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Phencyclidine: An Update

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Phencyclidine: An Update

Editor:

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Division of Preclinical Research
National Institute on Drug Abuse
and
New York State Division of
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Phencyclidine: An Update

This monograph is based upon papers and discussion from the technical review on phencyclidine which took place on May 7-9, 1985, at Rockville, Maryland. The review was sponsored by the Divisions of Preclinical Research, Clinical Research, and Epidemiology and Statistical Analysis of the National Institute on Drug Abuse.

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Foreword

This volume comes at an especially important time. PCP continues to be a significant problem in the U.S. with reports of epidemic levels of use in certain localities. Since 1978, NIDA has supported a substantial research program on this drug. The results of these studies demonstrated the biological and behavioral toxicity of PCP. Furthermore, PCP abuse presents a considerable hazard not only to the abuser, but to those in social contact with him/her. Particularly disconcerting were reports concerning the widespread occurrence of PCP-induced psychoses and neurological deficits and the number of PCP-abusing pregnant women.

In view of this, NIDA felt that it was important to convene a conference and prepare a monograph on a wide variety of issues relating to PCP. The present volume represents input from the preclinical, clinical, and epidemiological programs of the Institute. It is hoped that this state-of-the-science report on the basic biological mechanisms underlying PCP's action and current, as well as potential, treatment approaches to PCP abuse will prove useful to both researchers and health care personnel. This monograph also serves to document, once again, the harmful effects of PCP and should be useful in the development of specific prevention programs.

I would like to express my appreciation to Dr. Doris Clouet who undertook to organize the conference and edit the monograph while a Visiting Scientist at NIDA.

Marvin Snyder, Ph.D.
Director, Division of Preclinical
Research

Preface

Since the last Technical Review on phencyclidine (PCP) held by the National Institute on Drug Abuse was published in the NIDA Research Monograph series in 1978, there has been an explosion of new knowledge about drug actions in brain, including those of phencyclidine and related compounds, and during the same period, a new epidemic of PCP abuse has arisen in a few population centers in the country, resulting in greater clinical expertise in treating PCP abuse and PCP psychoses. In reports published in this Monograph, based on a Technical Review that was held May 7-9, 1985, at NIDA, both basic and clinical aspects of PCP abuse are discussed in detail by leading experts in each area.

In the first section of the Review, the basic neurobiology of PCP was emphasized. Studies on the binding of PCP to specific receptor molecules in brain have been confounded by the presence of two types of PCP-binding molecules. GUNDLACH reported that he was able to distinguish a PCP-binding site from an opiate-binding site that also binds PCP. The two sites had different localizations in brain and produced different behaviors. ZUKIN also separated the two receptors and reported on the early development of the PCP receptor in brain. He described the isolation from brain of a substance that reacts specifically with the PCP receptor. O'DONAHUE has isolated a naturally occurring peptide from brain that can produce responses similar to PCP when administered to animals. The results are reminiscent of the early studies of the opiopeptides that interact with opiate receptors and produce effects like narcotic drugs when administered to animals.

The binding of PCP to its receptor initiates a series of coupled neurochemical events eventually leading to the expression of behavior. One such coupling reaction was described by BLAUSTEIN as a blockade of transmembrane channels that transport K^+ into the neuronal cells. Since K^+ movements are part of the process of neurotransmission between neurons, this effect of PCP may explain the results of studies by MARWAH and by JOHNSON, in which several neurotransmitter systems were shown to be involved in the actions

of PCP. BUTERBAUGH also involved the K^+ channel in the dose-dependent convulsant and anticonvulsant actions of PCP. MORETON elaborated on the specific electrophysiological responses to PCP administration. JACOBSON has synthesized many components related to PCP, one of which, metaphit, was able to bind at the PCP receptor and display responses similar to PCP itself. CONTRERAS showed that metaphit had a dose-dependent effect on ataxia in rats acting like both agonist and antagonist.

OWENS has prepared antibodies to PCP in goats. When administered to mice the PCP levels in blood rose tenfold as an antibody-bound form that was readily excreted in urine. BROWNE tested the self-administration by rats of 1,000 compounds related (and not related) to PCP, some of which produced PCP-like effects. One compound that was self-administered prevented the entrance of PCP into brain. BALSTER gave a general review of the effects produced by PCP in laboratory animals and showed that some effects were similar to those produced by amphetamine , some to barbiturates, and some to antipsychotics. This response profile makes PCP a unique drug that stands alone in its complex effects and toxicity.

An epidemiological report by CRIDER showed high PCP abuse in Los Angeles, the Baltimore-Washington area and New York City, with part of the increase due to higher use by inner-city black males. WISH reported that urine tests on prison admissions show a high use of PCP, alone or in combination with alcohol and cocaine, in the New York City prison population. Signs of brain damage and motor impairment were found by LEWIS in PCP users subjected to a battery of psychological and motor tests. These subjects did not, in general, have toxic responses to PCP, raising the question of whether the symptoms preceded drug use. Many legal questions arise from incidents occurring while the PCP user is under the drug's influence or during psychotic episodes, including acts committed by police or others trying to restrain the psychotic individual. LERNER described three such cases that went to trial.

In the last section, clinicians discussed the treatment strategies for PCP abusers. MCCARRON described the presenting symptoms in prison admissions or emergency room admissions of over 1,000 PCP abusers with PCP toxicity. She divided responses in adults into four major patterns and suggested treatment for each group of symptoms. GORELICK explored the reasons for choosing PCP for use in a population entering a V.A. Hospital. The feelings of power, invulnerability, and great strength, followed by dysphoria, were the principal reasons. HOWARD showed the unfortunate condition of babies born to mothers using PCP. The babies at birth were smaller than usual, shaking and unconsolable. Some motor and mental deficits were seen in some of these babies after 6 months and 5 years. FRAM stated that the most successful treatment of middle-class adolescent PCP abusers was in a peer-group meeting attended daily. PAUL LUISADA of the Northern Virginia Institute of Psychiatry summed up the Technical Review meeting in a masterly fashion, blending basic and clinical reports into a coherent

whole. Unfortunately, this off-the-cuff summary was not recorded for publication.

Selecting from these presentations those that will prove most useful in the future, either clinically or mechanistically, is not easy. However, the potential value of some studies may be mentioned: (1) the separation and characterization of two PCP receptors; (2) the discovery of a naturally occurring brain substance with which PCP competes; (3) the synthesis of a long-lasting PCP analog; and (4) the successful preparation of antibodies to PCP. Clinically, we may mention: (1) the discovery that motor and psychological deficits are found in PCP abusers; (2) the categorization of responses in man to psychosis-producing doses of PCP, which has led to different treatment regimes depending on the group of presenting symptoms; and (3) the relative success of peer-group therapy programs in treating adolescent and young adult PCP abusers.

The editor would like to thank the participants, all of whom provided timely and complete reports in their areas of expertise, and Dr. J. Michael Walsh (Division of Clinical Research) and Nicholas J. Kozel (Division of Epidemiology and Statistical. Analysis) who cochaired the Technical Review. Special thanks go to Dr. R. Stanley Burns, who made a major contribution by suggesting suitable clinical investigators.

Doris H. Clouet, Ph.D.
Neuroscience Research Branch
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Characterization of Phencyclidine and Sigma Receptor-Binding Sites in Brain

Andrew L. Gundlach, Brian L. Largent, and Solomon H. Snyder

INTRODUCTION

Introduced in the late 1950s as a dissociative anesthetic, phencyclidine (PCP) has since become a major drug of abuse. PCP has strong, centrally mediated behavioral effects in animals and man and influences many different neuronal systems. PCP inhibits the uptake and increases the release of monoamines in brain (Smith et al. 1977; Doherty et al. 1980; Vickroy and Johnson 1983; Marwaha 1982; Johnson and Snell, this volume), interacts with cholinergic (Aronstam et al. 1980; Maayani et al. 1974) and serotonergic (Nabeshima et al. 1984) systems and antagonizes the neuronal stimulation caused by the excitatory amino acid, N-methyl aspartate (Anis et al. 1983). PCP may produce a general enhancement of neurotransmitter release by blocking voltage-sensitive potassium channels (Blaustein and Ickowicz 1983; Blaustein et al., this volume) and thus might act at several different loci.

Several groups have described specific receptor binding sites for PCP in brain, with a pharmacological selectivity consistent with effects of PCP and PCP analogues in animal behavioral tests (Vincent et al. 1979; Zukin and Zukin 1979). Classical neurotransmitters and neuropeptides fail to interact with ^{3}H-PCP binding sites. However, recently, a putative endogenous ligand for PCP receptor sites has been described (Quirion et al. 1984; DiMaggio et al., this volume; Sircar and Zukin, this volume).

Psychotomimetic effects of certain opioids in man (Keats and Telford 1964; Haertzen 1970) and unique behavioral effects of these drugs in animals have suggested the existence of specific receptor sites, designated sigma receptors (Martin et al. 1976). Many pharmacological and behavioral effects of the "sigma benzomorphans," such as N-allylnormetazocine (SKF-10,047) and cyclazotine, are not blocked by opioid antagonists, such as naloxone or naltrexone (Iwamoto 1981; Cowan 1981; Vaupel 1983; Young and Khazan 1984), suggesting that these drugs interact at sites very different from more classical opiate receptors. Furthermore,

other studies have suggested that the ability to produce "sigma" or psychotomimetic-like behavioral effects resides more in the (+) isomer of drugs such as SKF-10,047, with the (-) isomer being much weaker or inactive (Brady et al. 1982; Slifer and Balster 1983; Katz et al. 1985). This stereoselectivity is opposite to that at opiate receptors.

Assays of tritium-labeled (+) and (-) SKF-10,047 binding to brain membranes have suggested that the two isomers bind to distinct sites with different pharmacological profiles and regional distributions (Martin et al. 1984). Other behavioral and biochemical studies have suggested a commonality of effects of the sigma opioids and PCP and have suggested that these common actions are mediated through a common receptor binding site (Zukin and Zukin 1981; Shannon 1983). However, the regional distribution and pharmacology of (+)^{3}H-SKF-10,047 labeled sites appears to differ from sites labeled with ^{3}H-PCP (Tam 1983; Tam 1985; Martin et al. 1984).

3-(3-Hydroxyphenyl)-N-(1-propyl)piperidine (3-PPP) produces behavioral and biochemical effects in animals that are consistent with its having agonist actions at dopamine autoreceptors (Hjorth et al. 1981; Hjorth, et al. 1983; Arnt et al. 1983). However, in vitro assays reveal 3-PPP as a weak inhibitor of dopamine release and tyrosine hydroxylase activity, mechanisms thought to be under dopamine autoreceptor control (Sminia and Mulder 1983; Markstein and Lahaye 1983; Haubrich and Pflueger 1981; Mulder et al. 1985). Recently, specific binding sites in brain for (+) ^{3}H-3-PPP have been described (Largent et al. 1984). These apparently nondopaminergic binding sites have a distinctive pharmacological profile and regional distribution similar to that of putative sigma receptor sites labeled with (+)^{3}H-SKF-10,047 (Tam 1983; Tam 1985; Martin et al. 1984).

This study compares the pharmacological specificity and autoradiographic lotcalization of binding sites in brain for (+)^{3}H-SKF-10,047, (+) ^{3}H-3-PPP and ^{3}H-TCP (1-[l-(2-thienyl) cyclohexyl] piperidine), a PCP analogue that labels PCP receptor sites with high affinity (Vignon et al. 1983). Equilibrium-saturation and drug-inhibition binding studies using rat brain homogenates reveal that (+)^{3}H-SKF-10,047 binds to two sites on brain membranes and that (+)^{3}H-3-PPP and ^{3}H-TCP are selective radioligands for the high and low affinity (+)^{3}H-SKF-10,047 labeled sites respectively. Autoradiographic studies reveal a similar distribution of (+)^{3}H-3-PPP and high affinity (+)^{3}H-SKF-10,047 binding sites and the differential localization of these and ^{3}H-TCP (PCP-receptor) sites.

CHARACTERISTICS OF (+)^{3}H-3-PPP, (+)^{3}H-SKF-1Ø,Ø47 AND ^{3}H-TCP BINDING

Binding studies were carried out as previously described (Largent et al. 1984), except that in experiments utilizing (+) ^{3}H-SKF-10,047 or ^{3}H-TCP the incubation buffer was Tris pH 8.0 at a

concentration of 5 mM rather than 50 mM, as used in (+)^{3}H-3-PPP studies. All three ligands bind saturably and with high affinity to rat brain membranes. (+)^{3}H-3-PPP binds with an apparent dissociation constant (K_D) of 30 nM to a maximal number of binding sites (B_{max}) equal to 30 pmol/g wet wt (Largent et al. 1984). ^{3}H-TCP (0.5 - 50 nM) binds to a single population of sites with a K_D of 8 ± 1 nM and a B_{max} of 44 ± 4 pmol/g wet wt (n = 4). Computer-assisted analysis of saturation data suggests that (+)^{3}H-SKF-10,047 labels two sites in brain membranes with K_D values of 42 ± 12 and 615 ± 430 nM and B_{max} values of 18 ± 7 and 80 ± 25 pmol/g wet wt (n = 5) (see figure 1). In the presence of haloperidol (5 µM), a potent inhibitor of high affinity (+)^{3}H-SKF-10,047 binding (see figure 2), (+)^{3}H-SKF-10,047 labels a single low affinity site (K_D, 300 ± 24 nM) with a B_{max} of 74 ± 18 pmol/g wet wt (n = 3).

PHARMACOLOGY OF (+)^{3}H-3-PPP, (+)^{3}H-SKF-1Ø,Ø47 and (+)^{3}H-TCP BINDING

The drug specificity of sites labeled by (+)^{3}H-3-PPP has been extensively described previously (Largent et al. 1984) with binding being potently inhibited by haloperidol, phenothiazines such as perphenazine and psychotomimetic opioids such as pentazocine, SKF-10,047, and cyclazocine (see table 1). Stereoselectivity for different isomers of drugs at the binding site is seen for 3-PPP and many opioid derivatives, with the (+) isomer being a more potent inhibitor than its corresponding (-) isomer. However, little stereoselectivity occurs for isomers of PCP-like drugs, with dexoxadrol and levoxadrol having similar potency (see table 1). Furthermore, other potent PCP analogues have very low affinity for (+) ^{3}H-3-PPP labeled sites (data not shown).

^{3}H-TCP binding is inhibited potently by PCP and is stereoselective, with the potency of dexoxadrol exceeding that of levoxadrol by a factor of 400, in contrast to that seen at (+)^{3}H-3-PPP labeled Sites. Benzomorphans differ widely in their potency against ^{3}H-TCP binding with (+)SKF-10,047 being eight-fold more potent than pentazocine, a reversal of their relative potencies at (+)^{3}H-3-PPP labeled sites. Haloperidol and (+)3-PPP are very weak inhibitors of ^{3}H-TCP binding (see table 1).

The drug inhibition profile of (+)^{3}H-SKF-10,047 binding is similar in many ways to that of (+)^{3}H-3-PPP binding, but has some important differences. While pentazocine and SKF-10,047 are both potent inhibitors of (+)^{3}H-SKF-10,047 binding, haloperidol and (+)^{3}H-3-PPP inhibit only a portion of total specific (+)^{3}H-SKF-10,047 binding with high potency (see figure 2 and table 1). If (+)^{3}H-SKF-10,047 binding is measured in the presence of 5µM haloperidol to block binding to the haloperidol/(+)3-PPP-sensitive sites, the drug specificity of the remaining specific binding is similar to that for ^{3}H-TCP binding (see table 1). The decreased potency of pentazocine and the higher potencies of phencyclidine and dexoxadrol against (+)^{3}H-SKF-10,047 binding, relative to their potencies at (+)^{3}H-3-PPP sites, merely reflects the

contribution of the low-affinity PCP-like sites to the total specific (+)^{3}H-SKF-10,047 binding (see table 1). Although overall IC_{50} values are given in table 1, inhibition of (+)^{3}H-SKF-10,047 binding by drugs such as phencyclidine and pentazocine is consistent with displacement of binding from two sites (see figure 2).

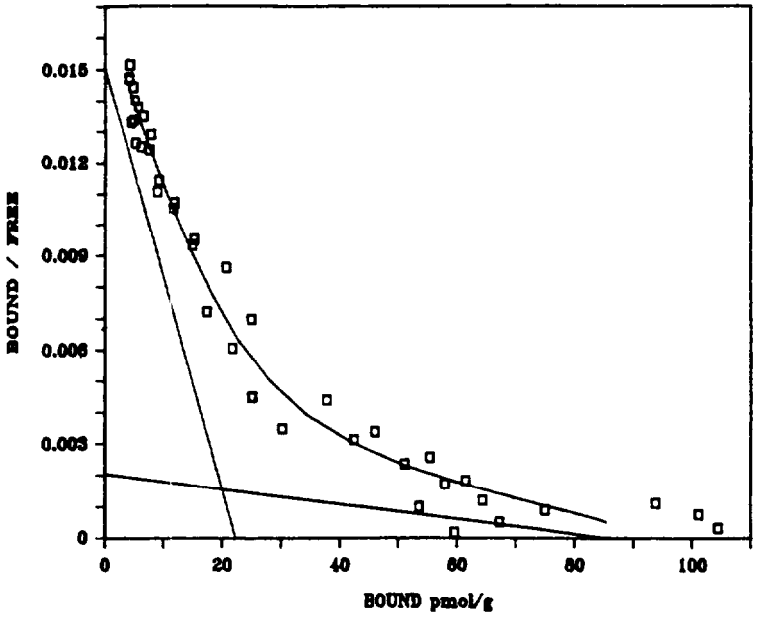

FIGURE 1. *Scatchard plot of equilibrium-saturation binding of (+)SKF-10,047 to rat brain membranes. Membranes were incubated with 8 nM (+)^{3}H-SKF-10,047 and various concentrations (1 - 64,000 nM)* of *(+)SKF-10,047* for *45 min at room temperature. Results are from a single experiment and values are the average of duplicate determinations. Lines indicate the high (K_D 45 nM; B_{max} 22 pmol/g) and low (K_D 110 nM; B_{max} 86 pmol/g) affinity components of total specific binding. Also shown is the computer-generated curve of best fit for the data points.*

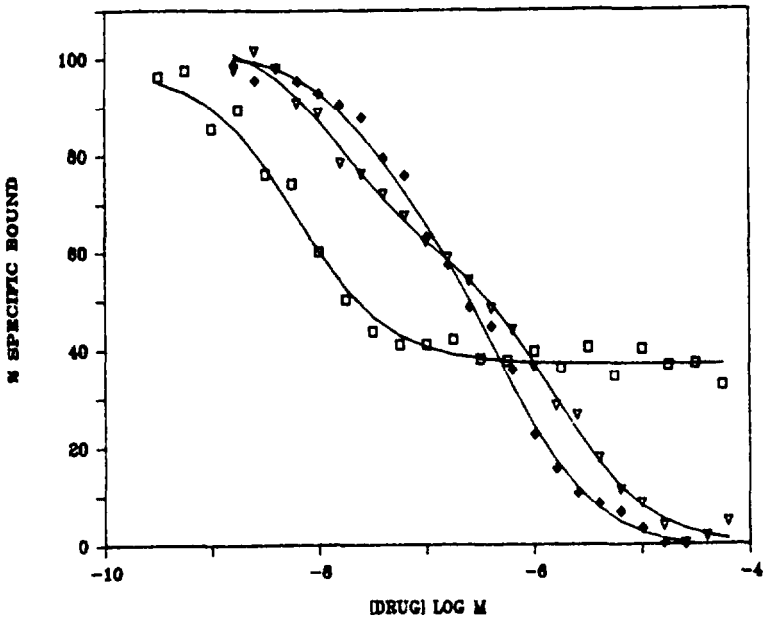

FIGURE 2. *Drug inhibition* **of** *(+)^{3}H-SKF-10,047* **binding** *to rat brain membranes. The data shown are from a typical experiment and represent the* **mean** *of duplicate determinations, replicated twice. Lines represent computer generated curves of best fit for drug displacement* **from** *one site (haloperidol □, K_i 4 nM) or two sites (pentazocine ▽, K_i values 13 and 1550 nM; phencyczidine ◆, K_i values 31 and 457 nM).*

AUTORADIOGRAPHIC LOCALIZATION OF (+)^{3}H-3-PPP, (+)^{3}H-SKF-10,047 AND ^{3}H-TCP BINDING SITES

Studies of the regional distribution of (+)^{3}H-3-PPP binding sites in brain homogenates reveals highest levels in the hindbrain, midbrain, cerebellum, and hypothalamus, with lower levels in cerebral cortex, corpus striatum, and olfactory tubercle. Similar studies reveal high levels of (+)^{3}H-SKF-10,047 binding site in hypothalamus, midbrain, pons, and medulla (Tam 1985), while ^{3}H-PCP binding is highest in hippocampus and cerebral cortex (Zukin and Zukin 1979). Autoradiographic studies provide details of these binding site localizations and alloy a better comparative analysis of the structures labeled by each ^{3}H-ligand. Slide mounted brain sections (8 microns) were incubated with 5 nM (+)^{3}H-3-PPP, 10 nM (+)^{3}H-SKF-10,047, or 5 nM ^{3}H-TCP for 45 minutes at room temperature, washed in buffer for the appropriate amount of time, rinsed in water, and dried. Autoradiograms were produced by apposing the labeled brain sections to tritium-sensitive film for 3 to 5 weeks at 4°C.

TABLE 1. *Drug inhibition of specific binding of various ^{3}H-ligands to sigma and PCP receptor sites in brain*

Drug	IC_{50} (nM) (+)^{3}H-3-PPP	(+)^{3}H-SKF-10,047	(+)^{3}H-SKF-10,047 (+ 5µH haloperidol)	(+)^{3}H-TCP
(+)SKF-10,047	340 ± 30	75 + 3	375 + 30	420 ± 7
(-)SKF-10,047	1350 ± 110	895 ± 175	530 ± 25	840 ± 35
(+)3-PPP	30 ± 2	49 + 6*	>100,000	>100,000
Haloperidol	2 ± 1	5 ± 1*	>50,000	>50,000
Pentazocine	23 ± 2	285 ± 50	1520 ± 220	3,200
Phencyclidine	710 ± 85	330 ± 40	48 ± 12	63 ± 6
Dexoxadrol	1880 ± 510	569 ± 140	46 ± 9	42 ± 5
Levoxadrol	2080 ± 490	3790 ± 70	9,500	17,000

NOTE: Membranes were Incubated with 10-12 concentrations of drug and 2-4 nM (+)^{3}H-J-PPP, 8-10 nM (+)^{3}H-SKF-10,047, or 1-3 nM ^{3}H-TCP respectively. The IC_{50} (concentration that inhibited 50% of specific binding) was calculated using an iterative curve fitting program (McPherson 1983). Nonspecific binding was determined in the presence of 1 µM haloperidol for (+)^{3}H-3-PPP, 100µM PCP for (+)^{3}H-SKF-10,047, and 100 µM (+)SKF-10,047 for ^{3}H-TCP.

*IC_{50} values for (+)3-PPP and haloperidol against the portion of specific (+)^{3}H-SKF-10,047 binding displaceable by these drugs.

(+)^{3}H-3-PPP labels a number of different areas in the brain, including a major group of structures associated with the limbic system, and another with the brainstem motor-regulatory system. Binding sites are concentrated in the pyramidal cell layer of the hippocampus and the granular layer of the dentate gyrus, with lower levels in the remaining hippocampal areas (see figure 3). Most of the cerebral cortex has low levels of binding, but the pyramidal cell layer of the pyriform cortex and a superficial layer of the cingulate cortex have higher levels. The hypothalamus, septal nuclei, diagonal band, and central grey also display high amounts of (+)^{3}H-3-PPP binding sites. Likewise several cranial nerve nuclei, reticular, and pontine nuclei all have high levels of binding. In the cerebellum the Purkinje and granule cell layers are heavily labeled, while high levels are also seen in the deep cerebellar nuclei and vestibular nuclei (see figure 4).

The distribution of ^{3}H-TCP labeled sites is similar to that described previously for ^{3}H-PCP (Quirion et al. 1981). Binding is densest in cortical regions, the strata oriens and radiatum of the hippocam us and the molecular layer of the dentate gyrus (see figure 3). There is negligible binding over the pyramidal cell layer of the hippocampus and the granular layer of the dentate gyrus. Moderate levels of binding sites are present in thalamic areas, the corpus striatum, nucleus accumbens, olfactory tubercle, septum, and interpeduncular nucleus, while low levels are found throughout the cerebellum, pons-medulla, midbrain, and hypothalamus (see figures 3 and 4).

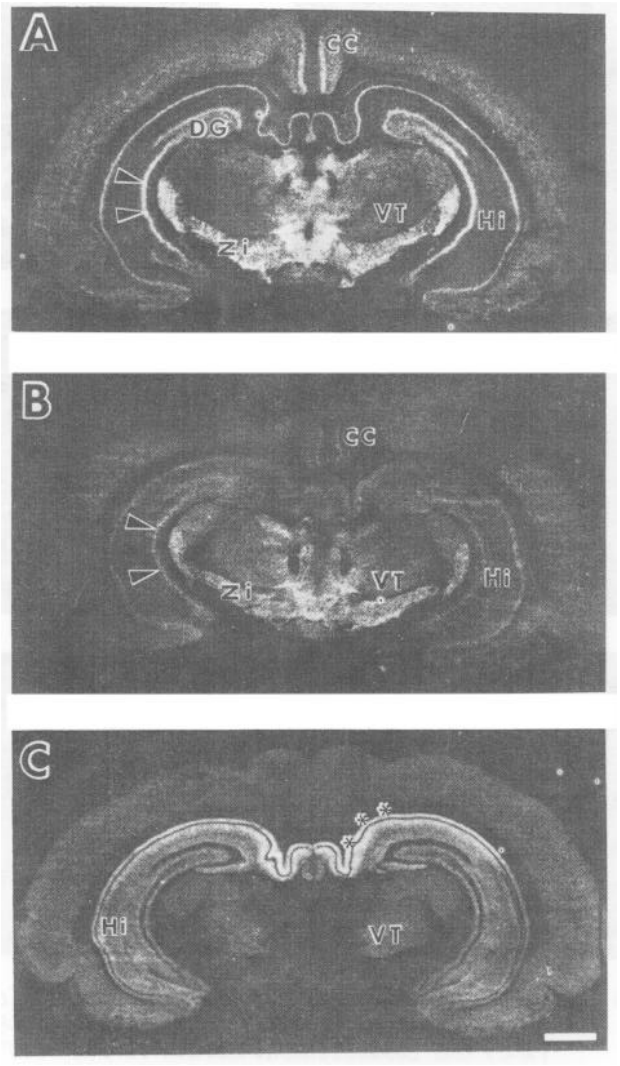

FIGURE 3. *Autoradiograms of (+)^{3}H-3-PPP, (+)^{3}H-SKF-10,047 and ^{3}H-TCP binding sites in coronal sections of guinea pig brain. Increased grain density is indicated by increased whiteness in the photograph. Distribution of (A) (+)^{3}H-3-PPP sites, (B) (+)^{3}H-SKF-10,047 sites, (C) ^{3}H-TCP sites. Nonspecific binding of each ligand was not significantly above film background to yield an image at a comparable exposure. Cingulate cortex, CC; dentate gyrus, DC; hippocampus, Hi (pyramidal Cell layer, arrows; Stratum oriens, asterisks); ventral thalamus, VT; zona incerta, Zi. (Bar = 2 mm).*

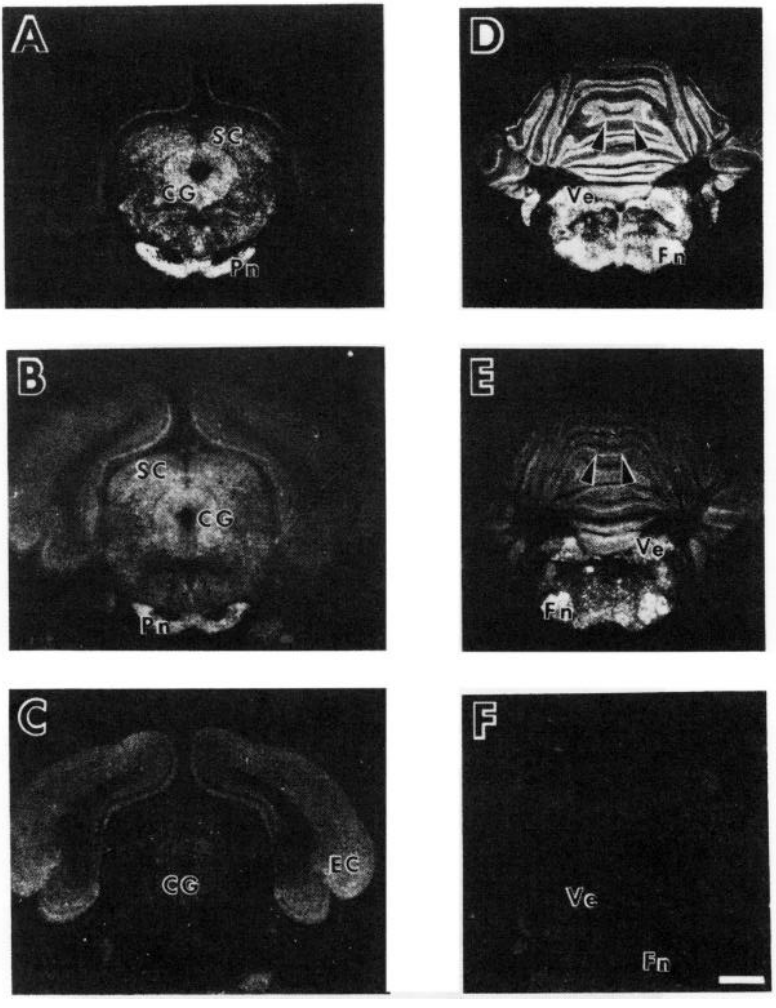

FIGURE 4. *Autoradiograms of (+)^{3}H-3-PPP, (+)^{3}H-SKF-10,047 and ^{3}H-TCP binding sites at the level of the midbrain (A-C) and cerebellum/hindbrain (D-F). (+)^{3}H-3-PPP binding is highest in the pontine nuclei and central grey (A), over the Purkinje and granular layers of the cerebellum and to cranial nerve nuclei (D). The distribution of (+)^{3}H-SKF-10.047 bindina sites is similar to that for, (+)^{3}H-3-PPP (B,E). Very low levels of ^{3}H-TCP associated arains are found at the level of the cerebellum and pons-medulla (C,F). Central grey, CG; cerebellum, Purkinje cell layer, arrows; entorhinal cortex, EC; facial nucleus, Fn; pontine nuclei Pn; Superior colliculus, SC; vestibutar nuclei, Ve. Bar = 2 mm.*

In several brain areas the distribution of (+)^{3}H-SKF-10,047 binding sites is strikingly similar to that of (+)^{3}H-3-PPP labeled sites. Structures labeled by both (+)^{3}H-SKF-10,047 and (+)^{3}H-3-PPP (but not by ^{3}H-TCP) include the pyramidal cell layer of the hippocampus, the granular layer of the dentate gyrus, the Purkinje cell layer of the cerebellum, cranial nerve and pontine nuclei, the central grey, the zona incerta and hypothalamic areas, among others (see figures 3 and 4). Additionally, (+)^{3}H-SKF-10,047 labels to some extent certain brain areas labeled heavily by ^{3}H-TCP, but not by (+)^{3}H-3-PPP. These include the thalamus, olfactory tubercle, and nonpyramidal layers of the hippocampus. One complicating methodological problem associated with (+)^{3}H-SKF-10,047 binding to brain slices is the somewhat low affinity of specific binding and high levels of nonspecific binding of the ligand, which makes interpretation of the autoradiograms more difficult. Initial attempts to examine sites labeled by (+)^{3}H-SKF-10,047 which are lower affinity and not labeled by haloperidol or (+)^{3}H-3-PPP, failed to produce visually convincing images. However, depletion of the concentrated binding over the pyramidal cell layer of the hippocampus, Purkinje cell layer of the cerebellum, and cranial nerve nuclei was apparent (data not shown). Likewise, examination of (+) ^{3}H-SKF-10,047 binding in the presence of a drug selective for PCP sites should give further confirmation of the similarity of high affinity (+)SKF-10,047 and (+)3-PPP/haloperidol labeled sites.

CONCLUSIONS

These studies have implications for research on both PCP and psychotomimetic opioids, as well as perhaps dopaminergic function. A major finding, which goes against previous suggestions, is that PCP and psychotomimetic opioid binding sites in brain are not identical with regard to pharmacology or distribution, at least when examined in an *in vitro* system. The benzomorphan, (+)SKF-10,047, labels at least two populations of nonopiate sites in brain. Sites for which (+)SKF-10,047 has higher affinity have a characteristic pharmacology having high affinity and selectivity for benzomorphans, haloperidol, and (+)3-PPP (this study, see also Martin et al. 1984; Tam 1985). Their distribution can be visualized autoradiographically, revealing high levels in hypothalamus, midbrain, cerebellum, pons, and medulla. Overall, the pharmacology and distribution of (+)3-PPP labeled sites and high affinity (+)SKF-10,047 sites are very similar, suggesting that these drugs at least label the same receptor-binding site complex, although there is not, as yet, conclusive evidence that they label the exact same site on the molecule. Further studies examining possible allosteric interactions and agonist-antagonist roles of the two types of drug are required to decide this issue.

The relative selectivity of drugs such as haloperidol for the higher affinity (+)SKF-10,047 labeled sites allowed the determination of the pharmacological profile of the low affinity sites, which was very similar to that of ^{3}H-TCP labeled sites. PCP and

PCP analogues had high affinity for the haloperidol-insensitive (+)SKF-10,047 binding, and stereoselectivity for dexoxadrol over levoxadrol was greater than that seen against total specific (+) ^{3}H-SKF-10,047 binding.

Although PCP has high affinity for ^{3}H-TCP labeled sites, it also has moderate potency against (+)^{3}H-3-PPP and (+)^{3}H-SKF-10,047 binding, suggesting that it may still have pharmacological activity at these sites, *in vivo*, when present at appropriate concentrations. This may explain the apparent contradiction between these *in vitro* results, revealing different binding sites for these two groups of drugs and differences in distribution of these sites, and the evidence cited in the introduction to this study, from *in vivo* behavioral and biochemical studies, which demonstrates common actions of PCP ard psychotomimetic opioids. For example, the number and regional concentration of PCP binding sites in the pons-medulla and hypothalamus is lower than that of (+)SKF-10,047 (and (+)3-PPP) sites in these same areas. Yet both SKF-10,047 and PCP produce effects-on cardiovascular parameters (Vaupel 1983), presumably through central actions at cardiovascular regulatory loci in these brain areas. Furthermore, in light of the common psychotic effects of PCP and SKF-10,047, it is possible that sites that are labeled by both PCP (TCP) and (+)SKF-10,047 such as in nonpyramidal cell areas of the hippocampus and in cortex may represent at least some of the sites at which these drugs mediate these effects. However, it is also possible that sites labeled with high affinity by (+)SKF-10,047 (and (+)3-PPP) throughout the brain, particularly in the hippocampus, hypothalamus, and brainstem reticular formation, are "psychotomimetic sites."

Experiments based on our results could be conducted to test the physiological and pharmacological relevance of these findings. Autoradiographic mapping studies should assist future work towards this end, as they provide new information that allows "site-directed experiments." The examination of the effects, *in vivo* and *in vitro*, of sigma and/or PCP drugs on biochemical, physiological, and behavioral parameters in discrete brain areas will best improve our knowledge of the true sites and mechanisms of action of PCP-like and psychotomimetic opioid drugs.

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Further Evidence of Phencyclidine/Sigma Opioid Receptor Commonality

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Phencyclidine (1-[1-phenylcyclohexyl]piperidine HCl; PCP) and its active derivatives produce unique behavioral effects in animals and psychotomimetic effects in humans. Drugs of this class have been demonstrated to bind saturably, reversibly, and with high affinity to specific binding sites in brain (Hampton et al. 1982; Quirion et al. 1981; Sircar and Zukin 1983; Vincent et al. 1979; Zukin and Zukin 1979). These sites have been shown to exhibit a characteristic heterogeneous regional distribution pattern (Quirion et al. 1981; Sircar et al., submitted for publication; Zukin and Zukin 1979) distinct from that of any other receptor type.

A variety of evidence suggests that PCP-like drugs and sigma opioids may bring about their common behavioral effects via activation of the same receptors. The existence of sigma opioid receptors was postulated by Martin to account for the behavioral pharmacology of the drug N-allylnormetazocine (SKF-10,047) and related benzomorphans, such as cyclazocine, which can produce psychosis in humans and "canine delirium," tachycardia, and tachypnea in animals (Martin et al. 1976). Sigma opioid receptors differ from mu, delta, and kappa receptors in terms of ligand selectivity. Specific sigma receptor ligands, such as (+)SKF-10,047, have very little affinity for mu, delta, or kappa receptors (Zukin et al. 1984), while prototypic mu, delta, and kappa opioids exhibit little or no affinity for sigma opioid receptors (Zukin and Zukin 1981a). Sigma opioid receptors labeled by ^{3}H-cyclazocine (ibid.) or ^{3}H-(-)SKF-10,047 (Zukin et al., submitted for publication) in homogenate binding studies under conditions blocking radioligand access to mu, delta, and kappa opioid receptors do, however, exhibit a ligand selectivity pattern in which not only sigma opioids but also PC and its derivatives are active. Similarly, receptors labeled by ^{3}H-PCP exhibit high affinity for sigma opioids (Zukin et al. 1983). Regional distributions of ^{3}H-PCP and ^{3}H-cyclazocine homogenate binding are similar (Zukin and Zukin 1981a). Behavioral studies utilizing the drug discrimination paradigm (Shannon 1981; Shannon 1982; Teal and Holtzman 1980; Holtzman 1980; Brady et al. 1982; Katz et al. 1985) have demonstrated cross-generaliza-

tion between PCP derivatives and sigma opioids. Such biochemical and behavioral findings have suggested the hypothesis that the sigma opioid and PCP receptors may represent the same entity (Zukin and Zukin 1981b; Quirion et al. 1981).

A problem in previous studies of sigma opioid receptors has been that racemic or (-) sigma opioid isomers interacted at multiple opioid receptor sites, requiring special blocking techniques to permit targeting of sigma receptors (Zukin and Zukin 1981b). The (+) isomers of sigma opioids, essentially devoid of mu, delta, and kappa activity (Zukin et al. 1984), thus seemed the ligands of choice for studies of sigma opioid receptors. This report documents the binding characteristics of ^{3}H-(+)SKF-10,047 to rat and mouse brain.

Among PCP derivatives, TCP (N-(1-[2-thienyl]cyclohexyl)piperidine) has been shown to be more potent than PCP itself (Vincent et al. 1979; Zukin and Zukin, 1979). In homogenate binding studies ^{3}H-TCP binds to brain PCP receptor sites more potently than ^{3}H-PCP (Vignon et al. 1983). Such findings raise the possibility that ^{3}H-TCP might prove a superior molecular probe of PCP/sigma opiate receptors.

In this chapter, the binding characteristics of the prototypical sigma opioid H-(+)SKF-10,047 are described, and the quantitative localization patterns of bits binding sites in brain are compared with those of ^{3}H-PCP and ^{3}H-TCP, the prototypic PCP receptor ligands, to address the questions of the extent and nature of PCP-sigma opioid receptor commonalities, and which radioligands constitute the best molecular probes of brain PCP/sigma opioid receptors.

CHARACTERIZATION OF ^{3}H-(+)SKF-1Ø,Ø47 BINDING IN RAT BRAIN

Specific binding of ^{3}H-(+)SKF-10,047 proved saturable with respect to increasing radioligand concentration. Scatchard analysis of ^{3}H-(+)SFK-10,047 binding gave a curvilinear plot suggestive of multiple ^{3}H-(+)SKF-10,047 binding sites or cooperativity of binding. Computer-assisted analysis (Munson and Rodbard 1980) revealed the best fit to be to a two-site model with apparent K_D values of 3.6 nM and 153 nM, and B_{Max} values of 40 fmol and 1.6 pmol/mg protein for the apparent high- and low-affinity binding sites, respectively. Scatchard analysis of complete binding isotherms in each of the four dissected brain regions (hippocampus, frontal cortex, cerebellum and pons-medulla) similarly gave curvilinear plots, which, in each case, displayed a good fit to a two-site model. For each of these regions, as well as for the whole-brain preparation, a valid fit to a one-site model could not be obtained (Sircar and Zukin, in press).

^{3}H-(+)SKF-10,047 binding was also measured in the presence of 100 nM haloperidol. This approach yielded a Scatchard plot in which the density of the apparent high-affinity sites was decreased by

greater than 90 percent (to 0.5 fmol/mg protein) relative to the value obtained in the absence of haloperidol, while the density of the apparent low-affinity binding sites showed little alteration (1.08 pmol/mg protein). This finding suggested that the curvilinear Scatchard plot was the result of independent interactions of ^{3}H-(+)SKF-10,047 with two distinct binding sites. To test this hypothesis, ligand selectivities of the two apparent classes of sites were characterized. The rank order of potency (PCE>dexoxadrol>PCP>pentazocine>ketamine>levoxadrol) of ligands for displacement of 100 nM ^{3}H-(t)SKF-10,047 from the predominant lower-affinity sites (in the presence of 100 nM haloperidol) was similar to that reported for displacement of ^{3}H-PCP (Zukin and Zukin 1979; Zukin et al. 1983). By contrast, the rank order of drugs inhibiting the binding of ^{3}H-(+)SKF-10,047 to the higher-affinity site (haloperidol>dexoxadrol>pentazocine>PCP>levoxadrol) proved distinct from the pattern for PCP receptors.

CHARACTERIZATION OF ^{3}H-(+)SKF-10,047 BINDING SITES IN MOUSE BRAIN

To assess possible species specificity of our findings, ^{3}H-(+)SKF-10,047 binding was carried out in mouse brain. Scatchard analysis of the binding data resulted in a biphasic Scatchard plot similar to that observed in rat brain. Computer-assisted analysis of the apparent two-site fit of the binding data yielded apparent K_D values of 4 and 227 nM, and B_{Max} values of 86 fmol and 3.8 pmol/mg protein, respectively. As in the rat, 100 nM haloperidol significantly reduced the high-affinity site while leaving the low-affinity site unaffected. Our finding of two distinct ^{3}H-(+)SKF-10,047 binding sites in mouse as well as rat brain is at variance with a recent study (Martin et al. 1984), which had reported mouse brain to possess a homogeneous population of haloperidol-sensitive ^{3}H-(+)SKF-10,047 binding sites. It may be that our extending the binding isotherm to higher radioligand concentrations (500 nM for our study as opposed to 100 nM for Martin et al.) was responsible for revealing the lower-affinity PCP/sigma opioid receptors.

VISUALIZATION OF PCP/SIGMA OPIOID RECEPTORS BY LIGHT HICROSCOPY AUTORADIOGRAPHY

The quantitative distribution patterns of PCP/sigma opioid receptors identified here from ^{3}H-TCP autoradiograms(Sircar and Zukin, in press), ^{3}H-(+)SKF-10,047 autoradiograms and ^{3}H-PCP autoradiograms (Sircar et al., submitted for publication) were remarkably similar (table l), and resembled the qualitative pattern of ^{3}H-PCP binding sites previously reported (Quirion et al 1981). Hippocampus was the most heavily labeled region in all 3 autoradiograms (figure 1). Dentate gyrus and hippocampal fields CA_1 and CA_2 were noticeably darker than hippocampal field CA_3 in PCP, TCP and (+)SKF-10,047 autoradiograms. Distinct laminar patterning in the hippocampus was seen with PCP and TCP, while lamination was less distinct in the case of (+)SKF-10,047. Diencephalic structures manifested moderate to low amounts of binding. In the thalamic region, the intermediodorsal nucleus had the highest concentration

of both ^{3}H-PCP and ^{3}H-(+)SKF-10,047 binding, while in the hypothalamus the dorsomedial nucleus had the highest levels of both. Midbrain/pontine areas also showed moderate to low levels of ^{3}H-PCP and ^{3}H-(+)SKF-10,047 binding. The superficial layer of the superior colliculus was substantially darker than the deeper layers. Another region in this area showing high concentrations of both ^{3}H-PCP and ^{3}H-(+)SKF-10,047 binding was the interpeduncular nucleus. Cerebellym had moderate levels of PCP binding, but fairly high levels of ^{3}H-(+)SKF-10,047 binding. In comparison, there were significantly lower levels of ^{3}H-TCP binding in central gray,

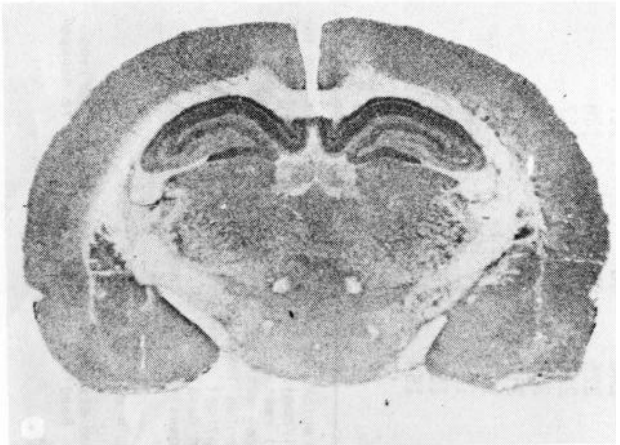
TABLE 1. *Receptor density values obtained from autoradiograms labeled with ^{3}H-PCP, ^{3}H-TCP and ^{3}H-(+)SKF-10,047 in rat brain*

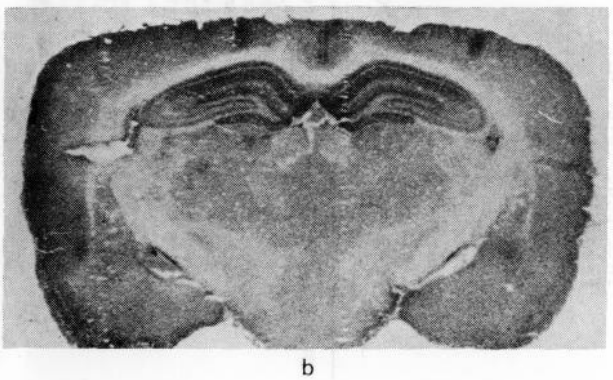
	Receptor Density (fmol/mg Tissue)		
Anatomical Region	PCP	TCP	(+)SKF-10,047
Hippocampus	296	91	194
CA 1	284	104	194
CA 2	272	105	211
CA 3	225	66	167
Dentate	378	111	194
Dorsomedial hypothalamus	284	40	156
Superior colliculus	260	65	128
Interpeduncular n.	248	40	117
Frontal cortex	225	83	128
Basolateral amygdaloid n.	225	42	117
Substantia nigra	225	14	139
Central gray	213	26	161
Nucleus accumbens	177	52	94
Cerebellum	154	47	139
Locus coeruleus	154	46	134
Striatum	154	46	94
Pons reticular formation	12	8	78
Corpus callosum	0	0	0

NOTE: 20-Micron sectlons from specific regions of rat brain were prepared and incubated with 10 nM H-PCP (49.9 Cl/mnol), 5 nM ^{3}H-TCP (58.2 Cl/mmol) and 10 nM ^{3}H-(+)SKF-10.047 (25.5 Cl/mmol) respectively. Sections were juxtaposed against trltlum-sensltlve film along with tritium standards, and-optical densities determined (Geary and Wooten 1983: Kuhar 1982: Sircar and Zukin. in press; Tempel et al. 1984). Optical density values from different brain regions were converted to receptor densities (nCl/mg tissue) using the tritium standards. The receptor density values have been expressed in fmol/mg tissue using the formula:

$$\frac{\text{CI/mg tissue}}{\text{speclflc actlvity}} = \text{mmol/mg tissue.}$$

Values represent mean readings from six sections for each region, derived from two Independent experiments. Readings have been normalized to nonspecific binding and to blank tissue.





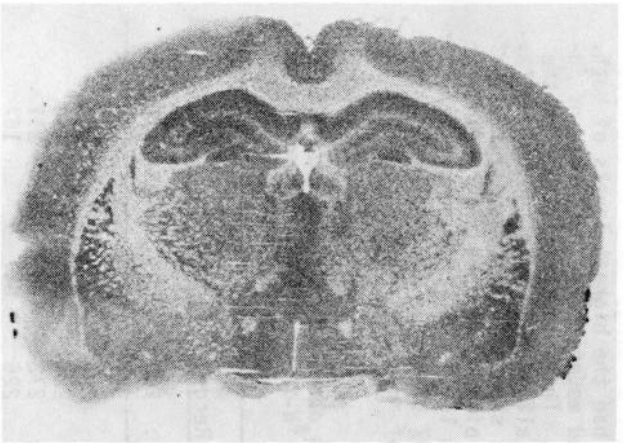


FIGURE 1. *Anatomical distrubtion of ^{3}H-PCP, ^{3}H-TCP, and ^{3}H-(+)SKF-10,047 bindings in rat brain*

NOTE: Brain sections are at the level of bregma -3.8 mm of the rat brain atlas (paxinos and Watson 1982). 20-Micron thick coronal sections of frozen rat brain were cut, thaw-mounted onto gelatin-coated slides, and incubated with (a) 10 nM ^{3}H-PCP (49.9 Ci/mmol) for 45 minutes; (b) 5 nm ^{3}H-TCP (58.2 Ci/mM) for 1 hour; (c) 10 nM ^{3}H-(+)SKF-10,047 (25.5 Ci/mmol) for 1 hour. Adjacent sections were incubated with the same radioligand concentrations, but in the presence of 1,000-fold excess of nonlabeled PCP, TCP or (+)SKF-10,047, respectively, for nonspecific binding. Sections were washed, dried, and exposed to tritium-sensitive film for 2 to 6 weeks. Note the dense labeling in CA_1, CA_2, and dentate gyrus of the hipocampus with all three radioligands. TeUnlike PCP and TCP, (+)SKF-10,047 labeled stratum pyramidale.

substantia nigra, dorsomedial hypothalamus, and interpeduncular nucleus. PCP is known to bind very weakly to mu opiate receptors (Vincent et al. 1978) but this property is not related to its discriminative stimulus behavioral effects or to its interaction with PCP/sigma opiate receptors. Areas such as central gray, substantia nigra, and interpeduncular nucleus are known to be rich in mu opiate receptors (Herkenham and Pert 1982). The fact that ^{3}H-TCP does not bind significantly in these areas suggests that, besides being a more potent analog of PCP than PCP itself (Vignon et al. 1983), it may also be a more specific PCP/sigma opioid receptor ligand, devoid of significant cross-activity at other classes of receptors.

The remarkable similarity in the regional distribution of binding sites for the arylcyclohexylamines PCP and TCP and those of the chemically unrelated benzomorphan (+)SKF-10,047 supports the hypothesis that PCP derivatives and sigma opioids may act via a common receptor site. The sigma opioid/PCP receptors are concentrated primarily in the limbic areas of the brain, including hippocampus, amygdala, striatum, and frontal cortex--regions that are involved in higher nervous functions, including memory, emotion, and behavior (Kimura 1958; Milner 1968). Autoradiograms obtained with ^{3}H-(-)SKF-10,047 in the presence of mu and delta blockers (Zukin et al., Submitted for publication are generally similar to those obtained with ^{3}H-(+)SKF-10,047 or ^{3}H-PCP. By contrast to ^{3}H-PCP, ^{3}H-TCP, and ^{3}H-(+)SKF-10,047 autoradiograms, ^{3}H-(-)SKF-10,047 autoradiograms show striosomes in the striatum and denser labeling in central gray, locus coeruleus, and nucleus accumbens, whereas hippocampus showed a lower relative concentration of ^{3}H-(-)SKF-10,047 binding. ^{3}H-(-)SKF-10,047 may thus label not only sigma opioid/PCP receptors, but also residual mu opioid receptors and other binding sites as well, perhaps including the haloperidol-sensitive sites described above. The differences between the autoradiographic patterns of ^{3}H-PCP and ^{3}H-(+)SKF-10,847 binding in the present study probably arise from the fact that ^{3}H-PCP, which gives a Scatchard analysis indicative of a single high-affinity site in binding studies (Vincent et al. 1979; Zukin and Zukin 1979; Quirion et al 1981; Mendelsohn et al. 1984) reveals the pattern of its homogenous class of PCP/sigma opioid receptors in autoradiograms, while ^{3}H-(+)SKF-10,047, which we have shown in this study to bind to two independent sites, reveals the autoradiographic pattern of the pattern of PCP/sigma opioid receptors plus that of the haloperidol-sensitive binding sites.

Our results suggest that the numerically predominant 153 nM ^{3}H-(+)SKF-10,047 site represents the PCP opioid receptor. The much less abundant haloperidol-sensitive 3.6 nM ^{3}H-SKF-10,047 binding site that we have described appears to represent the same entity as a class of sites reported by several other groups utilizing diverse strategies, including use of ^{3}H-SKF-10,047 in the presence of etorphine (Su 1982); ^{3}H-ethylketoSyclazocine (EKC) in the presence of excess naloxone (Tam 1983); ^{3}H-(+)SKF-10,047 or (+)^{3}H-haloperidol in guinea pig brain (Tam and Cook 1984); (+)^{3}H-3-PPP

(3-(3-hydroxyphenyl)-N-(1-propyl)piperidine) or ^{3}H-haloperidol (Largent et al. 1984); ^{3}H-EKC or ^{3}H-SKF-10,047 in cultured NCB20 cells (McLawhon et al. 1981; West et al. 1983); and ^{3}H-(+)SKF-10,047 in mouse brain (Martin et al. 1984). The pattern of areas where we have found relatively higher ^{3}H-(+)SKF-10,047 than ^{3}H-PCP binding, including central gray and cerebellum, is consistent with areas enriched in (+)^{3}H-3-PPP binding (Largent et al. 1984). As noted above, the latter radioligand labels sites identical to the haloperidol-sensitive ^{3}H-(+)SKF-10,047 sites but distinct from ^{3}H-PCP sites (ibid.). The behavioral significance of the haloperidol-sensitive (sigma) sites remains unknown. The striking PCP-like behavioral effects of (+)SKF-10,047 thus appear to be mediated at the haloperidol-insensitive sites, as well as at haloperidol-sensitive sites.

Because of its interactions with multiple binding sites, ^{3}H-(+)SKF-10,047 does not appear to be the ideal ligand for labeling PCP/sigma opioid receptors in binding assays. While its interaction with the non-PCP/sigma opioid sites can be blocked by inclusion of haloperidol in the incubation medium, ^{3}H-TCP, which binds exclusively and more potently to the nonhaloperidol-sensitive sigma opioid/PCP receptors (Vignon et al. 1983; Sircar and Zukin, in press), is clearly preprable to ^{3}H-(+)SKF-10,047 for targeting these sites. Indeed, ^{3}H-TCP appears to be the best ligand of PCP/sigma opioid receptors currently available.

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Isolation and Identification of an Endogenous Ligand for the Phencyclidine Receptor

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CLASSIFICATION OF OPIOID RECEPTORS

Opioid receptors comprise a heterogenous group that can be divided into at least four biochemically and topographically distinct subtypes, designated mu, kappa, sigma, and delta. Martin et al. (1976) proposed the existence of mu, kappa, and sigma opioid receptors based on observed differences in pharmacological profiles of drugs seen with variably selective opioid agonists and antagonists. Other groups have provided evidence for the delta subtype (Hughes et al. 1975).

The mu opioid receptor has been extensively characterized (Lord et al. 1976; Lord et al. 1977; Chang et al. 1979; Chang and Cuatrecasas 1981). Classical opioid effects, such as analgesia induced by morphine and its congeners, are thought to be mediated by the mu opioid receptor, which preferentially binds the levorotatory isomer. This stereoselective binding of the (-) enantiomer, which has greater analgesic and respiratory depressant properties than the (+) isomer, strongly supports the physiological relevance of specific mu opioid receptors. Delta receptors have also been well characterized (Simantov 1978). These opioid receptors are believed to be involved in reward processes and seizure. From the evidence available for kappa receptors (Kosterlitz and Paterson 1980, Chang and Cuatrecasas 1979), it appears that these sites are involved in mediating analgesia and sedation. Finally, it has been postulated that sigma receptors are involved in mediating the psychotomimetic actions seen with some of the benzomorphans, PCP, and PCP analogs (Quirion et al. 1981a).

INTERACTION OF OPIOID RECEPTORS WITH ENDOGENOUS PEPTIDE LIGANDS

The mu, kappa, and delta opioid receptors have been found to interact with endogenous peptide ligands that share certain pharmacologic properties with opioid drugs. These peptide ligands are derived from at least three different prohormones located in both

the central and peripheral nervous systems and also in the endocrine system.

Delta receptors are relatively selective for two related pentapeptides, methionine enkephalin and leucine enkephalin (met- and leu-enkephalin), which were isolated from porcine brain (Hughes 1975). Both met- and leu-enkephalin inhibit electrically induced contractions of guinea pig ileum, an effect that mimics those effects seen with opioid drugs, and is naloxone reversible. The enkephalins are processed posttranslationally from proenkephalin, and secreted from central and peripheral neurons and endocrine cells in the adrenal medulla.

Neurons in the brain and spinal cord process peptides derived from prodynorphin; these peptides appear to be kappa-preferring ligands. Dynorphin 1-13 was isolated from porcine pituitary by Goldstein et al. (1979). This pituitary opioid peptide contains within its sequence leu-enkephalin, which appears to be one of the products of posttranslational processing (Zamir et al. 1985; Palkovits et al. 1983). Dynorphin 1-13 is 700 times more potent than the enkephalins in inhibiting electrical contractions in guinea pig ileum longitudinal muscle (Goldstein 1979).

The third prohormone from which opioid peptides are derived is pro-opiomelanocortin, which yields a number of nonopioid and opioid peptide products (O'Donohue and Dorsa 1982). Of these products, beta-endorphin, an untriakontapeptide isolated from camel pituitary gland by Li and Chung (1976)) is thought to interact primarily with mu and delta receptors.

EVIDENCE OF SPECIFIC PCP BINDING SITES

In recent years, a number of groups have reported the presence of a class of high-affinity binding sites for phencyclidine (1-(1-cyclohexylphenyl)piperidine, PCP), a dissociative anesthetic with psychotomimetic properties. This binding was shown to be saturable, reversible, and selective (Vincent et al. 1979; Zukin and Zukin 1979; Quirion et al. 1981a; Vignon et al. 1982), as well as stereospecific (guirion et al 1981b). Furthermore receptor densities using ^{3}H-PCP (Quirion et al. 1981a) and ^{3}H-TCP (N-(1-(2-thienyl)cyclohexyl)3,4-^{3}(H)piperidine, (Contreras et al., submitted for publication) to label the binding sites were reported to be highest in cortical regions and hippocampus, indicating that the distribution of PCP binding sites correlates well with the psychotomimetic properties of the drug. The pharmacological relevance of the PCP receptor is supported by the fact that only those drugs with PCP-like properties *in vivo*, such as SKF-10,047 (N-allylnormetazocine), cyclazocine, PCP, and PCP analogs inhibit the binding of ^{3}H-PCP *in vitro* (Quirion et al. 1981a). Although PCP appears to bind to muscarinic and mu opioid receptors with very low affinity (Vincent et al. 1979), its action on these receptors is not compatible with its pharmacological profile (Vincent et al. 1979). Binding of PCP to the PCP receptor is not antagonized by

mu, delta, or muscarinic receptor ligands (Vincent et al. 1979). Finally, good correlation exists between the ability of PCP analogs to bind to the receptor and pharmacological potency as measured by a number of assays, including the rotarod assay (Vignon et al. 1982) and stereotypy (Contreras et al., submitted for publication).

Because the psychotomimetic benzomorphans, classed as sigma opioids, inhibit binding of ^{3}H-PCP and show PCP-like actions in several behavioral assays, it has been suggested that PCP and sigma opioids act through the same binding sites. However, recent work by a number of investigators (Su 1982; Tam 1983; Martin et al. 1984; Contreras et al., in press) indicate that PCP binding sites and sigma opioid sites may be distinct due to differences in drug selectivity and regional distribution.

ENDOGENOUS LIGAND FOR THE PCP/SIGMA RECEPTOR

The presence of highly specific and selective binding sites for PCP in brain strongly supported the presence of an endogenous ligand for these receptors. Quirion et al. (1984) and O'Donohue et al. (1983) have reported the isolation of an endogenous factor from preparative scale porcine brain acid extracts that inhibited the binding of ^{3}H-PCP in rat brain membranes. This paper summarizes those previous findings , and extends the data on this endogenous factor which has now been purified to homogeneity and has been given the name alpha-endopsychosin.

EXTRACTION AND PURIFICATION OF ALPHA-ENDOPSYCHOSIN

Porcine brains (200) were obtained from Gwaltney Co. and homogenized at 4 °C in five volumes of acid solution (Bennett et al. 1979) consisting of trifluoroacetic acid, formic acid, hydrochloric acid, and sodium chloride. Following centrifugation, the homogenate was extracted 1:1 with petroleum ether. The resulting supernatant (60 liters) was then filtered using a Minitan Ultrafiltration System, and chromatographed in a series of runs using preparative and semipreparative liquid chromatography followed by several analytical reverse phase high pressure liquid chromatography steps. Figure 1 provides an overview of the purification procedure. Throughout the purification, a binding assay using ^{3}H-PCP and rat brain membranes was used to assess the progress of this procedure.

ENZYMATIC INACTIVATION

The effects of various enzymes on the activity of HPLC fractions that inhibited ^{3}H-PCP binding were investigated. As shown in table 1, pronase (0.5 µg/ml), carboxypeptidase A (0.1 unit/ml), and trypsin (3.0 g/ml) markedly decreased the potency of 10 n units of PCP-like activity. No significant change in activity was. seen when fractions were incubated with alpha-chymotrypsin. Boiled enzymes did not alter the ability of active fractions to

inhibit the binding of ^{3}H-PCP to its receptor. These data suggest that the endogenous material is a protein or peptide.

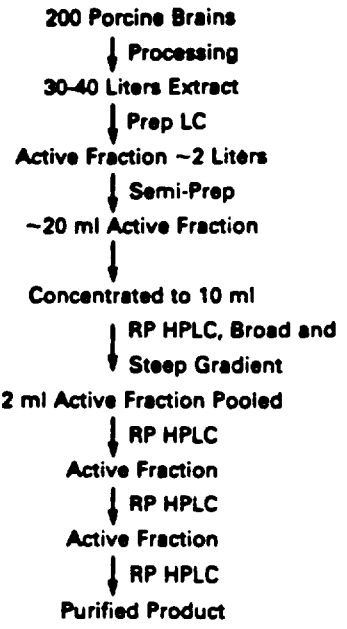

FIGURE 1. *Purification scheme of alpha-endopsychosin*

TABLE 1. *Effects of various enzymes on the activity of HPLC fractions which inhibited 3H-PCP binding*

Treatment	Control (Boiled Enzyme) n Unit PCP-Like Activity	Active Enzyme n Unit PCP-Like Activity
Pronase	8.9 ± 1.4	0
Trypsin	8.1 ± 1.6	2.3 ± 0.7
α-Chymotrypsin	7.7 ± 1.4	5.4 ± 1.0
Carboxypeptidase A	8.8 ± 1.3	3.1 ± 0.6

NOTE: 10 n units of PCP-like activity were incubated with various concentrations of active or inactive (boiled at 80 °C for 10 min) enzymes. The remaining activity was then evaluated by the ^{3}H-PCP binding assay. One unit of activity is equivalent to 1 mole of PCP. Mean ± SEM of three determinations.

GEL FILTRATION STUDIES

Supernatants were chromatographed over a column of Sephadex G-10, G-25, and G-50, and aliquots of collected fractions were assessed for their ability to displace ^{3}H-PCP from binding sites in rat brain preparations. Results indicated that the endogenous material has a molecule weight of about 3,000.

SELECTIVITY AND SPECIFICITY OF ACTIVE FRACTIONS

As Shown in table 2, a comparative dose of 10 n units of PCP-like activity inhibited ^{3}H-PCP binding in rat brain membranes, but did not inhibit binding of ^{3}H-dihydromorphine, ^{3}H-D-ala^{2}-D-leu^{5}-enkephalin, ^{3}H-ethylketocyclazocine, ^{3}H-diazepam, or ^{3}H-neurotensin. These results indicate that the active material is specific and selective from PCP receptors, as binding to the mu, delta, and kappa opioid receptors was unaffected, as was binding to benzodiazepine and neurotensin receptors.

Aliquots of fractions from an intermediate chromatography step were assayed for their ability to inhibit ^{3}H-PCP receptor binding. The endogenous material inhibited binding of ^{3}HPCP to rat brain membranes and did so in a dose-related fashion, but did not displace ^{3}H-SKF-10,047 in a separate binding study. Similarly, no displacement of ^{3}H-dexoxadrol or ^{3}H-haloperidol from rat brain preparations was apparent with aliquots taken from these same fractions.

TABLE 2. *Effect of endogenous 3H-PCP displacing material on the specific binding of various ligands*

Ligand	Specific Binding	
	Control (CPM)	10 n Units of Extract (CPM)*
^{3}H-PCP	2172 ± 201	409 ± 158^{+}
^{3}H-Dihydromorphipe	1737 ± 214	1664 ± 291
^{3}H-D-ala^{2}, D-leu^{5}-enkephalin	2474 ± 304	2435 ± 347
^{3}H-Ethylketocyclazocine	2691 ± 237	2831 ± 352
^{3}H-Diazepam	7211 ± 315	7337 ± 366
^{3}H-Neurotensin	1817 ± 207	1901 ± 291

Remaining specific binding (CPM) after incubation in presence of 10 n units of PCP-like activity as determined in a binding assay.

$^{+}p<0.001$

NOTE: One unit of activity is equivalent to 1 mole of PCP. Mean ± SEM of at least three determinations, each In triplicate.

REGIONAL DISTRIBUTION OF ACTIVE MATERIAL IN RAT BRAIN

The distribution of ^{3}H-PCP-displacing material correlated well with PCP receptor densities. Highest concentrations of endogenous material can be found in hippocampus and cortex, while relatively little material is detectable in striatum and brainstem (table 3).

TABLE 3. *Distribution of the endogenous PCP-like material (as measured in a PCP receptor assay) in porcine brain*

Region	N Units PCP Equivalents/g Wet Weight
Hippocampus	6.91 ± 1.31
Frontal cortex	5.80 ± 1.15
Cerebellum	1.27 ± 0.78
Striatum	0.12 ± 0.08
Brainstem	0.08 ± 0.04

BIOLOGICAL PROPERTIES OF PCP-LIKE FRACTIONS

Active fractions tested for electrophysiological actions on hippocampal and cortical cells mimicked the actions of PCP (Quirion et al. 1984). Iontophoresis of PCP inhibited spontaneous cortical and hippocampal cell firing, as did micropressure ejection of the PCP-like material. Fractions that did not possess PCP-like actions had no effect on spontaneous neuronal activity.

Similarly, using a behavioral paradigm where unilateral injection of PCP into substantia nigra induces contralateral turning behavior (Quirion et al. 1984), PCP-like fractions also mimicked the actions of PCP, producing significant rotational behavior contralateral to the injection site. Once again, inactive fractions elicited no response in this test. These two in vivo experiments demonstrate that the endogenous material is anagonist relative to PCP.

CHEMICAL CHARACTERIZATION OF PCP-LIKE MATERIAL

Figure 2 shows the elution profiles of several neuropeptides and the PCP-like material. When the PCP-active fractions were rechromatographed over a flatter gradient and in a different solvent system, it was clear that bombesin- and substance P-immunoreactivity no longer coeluted with the PCP-like material.

Figure 3 shows the final chromatogram and activity profile of purified alpha-endopsychosin. The first peak contained most of the PCP displacing activity as measured by its ability to inhibit ^{3}H-PCP. An aliquot of the most active material was hydrolyzed in acid and the amino acid composition was determined using OPA detection. It was determined that the peptide contained approximately 26 amino acids, in close agreement with the molecular weight predicted by Sephadex gel filtration studies. N-terminal analysis revealed that the peptide was blocked at this site. The nature of this blockade is yet to be determined. Studies are under way to determine the amino acid sequence of the peptide.

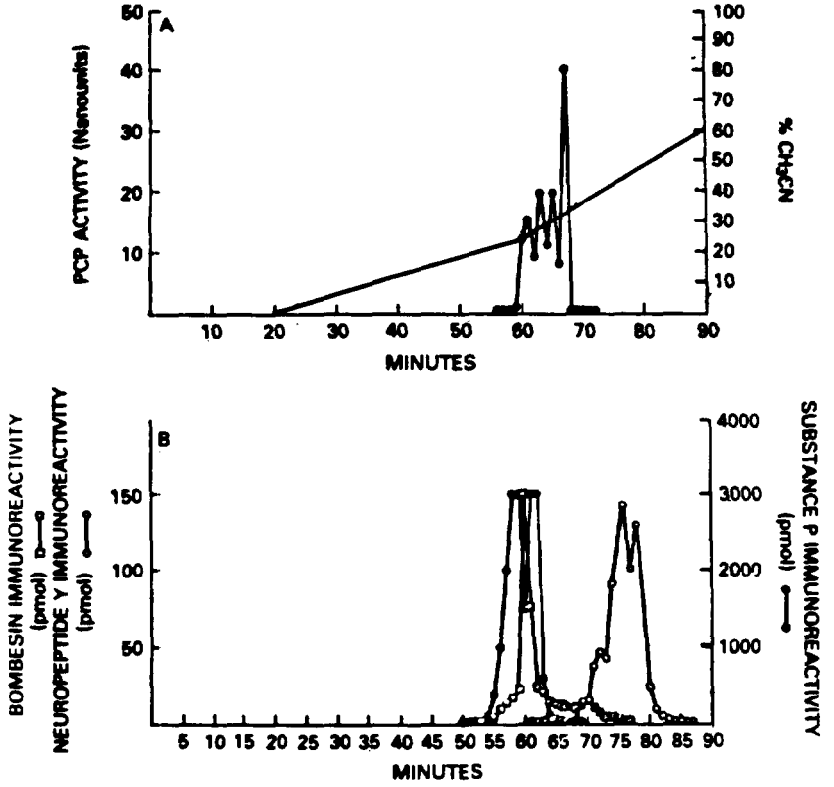

FIGURE 2. *Panel A: Elution pattern of endogenous PCP-like material from fractionated porcine brain. Activity is expressed in terms of equivalents of PCP required to inhibit 3H-PCP bindina to rat brain membranes. One unit of activity is eqivalent to 1 mole of PCP. Panel B: Activity profiles of bombesin, neuropeptide Y, and substance p from the same HPLC fractions.*

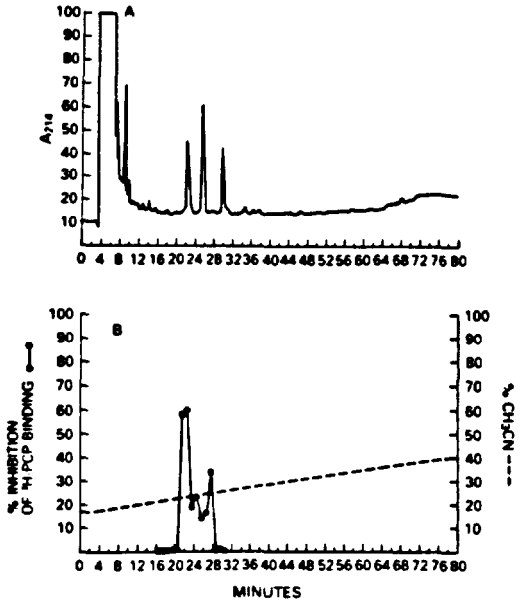

FIGURE 3. *Chromatogram and elution pattern of the purified material*

DISCUSSION

The existence of high affinity and stereoselective binding sites for PCP, a dissociative anesthetic with psychotomimetic properties, has been demonstrated in brain by a number of groups (Vincent et al. 1979; Zukin and Zukin 1979; Quirion et al. 1981a; Vignon et al. 1982). The identification of these PCP receptors in central nervous tissue suggested the existence of an endogenous ligand specific for these pharmacologically relevant binding sites. We have identified what appears to be a selective peptide ligand for the PCP receptor from porcine brain acid extracts and have named this compound alpha-endopsychosin due to its similarity in pharmacology to PCP. We have assigned the alpha designation to this peptide, since it is the first endogenous PCP ligand to be identified, and activity profiles of fractionated porcine brain show that other fractions are also PCP-active, although they do not appear to be as potent as the fraction characterized. This putative ligand for the PCP receptor, which is regionally distributed throughout the CNS and inhibits ^{3}H-PCP binding in rat brain membranes, appears to be an agonist relative to PCP, as indicated by its actions in electrophysiological and behavioral tests. The peptide appears to be selective for PCP receptors, since it does not interact with mu, kappa, or delta opioid receptors; nor does it interact with a number of other peptide binding sites.

Furthermore, the distribution of this peptide is compatible with PCP receptor densities, with highest concentrations of both ligand and receptor in areas that could be relevant to the psychotomimetic properties of PCP. Amino acid analysis of an aliquot of the purified fraction shows the peptide to contain at least 26 residues. Because the peptide is blocked at the N-terminus, enzyme fragments have been generated and purified over HPLC for sequence determination.

Without a specific PCP antagonist, it cannot be stated unequivocally that the endogenous ligand and PCP act at the same receptor to induce specific electrophysiological and behavioral actions. The discovery of specific PCP antagonists will facilitate complete characterization of the PCP-endogenous ligand system. Along this line of investigation, Rafferty et al. (in press) have reported the discovery of an acylating agent which specifically reacts with PCP receptors. This agent effectively blocks PCP-induced stereotypic behavior and electrophysiological actions in rats (Contreras et al. 1985). an effect that has been shown to be the result of PCP receptor-binding. It will be interesting to study the effects of this specific acylating agent on the interaction of PCP receptors with the endogenous ligand.

Although PCP affects several ion channels (Aguayo et al. 1982; Albuquerque et al. 1980) and numerous neurotransmitter systems, it is believed to exert its psychotomimetic effects via interaction with a specific receptor. It has been suggested that PCP receptor sites are actually sigma opioid sites, since SKF-10,047 and Syclazocine, sigma opioid psychotomimetics, inhibit the binding of ^{3}H-PCP to membranes in vitro. PCP analogs have been shown to inhibit binding of ^{3}H-cyclazocine and ^{3}H-SKF-10,047 (Quirion et al. 1981b). Furthermore, sigma opioids generalize to PCP stimulus In drug discrimination paradigms (Brady et al. 1982; Shannon 1981). and PCP has been shown to generalize to sigma opioid stimulus (Shannon 1983). However, Contreras et al. (1985) have shown that Metaphit, an acylating agent specific for PCP receptors, inhibits PCP-induced stereotypy but does not inhibit stereotyped behavior typically seen with cyclazocine treatment. In addition, evidence exists that suggests that PCP, SKF-10,047, and cyclazocine do not bind to a homogenous population of receptors (Contreras et al., in press). Recent work presented by a number of investigators (Su 1982; Tam 1983; Martin et al. 1984; and Contreras et al., in press) also indicates that, due to differences in regional distribution of drug selectivity, PCP receptors and sigma opioid sites represent different binding sites. Largent et al. (1984) have shown that sites labeled with ^{3}H-PPP (3-(3-hydroxyphenyl)-N-(1-propyl)piperidine) are specific for sites that are distinct from PCP sites. Finally, Pilapil et al. (in press) have delineated a binding profile for dexoxadrol, a putative sigma agonist, that is distinct from PCP binding. In this light, it is particularly interesting to note that the PCP-like peptide inhibits binding of ^{3}H-PCP but not of ^{3}H-(+)SKF-10,047, ^{3}H-dexoxadrol or ^{3}H-haloperidol. The endogenous ligand for the PCP receptor may therefore

be a far more selective ligand than any of the synthetic compounds.

A controversial issue concerns whether PCP/sigma opioids are in fact opioids at all, as their "sigma" psychotomimetic actions are not antagonized by naloxone. The three known opioid peptide precursors share marked structural homology in that they all contain multiple cysteine residues in the N-terminal region, they are all approximately the same size, and they all contain an enkephalin sequence (Douglass et al. 1984). It will be interesting to see whether alpha-endopsychosin is the peptide product of a distinct yet similar prohormone. If so, then perhaps alpha-endopsychosin and PCP binding sites may belong to the superfamily of opioid peptides and receptors.

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Phencyclidine (PCP) Selectively Blocks Certain Presynaptic Potassium Channels

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INTRODUCTION

Phencyclidine (1-[1-phenylcyclohexyl] piperidine; "PCP"; "angel dust") is a major drug of abuse in the United States. It is a particularly interesting pharmacological tool because it induces a toxic confusional psychosis in man that reproduces many of the primary symptoms of schizophrenia (Domino and Luby 1981). The precise mechanism of action is not known, but many studies suggest that the complex behavioral syndrome elicited by PCP is a consequence of altered central synaptic transmission (Petersen and Stillman 1978). PCP is known to bind with high affinity to brain membranes (Vincent et al. 1978: Zukin and Zukin 19791: however, the physiological activity of these receptors has not-yet beenelucidated, nor have these receptors been identified. One effect of low concentrations of PCP is a blockade of a portion of the potassium-stimulated ^{86}Rb efflux from rat brain presynaptic nerve terminals (synaptosomes) (Albuquerque et al. 1981; Albuquerque et al. 1983; Blaustein and Ickowicz 1983). These studies led to the suggestion that PCP may selectively block certain potassium channels, and that this effect might account for the behavioral action of the drug (Albuquerque et al. 1981; Albuquerque et al. 1983; Blaustein and Ickowicz 1983).

Recently, we succeeded in separating four pharmacologically-different fractions of ^{86}Rb efflux from synaptosomes (Bartschat and Blaustein 1985a; Bartschat and Blaustein 1985b), which correspond to four different types of K channels. Submicromolar to micromolar concentrations of PCP and behaviorally-active congeners selectively block one of these channels--a voltage-regulated, noninactivating (or very slowly inactivating) K channel in nerve terminals. The rank order of potency for block of these K channels paralleled both the relative ability of these agents to produce characteristic behavioral deficits in rats (Shannon, 1983), and their ability to displace ^{3}H-PCP from its high affinity binding sites in brain (Vincent et al. 1978; Zukin and Zukin 1979;

Sorensen and Blaustein 1985a). In view of the enhanced neurotransmitter release that would be expected to accompany block of presynaptic K channels (Llinas et al. 1976), this mechanism could explain the PCP-induced "dopamine storm" (Rappolt et al. 1980). Such altered synaptic transmission at central synapses may underlie the disordered behavior characteristic of PCP intoxication.

The aforementioned observations imply that the high affinity PCP binding sites in the brain are K channels. Therefore, as a prelude to the eventual isolation and characterization of these PCP "receptors"/K channels, we employed a tritiated photo affinity analogue of PCP, m-azido-^{3}H-PCP (^{3}H-Az-PCP) to label rat brain, synaptic membrane proteins. The results indicate that this analogue binds specifically to two membrane polypeptides of a parent M_R 80,000 and 95,000 Daltons (Sorensen and Blaustein 1985b).

IDENTIFICATION OF K CHANNELS IN SYNAPTOSOMES WITH TRACER ^{86}Rb EFFLUX

Rb efflux from synaptosomes loaded with ^{86}Rb was used to assess the K permeability of the nerve terminals under "resting" conditions, and under conditions in which the terminals were depolarized by elevating the external k concentration, $[K]_o$. With a half-life 36 times longer than ^{42}K, ^{86}Rb is a suitable tracer for K because (Bartschat and Blaustein 1985a; Bartschat and Blaustein 1985b): (1) Rb, like K, is accumulated by synaptosomes via a metabolically active, ouabain-sensitive route; (2) Rb permeates most neuronal K channels nearly as well as does K itself; and (3) synaptosomes preloaded with both ^{42}K and ^{86}Rb have qualitatively similar K and Rb effluxes.

Voltage-regulated K channel activity in synaptosomes was measured as described in the figure 1 legend. For further details, see Bartschat and Blaustein (1985a). Under "resting" conditions (5 mM $[K]_o$; open circles in figure 1), ^{86}Rb efflux was about 0.3 to 0.4%/sec (component "R"), which corresponds to a resting K permeability of 2.4×10^{-7}cm/sec (Bartschat and Blaustein 1985a). Rb efflux under these conditions probably reflects the mechanism(s) responsible for the normal K permeability of the resting terminals.

Depolarization of the synaptosomes with Ca-free media containing 100mM K increased ^{86}Rb efflux (figure 1, open squares); two kinetically and pharmacologically distinct K conductances could be discerned. Between 1 and 4 seconds, Rb efflux was linear and was 2.2 to 2.4%/sec (component "S"). Extrapolation of Rb efflux to the ordinate ("zero time") exposed an additional, rapid component of ^{86}Rb efflux (component "T"). Component T reflects a distinct K channel that, unlike component S, appeared to inactivate in less than 1 second (Bartschat and Blaustein 1985a).

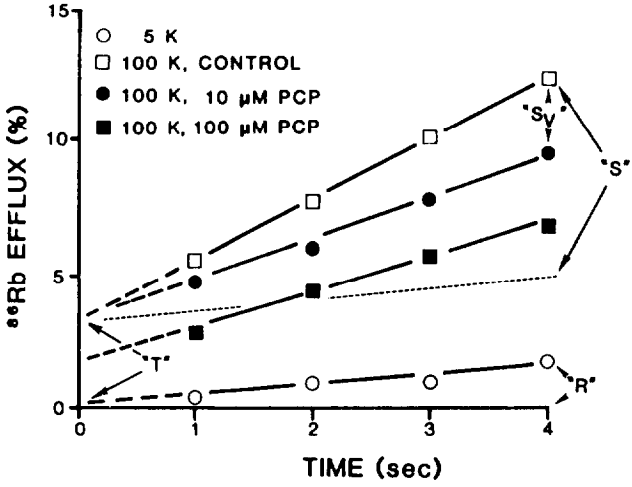

FIGURE 1. *Time course of ^{86}Rb efflux from synaptosomes; the effect of PCP*

NOTE: Synaptosomes were prepared as described (Krueger et al. 1979), were equilibrated with hysiologlcal salt solution (PSS). and were allowed to accumulate tracer ^{86}Rb (20 µCi/ml in PSS) at 30 °C for 30 minutes. PSS contained (mM): KCI, 5; NaCl, 145; $MgCI_2$, 2; glucose, 10; HEPES buffer, 10, titrated to ph 7.4 with NaOH; $Na_2 HPO_4$, 0.5; and unlabelled RbCI, 0.1. Aliquots (30 µl) of the synaptosomal suspension were then pipetted onto glass fiber filters, were washed free of extracellular tracer, and then exposed to efflux media for various lengths of time (1 to 4 seconds). Efflux was terminated by rapid addition of "stopping solution" containing the K channel blockers tetraethylamnonium (145 mM) and tetrabutylamnonium (5 mM), but no NaCl or KCI. Suction was rapidly applied, and the filters and filtrates were counted by Iiquid scintillation spectroscopy; Rb efflux was expressed as:

$$^{86}Rb\ efflux\ (\%) = \frac{^{86}Rb_{filtrate}}{^{86}Rb_{filtrate} + {}^{86}Rb_{filter}} \times 100$$

The efflux medium was similar to the loading medium; however, In experiments involving elevated $[K]_o$, K replaced Na mole-for-mole. When drugs were tested, they were Included In the wash media facilitate equilibration with the synaptosomes. Symbols correspond to Rb efflux in: 5 mM K (0), 100 mM K (control; □), 100 mM K + 10 µM PCP (●). or 100 mH K + 100 µM PCP■]. The data points are the means of six determinations. The components of ^{86}Rb efflux indicated in the figure represent: R = Rb efflux in 5 mH K media (expressed in %/sec); S = Rb efflux between 1 and 4 seconds (%/set) in K-rich media minus component R; T = K-dependent increment (%) In Rb efflux when S is extrapolated back to zero time. S_V = component of S that is blocked by PCP; S_R = PCP-lnsensltive portion of component S.

Inclusion of Ca in the efflux media enhanced ^{86}Rb efflux in 100 mM $[K]_o$ but not 5 mM $[K]_o$ (data not shown). This Ca-dependent ^{86}Rb efflux (component "C") appears to be a manifestation of TEA-sensitive, Ca-regulated K channels (Bartschat and Blaustein 1985a; Bartschat and Blaustein 1985b).

Pharmacological evidence indicates that components R, S, T, and C correspond to distinct classes of K channels (Bartschat and Blaustein 1985a; Bartschat and Blaustein 1985b). Component T is blocked by low concentrations of 4-aminopyridine (4-AP); component C is selectively blocked by micromolar quinine sulfate, but not by 4-AP. Components R and S are much less sensitive to both drugs.

EFFECTS OF PCP ON K CHANNELS IN SYNAPTOSOMES

To determine which of these K channels are inhibited by PCP, this drug was tested for its ability to block the various components of Rb efflux. In the experiment of figure 1, the effects of 10 μM PCP (closed circles) and 100 μM PCP (closed squares) were examined in nominally Ca-free solutions. In 100 mM $[K]_o$ medium, 10 μM PCP depressed ^{86}Rb efflux through S by about 35 percent, but had negligible effect on component T. Increasing PCP to 100 μM had no additional effect on S, but blocked component T by about 45 percent. Although not shown here, component R and the Ca-dependent component, C, were virtually unchanged by 100 μM PCP.

The dose-response curves for the effects of PCP on components S and T are illustrated in figure 2. Note that low doses of PCP selectively blocked a portion (about one-third) of component S (S_V); higher doses inhibited T, as well, with but little additional effect on S.

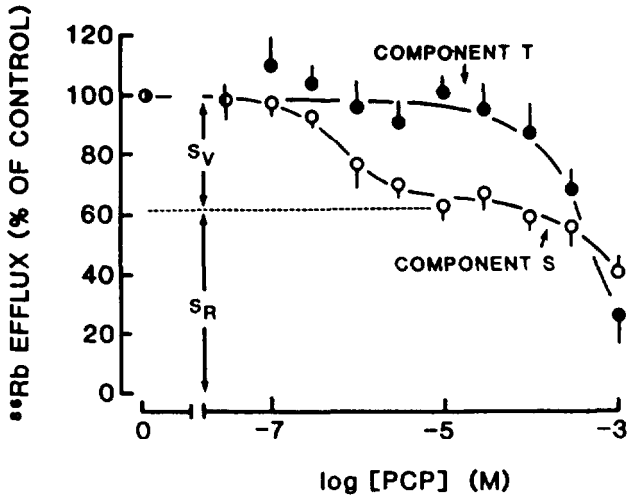

FIGURE 2. *PCP dose-response curves for the inhibition of components S (○) and T (●)*

NOTE: The data points are the means of 4 determinations, ± SEW. SimiIar results were obtained in 3 other experlments.

EFFLUX COMPONENT S CAN BE DIVIDED INTO TWO FRACTIONS, S_R AND S_V, WITH DIFFERENT PROPERTIES

Before trying to interpret this partial inhibition of S by PCP, we need to consider the influence of membrane potential on the ^{86}Rb efflux. To obtain information about the relationship between component S and membrane potential, we measured S (increase in the slope of ^{86}Rb efflux between 2 and 4 seconds) as a function of $[K]_o$ in the efflux solution, in the absence of drug. These data are shown in figure 3 (solid circles); the calculated depolarization, due to increasing $[K]_o$, is given in the upper abscissa scale.

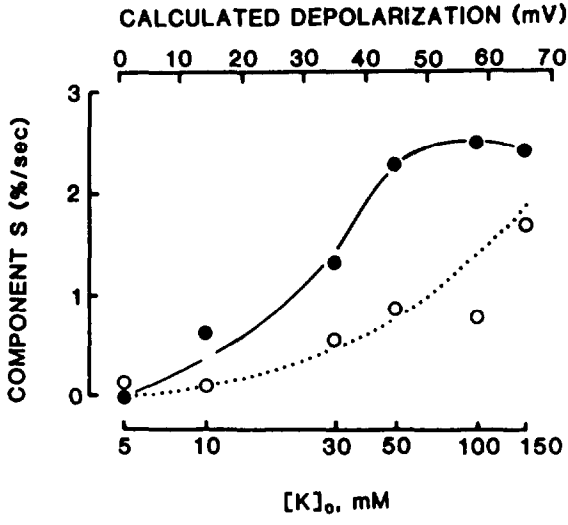

FIGURE 3. *Effect of PCP on ^{86}Rb efflux component S*

NOTE: The magnitude of component S at the indicated [K] was expressed as the slops of the least squares line fitting Rb efflox°between 2 and 4 seconds for control (•) and 100 µM PCP-containing solution (o). The dotted line Is the expected contrlbutlon of the "resting" K permeabllity (R) to component S due to electrodiffusion effects (i.e., S_R) when the synaptosomes are depolarized to the level lndicated In the upper abscissa (also see Bartschat and Elsusteln 1985a). The data points are the means of 4 determinatlons.

As discussed previously (Bartschat and Blaustein 1985a), depolarization of the terminals should increase the driving force for efflux of ^{86}Rb through the "resting" K permeability (component R), even if there is no increase in conductance (i.e., no voltage gating of R). The magnitude of this calculated electrodiffusion component of ^{86}Rb efflux through the "resting" K conductance, denoted as S_R, is shown as the dotted line in figure 3 (also see figure 6c in Bartschat and Blaustein 1985a). The difference between this

dotted line (fraction S_R) and the solid line (component S) presumably represents the voltage-regulated fraction of component S, denoted as S_V.

THE EFFECT OF PCP ON ^{86}Rb EFFLUX THROUGH COMPONENT S

If two different types of K conductances contribute to component S, we might anticipate that some drugs will affect the two conductances differently. Indeed, the dose-response curves for inhibition of S by tetra-alkylamines and 4-AP appear to be biphasic (Bartschat and Blaustein 1985a), which is consistent with this prediction. The obviously biphasic dose-response curve for PCP inhibition of component S (figure 2, open circles) provides further evidence for this view.

Note that the magnitude of component S measured as a function of $[K]_o$ in the presence of 100 μM PCP (figure 3, open circles) corresponds very closely to the calculated magnitude of S_R (figure 3, dotted line). These data clearly indicate that components S_R and S_v are different. Component S_V apparently is a manifestation of voltage-regulated, noninactivating K channels, and is blocked selectively by low concentrations of PCP. Since the "resting" ^{86}Rb efflux is unaffected by these concentrations of PCP (not shown), we would not expect PCP to affect ^{86}Rb efflux component S_R if this flux is mediated by the resting K conductance, as described.

The concentration of PCP that inhibits S_V by 50 percent (IC_{50}) is about 1 μM (figure 2, open circles). This is within the range of doses that produce confusional psychosis (0.1 to 1.0 mg/kg, corresponding to about 0.1 to 1 μM) (Burns and Lerner 1981). Higher concentrations of PCP induce convulsions and coma (Burns and Lerner 1981). Assuming that block of the K channels corresponding to S_V does cause the behavioral deficit, it is important to consider the possibility that block of only a small fraction of these K channels may be sufficient to induce behavioral change.

THE EFFECTS OF PCP ANALOGUES ON COMPONENT S_v

If the behavioral activity of PCP is related to its block of presynaptic K channels (Albuquerque et al. 1981; Albuquerque et al. 1983; Blaustein and Ickowicz 1983), PCP-like analogues should block these same K channels with a rank order of potency that parallels their relative <u>in vivo</u> psychotomimetic activity. One of the most behaviorally potent PCP-like agents is TCP (1-[1-(2-thienyl)-cyclohexyl] piperidine) (Shannon 1983). Figure 4 illustrates the dose-response curves for the block of components S and T by this drug. The data indicate that TCP is a more potent blocker of S_v than is PCP (figure 2). TCP blocked component T only at high concentrations ($>10^{-5}$ M), and in this respect was approximately equivalent in potency to PCP (figure 2).

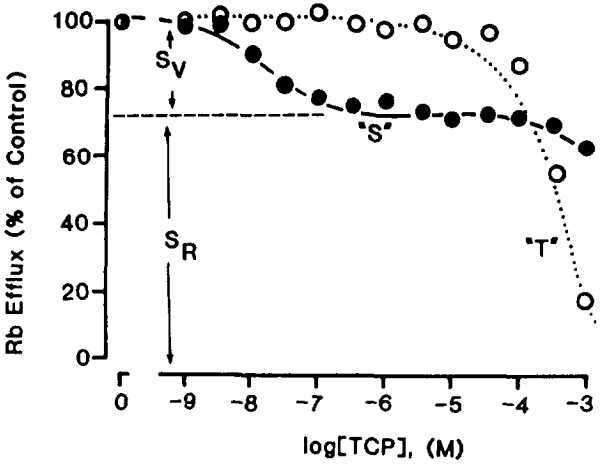

FIGURE 4. *Dose-response curve illustrating the effects of the PCP analogue TCP on components (●) and T (o)*

NOTE: The experiment was carried out as described in the figure 1 legend. The data points are the means of 6 determinations.

Figure 5 compares the ability of PCP and two of its congeners, meta-amino-PCP (m-NH_2-PCP) and meta-nitro-PCP (m-NO_2-PCP), to block component S. All three drugs selectively blocked S_v, but with very different affinities. The rank order of potency for block of S_v by these three drugs and TCP (figure 4) was: TCP, m-NH_2-PCP>PCP>m-NO_2-PCP. This same sequence was observed when these agents were examined in various behavioral impairment paradigms that have been used to assess the psychotomimetic liability of these and related agents (Albuquerque et al. 1981; Shannon 1983; Aguayo et al. 1984). In contrast, all of these agents blocked T only at higher concentrations (IC_{50}'s=100-500 µM; data not shown). The similarity between the relative potency of block of S_v by PCP-like drugs and the effects of these drugs in the behavioral impairment paradigms strongly supports the view that blockade of voltage-regulated, noninactivating K channels may be directly involved in the psychotomimetic actions of these drugs.

THE EFFECTS OF "SIGMA OPIATES" ON COMPONENT S_V

Several "sigma opiates," which differ structurally from PCP, are known to induce a PCP-like toxic psychosis, and to displace PCP from rat brain membranes (Zukin 1982; Hampton et al. 1982;

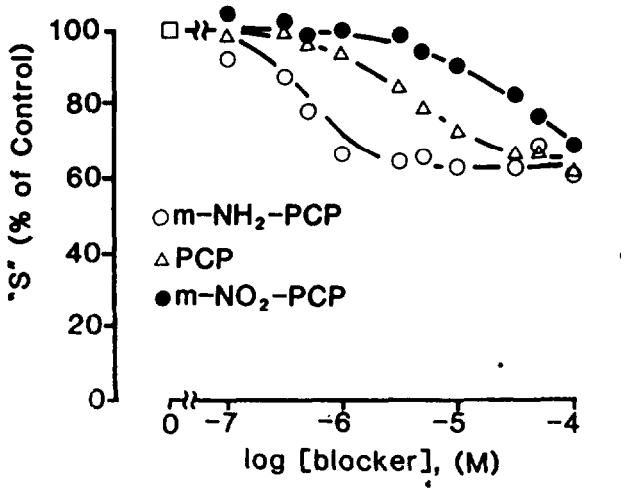

FIGURE 5. *The effects of the PCP (Δ), m-NH_2-PCP (o), and m-NO_2-PCP (●.) on component S*

NOTE: The experiments were carried out as described in the figure 1 legend. The data points are the means of six determinations.

Mendelsohn et al. 1984; Murray and Leid 1984). Of particular interest are several stereoisomer pairs of "sigma opiates," one isomer of which produces PCP-like behavioral effects and displaces bound ^{3}H-PCP more potently than the other. These agents should be especially well suited for a test of the hypothesis mentioned in the preceding section, namely, that induction of the PCP-like behavioral deficit can be correlated with block of S_V.

We examined the effects of three such stereoisomer pairs of "sigma opiates" on ^{86}Rb efflux in synaptosomes in the presence of 10 μM naloxone (to avoid classical opiate effects). Our data show (Bartschat et al. 1985) that dexoxadrol blocks S_V at one-thousandth the concentration of its stereoisomer, levoxadrol; (+)NANM (N-allyl-normetazocine or SKF-10,047) is tenfold more potent than (-)NANM; and (-)cyclazocine is two- to threefold more potent than (+)cyclarocine. This stereoselectivity for block of S_V closely parallels the effects of these stereoisomers in behavioral and binding experiments (table 1). Furthermore, block of S_V occurs at nano- to micromolar concentrations of the more potent "sigma opiates"--comparable to the concentrations at which PCP and its more potent congeners act.

TABLE 1. *Comparison of actions of stereoisomer pairs of "sigma opiates"*

Drug Pair	Relative Potency for: Block of S_V	Displacement of Bound ^{3}H-PCP	PCP-Like Behavior
Dexoxadrol: Levoxadrol	~1,000:1	418: 1	>1,000:1[a]
(+)NANM:(-)NANM	~10:1	6.4:1	3:1[b]
(-)Cyclazocine: (+)Cyclazocine	1-2:1	1.8:1	5:1[c]

SOURCES: [a]Cone et al. 1984; [b]Shannon 1982a; [c]Shannon 1982b.

IDENTIFICATION OF THE RAT BRAIN PCP RECEPTOR

The aforementioned results are consistent with the view that the rat brain PCP/"sigma opiate" high-affinity receptor is associated with the voltage-regulated, noninactivating K channels in the presynaptic terminals. Thus, we reasoned that the elucidation of the molecular composition of this PCP "receptor" might provide direct information about the subunit composition of these K channels. This could also prove to be a very useful first step in the effort to purify and characterize the channel protein. To label and identify the brain PCP receptor, we synthesized a tritiated photo affinity analogue of PCP, m-azido-^{3}H-phencyclidine (^{3}H-Az-PCP) (Haring and Kloog 1984). This photolabile ligand binds with high affinity ($K_{0.5} \simeq 0.9$ μM) to the rat brain PCP receptor (Sorensen and Blaustein 1984) As illustrated by the fluorogram in figure 6, when rat brain sinaptic membranes were incubated with ^{3}H-Az-PCP and irradiated, several polypeptides incorporated the label. However, when excess unlabelled PCP was added before the samples were irradiated, incorporation of the label was markedly reduced in only two of the polypeptides, M_R=80 kD (80,000 Daltons; P80) and 95 kD (P95). respectively. P95 was labelled more heavily than P80, and may, therefore, include the primary PCP binding site; however, we have not yet ruled out the possibility that P80 is a product of proteolytic cleavage (Sorensen and Blaustein 1985b).

Covalent labelling of these two polypeptides was also specifically blocked by other PCP analogues such as TCP, by some K channel blockers (4-AP and tetrabutylammonium ions), and stereoselectively by certain PCP-like "sigma opiates" (dexoxadrol >> levoxadrol) (not shown). The latter results parallel the ability of these ligands to displace ^{3}H-PCP from rat brain membranes and to block ^{86}Rb efflux component S_v in synaptosomes (Sorensen and Blaustein 1985a; Bartschat et al. 1985).

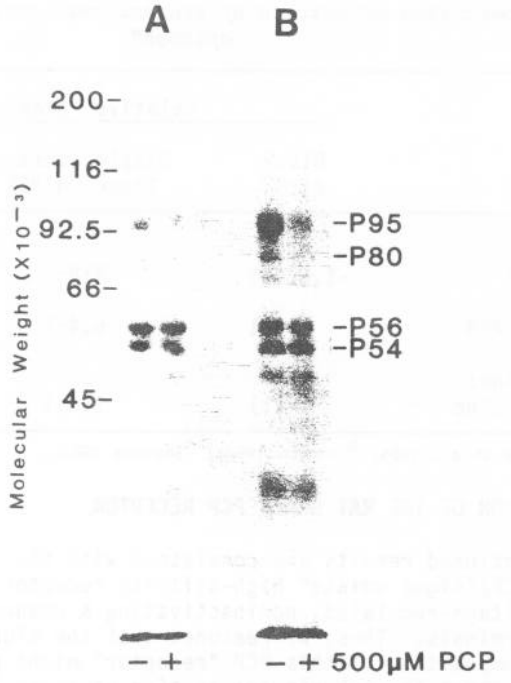

FIGURE 6. *Fluorogram showing the covalent attachment of ^{3}H-Az-PCP to rat brain synaptic membrane polypeptides*

NOTE: Synaptic membranes were incubated in the dark for 60 minutes at 0 °C in either 54 mM$_3$Tris-HEPES (A) or 5 mM sodium phosphate (B) buffers at pH 7.0, with 1.0 µM H-Az-PCP, without (-) or with (+) a five hundredfold excess of unlabelled PCP. The samples were then Irradiated with 366 nm UV light for 15 minutes (irradiation at 254 nm UV light for 5 minutes gives similar results) to pnotolyze the Az-PCP. The membranes were solubilized in sodium dodecyl sulfate (SDS) dissociation buffer overnight. and subjected to SDS-polyacrylamide gel electrophoresis. The resulting geIs were impregnated with "Fluore-Hance" (RPI, Mt. Prospect, III.) dried, and exposed to Kodak X-Omat AR film for several weeks to obtain fluorographic patterns of the labelled polypeptides. Several polypeptIdes that incorporate label are lndlcated as PN where N is defined as the apparent molecular weight (kD) of the polypeptIde x 10^{-3}. Molecular weight standards are also Indicated.

The acetylcholine receptor (AChR) of Torpedo electric organ is also a PCP "receptor." However, this nicotinic AChR has about one-tenth the affinity for PCP than that of the rat brain PCP receptor [$K_{0.5} \simeq 0.3$ µM, versus $\simeq$ 4-6 µM for Torpedo (Heidmann et al. 1983; flaring et al. 1984)]. Moreover, the nicotinic AChR has subunits of M_R<66 kD, and these are the subunits that are specifically labelled with ^{3}H-Az-PCP in the Torpedo electroplax membranes (Heidmann et al. 1983; Haring and Kloog 1984; Haring et al. 1984). These data indicate that the nicotinic AChR-PCP receptor differs from the rat brain PCP receptor. Furthermore, our findings are

consistent with the view that the rat brain PCP receptor is the voltage-regulated, noninactivating K channel in the nerve terminals, and that this channel consists of at least two subunits of M_R=80 kD and 95 kD.

HOW DOES PCP PRODUCE ITS BEHAVIORAL EFFECTS?

The striking correlation between behavioral potency and block of ^{86}Rb efflux component S_V, for PCP analogues and the stereoisomer pairs of "sigma opiates," provides strong circumstantial evidence that the K channel block may underlie the behavioral effects of these drugs. Block of K channels at the nerve tetminals should prolong the nerve action potential and thereby enhance Ca entry into the terminals. This would in turn, alter synaptic transmission by increasing Ca-dependent neurotransmitter release; virtually all neurotransmitter types might be affected, depending upon the distribution in the brain of these PCP-sensitive, voltage-regulated K channels. Such disruption of synaptic transmission at central synapses could induce the disordered behavior that is characteristic of PCP intoxication. Thus, our observations may provide the physiological link between the binding of PCP to its high-affinity receptor in the brain and the ultimate behavioral effects of PCP intoxication.

It should be pointed out that PCP analogues also have a prominent postsynaptic action: they block the channels associated with the nicotinic cholinergic receptors (Albuquerque et al. 1981; Albuquerque et al. 1983). However, many of the analogues that display potent antinicotinic activity are behaviorally inactive (Albuquerque et al. 1983), whereas our data demonstrate that there is a direct relationship between block of certain presynaptic K channels and behavioral potency; the stereoselective effects of the "sigma opiates" are particularly striking in this regard (table 1). This supports the view that presynaptic K channels are the primary sites of action of these drugs in the brain. Moreover, our data indicate that the voltage-regulated, noninactivating K channels may be the high-affinity PCP binding sites, and that PCP may be a useful ligand to help identify and isolate these K channels.

The behavioral effects of PCP have been associated with excessive release of a wide variety of neurotransmitters: in particular, a massive dopamine release may underlie some of the most prominent symptoms of PCP intoxication (Rappolt et al. 1980). Our results readily explain the genesis of such an effect, because activation of presynaptic K channels is one of the primary factors that influences Ca entry into nerve terminals and Ca-dependent transmitter release by limiting action-potential duration and regulating excitability.

There is ample precedent for a modulatory role of K channels in behavior. The K channel blocker, 4-AP, selectively blocks component T (Bartschat and Blaustein 1985a). prolongs nerve action potentials, and enhances neurotransmitter release (Llinas et al. 1976). In man, intoxication with this agent may lead to dissociative behavior, agitation, confusion, convulsions, and coma (Spyker et al. 1980). However, the behavioral aberrations induced by 4-AP differ qualitatively from those induced by PCP. This implies that block of various types of presynaptic K channels may modify behavior and mental activity; however, the precise nature of the behavioral manifestations is likely to depend upon the specific type of K channel that is affected.

In man, PCP intoxication causes a profound perceptual and cognitive disturbance that resembles the primary symptoms of schizophrenia (Domino and Luby 1981). According to the popular "dopamine hypothesis," the positive symptoms (e.g., thought disorder and delusions) of schizophrenia are associated with an excessive release of dopamine (by an unknown mechanism). These symptoms can often be curtailed by treatment with neuroleptics, agents that block dopamine receptors (Seeman 1980). However, the negative symptoms (e.g., flattened affect and anhedonia) are not alleviated by the neuroleptics, and are likely to be associated with other, nondopaminergic pathways (Crow 1980). PCP intoxication reproduces both the positive and negative symptoms of schizophrenia (Domino and Luby 1981). In view of the evidence that schizophrenia may be an inherited disorder (Kety et al. 1978), and that neurotransmitter pathways other than dopaminergic pathways may be involved in producing some of the behavioral aberrations (Hornykiewicz 1982; Henn 1983), recent findings (Albuquerque et al. 1981; Albuquerque et al. 1983; Blaustein and Ickowicz 1983) raise the possibility that the inherited defect could involve a primary alteration in the ion channels responsible for the maintenance of normal electrical activity in the nervous system. For example, a defect in K channel activation could lead to prolongation of action potentials at nerve terminals and, thus, to excessive release of a wide variety of neurotransmitters, including dopamine.

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Involvement of Dopaminergic, Cholinergic, and Glutamatergic Mechanisms in the Actions of Phencyclidine-Like Drugs

Kenneth M. Johnson and Lawrence D. Snell

INTRODUCTION

Although there is good evidence that administration of phencyclidine (PCP) to rodents alters the synthesis, metabolism, release, or reuptake of several neurotransmitters, including serotonin, norepinephrine, GABA, acetylcholine (ACh), and methionine enkephalin, most of the research in this area has been on dopamine (DA). The reasons underlying the interest in DA are several. Perhaps the most important is the similarity seen by most investigators between schizophrenia and PCP-induced psychosis in humans. This has been coupled with the observation that PCP-induced stereotypy, locomotor activity, and rotational behavior can be blocked by antischizophrenic agents that are DA receptor antagonists. The DA connection has been strengthened substantially by studies from several laboratories showing that PCP, like amfonelic acid, enhances DA synthesis and release, and blocks its subsequent reuptake (Johnson 1983). However, because of the complexity of the neuronal systems subserving even relatively simple behaviors such as stereotypy or circling behavior in rats with unilateral destruction of the nigrostriatal dopaminergic pathway, it is possible that the dopaminergic properties of PCP are not the primary factors that underlie these behavioral properties. One of the primary goals of the studies presented here was to determine the relevance of the known dopaminergic properties of PCP to the ipsilateral turning produced by PCP administration to rats.

Another characteristic of PCP which has been studied with great interest over the last 5 years, is the ability of PCP to produce a discriminative stimulus in monkeys, rats, and pigeons. As discussed elsewhere in this volume, by Browne, the discriminative stimulus properties of PCP are shared not only by other members of the arylcycloalkylamine class, but by psychotomimetic benzomorphans and substituted dioxolanes. The structure-activity relationships (SAR) within and between these classes are virtually identical to those found when studying the displacement of ^{3}H-PCP from its binding site in rat brain membranes. This correlation

between the behavioral and binding data suggests that this binding site could be part of a physiologically relevant receptor. Although some progress is being made toward the identification of an endogenous ligand for this receptor (DiMaggio et al., this volume), many questions remain unanswered. For example, on what kinds of neurons are these receptors located? What is their function? How is this function carried out? A more specific question, which we sought to answer, was whether facilitation of DA release or blockade of its reuptake could be mediated by an action at this receptor.

One of the difficulties in the pharmacological analysis of drug-induced behavior is that the same behavior may be affected in a similar fashion by a variety of drugs. For example, PCP-induced turning is inhibited by alpha-methyl-p-tyrosine (an inhibitor of tyrosine hydroxylase) and arecoline (a muscarininc agonist) (Finnegan et al. 1976). Similarly, PCP-induced behaviors are facilitated by amphetamine (Balster and Chait 1978) and physostigmine (Finnegan et al. 1976). Thus, behaviors such as turning, which are thought to be largely mediated in the striatum, are somewhat difficult to analyze because of the balance between cholinergic and dopaminergic neurons in that area (Pycock et al. 1978). That balance may be influenced considerably by the excitatory (presumably glutamatergic) input from the cortex. The potential importance of this input was revealed by studies that showed that PCP and several drugs with PCP-like discriminative stimulus properties selectively antagonized spinal neuron excitation by N-methyl-D-aspartate (NMDA), an agent believed to selectively activate one of three putative glutamate receptors (Lodge et al. 1982; Berry et al. 1984a; Berry et al. 1984b). In addition, this laboratory recently reported that PCP potently inhibited NMDA-induced ACh release from the rat striatum (Snell and Johnson 1984; Snell and Johnson, in press). Therefore, another goal of the studies reported here was to determine whether ACh release could be influenced by PCP, either by virtue of its ability to release DA or by antagonism of glutamate, in a way that was correlated with turning behavior. By using the SAR approach, we also hoped to determine whether PCP/sigma receptors might be mediating any of the effects we observed on DA or ACh function in the striatum.

METHODS

Male Sprague-Dawley rats (200-300 gm) were used in all experiments. Dopamine uptake was measured using the accumulation of tritium into a striatal synaptosomal fraction in the presence of an MAO inhibitor following a 5-minute incubation period with 10 nM ^{3}H-DA at 37 °C. Uptake at 2 °C was used as a control for uptake by diffusion and was subtracted from uptake at 37 °C. Other details have been published previously (Johnson and Snell 1985).

To measure the spontaneous efflux of DA, we preincubated striatal slices (0.4 mm) in a modified Tyrode's buffer containing pargyline

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and 10 nM ^{3}H-DA for 30 minutes. Slices were loaded into plexiglas superfusion chambers (0.4 ml) and superfused with buffer at a constant rate of 0.7 ml/min. Superfusate was collected in 5-minute fractions and radioactivity estimated by liquid scintillation spectrometry. Fractional release was calculated as the percent of radioactivity in each fraction, relative to that which was in the slice at that time (radioactivity in the slice was counted at the end of the experiment). Fractional release reached a stable baseline of about 1 percent after 30 minutes of superfusion. Drugs were added in various concentrations 15 minutes later, for a period of 15 minutes. Drug-induced increases in spontaneous ^{3}H-DA efflux were estimated by subtracting the average of the fraction before addition of drug and the fraction collecting 25 minutes after the removal of drug from each of the eight fractions in between. This technique is published in detail elsewhere (Snell et al. 1984).

The effects of various PCP-like drugs on K^{+} and NMDA-induced ACh release were studied in a similar superfusion paradigm. KCl (30 mM) was used as a depolarizing stimulus as previously described (Leventer and Johnson 1983). As with K^{+} stimulation, in the study of NMDA-induced ACh release, slices were loaded with ^{3}H-choline (50 nM) and then superfused with buffer containing hemicholinium-3 (to prevent the reuptake of ^{3}H-choline formed from the extraneuronal hydrolysis of newly synthesized and released ^{3}H-acetylcholine), until a stable baseline was reached (60 minutes). Superfusion was continued and the collection of 3-minute fractions was begun. Buffer containing test drug or vehicle was added 9 minutes prior to the addition of an excitatory amino acid (usually 1 mM NMDA) for 2 minutes. Fractional release over baseline was estimated in a manner similar to that described above for ^{3}H-DA release. This paradigm was slightly modified to allow the study of NMDA-induced ^{3}H-DA release as well.

The effect of PCP-like drugs was also studied <u>in vivo.</u> In these experiments, the ability of these drugs to enhance haloperidol-induced DA metabolism was assessed by measuring DA and homovanillic acid (HVA) concentrations in the striatum. In this paradigm, saline or drug was administered (SC) immediately after the administration of 0.1. mg/kg haloperidol. The rats were killed 45 minutes later, and DA and HVA levels were estimated fluorometritally (Snell et al. 1984).

Turning behavior in rats was measured after unilateral administration of 8 µg of 6-hydroxydopamine into the substantia nigra. Details of the injection procedure and experimental protocol were described in Johnson and Snell, 1985.

In order to determine the potential correlation between any of these variables and affinity for the PCP/sigma receptor, we determined the concentration of these drugs required to displace specific binding of ^{3}H-PCP to rat cortical membranes (Johnson and Snell 1985). In other experiments, we determined the effect of

NMDA on the affinity and binding site density by Scatchard analysis, as described in the note with table 4.

RESULTS

Turning Behavior

All the drugs tested in these experiments were administered (IP) at doses ranging from 3 to 10 mg/kg (except for ketamine, which was tested at 10, 30, and 100 mg/kg). All the rats used had previously turned contralaterally in response to 0.05 mg/kg apomorphine HCl. Net ipsilateral rotations were counted in two consecutive 15-minute bins, immediately following drug (or saline) administration.

PCP produced a dose-related increase in ipsilateral turning, as reported previously (Fessler et al. 1979). However, the effects of N-ethyl-phenylcyclohexylamine (PCE) and ketamine were related to dose in an inverse manner. This inverse dose-relationship was apparent in both 15-minute periods, and appeared to be due to a general motor incapacitation. With PCE, ipsilateral posturing was apparent, but hindlimb coordination was grossly impaired. Ketamine, on the other hand, seemed to reduce turning by virtue of gross sedation (after 100 mg/kg, the rats were totally akinetic). N-Allylnormetazocine (NANM) produced results virtually identical with those of PCP (about 25 turns in the first 15-minute period after 10 mg/kg). Cyclazocine was a little more potent than PCP, and etoxadrol was more potent than cyclazocine, although turning was impaired by ataxia at the higher dose of each. Neither ketocyclazocine nor ethylketocyclazocine (EKC) produced any significant rotation at the doses tested. If these drugs are ranked for effectiveness in the first 15-minute period (without regard to dose), one obtains the following rank: PCE, etoxadrol > cyclazotine, NANM, PCP > ketamine >> EKC, ketocyclazocine (Johnson and Snell 1985).

The ineffectiveness of the latter two kappa agonists suggested that this effect might be partially mediated via the PCP/sigma receptor. To test this notion further, we utilized three related pairs of drugs, each of which has one member that is more potent than the other in displacing ^{3}H-PCP from its binding site, and in eliciting PCP-like responding in rats trained to discriminate PCP from saline. These data are shown in table 1. In the first 15 minutes following administration, 1-[1-(napthyl)cyclohexyllpiperidine, (m-NH_2-PCP), dexoxadrol and (-) cyclazocine induced significant ipsilateral turning, while their counterparts, 1-[(m-nitrophenyl)cyclohexyl]piperidine, (m-NO_2-PCP), levoxadrol, and (+) cyclazocine did not. (-) Cyclazocine and m-NH_2-PCP caused significant ataxia, as evidenced by reduced turning rates in the second 15-minute time period. Ataxia produced by dexoxadrol and etoxadrol (data not shown) was less severe. Although (-) cyclazocine was clearly more effective than (+) cyclazocine in the first 15-minute period, it was somewhat less active than (+) cyclazocine

TABLE 1. *Effect of some PCP-like drugs on turning behavior*

Drug	Mg/ Kg	(N)	Net Ipsilateral Turns 0-15 Min	15-30 Min
m-NH_2-PCP	10	(3)	63 ± 2	1_+l
m-NO_2-PCP	10	(3)	8.0 ± 3.5	5.3 ± 2.9
Dexoxadrol	10	(6)	50 ± 15*	105 ± 17**
Levoxadrol	10	(6)	4.0 ± 1.0	2.5 ± 1.5
(-) Cyclazocine	5	(6)	48 ± 13*	11 ± 6.0
(+) Cyclazocine	5	(3)	6.3 ± 5.3	19 ± 0.9**

*Slgnlflcantly different from the turning rate produced by 0.9% NaCl (6.8 ± 2.1).

**Slgnlflcantly different from the turning rate produced by 0.9% NaCl (5.0 ± 1.1); P<.05 (Mann-Whitney U test).

in the second time period. This was probably due to the greater ataxia produced by the (-) isomer. Thus, the differences between dexoxadrol and levoxadrol, and between m-NH_2-PCP and m-NO_2-PCP are obvious, while the difference between the enantiomers of cyclazocine are more subtle, in that each produces turning at different times following administration. Similar differences between the enantiomers of dioxadrol and cyclazocine in producing stereotypy are presented elsewhere in this volume (Contreras et al.).

Uptake of ^{3}H-DA

PCP is a potent, competitive inhibitor of synaptosomal uptake of ^{3}H-DA, ^{3}H-norepinephrine, and ^{3}H-serotonin) (Garey and Heath 1976; Smith et al. 1977). In addition, we found that PCP administration *in vivo* resulted in a time- and dose-dependent inhibition of ^{3}H-DA uptake into striatal slices (Vickroy and Johnson 1980). More recently, we compared the effects of amphetamine and representatives from each of the three chemical classes known to produce PCP-like behavioral effects in rats on high-affinity, synaptosomal uptake of H-DA (Johnson and Snell 1985). IC_{50} values ($x10^{-6}$M) were as follows: amphetamine (0.06), PCP (0.58), N-ethyl-phenylcyclohexylamine (PCE) (9.4), ketamine (24), etoxadrol (38), and N-allylnormetazocine (NANM or SKF-10,047) (46). Cyclazocine and EKC were extremely weak inhibitors, producing minimal inhibition even at $1x10^{-4}$ M. Thus, although PCP unquestionably can inhibit DA reuptake, other drugs with similar behavioral effects (and similar potency) like PCE, etoxadrol, and cyclazocine are either much weaker inhibitors or simply lack this property entirely. Further, the abilities of these drugs to inhibit ^{3}H-DA uptake and to displace ^{3}H-PCP from its binding site in brain membranes were not significantly correlated (Johnson and Snell 1985).

Release of ^{3}H-DA

Complete concentration-response curves for representatives from several chemical classes with PCP-like behavioral properties were obtained using the in vitro release of ^{3}H-DA from striatal slices (Snell et al. 1984). Every agent tested produced a significant increase in spontaneous ^{3}H-DA efflux at 30-100x10^{-6}M. Since none of the compounds tested appeared to exhibit a maximal effect even at 1x10^{-4}M, potency was difficult to estimate. In lieu of an estimate of potency, we report here a simple comparison between these drugs at the somewhat arbitrary concentration of 1x10^{-5} M (table 2). This shows that drugs that are approximately equipotent with PCP in producing turning are much less effective at this concentration than PCP. Further, the differences between m-NH_2-PCP and m-NO_2-PCP, and between dexoxadrol and levoxadrol are insignificant.

Inasmuch as the effects of PCP can be distinguished from those of amphetamine, at a biochemical level, by measuring the effect of each on haloperidol-induced DA metabolism, we also determined the effect of these same drugs, in combination with haloperidol, on the ratio of HVA to DA, which was used as an index of DA metabolism. In preliminary experiments, 0.1 mg/kg haloperidol increased the striatal concentration of HVA from 1.20 ± 0.05 µg/g to 2.94 ± 0.26 µg/g while not significantly changing the concentration of DA (7.95 ± 1.65 µg/g). Thus, the HVA/DA ratio was increased from 0.12 to 0.36 by haloperidol. The data presented in table 2 represent the percent of the HVA/DA ratio for a haloperidol control group run the same day for the indicated drug (given immediately after haloperidol). Amfonelic acid, PCP, and m-NH_2-PCP significantly enhanced haloperidol-induced DA metabolism as indicated by an increased HVA/DA ratio. Amphetamine reversed the effect of haloperidol on HVA/DA, primarily by increasing the concentration of DA. EKC decreased the HVA level and increased the DA level significantly. All other drugs tested had no significant effect on this index of haloperidol-induced DA metabolism.

ACh Release: Depolarization with K^+ and Excitatory Amino Acids

The effects of PCP and related compounds on ACh release have been studied using two modes of depolarization: high K^+ and excitatory amino acids. Both modes result in Ca^{++}-dependent release, but only the mode of excitatory amino acids is sensitive to tetrodotoxin, suggesting that excitatory amino acids elicit an action potential that is requisite for ACh release. Using K^+ (30mM KCl)-stimulated AC release as the dependent variable, we found that PCP (3-10x10^{-6}M) and amphetamine (1x10^{-6}M) inhibited release by 17 to 28 percent, in a manner that was reversible by haloperidol (Leventer and Johnson 1983). We postulated that PCP inhibited K^+-stimulated ACh release via a release of DA. Later, we found that (+) NANM and EKC, but not (-) NANM or morphine, also inhibited K^+-stimulated release. This was reversed by naloxone as well as by haloperidol (Leventer and Johnson 1984). This led us to amend our

hypothesis to include the possibility that PCP was acting through delta or possibly kappa opiate receptors to release DA, which then inhibited ACh release. Although an action at these sites has not been ruled out, it is apparent from our work with (+) and (-) NANM and EKC that DA release is probably not a relevant intermediate (table 2) (Snell et al. 1984).

TABLE 2. *Comparative effects of several aryLcycLoalkylamines, benzomorphans, and substituted dioxolanes on striatal release of ^{3}H-DA and hatoperidol-induced DA metabolism*

Drug*	Fractional Release of ^{3}H-DA (x100) at $1x10^{-5}$ M**	HVA/DA (% Haloperidol Control)
Amphetamine	34.0 ± 3.7	65.1 ± 1.4***
Amfonelic acid	5.9 ± 0.5	197.0 ± 13
PCP	8.9 ± 1.4	139.0 ± 3.8***
PCE	0.53 ± 0.19	113.0 ± 4.7
Ketamine	0.44 ± 0.28	92.4 ± 15
m-NH_2-PCP	4.14 ± 0.55	126.0 ± 5.1***
m-NO_2-PCP	2.68 ± 0.29	88.6 ± 7.7
NANM	0.91 ± 0.33	88.5 ± 8.5
EKC	0.47 ± 0.15	45.4 ± 3.0
Etoxadrol	0.68 ± 0.28	114.0 ± 11
Dexoxadrol	0.86 ± 0.25	108 ± 2.7
Levoxadrol	1.9 ± 0.28	83.8 ± 2.7

*All drugs were administered at a dose of 10 mg/kg (except ketamine, dexoxadrol, and levoxadrol, which were used at 30 mg/kg).

**At $1x10^{-5}$ each of the drugs tested, except ketamine and etoxadrol, signiflcantly enhanced release above buffer controls (-0.38 ± 0.23).

***Significantly different from haloperidol control ($p<0.05$, Student's t-test).

Since there is a cortico-striatal glutamatergic pathway that provides excitatory input onto both dopaminergic terminals and cholinergic interneurons, we followed the lead of Lodge and coworkers (Lodge et al. 1983), and determined the effect of PCP on glutamate-stimulated ACh and DA release. We found that glutamate-induced release of ACh was mediated primarily through a glutamate receptor subtype characterized by a selective affinity for the antagonist 2-aminophosphonovalerate (2-APV) and the agonist, NMDA. ACh release induced by NMDA is apparently mediated by a Mg^{++}-gated conductance, as 1.2mM $MgCl_2$ inhibited ACh release stimulated by NMDA by about 80 percent. Release induced by the prototypic agonists of the other receptor subtypes (quisqualate and kainate) were unaffected by physiologic concentrations of Mg^{++}. PCP inhibited ACh release induced by NMDA, but not that induced by

quisqualate or kainate. Since PCP enhances the spontaneous efflux of DA, and DA is known to inhibit ACh release, we examined the possibility that DA release may be involved in the inhibition of NMDA-induced ACh release by PCP. We believe that it is not involved, for the following reasons: (1) the concentrations of PCP required to inhibit NMDA-induced release of ACh are at least one-thirty-third of those required to elicit DA release, (2) DA antagonists such as haloperidol, chlorpromazine, and clozapine do not reverse the inhibition of ACh release by PCP, and (3) drugs like etoxadrol, which have little or no potency as indirect DA agonists, are potent inhibitors of NMDA-induced ACh release. The concentration of several representatives from the drug classes with PCP-like behavioral properties required to inhibit NMDA-induced ACh release by 50 percent are shown in table 3.

TABLE 3. *Inhibition of NMDA-induced transmitter release*

Drug	IC_{50}(nM) ACh	DA
PCP	69	290
Etoxadrol	98	590
(-)Cyclazocine	120	220
(+)Cyclazocine	630	1,900
Dexoxadrol	N.D.*	1,700
Levoxadrol	N.D.	5,700
N-allylnormetazocine	940	N.D.
Ketamine	1,600	N.D.
Ethylketocyclazocine	8,300	N.D.
Morphine	30,000	N.D.

*N.D. = not determined

Two points need to be emphasized concerning the data on ACh release. First, PCP, etoxadrol, and cyclazocine are very potent, being effective in the same range in which they compete with ^{3}H-PCP for binding to the PCP/sigma receptor recognition site. Second, the rank order potency of these drugs in this preparation correlates very highly with their ability to compete for ^{3}H-PCP binding sites (r=0.98, unpublished observation) and to mimic the discriminative stimulus and reinforcing properties of PCP (Balster, this volume; Browne, this volume). In addition, using a single concentration of $1x10^{-7}$M, we found that the paired drugs shown in table 1, which produced significant ipsilateral turning, significantly inhibited NMDA-induced release. Their inactive counterpart was also inactive at this concentration in inhibiting ACh release.

In other experiments, we found that PCP also inhibited ACh release induced by the amino acid transmitter candidates, L-glutamate and L-aspartate. Release of ACh by these amino acids had a similar Mg^{++}sensitivity to that induced by NMDA, suggesting an action of these amino acids on the N-type receptor. No inhibition of release by PCP could be seen in the presence of Mg^{++}.

Although inhibition of NMDA-induced DA release by all the drugs studied was one-sixth to one-half that of inhibition of ACh release (table 3), the rank order potencies and stereoselectivity of the effect was similar. One major difference, however, was noted in our characterization of the response of dopaminergic nerves to excitatory amino acids. That is, the responses to quisqualate and kainate were inhibited by both Mg^{++} and PCP. Thus, the receptor mediating the response of excitatory amino acids is less selective in that quisqualate and kainate apparently can stimulate N-type receptors on dopaminergic terminals (or other neurons modulating DA release), to cause the release of DA. Further, even in the presence of Mg^{++}, PCP ($1x10^{-6}$M) can inhibit release induced by L-glutamate, quisqialate, and kainate. This could mean that PCP is somewhat less selective than one would predict from the ACh release experiments, or that the presence of Mg^{++} does not totally inactivate the conductance channel activated by NMDA on these neurons. Alternatively, since Mg^{++} completely abolishes NMDA-induced DA release, PCP may also block quisqualate and kainate receptors in this preparation.

Analysis of PCP-NHDA Interactions

Since the actions of PCP and related compounds in blocking the response to NMDA appear to be well correlated with their affinity for the PCP/sigma receptor, we wondered whether NMDA and PCP might compete for the same binding site. Although glutamate had been shown not to inhibit ^{3}H-PCP binding (Zukin and Zukin 1979), we thought that glutamate might not have a very high affinity for the NMDA (PCP?) receptor. The effects of several concentrations of NMDA on the specific, saturable binding of ^{3}H-PCP at equilibrium to rat cortical membranes were analyzed according to Scatchard; the results are shown in table 4.

These data show that NMDA does not compete for ^{3}H-PCP binding sites at co centrations that elicit significant ACh release (EC_{50}=$5x10^{-5}$M). The apparent competition observed at the higher concentrations may be irrelevant to this question, as significant inhibition of the ACh or DA release can be observed using $3x10\text{-}5_{M}$ MDA. However, the competitive inhibition observed at higher NMDA concentrations may indicate that NMDA binding can influence the conformation of the PCP/sigma recognition site via an allosteric mechanism.

In perhaps a more physiologic assessment of the nature of the PCP-NMDA interaction, we determined the effect of fixed concentrations of PCP and a classic NMDA antagonist (2-APV) on both ACh and DA

release stimulated by increasing concentrations of NMDA. As shown in figure 1, 2-APY ($3x10^{-4}$M) produced a parallel shift to the right in the concentration response curve, while PCP ($1x10^{-7}$M) produced a nonparallel shift to the right. This suggests that

TABLE 4. *Effect of NMDA on ^{3}H-PCP binding to rat cortex*

NMDA	K_D(nM)	B_{mx}(p moles/mg protein)
0	256 ± 26	5.83 ± 0.35
$3x10^{-5}$M	261 ± 17	6.38 ± 0.16
$3x10^{-4}$M	376 ± 26	6.21 ± 0.59
$3x10^{-3}$M	515 ± 68	6.66 ± 1.1

NOTE: Each value is the mean ±S.E. of 3 independent experiments, in which specific binding of ^{3}H-PCP (defined as that displaceable by $3x10^{-5}$M PCP) measured at six concentrations ranging from 10 to 1,000 nM.

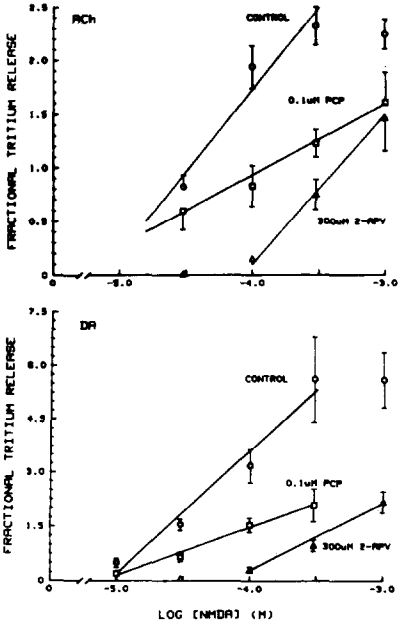

FIGURE 1. *Effect of 2-APV and PCP on NMDA-induced ACh release (upper panel) and DA release (lower panel). Each point is the mean ±S.E. of 4-7 experiments.*

PCP is not acting as a competitive inhibitor at the NMDA receptor; thus, PCP and NMDA probably do not share a common recognition site. Examination of the effect of PCP on NMDA-induced DA release (figure 1, lower panel) tends to support this conclusion, but is compromised somewhat by the slightly nonparallel shift produced by 2-APV. This may be due to the fact that NMDA may partially activate quisqualate and kainate receptors on those neurons that are not antagonized by 2-APV.

DISCUSSION

This laboratory, as well as others, has shown unequivocally that PCP affects a variety of parameters related to neurotransmission in several neuronal systems. This paper has focused on evidence for the involvement of dopaminergic, cholinergic, and glutamatergic pathways, and evidence of their interactions in the rat striatum. However, the effects of PCP undoubtedly involve other neuronal systems in other brain areas. Thus, it must be borne in mind that the data discussed in this paper cannot possibly account for the more complex behavioral effects of PCP.

On the other hand, restriction of our experimental paradigms to the striatum does have some advantages. First, the involvement of the striatum in locomotor activity, stereotypy, and circling behavior are relatively well understood on anatomical, physiological, and neuropharmacological grounds. Although these behaviors are in no way selectively affected by PCP, the relatively circumscribed anatomical and physiological substrates underlying these behaviors make their study seem attractive. Our approach has been to determine, using structure-activity relationships, the correlation between circling behavior and a variety of neurochemical indices of transmitter function. Once the structure-activity relationships have been established for a given parameter, one can determine the correlation with other behaviors, or with other measures of biological function, in an attempt to identify cause and effect relationships. However, the urge to jump from a simple correlation between a given neurochemical parameter and a more complex behavior such as drug discrimination should be resisted until appropriate hypotheses can be constructed and tested. Another advantage in studying the striatum, with particular emphasis on dopaminergic mechanisms, is that we may gain some insight into the factor underlying the production, by PCP, of schizophrenic symptoms in humans.

In this regard, considerable evidence shows that PCP increases dopaminergic transmission in the striatum (Johnson 1983) and, more recently, evidence indicates that DA function is increased in the mesolimbic and mesocortical pathways as well. For example, PCP administration has been shown to inhibit the firing of cells found in the ventral tegmental area (Freeman and Bunney 1984) similar to that observed in the substantia nigra (Raja and Guyenet 1980). This effect was reversed by haloperidol. On the other hand, lower doses of PCP (and NANM) increased cell firing in both areas in a

manner that is insensitive to haloperidol, suggesting significant nondopaminergic influences on dopamine cells as well (Freeman and Bunney 1984). In spite of the fact that PCP is a competitive inhibitor of ^{3}H-DA uptake, which also enhances impulse-dependent release of DA (Doherty et al, 1980; Johnson and Oeffinger 1981) in a manner similar to nonamphetamine stimulants such as amfonelic acid (Doherty et al. 1980; Vickroy and Johnson 1982), the apparent increased dopaminergic tone produced by PCP administration may not be a major factor in behavioral alteration. The major argument in favor of dopaminergic involvement in PCP-induced behaviors (aside from the neurochemical data) is that DA antagonists reversed the behavior. Unfortunately, the effects of DA antagonists on behaviors such as stereotypy and turning (which are strongly influenced by DA) could dampen the behavior by acting at a site distinct from that of the primary site of PCP action. The very weak dopaminergic properties of drugs like NANM, cyclazocine, and dexoxadrol (Snell et al. 1984; Johnson and Snell 1985), which elicit turning behavior (Johnson and Snell 1985; Snell and Johnson, in press) and stereotypy (Contreras et al. 1984; Contreras et al., this volume), argue in favor of this interpretation of the haloperidol-induced inhibition of these behaviors. Haloperidol has also been shown to antagonize PCP- and NANM-induced increases in locomotor activity (Iwamoto 1981). Destruction of the nucleus accumbens and ventral tegmental area with 6-OHDA prevented the increased locomotor activity produced by PCP, but not that produced by caffeine or scopolamine (French et al. 1984). Administration of 6-OHDA in either area resulted in a decrease in the binding site density found for ^{3}H-PCP. These authors have suggested that PCP and NANM may induce locomotor activity by interacting with PCP/sigma receptors located presynaptically on terminals of the mesolimbic DA system (Iwamoto 1981; French et al. 1984). There may, therefore, be a better case for the involvement of DA in PCP-induced locomotor activity than for stereotypy or rotational behavior, but more detailed SAR studies are need to confirm this.

A final comment on the DA studies reviewed here: although PCP does act as an indirect DA agonist similar to methylphenidate and amfonelic acid, the effects are apparently not mediated via an action on PCP/sigma receptors. This conclusion is based on the absence of a significant correlation between (1) the effects of several drugs from three chemical classes on DA reuptake, DA release, or haloperidol-induced DA metabolism, and (2) either drug discrimination behavior or affinity for the site labelled by ^{3}H-PCP. This does not rule out the possibility that nonstriatal dopaminergic mechanisms are important in the general pharmacology of PCP and related drugs.

The most interesting aspects of the studies reviewed here are that the drugs having discriminative stimulus properties similar to PCP also produce ipsilateral turning; and that this behavior is well correlated with both affinity for the PCP/sigma receptor and the ability to inhibit the effects of NMDA on transmitter release in the striatum. Although inhibition of NMDA-induced DA release was

not as extensively characterized from an SAR standpoint as was the inhibition of NMDA-induced ACh release, similar rank order potency and stereoselectivity were apparent. Since striatal DA neurons inhibit cholinergic interneurons, blockade of an excitatory input onto both neurons would effectively cancel any effect on net output from the striatum. However, two points should be considered. First, the pharmacologic effect in vivo would be dependent on the endogenous excitatory input (or tone) on these neuronal elements. That is, if there is very little excitatory input to the dopaminergic terminals relative to the cholinergic interneurons, then the blockade of excitation by PCP would significantly reduce cholinergic output. However, the relative excitatory tone on these nerves is unknown. Second, the two- to sixfold greater potency of PCP-like drugs on ACh release may relegate the effects on DA release to secondary importance. If this were not the case, one might expect to observe an increase in ACh release following blockade of an excitatory input onto the inhibitory dopaminergic neurons. We never observed this at concentrations as high as $1x10^{-6}$ M PCP. It would appear that the inhibition of ACh release is most important. This indirect anticholinergic effect could be the basis for PCP-induced turning in this model.

The global nature of glutamate/aspartate distribution and function suggests the tremendous potential of this mechanism in other PCP-induced behaviors. To determine something of the universality of this phenomenon, we have conducted preliminary studies in several brain areas. We have found that PCP inhibits NMDA-induced ACh release from the nucleus accumbens and dendritic DA release from the substantia nicra. It would be easy to imagine that PCP modulates excitatory transmission in numerous CNS pathways in addition. How this occurs at a molecular level is open to speculation. Since PCP is known to block both Na^+ and K^+ conductances, and since NMDA is thought to activate a channel possibly conducting both Na^+ and K^+, our working hypothesis is that PCP and glutamate (or aspartate) modulate the same conductance channel. At very high concentrations of NMDA, the configuration of the channel and the nearby PCP/sigma site may be sufficiently altered to account for the apparent decreased affinity that we observed for ^{3}H-PCP in the presence of NMDA. At this point, this hypothesis is very tentative, but it will be actively investigated by our laboratory in the future.

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Anticonvulsant Properties of Phencyclidine and Ketamine

Gary G. Buterbaugh and Hillary B. Michelson

INTRODUCTION

Phencyclidine (1-(1-phenylcyclohexyl)piperidine (PCP)) was the first in a series of arylcycloalkylamines synthesized in an attempt to develop an intravenous general anesthetic agent. The compound was subsequently found to produce a complex profile of acute and chronic effects on overt behavior in animals and humans (Balster and Chait 1976; Domino 1964; Luby et al. 1958) and central nervous system function, including convulsions (Chen et al. 1959; Matsuzaki and Dowling 1984; Snyder et al. 1981; Winters 1976). In humans, the acute effects of PCP overdosage implicated in fatalities include seizures and cardiovascular collapse (Burns and Lerner 1981)) although the most probable cause of death in humans (Burns and Lerner 1978) and in animals (Chen et al. 1959; Hackett et al. 1981) is respiratory depression. The production of end-state convulsive-like activity at lethal doses is common to many analogs of PCP, with the possible exception of ketamine (Mattia et al., this volume). Animals administered PCP or PCP analogs do not move through a dose-related progression of clonic followed by tonic-clonic convulsions, as is typical of classical convulsant compounds. The convulsive-like behavior associated with high doses of PCP-like agents is superimposed upon a background of severe overt behavioral disruption, and is probably a reflection of a more generalized toxic insult to the central nervous system (CNS) caused by high doses of the compounds.

In contrast to the convulsive-like effects of high doses of PCP compounds, several models of convulsions have been used to demonstrate anticonvulsant properties of PCP in a variety of species. In mice, PCP is effective in antagonizing electroshock- or pentylenetetrazol (PTZ)-induced tonic extensor convulsions and audiogenic seizures (Chen et al. 1959; Chen and Bohner 1961). In dogs, PCP raises the threshold and decreases the duration of the afterdischarge produced by electrical stimulation of the suprasylvian gyrus (Domino 1964). In rats, the latency for seizures produced by fluorothyl is prolonged by PCP (Geller et al. 1981). The doses

of PCP required to demonstrate anticonvulsant effects are sufficient to cause mild to severe impairment of behavior, but are well below lethal levels.

The effects of PCP on the amygdala-kindled seizure model have been reported by Freeman et al. (1982). A 5 mg/kg dose IP results in a slightly greater than twofold elevation of the threshold for producing amygdala-kindled seizures, but has little effect on the duration of the EEG afterdischarge or motor seizure. This profile of effects on the amygdala-kindled seizure does not resemble that of the convulsant compound pentylenetetrazol, which has no effect on the threshold but prolongs the duration of the EEG and motor seizure (Bowyer and Albertson 1982). In addition, PCP and ketamine are effective in antagonizing seizures kindled by repeated stimulation of the cerebral cortex (Bowyer et al. 1983).

This laboratory has utilized two approaches to define further the anticonvulsant properties of PCP. One approach involved a relatively simple convulsant model, pentylenetetrazol-induced convulsions. In this model, the administration of ketamine alone, or in combination with several known anticonvulsants, was tested. Ketamine, as a structural analog of PCP, shares many of the pharmacological properties associated with PCP. The second approach involved a more complex model, hippocampal-kindled seizures. Using this model, the ability of PCP, ketamine, and several anticonvulsants to antagonize hippocampal seizures and elevate seizure thresholds was tested both before and after kindling.

ANTIPENTYLENETETRAZOL ACTIVITY

Male Dublin-ICR white mice were administered pentylenetetrazol (dissolved in normal saline) by tail vein infusion. This slow intravenous infusion of PTZ to mice provided three consistent and easily measured endpoints for assessing anticonvulsant effects: (a) an initial clonic body jerk followed by (b) tonic limb extension, and (c) lethality. Mice were pretreated with ketamine 15 minutes, and anticonvulsants 30 minutes, prior to PTZ infusion. All drugs were administered by IP injection.

Figure 1 illustrates the dose-dependent effects of ketamine on these three endpoints. A dose of 20 mg/kg significantly delayed tonic limb extension but did not protect against the lethality associated with this severe convulsive response. Higher doses significantly delayed the initial clonic convulsive response and prevented tonic limb extension. At these doses, the tonic extension response was replaced-with the abrupt onset of continuous clonic limb convulsions, which persisted until death from apparent respiratory depression. The onset of the continuous clonic convulsions and lethality was also delayed in a dose-dependent manner, at the higher doses of ketamine.

The profiles of anticonvulsant effects for phenobarbital, phenytoin, and trimethadione were also determined in the PTZ model.

Phenobarbital closely resembled ketamine, but was more effective in delaying clonic and tonic convulsions (figure 1). In contrast, phenytoin was effective only in preventing tonic extension convulsions and delaying lethality (figure 2). Trimethadione delayed the clonic and tonic endpoints but did not prevent tonic extension convulsions or the lethal effect of the tonic convulsion (figure 2).

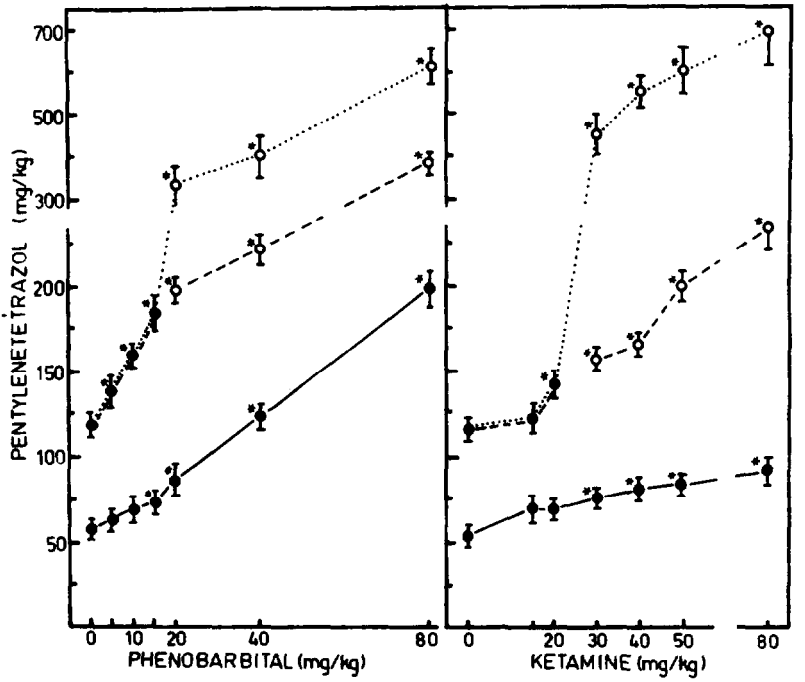

FIGURE 1. *Effect of phenobarbital and ketamine on pentylenetetrazol convulsions*

NOTE: Solid lines = clonic convulsions, dashed lines = tonic extensor convulsions and dotted lines = lethality. Open circles represent doses preventing extension and delaying lethality (see text). Data are expressed as mean + s.e.m., n=6-7 mice per point. *indicates significant difference from control, $P \leq .05$.

The interaction of ketamine with each of the three anticonvulsant compounds was also tested. Ketamine, 15 mg/kg, a dose showing no anti-PTZ effect and causing no overt behavioral changes, potentiated the effect of phenobarbital (20 mg/kg) in delaying the clonic and tonic convulsive responses and lethality (figure 3). Ketamine also potentiated the ability of phenytoin (20 mg/kg) to delay

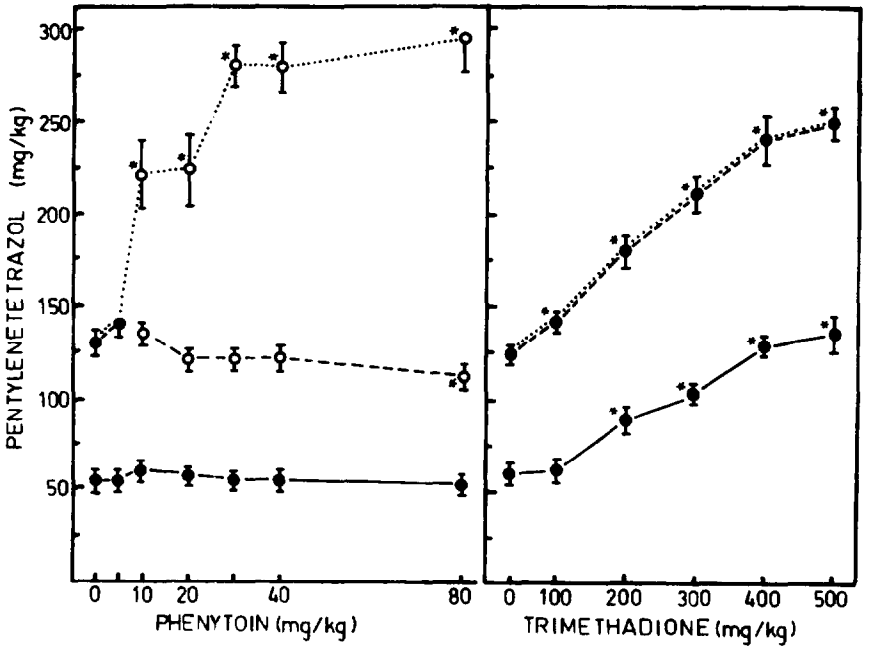

FIGURE 2. *Effects of Phenytoin and Trimethadione on Pentylenetetrazol convulsions (see legend for figure 1 for details)*

lethality (not shown). No interaction was found between ketamine and trimethadione (200 mg/kg).

KINDLED SEIZURES

A model of seizures that many consider to resemble human epileptogenesis closely is the kindling model of epilepsy. Kindling involves the administration of low intensity stimulation to a specific brain region (e.g., the amygdala) at regular intervals. Initially, the stimulation produces a synchronous electrical afterdischarge with no behavioral correlates; however, as kindling progresses, a stable clonic convulsive response, which is retained for long periods of stimulation-free time, gradually results (Goddard et al. 1969). The kindling model provides the unique opportunity to assess the effect of a compound on the threshold for initiating a seizure, the initial prekindled seizure, and the fully kindled seizure. Many anticonvulsant compounds that are ineffective against the prekindling afterdischarge are very active in antagonizing some component of the fully kindled seizure.

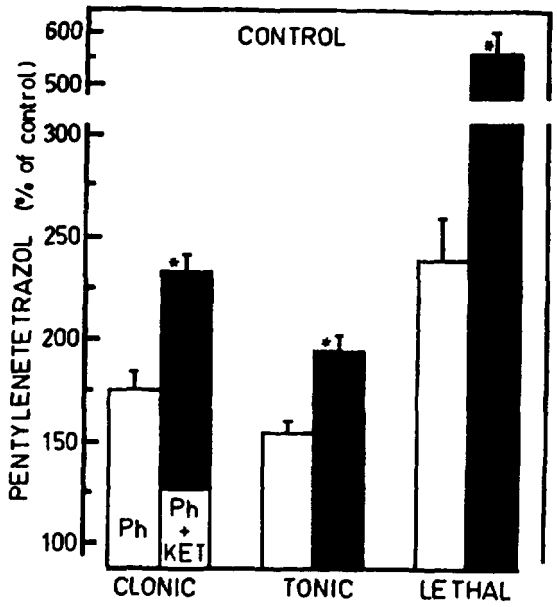

FIGURE 3. *Interaction between ketamine and phenobarbital against pentylenetetrazol convulsions*

NOTE: Ketamine, 17.5 mg/kg and phenobarbital, 20 mg/kg, were Injected 15 and 30 min., respectively, prior to pentylenetetrarol Infusion. Data are expressed as mean ± s.e.m., n=5-6 mice per point. *indicates significant difference from control, P≤ .05.

We have evaluated the dose-related effects of PCP, ketamine, and selected anticonvulsant drugs on seizure activity in the hippocampal model of kindled seizures. The hippocampal model is particularly well suited for the study of the anticonvulsant effects of drugs because of the slow rate of acquisition of the fully kindled seizure. Electrical stimulation of the dorsal hippocampus initially evokes a stereotyped sequence of behavior, accompanied by a characteristic EEG pattern. Repeated electrical stimulation eventually results in generalized kindled seizures. This allows the testing of drugs on the unkindled hippocampal seizure (afterdischarge) to be compared to effects on the fully kindled seizure in the same rats.

Male, Sprague-Dawley rats were implanted under pentobarbital anesthesia with a bipolar electrode in the right dorsal hippocampus for hippocampal stimulation and recording. Stainless steel screws were also placed over the contralateral frontal and parietal cortices for recording cortical seizure activity. The electrodes

were connected to an Ampherol headpiece and the assembly affixed to the skull with dental acrylic. Ten days later, the threshold for eliciting hippocampal afterdischarge (AD) was determined with an ascending series of stimulations (1 second of 60 Hz, biphasic square-wave pulses of 1 millisecond duration) at 5-minute intervals. At 7-day intervals, the rats were administered either vehicle or drug, and the threshold determined as above. EEG was recorded (Grass Model 7 polygraph) 2 minutes prior to stimulation, and continued for 2 minutes following termination of the seizure. Each rat received a maximum of four drug trials.

The rats were next administered twice daily hippocampal stimulation (2xthreshold) until three consecutive stage V convulsive responses (Racine 1972) were obtained, indicating that the rats were fully kindled. The average number of stimulations to achieve the kindled state was 41.4 ± 2.3 stimulations. Drug effects on seizure threshold and the kindled seizure were assessed as described above for the prekindled seizure.

Effect on Hippocampal Seizures (Prekindling)

The control EEG records in figure 4 illustrate the typical EEG response produced by hippocampal stimulation in unkindled rats. An initial afterdischarge is followed by a period of postictal depression, which is interrupted by a brief episode of rebound spiking. The effects of PCP and ketamine on the hippocampal seizure are also illustrated in figure 4. Doses of PCP and ketamine (IP administration, 15 minutes prior to stimulation) causing equivalent overt behavioral effects were chosen, and produced nearly identical effects on the hippocampal response. The initial AD was slightly prolonged, and the period of postictal depression was shortened, allowing the rebound spiking to appear earlier, thus decreasing the total seizure duration. Ketamine, at an anesthetic dose of 80 mg/kg, resulted in suppression of the rebound spiking.

Anticonvulsant drugs such as carbamazepine, diazepam, valproic acid, and phenobarbital also slightly increased the duration of the initial AD. However, the effects of these drugs on the other associated seizure events were quite different from PCP and ketamine. The effects of carbamazepine and diazepam, typical of the four compounds, are illustrated in figure 4. These compounds either suppressed the rebound spiking (diazepam, valproic acid, and phenobarbital) or lengthened the total seizure duration with no rebound suppression (carbamazepine).

Effects on Kindled Hippocampal Seizures

The fully kindled hippocampal seizure is quite different from the prekindled seizure described above. The hippocampal response typically appears as a continuous AD, with a duration similar to the total duration of the unkindled response. In other words, the unkindled EEG response of initial AD, postictal depression, and

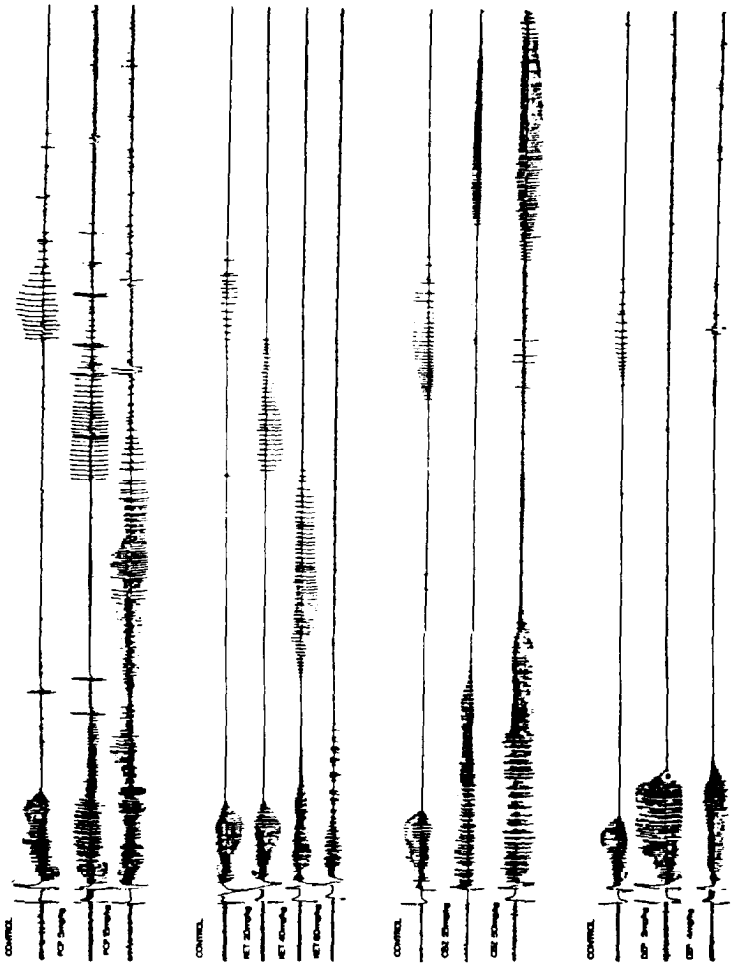

FIGURE 4. *Effect of phencyclidine (PCP) and ketamine (KET) on the prekindling hippocampal seizure (afterdischarge)*

NOTE: The effects of carbamarepine (CBZ) and diazepam (DZP) are Included as representative of antlconvulsant drugs. Total seizure duration (control) averaged 110 seconds. See text for details of seizure response.

rebound spiking is replaced by continuous AD activity. Moreover, prominent spiking activity is also continuously recorded from the cerebral cortex, and the characteristic motor seizure responses occur. Drug effects on the fully kindled hippocampal seizure were much different from those seen on the prekindled seizure. Moreover, in marked contrast to the effects on the unkindled seizure, the effects of PCP, ketamine, and the four anticonvulsants on the kindled seizure were quite similar. PCP, ketamine, and the four anticonvulsants all significantly decreased the duration of the hippocampal EEG seizure and reduced the severity of the motor seizures (table 1). However, none of the six compounds, even in doses resulting in loss of righting reflex, completely prevented the kindled seizure response. The EEG seizure response was less sensitive to the drug effects than was the motor convulsive response.

TABLE 1. *Effect of PCP, ketamine and selected anticonvulsants on the duration and severity of hippocampal kindled seizures*

Compound	Dose (Mg/Kg)	Seizure Duration (Seconds)	Convulsive Response (Stage)
PCP	0	121 ± 8	5.0
	5	84 ± 9 *	4.0
	15	76 ± 11*	1.8
Ketamine	0	119 ± 7	5.0
	20	79 ± 4 *	3.0
	40	71 ± 6 *	2.4
Phenobarbital	0	124 ± 9	5.0
	25	79 ± 19*	1.8
	50	42 ± 7*	0.5
Valproic acid	0	123 ± 7	5.0
	125	69 ± 14*	1.0
	225	24 ± 10*	0.8
Carbamazepine	0	130 ± 8	5.0
	25	107 ± 24	1.3
Diazepam	0	128 ± 7	5.0
	2	31 ± 4 *	0.0
	8	17 ± 6 *	0.0

*Indicates significant difference from control, $P \leq .05$.

NOTE: Data expressed as mean ± s.e.m., n=4-6 rats per dose.

Effects on After discharge and Seizure Threshold

PCP, 15 mg/kg, and ketamine, 40 mg/kg, elevated the threshold for eliciting hippocampal afterdischarge (prekindling) by 61 percent and 267 percent, respectively (table 2). Valproic acid and carbamazepine also elevated the threshold. In contrast, phenobarbital and diazepam had no effect on the prekindling afterdischarge threshold, even at doses capable of altering the AD.

TABLE 2. *Increased sensitivity of hippocampal seizure threshold to drug effects following kindling*

Compound	Dose (Mg/Kg)	Percent Increase in Threshold Before Kindling	Following Kindling
PCP	5	11 ± 11	16 ± 13
	15	267 ± 90*	631 ± 89 **
Ketamine	20	15 ± 7	381 ± 83 **
	40	61 ± 21*	786 ± 98 **
Phenobarbital	25	10 ± 7	214 ± 66 **
	50	7 ± 7	389 ± 120 **
Valproic acid	150		272 ± 90 **
	225	75 ± 29 *	272 ± 50 **
Carbamazepine	25	180 ± 26 *	657 ± 150 **
Diazepam	2	5 ± 3	10 ± 4
	8	18 ± 12	24 ± 14

*Indicates significant difference from vehicle control before kindling, $P \leq .05$.

**Indicates significant difference from prekindling threshold, $P \leq .05$.

NOTE: Data expressed as mean ± s.e.m., n=4-6 per dose.

Following the completion of kindling, the seizure threshold was not significantly different from the prekindling threshold. However, there was a marked increase in the sensitivity of the kindled seizure threshold to all drugs except diazepam and the lower dose of PCP (table 2). The most dramatic increase in threshold sensitivity was with ketamine, 40 mg/kg. Before kindling, this dose of ketamine elevated the AD threshold by 61 percent; following kindling, this dose elevated the AD and seizure threshold by 786 percent. In contrast, diazepam, even at a dose

(8 mg/kg) resulting in marked sedation and akinesia, had no effect on the kindled seizure threshold.

DISCUSSION

The results demonstrate anticonvulsant properties of PCP and ketamine in two quite different seizure models. On the one hand, ketamine was effective in antagonizing several components of PTZ activity. Others have previously reported anti-PTZ effects of ketamine. However, the present results demonstrate that the anticonvulsant effects of ketamine against PTZ seizures closely resembled the effects of phenobarbital in that both compounds delayed clonic convulsions and prevented tonic extension. Moreover, a low dose of ketamine, which alone showed no anticonvulsant effect or overt behavioral changes, potentiated the anti-PTZ effects of phenobarbital. These findings suggest that ketamine possesses selective anticonvulsant properties. The anticonvulsant mechanism of action for phenobarbital is not known. However, the similarities between ketamine and phenobarbital, and the interaction between the two compounds, suggest a common mechanism or site of action.

Although PCP was not included in these experiments using the PTZ model, PCP has been shown previously to antagonize PTZ convulsions (see above). Since ketamine and PCP share many common pharmacological properties, it is reasonable to expect that PCP would show effects similar to those seen with ketamine. In fact, since these experiments were done, others have compared the anticonvulsant effects of structural analogs of PCP. For example, all compounds tested thus far are active against electroshock-induced convulsions, with some analogs more active than PCP or ketamine at behaviorally equivalent doses (Mattia et al., this volume). Further study of the anticonvulsant properties of PCP derivatives may thus provide clues to anticonvulsant drug mechanisms of action.

On the other hand, the results using the hippocampal seizure model revealed an interesting profile of anticonvulsant effects for PCP and ketamine, compared to several classical anticonvulsant compounds. When tested against the unkindled hippocampal seizure, the effects of behaviorally equivalent doses of PCP and ketamine were remarkably similar, but differed substantially from the effects of the anticonvulsant drugs. The compression of the entire EEG seizure episode to a shorter duration was unique to PCP and ketamine, and suggests an anticonvulsant effect. Conversely, the small prolongation of the initial AD episode, and the decreased duration of the postictal depression, could be reflective of proconvulsive influences. There were, however, no other indications of enhanced seizure activity, such as the appearance of motor convulsions or spread of seizure activity to the cerebral cortex.

The four anticonvulsant compounds, like PCP and ketamine, prolonged the initial AD of the prekindled hippocampal seizure. However, diazepam, valprok acid, and phenobarbital, unlike PCP or ketamine, also suppressed the rebound spiking. Carbamazepine showed an even different profile of effects, causing a marked prolongation of the initial AD, rebound spiking, and the total seizure duration. Thus, although the seizure discharge evoked by hippocampal stimulation was altered in a similar manner by both PCP and ketamine, the seizure activity responded differently to the anticonvulsant compounds. Moreover, unlike the results with the PTZ model, ketamine did not resemble phenobarbital in the hippocampal model. These differences may be a reflection of the focal character of the prekindled hippocampal seizure, in contrast to the more widespread CNS stimulatlon following PTZ administration.

During the acquisition of kindled seizures, a progressive recruitment of structures into a network of neuronal circuits capable of supporting seizures has been described (Engel et al. 1978). During this process, the changes in seizure discharge and motor convulsions characteristic of kindling appear. Therefore, the kindled seizure reflects altered CNS function, and may more closely approximate the underlying conditions of epileptogenesis. When the compounds were tested against the fully kindled hippocampal seizure, a different pattern emerged. PCP and ketamine now exerted anticonvulsant effects similar to the four anticonvulsant compounds. All six agents caused a dose-related reduction of the duration of the kindled seizure, and decreased the severity of the motor convulsions. This similarity suggests that kindled epileptogenesis is associated with altered substrates or the formation of additional substrates necessary for the support of seizure activity. It is possible that it is against these altered or new substrates that drugs with anticonvulsant properties are effective.

This speculation is supported by the marked increase in the sensitivity of the seizure threshold to drug-induced elevation following kindling. Clearly, the process of kindling produces alterations in the manner in which the existing neuronal circuitry responds to drug administration. Interestingly, diazepam, at doses capable of altering both the prekindled and kindled seizure, had no effect on either the prekindling or kindled seizure threshold. Therefore, the change in sensitivity of the seizure threshold following kindling, while related to other kindling-induced alterations in brain function, is nonetheless distinct from them. Further studies of the mechanisms of action by which PCP and ketamine alter seizures and thresholds, particularly involving comparisons before and after kindling , and with classical anticonvulsant drugs, may provide clues to mechanisms of epileptogenesis.

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Agonistic and Antagonistic Effects of PCP-Derivatives and Sigma Opioids in PCP Behavioral and Receptor Assays

Patricia C. Contreras, Remi Quirion, and Thomas L. O'Donohue

Phencyclidine (PCP, 1-(1-phenylcyclohexyl)piperidine, angel dust) was first synthesized in 1957 as an anesthetic by the Parke Davis pharmaceutical company. PCP is a "dissociative" anesthetic with minimal respiratory and cardiovascular depression. However, clinical use of PCP was discontinued because it produced post-anesthetic hallucinations often lasting more than 12 hours in about 30 percent of patients (Greifenstein et al. 1958). Today, PCP is one of the most abused drugs, due in part to its ability to elicit hallucinations, excitation, and feelings of tranquility. PCP can also produce very violent aggressive behavior and a psychosis that resembles the acute symptoms of schizophrenia. Thus, it has been suggested that PCP may be a better drug model for schizophrenia than amphetamine (Allen and Young 1978). So far, there is no specific treatment for PCP intoxication or the schizophrenia-like psychosis because the mechanisms responsible for the effects of PCP are not known.

It is believed that many of the behavioral effects of PCP are due to interactions with specific PCP receptors, which were first characterized by Vincent et al. (1979) and Zukin and Zukin (1979). These binding sites appear to satisfy many of the criteria for a PCP receptor because the binding of ^{3}H-PCP to brain homogenates is reversible, saturable, stereoselective, occurs with a relatively high affinity (Vincent et al. 1979; Zukin and Zukin 1979; Quirion et al. 1981a), and has a selective regional distribution (Quirion et al. 1981b). Furthermore, the binding of ^{3}H-PCP was rapidly inactivated by heat and destroyed by proteases, indicating that the PCP receptor is a protein (Vignon et al. 1982). In addition, serotonin, LSD, benzodiazepines, cholinergic, dopaminergic, and adrenergic agonists and antagonists did not inhibit the binding of ^{3}H-PCP. Only drugs that produced PCP-like psychotomimetic effects--PCP analogs, dexoxadrol, and sigma opioids--were able to displace the binding of ^{3}H-PCP at low concentrations, which has led to the suggestion that the PCP receptor is also the sigma opioid receptor (Quirion et al. 1981b). This possibility is supported by the Finding that PCP analogs inhibit the binding of

^{3}H-cyclazocine (Zukin and Zukin 1981), sigma opioids generalize to PCP stimulus (Shannon 1981; Brady et al. 1982) and conversely PCP generalizes to many sigma opioids in drug discrimination paradigms (Teal and Holtzman 1980; Shannon 1983). But these are repasts showing that differences between the binding of ^{3}H-PCP and ^{3}H-SKF-10,047 are significant (Tam 1983; Martin et al. 1985).

The relevance of PCP receptors is supported by reports that the ability of PCP-like drugs to produce PCP-like stimulus in drug discrimination paradigms (Shannon 1981; Holtzman 1980; Brad and Balster 1981), produce vasoconstriction (Altura et al. 1983) and produce ataxia (Vincent et al. 1979; Vignon et al. 1982; Vaupel et al. 1984) correlates well with their ability to bind to PCP receptors.

In rodents, PCP produces not only ataxia, but also stereotyped behavior and hyperactivity. The PCP-induced stereotyped behavior is thought to be due to changes in serotonergic and dopaminergic systems (Nabeshima et al. 1983; Martin et al. 1979; Sturgeon et al. 1981). It is not known whether PCP receptors mediate PCP-induced hyperactivity or stereotyped behavior or even the effect on neurotransmitter systems. It is also possible that mu, kappa, or sigma opioid receptors are involved (Castellani et al. 1982).

The purpose of these studies was to determine whether stereotyped behavior and ataxia induced by PCP-like drugs and sigma opioids is mediated by PCP receptors. Also, we wanted to investigate whether sigma opioid and PCP receptors are the same receptors using behavioral and radioreceptor assays.

COMPARISON BETWEEN INDUCTION OF PCP-LIKE STEREOTYPED BEHAVIOR AND ATAXIA TO INTERACTIONS WITH PCP RECEPTORS

Using the PCP rating scale for stereotyped behavior and ataxia as described by Sturgeon et al. (1979), the central effects of PCP analogs, dexoxadrol, and its levo-isomer, levoxadrol, were determined. As shown in figure 1, all drugs except the (-) isomers produced dose-dependent stereotyped behavior. In contrast, (-)PCMP was equipotent with (+)PCMP in induction of ataxia (figure 2). Furthermore, TCM, which was one-fifth as potent as PCP in the induction of stereotyped behavior, was as potent as PCP in induction of ataxia. The ability of PCP-like drugs to bind to PCP receptors, as measured by their ability to inhibit the binding of ^{3}H-PCP, was determined as described by Contreras et al. (in preparation). The order of relative potencies of drugs as compared to PCP was TCP > PCE > PCP = NIPCA $\geq$ dexoxadrol $\geq$ (+) PCMP > TCM = (-) PCMP >> levoxadrol. A comparison of the ability of drugs to bind to PCP receptors and induce stereotyped behavior (figure 3A) resulted in a straight line (r=0.98), that intersected the origin. However, the correlation between a drug's ability to bind to PCP receptors and to induce ataxia (figure 3B) did result in a good fit to a straight line (r=0.80) but did not intersect the origin.

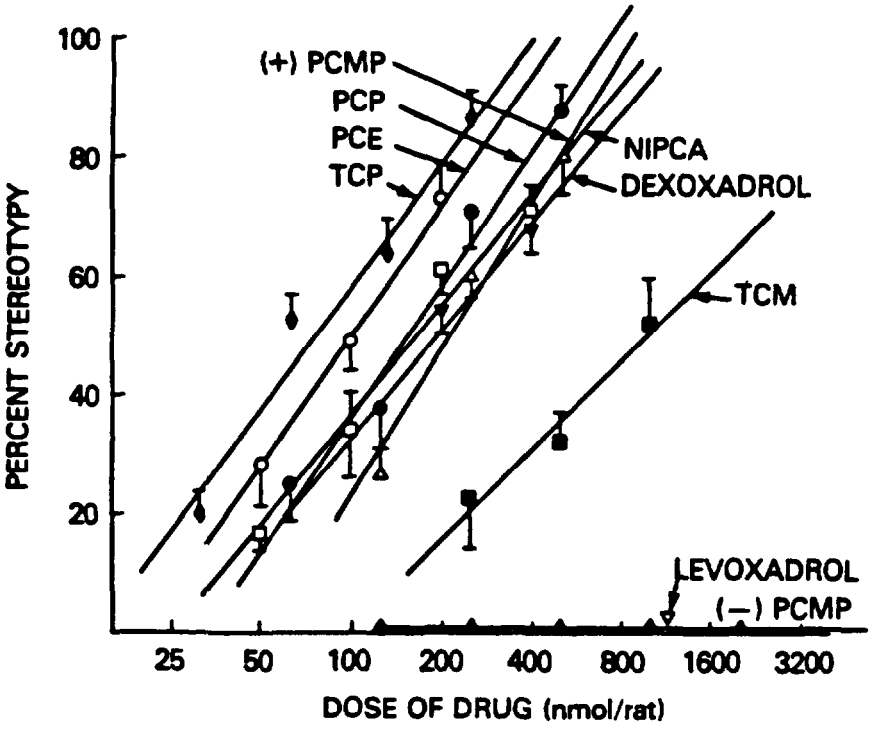

FIGURE 1. *Dose-response curves for induction of stereotyped behavior. Ratings for each animal were determined 5 minutes after ICV administration of each drug. At least 21 rats were used to determine each dose-response curve.*

Thus, stereotyped behavior appears to be mediated by PCP receptors, but ataxia appears to be mediated by more than just an interaction with PCP receptors.

Only the (+) isomer of SKF-10,047, which very weakly inhibited the binding of ^{3}H-PCP, induced stereotyped behavior. This finding is consistent with the results of the PCP receptor assay showing that (+)SKF-10,047 is one-tenth as potent as PCP, but is fivefold more potent than (-)SKF-10,047 (table 1). However, it was not possible to determine whether SKF-10,047 was a full agonist because of its poor solubility in saline. Also, SKF-10,047 produced weaving and circling behavior that was much less pronounced than that induced by PCP. In contrast to the results of the assays for stereotyped

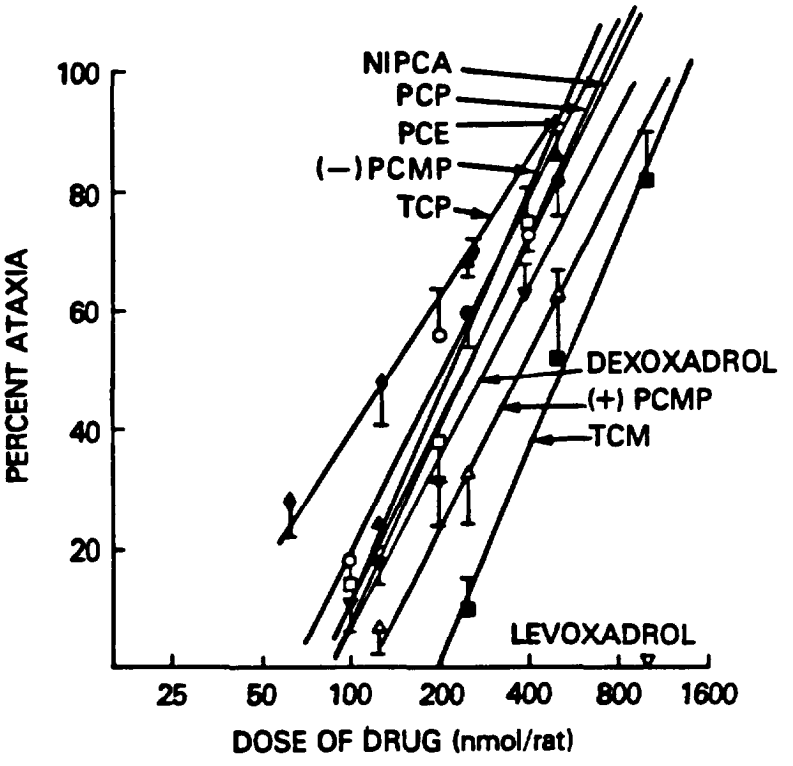

FIGURE 2. *Dose-response curves for induction of atazia. Behavioral ratings were determined 5 minutes after drug administration ICV. At least 21 rate were used to determine each dose-response curve.*

behavior and binding to PCP receptors, the (-) isomer of SKF-0,047 was more potent than the (+) isomer in induction of ataxia.

Stereoselectivity was evident in the assays for stereotyped behavior and PCP receptor interaction, but not in the assay for ataxia as the (+) isomers of the PCP-like drugs and SKF-10,047 were more potent than the (-) isomers in induction of stereotyped behavior and inhibition of binding of ^{3}H-PCP. However, one exception to this trend is that the (-) isomer of cyclazocine was more potent than the (+) isomer in industion of stereotyped behavior and inhibition of the binding of ^{3}H-PCP.

Since large doses of naloxone (10 and 50 m/kg) did not antagonize the ability of PCP or cyclazocine to induce stereotyped behavior

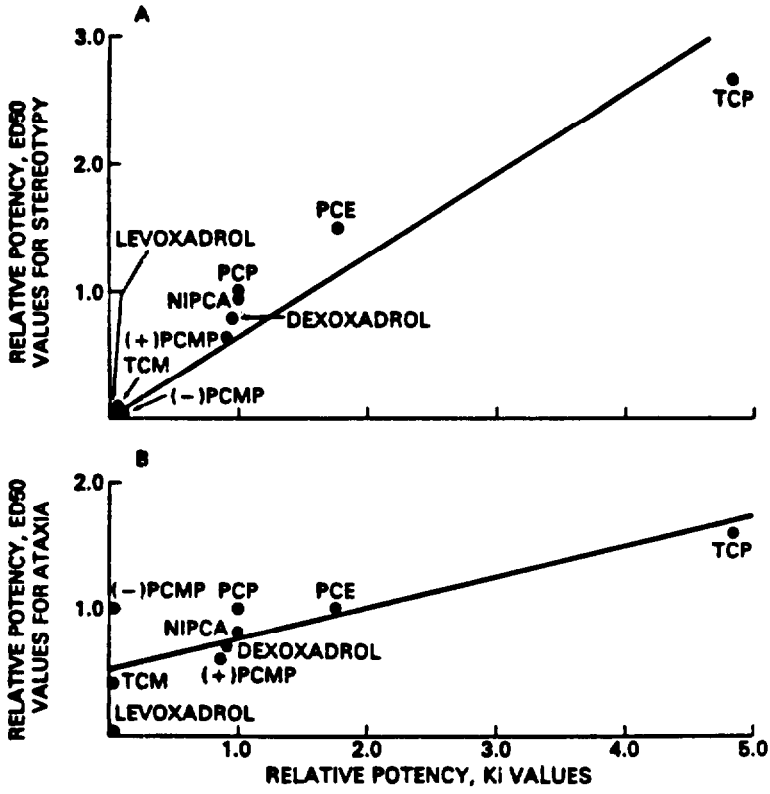

FIGURE 3. *Comparison of the relative potency (ED50 of PCP/ED50 of drug) for induction of (A) stereotyped behavior or (B) ataxia to the relative potency (IC50 of PCP/IC50 of drug) for inhibition of the binding of ^{3}H-PCP*

or ataxia, it is unlikely that mu, kappa, or sigma opioid receptors play a role in mediating these PCP-like behavioral effects. In addition, naloxone pretreatment did not antagonize the ability of (-)SKF-10,047 to induce ataxia.

EFFECT OF METAPHIT ON PCP-INDUCED BEHAVIORAL EFFECTS AND PCP RECEPTORS

Metaphit, (1-(1-(3-isothiocyanatophenyl)cyclohexyl)piperidine), is a PCP analog that specifically acylates PCP receptors in vitro (Rafferty et al. 1985). Additional experiments were performed to determine whether metaphit could acylate PCP receptors in vivo and

antagonize PCP induction of stereotyped behavior and ataxia. Pretreatment of rats with 1 or 2 µmol/rat of metaphit intracerebroventricular (ICV) 24 hours prior to sacrifice, resulted in a 25 percent and 40 percent decrease in the B_{max}, but no change in the Kd of binding of ^{3}H-PCP. Metaphit pretreatment did not alter the binding of ^{3}H-etorphine or ^{3}H-spiroperidol. Since the preparation of the brain homogenates for the binding assays consisted of two washes and was prepared 24 hours after metaphit pretreatment, these results demonstrated that metaphit specifically binds irreversibly to PCP receptors after in vivo administration.

Metaphit administered alone at doses up to 1 µmol/rat did not produce any significant behavioral effects. However at doses of 2 µmol/rat and larger, metaphit produced PCP-like stereotyped behavior and ataxia. Thus, metaphit is a very weak PCP agonist. In addition to acute effects, metaphit produced convulsions, which were evident between 5 and 24 hours after ICV administration of 2 µmol/rat.

Metaphit administered ICV prior to PCP administered ICV antagonized PCP induction of stereotyped behavior and ataxia up to 5 days after metaphit pretreatment. The antagonism of the behavioral effects of PCP by metaphit was dose dependent as is shown in figure 4. Furthermore, this antagonism by metaphit is specific as metaphit pretreatment ICV did not antagonize amphetamine-induced stereotyped behavior and could be prevented by pretreating rats with PCP just prior to metaphit administration. These results indicate that acylation of PCP receptors results in decreased ability of PCP to induce stereotyped behavior.

Since metaphit appears to specifically acylate PCP receptors, metaphit is a useful tool with which to study the physiological role of PCP receptors. When metaphit was administered ICV prior to IP administration of PCP, metaphit antagonized the ability of PCP to induce stereotyped behavior, but not its ability to induce ataxia. Thus, it appears that ataxia is mediated by both central and peripheral mechanisms. It is unlikely that the peripheral effect of PCP in induction of ataxia is mediated by PCP receptors as 20 mg/kg of metaphit administered IV only antagonized PCP-induced stereotyped behavior when PCP was also administered peripherally.

Cyclazocine and PCP probably do not induce stereotyped behavior and ataxia through an interaction with the same receptor, as metaphit did not antagonize the behavioral effects of cyclazocine. Yet, cyclazocine was able to displace the binding of ^{3}H-PCP. These findings are consistent with the finding that metaphit can only bind irreversibly to about 50 percent of the receptors labeled by ^{3}H-PCP (Rafferty et al. 1985), which indicates that ^{3}H-PCP binds to more than one type of receptor. Thus, PCP and cyclazocine probably exert their effects through different receptors.

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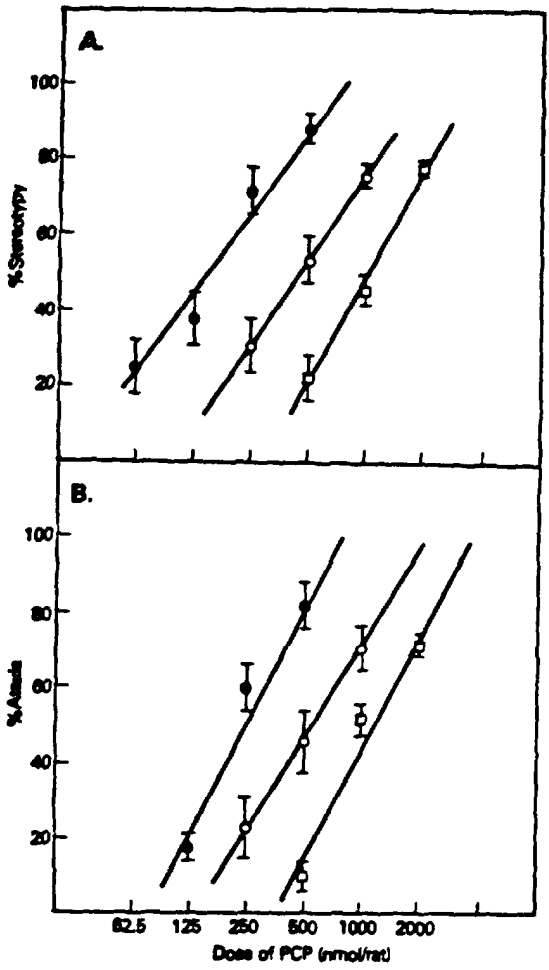

FIGURE 4. *PCP (ICV) dose-response curves for induction of (A) stereotyped behavior and (B) ataxia in control animals (●) or 24 hours after ICV administration of 1 μmoZ/rat (○) or 2 μmol/rat (□) of metaphit*

COMPARISON OF THE BINDING OF ^{3}H-PCP, ^{3}H-TCP, ^{3}H-DEXOXADROL AND ^{3}H-(+)SKF 10,047

The question whether PCP and sigma opioids bind to more than one receptor was studied by comparing the binding and regional distribution of binding sites labeled by ^{3}H-PCP, ^{3}H-TCP, ^{3}H-dexoxadrol,

and ^{3}H-(+)SKF-10,047. ^{3}H-dexoxadrol, ^{3}H-TCP, ^{3}H-PCP, and ^{3}H-(+)SKF-10,047 did not bind to mu, kappa, or sigma opioid receptors or to alpha or beta adrenergic, serotonin, benzodiazepine, or GABA receptors. Only very large concentrations of cholinergic drugs displaced the binding of ^{3}H-PCP. Also dopamine, apomorphine, (+)butaclamol did not inhibit the binding of ^{3}H-PCP. However, the rank orders of potency for inhibition of binding of ^{3}H-PCP, ^{3}H-dexoxadrol and ^{3}H-(+)SKF-10,047 by PCP analogs and sigma opioids were different (table 1). Although the PCP analogs appeared to bind to the tritiated ligands with about the same degree of potency, dexoxadrol, levoxadrol, and the sigma opioids varied greatly in their ability to displace the tritiated ligands. Also, the difference in potency of the isomers varied depending upon the tritiated ligand. These results indicate that PCP, (+)SKF-10,047 and dexoxadrol do not interact with a homogenous population of binding sites.

TABLE 1. *Relative potency of drugs for inhibition of binding of ^{3}H-PCP, ^{3}H-(+)SKF-10,047 and ^{3}H-dexoxadrol*

Drug	Relative potency* for inhibition of the binding of		
	^{3}H-PCP	^{3}H-(+)SKF-10,047	^{3}H-dexoxadrol
PCP	1.0	1.0	1.0
TCP	4.8	4.9	1.8
PCE	1.6	-	0.6
NIPCA	1.0	1.7	-
TCM	<0.1	0.6	0.2
PHP	1.4	-	1.4
THP	0.8	-	0.9
PCDEA	0.3	-	0.2
Dexoxadrol	0.9	0.3	50.9
Levoxadrol	<0.1	0.4	-
(±)SKF-10,047	<0.1	4.0	0.2
(+)SKF-10,047	0.1	11.8	0.3
(-)SKF-10,047	<0.1	0.5	0.2
(+)cyclazocine	0.1	1.7	0.8
(-)cyclazocine	0.5	1.4	0.9
Dextrorphan	0.6	1.6	-

*Relative potency = IC50 of PCP/IC50 of drug for dlsplaclng 8 nM of ^{3}H-PCP, 6 nM of ^{3}H-(+)SKF-10,047, or 7 nH of ^{3}H-deroxadrol.

Another method used to study whether these tritiated ligands bind to different groups of binding sites was to determine the regional distribution of binding sites labeled by ^{3}H-TCP and ^{3}H-dexoxadrol. ^{3}H-TCP was used to label PCP receptors because PCP receptors have

a higher affinity for TCP than for PCP and the degree of non-specific binding is lower for ^{3}H-TCP than for ^{3}H-PCP. Thus, the distributiog of binding sites was more clearly defined when labeled by ^{3}H-TCP than when labeled with ^{3}H-PCP. ^{3}H-TCP appeared to bind to the same receptors as ^{3}H-PCP because the order of potencies for inhibition of binding of ^{3}H-TCP and ^{3}H-PCP by PCP analogs and sigma opioids were the same. The areas of the rat brain with the highest density of binding sites labeled by 3H-TCP were the superficial layers of cerebral cortex, dentate gyrus, subiculum and hippocampus, with much lower densities of binding sites in the olfactory bulb, olfactory tubercle, caudate nucleus, nucleus accumbens, interpeduncular nucleus, periaqueductal gray, superior colliculus, and cerebellum. Very low densities of binding sites were found in most of brainstem, spinal cord, and hypothalamus. ^{3}H-dexoxadrol labeled many more areas of the rat brain than ^{3}H-TCP (Pilapil et al., in press), For example, in the hypothalamus, which was poorly labeled by ^{3}H-TCP, there was a large density of binding sites labeled by ^{3}H-dexoadrol (figure 5). Analysis of the binding sites labeled by H-dexoxadrol in the hypothalamus and cortex, as measured by displacement curves of ^{3}H-dexoxadrol by a variety of ligands, indicated that the binding sites in the cortex and hypothalamus were different (table 2). The order of drug potencies of the PCP analogs for inhibition of binding of ^{3}H-dexoxadrol were similar in the cortex and hypothalamus, but the order of potency for the isomers of SKF-10,047 were reversed in the hypothalamus as compared to binding in the cortex. This is the same order of potency for the isomers of ^{3}H-SKF-10,047 for induction of ataxia and analgesia (Aceto and May 1983), but ^{3}H-dexoxadrol does not bind to mu, kappa, or sigma opioid receptors as mu, kappa, or sigma opioid ligands did not displace the binding of ^{3}H-dexoxadrol in the hypothalamus. Haloperidol only displaced binding of ^{3}H-dexoxadrol in the hypothalamus. Thus, ^{3}H-dexoxadrol labels more than one kind of binding site.

CONCLUSIONS

These results clearly demonstrate that PCP-like drugs administered centrally produce stereotyped behavior that is mediated by PCP receptors. A causal relationship between binding to PCP receptors and induction of stereotyped behavior is also supported by the ability of metaphit, which specifically acylates PCP receptors *in vivo*, to antagonize induction of stereotyped behavior. The order of drug potency of PCP analogs and dexoxadrol to induce stereotyped behavior is similar to that seen in other studies on the binding of ^{3}H-PCP (Hampton et al. 1982; Murray and Leid 1984) and in drug discrimination assays (Shannon 1981; Shannon 1982). Also, the finding that the (+)SFK-10,047 and (-)cyclazocine were the more potent isomers in inducing stereotyped behavior and inhibiting the binding of ^{3}H-PCP is consistent with results from drug discrimination paradigms (Herling et al. 1983; Shannon 1983; Shearman and Herz 1982). Thus, stereotyped behavior, like drug discrimination paradigms, is a good behavioral assay for studying PCP receptor interaction.

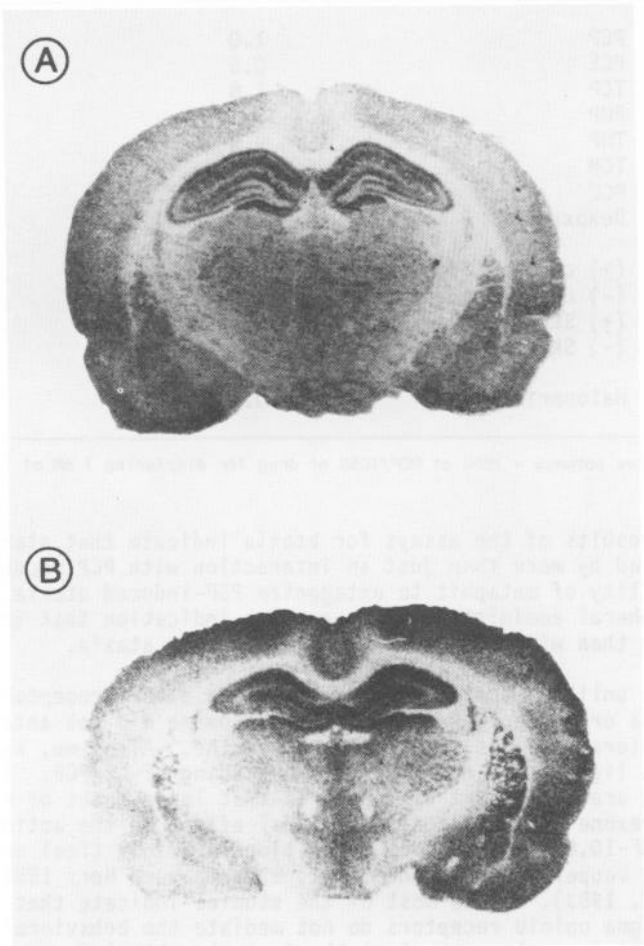

FIGURE 5. *Automdiograms of binding sites labeled by (A) ^{3}H-TCP and (B) ^{3}H-dexoxadrol in coronal sections of rat brain*

TABLE 2. *Inhibition of binding of ^{3}H-dexoxadrol in cortex and hypothalamus*

Drug	Relative Potency*	
	Cortex	Hypothalamus
PCP	1.0	1.0
PCE	0.6	0.5
TCP	1.8	1.3
PHP	1.4	0.7
THP	0.9	1.1
TCM	0.2	<0.4
PCC	<0.1	<0.4
Dexoxadrol	51	137
(+) cyclazocine	0.8	1.0
(-) cyclazocine	0.9	3.8
(+) SKF-10,047	0.3	0.9
(-) SKF-10,047	0.2	3.4
Haloperidol	<0.1	10

*Relative potency = IC50 of PCP/IC50 of drug for displacing 7 nM of ^{3}H-dexoxadrol.

The results of the assays for ataxia indicate that ataxia is induced by more than just an interaction with PCP receptors. The inability of metaphit to antagonize PCP-induced ataxia after peripheral administration is another indication that interactions other than with PCP receptors also mediate ataxia.

It is unlikely that mu, kappa, or sigma opioid receptors mediate ataxia or stereotyped behavior as naloxone did not antagonize the behavioral effects of PCP or cyclazocine. Also, mu, kappa, or sigma ligands did not inhibit the binding of ^{3}H-PCP. These results are consistent with reports that large doses of naloxone or naltrexone had no effect or minimal effect on the actions of PCP or SKF-10,047 in drug discrimination paradigms (Teal and Holtzman 1980; Vaupel 1983; Shannon 1982; Shearman and Herz 1982; Herling et al. 1983). Since most of the studies indicate that mu, kappa, or sigma opioid receptors do not mediate the behavioral effects of PCP, it is unclear why Castellani et al. (1982) found naloxone to antagonize PCP-induced stereotyped behavior and ataxia.

The finding that metaphit did not antagonize (-)cyclazocine induction of stereotyped behavior or ataxia is evidence that PCP receptors and sigma opioid receptors are different receptors. Also, it is clear that ^{3}H-PCP labels more than one binding site because metaphit can only bind irreversibly to about 50 percent of

the binding sites labeled by ^{3}H-PCP. It is also evident that ^{3}H-dexoxadrol, and probably ^{3}H-SKF-10,047, do not bind to a homogenous population of binding sites. The binding sites labeled by ^{3}H-dexoxadrol in the hypothalamus appear to be similar to the sigma opioid binding sites described by Tam (1983) because haloperidol displaced the binding of ^{3}H-dexoxadrol in this region.

In summary, induction of stereotyped behavior appears to be mediated by PCP receptors, whereas induction of ataxia is due to more than one mechanism. Metaphit is a useful tool for studying the role of PCP receptors, as it specifically acylates PCP receptors. The question whether PCP and sigma opioid receptors are the same receptors is complicated by the fact that none of the tritiated ligands used to label PCP and sigma opioid receptors studied binds to a homogenous population of receptors. However, it does not appear that sigma opioids and PCP analogs exert their behavioral effects through a common receptor.

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Electroencephalographic (EEG), Psychopharmacological, and Receptor-Binding Profiles of 'Phencyclinoids'

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INTRODUCTION

Phencyclidine (1-(1-phencyclohexyl)piperidine HCl, PCP) is a widely abused (Petersen and Stillman 1978) psychoactive agent with a broad spectrum of activity. PCP's effects have been assessed in a number of diverse experimental protocols producing behavioral, electraphysiological, and biochemical data (Kamenka et al. 1983; Domino 1981). Unfortunately, despite its potency in many experimental models, it is not known which of PCP's experimental effects in these animal models (motor incoordination, analgesia, stereotypy, etc.) are most relevant to its pharmacologic and toxic effects in humans (anesthesia, analgesia, psychosis). This is at least partially related to the complexity of PCP's actions. For example, even seemingly simple protocols of gross behavioral observations of PCP effects can be difficult since stereotypy, ataxia, and locomotion occur simultaneously, tend to be fragmented in nature, and compete with each other for expression. Fortunately, however, a number of phencyclidine analogues (Kalir et al. 1969) and compounds from other chemical classes that possess phencyclidine-like activity (benzomorphan, benz(f)isoquinoline, and dioxolane derivatives) are available and will no doubt be helpful in elucidating PCP's spectrum of pharmacologic activity and mechanism of action. We propose that these and other compounds that exhibit significant phencyclidine-like activity be referred to collectively as "phencyclinoids." In order to obtain useful information on the basic pharmacology of PCP, which may help to understand its mechanism of action, comprehensive profiles are being developed for a series of phencyclinoids in several assays which progress from simpler to more complex. This report will describe the results of EEG, behavioral, and receptor binding studies conducted to date.

METHODS

Animals and Surgical Procedures

Throughout these studies, adult female Sprague-Dawley rats weighing about 250 gm were used. During experimentation, they were housed in individual plastic cages. Purina Rat Chow and water were available ad libitum, and they were maintained under an automated light cycle with illumination from 6 a.m. to 10 p.m. daily.

Rats were implanted with indwelling jugular cannulae for intravenous (IV) administration of drugs (Weeks and Davis 1964). To monitor cortical EEG and electromyographic (EMG) activity, respectively, they were also prepared with chronic cerebrocortical electrodes and temporalis muscle electrodes (Khazan 1975). One week was allowed for recovery from surgery before experimentation.

Drugs and Drug Administration

The phencyclinoids used in this study are listed in table 1. PCP analogues were chosen with modifications of the piperidine (PCA, NMPCA, PCE, NsBPCA, PCPY) or phenyl (TCP and TCPY) ring systems. Ketamine, also an analogue of PCP, has a piperidine ring replacement and additional modifications at the cyclohexyl and phenyl rings. SKF-10,047 is a benzomorphan opioid derivative. PCP, its analogues, and the racemate of SKF-10,047 were obtained from the National Institute on Drug Abuse. ^{3}H-PCP (49.9 Ci/mmol) was obtained from New England Nuclear Company for receptor binding studies. Dextroamphetamine, ketamine, sodium pentobarbital, and morphine were obtained commercially.

TABLE 1. *Chemical names and abbreviations*

Abbreviation	Chemical Name
PCP	1-(1-phenylcyclohexyl)piperidine HCl
PCA	1-phenylcyclohexylamine HCl
NMPCA	N-methyl-1-phenylcyclohexylamine HCl
PCE	N-ethyl-1-phenylcyclohexylamine HCl
NsBPCA	N-(s-butyl)-1-phenylcyclohexylamine HCl
PCPY	1-(1-phenylcyclohexyl)pyrrolidine HCl
TCP	1-(1-(2-thienyl)cyclohexyl)piperidine HCl
TCPY	1-(1-(2-thienyl)cyclohexyl)pyrrolidine HCl
Ketamine	2-(o-chlorophenyl)-2-methylaminocyclohexamine HCl
SKF-10,047	N-allylnormetazocine HCl

Drugs were prepared biweekly in physiological saline and administered via cumulative IV injections. Acute dose-response data were generated for each drug in one test session by giving each rat a series of drug injections beginning at 0.1 mg/kg, and then doubling the dose at successive 30-minute intervals. Rats received bolus injections of 0.5 ml or less saline alone or 0.1 to 0.2 ml of drug solution flushed with saline through jugular cannulae. In anticonvulsant studies, intraperitoneal (IP) drug administration was used. In the EEG studies, a one-quarter logarithmic dilution was used for ketamine. Doses are expressed as the hydrochloride salts.

Direct EEG and EEG Power Spectra

Rats were acclimated to the EEG recording cages and connected by flexible cables through mercury commutators to a Grass Model 7D Polygraph. The direct EEG was filtered at the polygraph at 35 Hz. On the day of an experiment, in addition to paper EEG and EMG recordings, the EEG was collected on FM magnetic tape using a Sony TC-277-4 quadradial tape recording system in conjunction with a Model 4 FM recording adaptor. Spectral analysis of the EEG was performed using the Fast-Fourier-Transformation on digitized data points from 0 to 25 Hz with the Nicolet Med-80 and Pathfinder I computers and software. Sampling was performed at the Nyquist sampling rate of 50 Hz. Sequential spectra were plotted during saline and cumulative IV drug injections from 0.1 to 12.8 mg/kg. Utilizing the overt behavioral assessment described below, doses were chosen that produced behaviorally similar responses. For all compounds tested, the peak total power and predominant frequency of 5 or 6 EEG samples of 10- or 12-second duration were averaged for each dose. To normalize the data, the absolute power values were converted to root-mean-square (RMS) voltage and expressed relative to saline quiet awake baseline for each rat; each rat, therefore, served as its own control.

Overt Behavior

Locomotion, stereotypy, and ataxia were rated via behavioral observations for all compounds, using behavioral rating scales devised specifically for PCP (Sturgeon et al. 1979). Behaviors were rated by observing each animal for 1 or 2 minutes at the midpoint of each 30-minute dosing interval during collection of the EEG.

Spontaneous Locomotor Activity

Spontaneous locomotor activity (SLA) was measured in photocell activity cages isolated in light- and sound-attenuated boxes. Each cage contained six infrared photocell beams arranged around the base of a circular tract. Each interruption of a beam registered a count on a total-event counter and on a cumulative recorder. Cumulative IV doses at 30-minute intervals were administered over dose ranges that included the complete spectrum of effects on SLA.

Analgesic Activity

The hot plate test with a 55 °C platform was used to measure latency to hindlimb lick at 12 or 18 minutes postinjection in rats. A maximum latency of 60 seconds was allowed to prevent tissue damage and to enable multiple testing. Drugs were given by cumulative IV injections at 42-minute intervals up to a maximum dose one unit below the dose which produced rotarod failure.

Rotarod Performance, Righting Reflex, Convulsant Activity, and Lethality

Rotarod performance, righting reflex, convulsant activity, and lethality were evaluated in the same rats, which were given saline followed by cumulative IV drug injections from 0.1 to 51.2 mg/kg at intervals of 30 minutes. Two-minute rotarod trials at 20 revolutions per minute were conducted at 12 and 18 minutes after injections, to measure motor coordination. After completion of rotarod testing, subsequent drug doses were administered to determine the doses at which loss of righting reflex, motor signs of convulsant activity, and lethality occurred. The doses producing the maximal effects on each parameter were recorded.

Pro- and Anticonvulsant Activity

The pro- and anticonvulsant effects of the phencyclinoids were studied by assessing their ability to increase or decrease the intensity of electrically-induced convulsions. A 32 mA, 0.2-second stimulus was delivered via corneal electrodes with a constant-current electroshock apparatus. The shock parameters were chosen to produce a convulsion intensity of "3" on a five-point rating scale as follows: 0 = stunned only, 1 = facial and vibrissae tremor, 2 = clonic forepaw treading, 3 = tonic forelimb extension, 4 = tonic forelimb and hindlimb extension, and 5 = death. Thus, both increases and decreases in the convulsion intensity subsequent to drug administration could be observed. Drugs were given IP in selected doses based on rotarod test results. The rats received saline and shock on day one, drug and shock on day three, and saline and shock again on day five. Data are presented as difference scores in convulsant intensity for saline versus drug within animals.

Receptor Binding

Displacement binding experiments with ^{3}H-PCP were conducted with minor modifications of the filtration method described in the literature (Zukin and Zukin 1979; Vincent et al. 1979; Hampton et al. 1982) in crude tissue preparations of rat whole brain homogenates in 5 mM Tris-HCl (pH 7.4).

RESULTS

Direct EEC and EEC Power Spectra

Representations of the direct cortical EEG effects and sequential 1-minute power spectra after cumulative IV doses of 0.4. 0.8, 1.6, and 3.2 mg/kg PCP are provided in figure 1 (A, B). The direct EEG and EEG power spectra correlated in a dose-related manner with PCP's behavioral effects. At 0.4 mg/kg, PCP produced increased locomotor activity and stereotypy associated with predominant spectral power in the 5- to 10-Hz range. At 0.8 mg/kg, locomotor activity and stereotypy intensified and ataxia emerged. In conjunction with ataxia, high-amplitude slower waves were present and more power was contained in the 0- to 5-Hz band. At the higher doses of 1.6 and 3.2 mg/kg, the EEG activity consisted primarily of high-amplitude, slow-frequency waves superimposed upon background theta activity. At the highest doses, severe ataxia and dyskinetic head and forepaw movements occurred in association with spectral power concentrated in the 0- to 5-Hz band.

Spectral analysis of the EEG effects of PCP and related compounds-on peak RMS voltage revealed similarities and differences between the compounds tested. In general, moderate increases in peak RMS voltage occurred as a function of dose, producing relatively flat dose-response curves, as shown in figure 2, for 6 of the 10 compounds tested. The N-piperidine derivatives were qualitatively similar to PCP and differed primarily in that they were less potent. NMPCA, about one-fourth as potent as PCP, and ketamine, about one-eighth as potent as PCP, also differed in that the slopes of their increase in RMS voltages were steeper, and greater maximal increases were obtained. TCP (data not shown) was most potent and SKF-10,047 was least potent with respect to effects on RMS voltage. Despite its PCP-like effects on the EEG, PCA produced less intense behavioral effects.

Dose-related shifts in predominant EEG frequency for PCP and several phencyclinoids are shown in figure 3. For all 10 compounds tested, there was a shift in predominant EEG frequency into the theta range across the lower doses , associated primarily with increased locomotor activity and stereotyped behaviors. With further increases in dose, PCP and all of its analogues produced shifts to lower predominant frequencies, which typically fell between 2 and 4 Hz. As the dose was incremented geometrically, the lower frequency EEG waves were associated first with ataxia, then with dyskinetic movements , catalepsy, and possibly seizure activity. SKF-10,047 also produced ataxia, but was unique in that it did not cause a shift to a lower predominant frequency and produced only EEG theta activity at all subconvulsant doses.

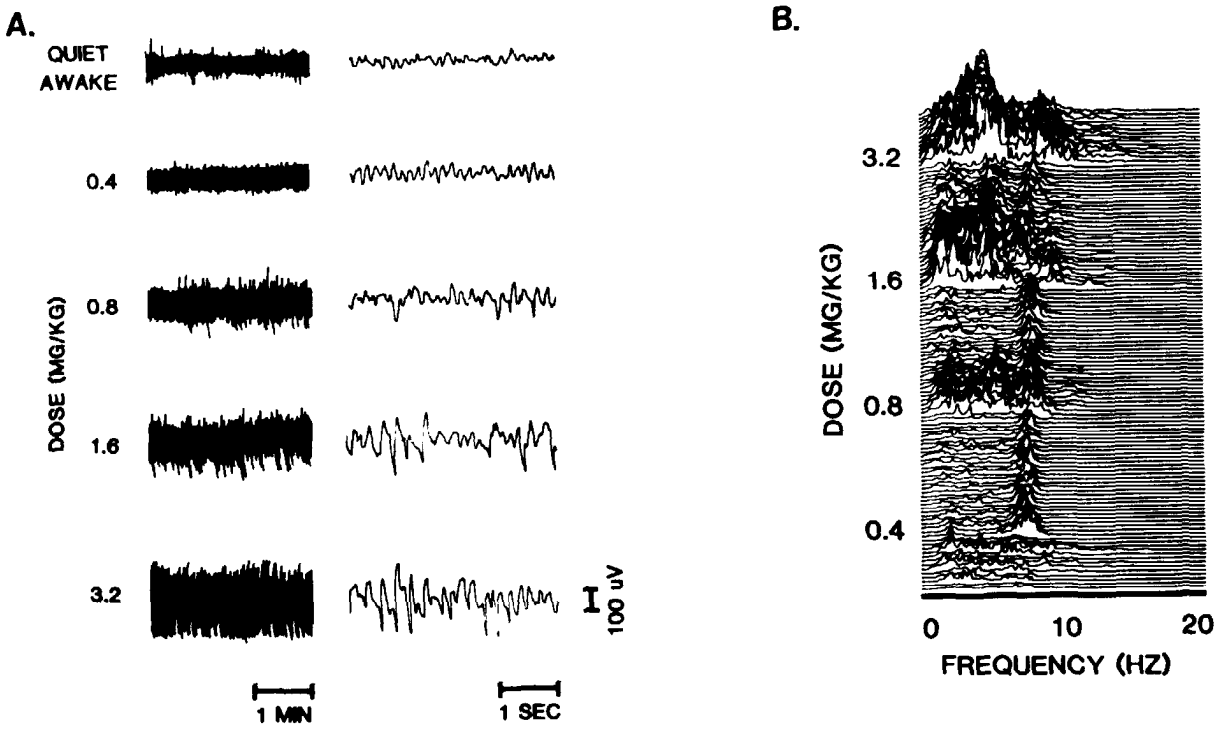

FIGURE 1. *The effects of cumulative intravenous PCP on (A) the direct cortical EEG recorded in freely moving rats, and (B) the associated sequential l-minute EEG power spectra*

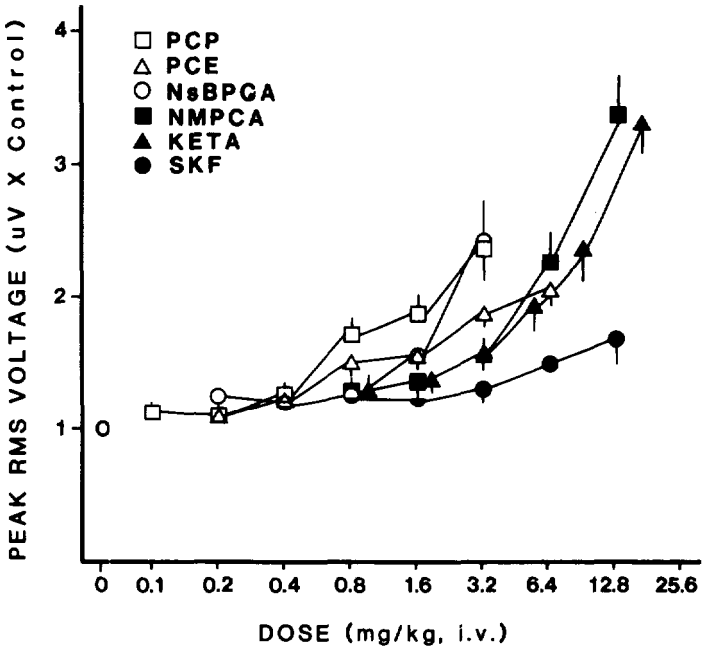

FIGURE 2. *Peak EEG root-mean-square (RMS) voltage from 0-20 hertz (Hz) as a function of dose for phencyclinoids*

PCP produced electrical seizure activity at 12.8 mg/kg IV, EEG spectra were clearly different from those produced by lower doses in that fast-frequency, high-amplitude EEG waves occurred and resulted in a spectral peak at about 15 Hz. EEG activity from 0 to 35 Hz occurred during seizures in contrast to subseizure doses, which produced EEG with little activity beyond 10 Hz. Generally, these seizures occurred immediately after IV injections and lasted 1 to 3 minutes. Similar spectra were obtained with NsBPCA (12.8 mg/kg), SKF-10,047 (25.6 mg/kg), and even with ketamine despite the absence of overt convulsant activity. Motor manifestations of EEG seizure activity included whole body tremors and vigorous twitches of the face and vibrissae.

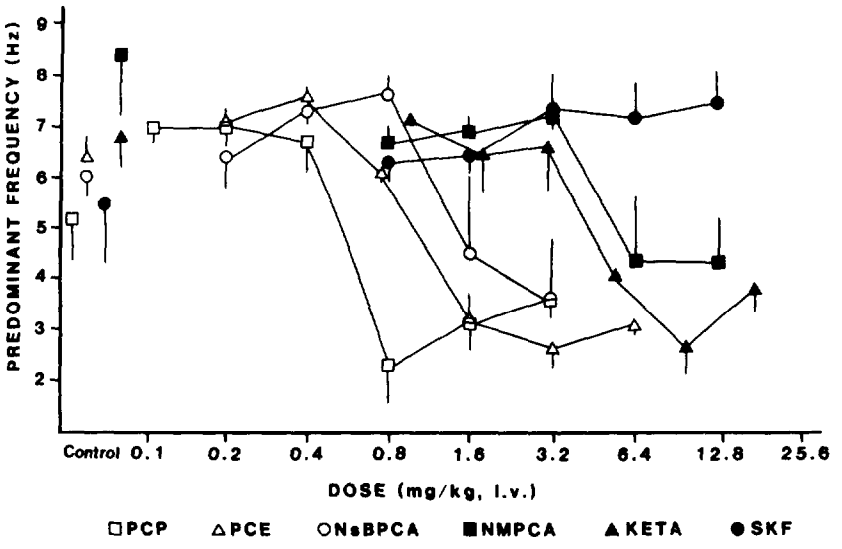

FIGURE 3. *Predominant EEG frequency as a function of dose for phencyclinoids*

Overt Behavior

Dose-response curves for the effects of PCP and several compounds on locomotion, stereotypy, and ataxia are shown in figure 4 (A, B, C). PCP increased behavioral rating scores for stereotypy and ataxia as a function of increasing dose, from 0.2 to 3.2 mg/kg cumulative IV. For PCP-induced locomotion, behavioral rating scores increased up to 1.6 mg/kg, and declined at 3.2 mg/kg. Similar scores were generated for the other compounds over doses ranging from 0.1 to 12.8 mg/kg. When scores for one behavior increased, concomitant increases in the scores for each of the behaviors resulted, making only quantitative differences between these phencyclinoids observable. Consequently, similar relative potencies were obtained from consideration of any one of these three behaviors. The rank order of potency for locomotion, stereotypy, and ataxia was TCP > PCP = PCPY = TCPY > PCE = NsBPCA > NMPCA > ketamine = PCA = SKF-10,047. PCE was unusual in that its potency for ataxia was nearly equal to PCP's, yet it was only about one-third as potent in inducing locomotion and about two-thirds as potent for producing stereotypy. TCP was more potent, TCPY and PCPY were about equipotent, and PCA was less potent than PCP (data not shown).

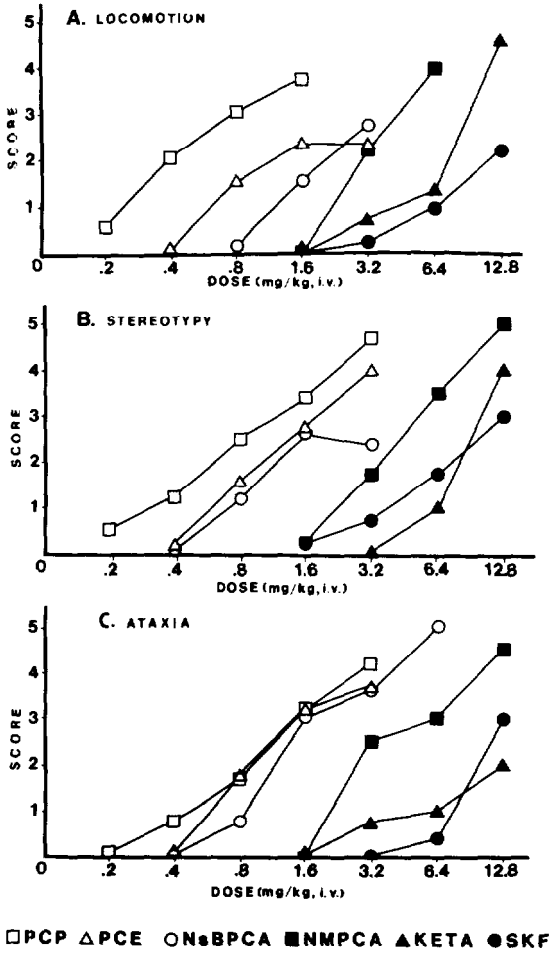

FIGURE 4. *Dose-response-curves for the effects of phencyclinoids on: (A) locomotion; (B) stereotypy; and (C) ataxia. Overt behaviors were scored using the behavioral rating scales of Sturgeon et al. (1979).*

Spontaneous Locomotor Activity

The relationship between dose and SLA was characterized by an inverted U-shaped curve for the phencyclinoids tested and dextro-amphetamine. Geometric increases in cumulative IV doses produced nearly linear increases followed by decreases in SLA for each

compound, while repeated saline injections resulted only in diminished motor activity. Dose-response curves for the rate-increasing effects of the phencyclinoids were similar and are shown in figure 5. The psychomotor stimulant dextroamphetamine was nearly equipotent with PCP. All the drugs tested were significantly less efficacious than PCP (ANOVA, Dunnett's comparison of means, $p < 0.05$) with respect to peak increases in SLA, regardless of their potency. For example, PCE was the least efficacious, yet produced its maximal effect at 0.8 mg/kg, as did PCP. The doses of phencyclinoids producing peak SLA and maximal disruption of rotarod performance are strongly correlated (r=0.99). Furthermore, a good correlation (r=0.77) exists between the doses of phencyclinoids producing peak SLA and maximum EEG theta activity.

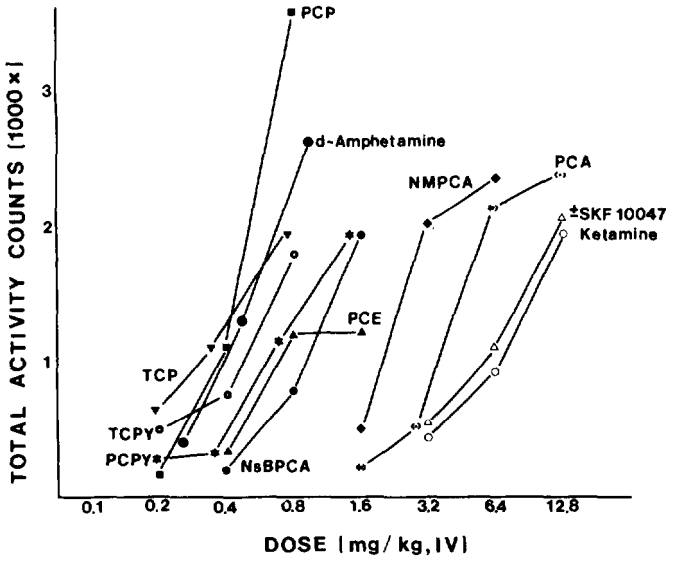

FIGURE 5. *Dose-response curves for the rate-increasing effects of phencyclinoids and dextroamphetamine on spontaneous locomotor activity.*

Analgesic Activity

Analgesic data, expressed as ED_{50} values and their confidence limits, are summarized in table 2. All 10 compounds possessed analgesic activity at doses below those inducing severe ataxia. Ataxia at higher doses prevented accurate measurement of the response, resulting in a ceiling effect. The rank order of analgesic potency for the phencyclinoids was TCP > PCE > PCP > PCPY = TCPY > NsBPCA > ketamine > SKF-10,047 > NMPCA > PCA, which varied

somewhat from their rank order of potency for disruption of rotarod performance (figure 6A) and effects on SLA (figure 5). More important, as was also true in the case of SLA, analgesic potency was distinguished from analgesic efficacy. But, none of the phencyclinoids was as efficacious as morphine in producing analgesia.

TABLE 2. *Analgesic effects of phencyclinoide and morphine*

Drug	Time (Min Postdrug)	ED_{50}	Max Analgesia (Percent)
PCP	18	0.19 (0.10-0.36)	80.9
NMPCA	12	1.69 (0.44-6.50)	68.8
Ketamine	18	0.48 (0.17-1.36)	54.8
NsBPCA	18	0.23 (0.13-0.38)	50.7
PCE	18	0.10 (0.05-0.22)	48.8
PCPY	12	0.20 (0.12-0.31)	32.8
TCP	18	0.02 (0.01-0.07)	31.9
TCPY	12	0.20 (0.12-0.31)	29.8
SKF-10,047	18	1.49 (0.69-3.31)	27.4
PCA	18	3.94 (0.70-22.2)	15.0
Morphine	12	0.48 (0.11-2.07)	98.4

NOTE: ED_{50} values determined by the method of Litchfield and Wilcoxon (1949).

Rotarod, Righting Reflex, Convulsant Activity, and Lethality

Figure 6 (A, B, C, D) summarizes the data for 10 phencyclinoids for disruption of rotarod performance, loss of righting reflex, convulsant activity, and lethality. The rotarod test proved most useful in differentiating compounds. The rank order of potency for the disruption of rotarod performance was TCP > TCPY = PCPY = PCE > PCP = NsBPCA > PCA = NMPCA > ketamine = SKF-10,047. When the doses producing disruption of rotarod performance were corn-pared to lethal doses, none of the compounds demonstrated an exceptional margin of safety. Distinctions between the drugs were also made via behavioral observations of convulsant effects. Ex-cept for ketamine, overt motor manifestations of convulsant activ-ity, including full body extensions and vigorous twitches of the face and vibrissae, were noted for each compound at high doses. Since ketamine lacked convulsant activity and was not very potent in disrupting rotarod performance, it had the largest margin of safety when these drug properties were considered relative to lethality. Loss of righting reflex and lethality were less useful parameters for discriminating between drugs, at least with the dosing schedule used in this assay.

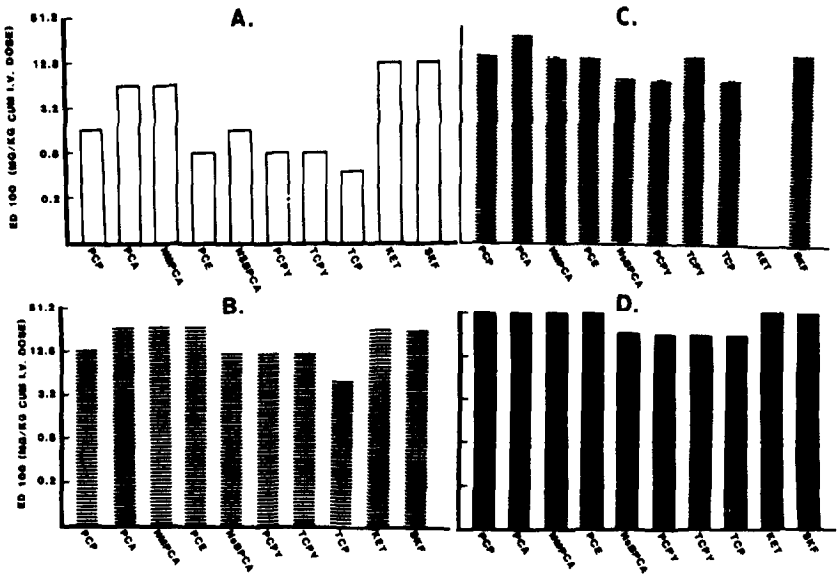

FIGURE 6. *Histograms depicting doses of PCP and related compounds which produced: (A) maximal disruption of rotarod performance; (B) loss of righting reflex; (C) clonic and/or toxic convulsions; and (D) lethality in rats (n=6) given cumulative intravenous doses*

Pro- and Anticonvulsant Activity

A complete dose-response analysis was generated for PCP for doses from 0.625 to 20 mg/kg IP (data not shown). PCP exhibited dose-related anticonvulsant action when day one minus day three difference scores were compared for all doses tested. When retested with saline only on day five, no reduction in convulsant severit or super-sensitive response was observed (day one minus day five), indicating no carryover drug effect 48 hours after dosing. At behaviorally equivalent doses, all compounds assayed were clearly anticonvulsant (table 3). TCP was most potent at the doses tested. PCA was the most efficacious, and reduced convulsant severity by 2.58 points. As with PCP, none of the other phencyclinoids had any carryover effects 48 hours after dosing (day one minus day five).

TABLE 3. *The effects of phencyclinoids on electrically induced convulsions*

Drug	Dose (mg/kg IP)	Mean Difference Score Days 1-3	Days 1-5
Saline	-	0.42	0.13
PCP	2.500	-0.83*	0.17
	10.000	-0.92**	0.17
PCE	1.250	-0.66*	0.83
	5.000	-0.75*	0.17
NsBPCA	2.500	-0.75*	0.33
	10.000	-0.83*	-0.33
PCA	10.000	-0.75*	0.00
	40.000	-2.58**	0.17
NMPCA	5.000	-0.83*	0.50
	20.000	-1.40*	0.33
PCPY	1.250	-0.75*	-0.17
	5.000	-0.83*	0.00
TCP	0.625	-0.33*	0.17
	2.500	-0.33*	0.33
TCPY	1.250	-0.33*	0.50
	5.000	-0.83*	0.50
Ketamine	5.000	-0.50*	0.00
	20.000	-0.50*	0.83
SKF-10,047	5.000	-0.50*	-0.17
	20.000	-0.50*	-0.33

*p<0.05

**p<0.01

NOTE: A mean difference score of zero lndicates no change; a negative score denotes ant convulsant action; a positive score denotes a proconvulsant action of the drug. n=6.

Receptor Binding

The binding of ^{3}H-PCP to whole brain homogenates was saturable and completely displaced by unlabeled PCP at a concentration of 10^{-5} M. PCP-related compounds displaced ^{3}H-PCP and varied in potency. Although this work is still in progress, preliminary results indicate a rank order of potency for the displacement of ^{3}H-PCP from its receptor similar to those reported for effects on EEG, rotarod performance, and SLA.

DISCUSSION

These studies provide pharmacologic profiles of PCP and related compounds ("phencyclinoids") derived from *in vivo* and *in vitro*

assays relevant to the general pharmacology of this class of psychoactive agents. While a comprehensive discussion of all the data is not possible here, several important points can be made regarding the data and approach employed to study PCP.

Although some EEG data for PCP and/or related compounds can be found in the literature (Vanderwolf and Leung 1983; Domino et al. 1983a; Domino et al. 1983b; Young et al. 1981; Gerhmann and Killam 1979), no comprehensive EEG studies systematically associated with behavioral effects of PCP have been reported. In this study, characteristic EEG effects, produced by PCP, that are dose related have been described using computer-assisted EEG analysis. At low doses of PCP, the predominant EEG effect was theta activity (5 to 10 Hz). At moderate doses, the predominant EEG activity consisted of high-amplitude slow waves (0 to 5 Hz). At high doses, there was activity over a wider range of frequencies, which was associated with seizure-like activity. There were dose-related behavioral effects that correlated well with the EEG changes. Characterization of these EEG and behavioral effects enabled replication and extension of previous descriptions of qualitative and quantitative differences between PCP and a more limited sample of related compounds (Mattia and Moreton 1981). The behavioral rating scales of Sturgeon et al. (1979) were very useful in conjunction with EEG recordings, since behaviorally equivalent doses could be selected for EEG comparisons. However, when used alone, these behavioral rating scales did not permit qualitative differences in compounds to be observed.

Summarizing the results of the other pharmacologic assays, our data for the analgesic effects of phencyclinoids are in agreement with other published data (Itzhak et al. 1981; Itzhak and Simon 1984; Kalir et al. 1978), but extensive analgesic studies of the analogues have not previously been reported. On the whole, our results also support existing data for the effects of phencyclinoids on spontaneous locomotor activity (Lozovsky et al. 1983; Castellani and Adams 1981), and for their pro- and anticonvulsant effects (Chen et al. 1959; Snyder et al. 1981; Hayes and Balster 1985; Zimmerman et al. 1985). The rotarod test of motor coordination, in agreement with other published data (Vaupel et al. 1984; Vignon et al. 1982; Cone et al. 1984), proved reliable in separating the compounds with respect to potency. Both quantitative and qualitative differences were discernible via observations of convulsant activity occurring at higher doses. Measurements of righting reflex and lethality, however, were less discriminating, probably because of the narrow range of potencies of the compounds tested and the use of dose doublings at successive dosing intervals. Given a broader range of potencies, these parameters might have been more useful. Furthermore, changing the dosing increments or time interval between doses might enhance the utility of measuring these parameters during cumulative dosing.

Although still in progress, correlations of PCP receptor binding with the results of the other assays should prove valuable in

completing the pharmacologic profiles of the phencyclinoids studied thus far. Such correlations have already been obtained by others for rotarod performance (Vaupel et al. 1984; Vignon et al. 1982; Cone et al. 1984), drug discriminations (Shannon 1981). and catalepsy (Mendelsohn et al. 1984). It may also be possible to relate various pharmacologic effects of phencyclinoids to PCP receptor subtypes recently described in the literature (Mendelsohn et al. 1984; Sethy and McCall 1984).

Although generally similar pharmacologic profiles were obtained for the phencyclinoids, subtle but perhaps important differences in these compounds were discernible depending upon the individual assay employed. For example, ketamine never produced behavioral convulsions and was least potent with respect to SLA and disruption of rotarod performance, but was more potent than PCPY, TCPY, TCP, and PCA in the assessment of analgesic activity. PCA, which was very effective in decreasing the severity of electroshock convulsions, was not particularly efficacious or potent in other assays. While PCE was equipotent with PCP in stimulating SLA, it was least efficacious of all compounds with respect to peak SLA achieved.

Cumulative dosing schedules are useful and have practical application in psychopharmacology (Wenger 1980). The use of the cumulative IV dosing schedule in these studies permitted the full range of activities for each compound to be observed in a group of animals in one test session.

In conclusion, these data emphasize the need for multiple assays to discern differences among compounds otherwise regarded as pharmacologically more similar than different. Measurements of EEG and convulsant activity are useful because each permits qualitative and quantitative differences in the compounds to be observed. SLA and analgesia are also useful tests which provide information regarding potency and efficacy. Rotarod performance is helpful in determining potency but this paradigm does not permit differences in efficacy to be observed. The binding studies should be of use in relating diverse pharmacologic effects to specific drug receptor interactions. This integrated approach utilizing multiple assays to develop pharmacologic profiles, as first accomplished by Chen et al. (1959) for PCP, should help to better define the agonist properties and mechanism of action of the phencyclinoids. This would facilitate investigations regarding the physiological consequences and determinants of drug abuse, and contribute to the search for antagonists, potentially useful research tools, and therapeutic agents.

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Modulation of Phencyclidine (PCP) Pharmacokinetics With PCP-Specific Fab Fragments

S. Michael Owens and Michael Mayersohn

At high doses, phencyclidine (PCP) abuse sometimes leads to a schizophrenic-like condition as well as violent and destructive behavior (Lerner and Burns 1978; Fauman and Fauman 1979). As with most drugs, there is no specific antagonist for reversing effects from PCP. Therefore, conventional therapy, such as urine acidification and forced diuresis. have been the only available treatments (Domino and Wilson 1977; Aronow et al. 1978). Although these techniques may aid in the elimination of PCP, there are several criteria which must be met before these approaches can be considered clinically effective. First, the degree of ionization of the drug should be alterable within the physiological urine pH range. Second, the drug needs to have a fairly small volume of distribution. Finally, the therapy should cause renal excretion to become a major route of elimination. PCP meets only the first of these criteria. In both humans and animals, PCP has been shown to have a very large volume of distribution (i.e., very little of the drug is present in the blood stream), and to be primarily eliminated through metabolism (Cook et al. 1982a; Cook et al. 1982b; Woodworth et al., in press). Therefore, a more effective detoxification procedure is needed.

A promising technique for detoxification of certain drugs is the use of drug-specific antibody fragments (Fab, the antigen-binding fragment of IgG). This type of treatment has been shown to reverse digoxin and digitoxin toxicity rapidly in both animals and humans (Lloyd and Smith 1978; Smith et al. 1982). The purpose of this paper is to discuss the important factors in the use of immunotherapy for treating PCP toxicity and to present preliminary data on the effects of anti-PCP Fab fragments on PCP pharmacokinetics in dogs.

PHARMACOKINETIC CONSIDERATIONS FOR DETOXIFICATION OF PCP BY IMMUNOTHERAPY

Immunotherapy for drug overdose is a fairly recent medical development (Lloyd and Smith 1978; Smith et al. 1979; Smith et al.

1982). The advantages and disadvantages of choosing immunotherapy as a treatment for drug toxicity have been reviewed by Colburn (1980). The reasons for choosing immunotherapy for PCP are based on two important characteristics of the drug: an extremely large volume of distribution, and pharmacological effects that are mediated through reversible binding to a drug/receptor complex.

The large volume of distribution of PCP precludes effective detoxification by passive procedures, which are dependent on access to the drug in the blood stream. For instance, Allen et al. (1985) have shown that charcoal hemoperfusion of the blood of dogs after a 5 mg/kg dose of PCP does not affect the pharmacokinetics of PCP, nor does it alter the pharmacological response to the drug. To demonstrate the point regarding the large volume of distribution of PCP, figure 1 illustrates the change in the apparent volume of distribution of PCP with time, after an intravenous bolus dose of ^{3}H-PCP in one of our control animals (i.e., no antibody was administered in this experiment).

Fab fragments (M.W. 50,000) have several advantages over IgG (M.W. 150,000) for use as the immunotherapeutic reagent (Smith et al. 1979). The Fab fragments distribute more rapidly and extensively than intact IgG. In addition, they are catabolized and excreted earlier than intact IgG. A final important advantage is that the Fab fragments are less antigenic than the intact IgG.

Even though the Fab fragments can probably distribute throughout the plasma and interstitial space (i.e., extracellular water) (Colburn 1980) after intravenous administration, they most likely will not penetrate directly to sites of action of PCP in the central nervous system. Therefore, the effectiveness of the Fab fragments will depend on a number of interrelated factors. These factors include the affinity constant of the Fab fragments relative to other binding sites in the body (i.e., particularly the PCP neuroreceptor), the binding capacity of the Fab fragments (i.e., the amount of antibody administered and its affinity for the drug), and the accessibility of antibody fragments to PCP in the peripheral compartment, as judged by the magnitude of clearance from the peripheral to the central compartment (see figure 1). The significance of each point will be discussed separately.

Intravenously administered anti-PCP Fab fragments would be expected to "neutralize" drug effects by decreasing the concentration of PCP at the site of action (i.e., particularly the PCP neuroreceptor). Since the antibody fragment may not be able to penetrate directly to the sites of action of PCP, it must shift the in vivo equilibrium of the drug through reversible, high-affinity binding. Therefore, the affinity of the Fab fragments for PCP needs to be much greater than the affinity of in vivo binding sites for PCP. The highest reported in vivo binding site for PCP is the PCP neuroreceptor. Vincent et al. (1979) and Quirion et al. (1981) have reported affinity constants for this binding site of 4.0×10^{6} M^{-1} and 2.17×10^{7} M^{-1}, respectively (i.e. Ka or 1/Kd).

The affinity constant of the Fab fragments we produced for these studies (discussed below) was approximately 3.0×10^9 M^{-1}. This means that the Fab fragments would have about 138 to 750 times greater affinity for PCP than for the receptor.

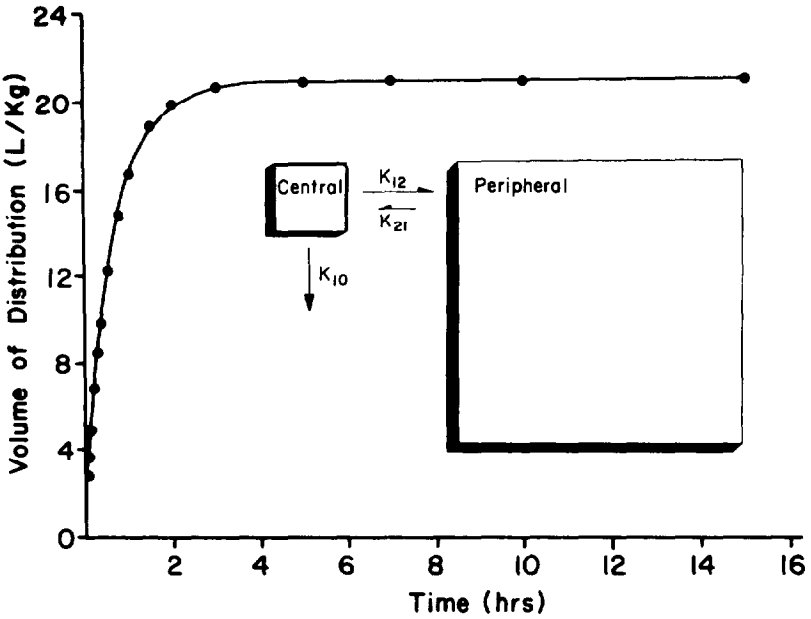

FIGURE 1. *Change in the apparent volume of distribution of PCP as a function of time following administration of an intravenous bolus dose of ^{3}H-PCP (6.4 μg) in a male dog (19.5 kg)*

NOTE: These results are the predicted values of a nonlinear regression fit of the concentration-time data, calculated according the method of Colburn (1983). Note that 2 hours after administration of PCP, the apparent volume of distribution is greater than 95 percent of its maximum value. This dog (dog C) was also used In the anti-PCP Fab fragment studies discussed below. The inset figure shoes a schematic representation of PCP in the dog as a two-compartment open model with elimination from the central compartment. The constant k_{10} is the apparent first-order elimination rate constant. The constants K_{12} and K_{21} are the Intercompartmental transfer rate constants.

In addition to having a high affinity, the amount of antibody administered must be sufficient to reduce the body burden of PCP below that of toxic levels. Therefore, the effectiveness of a given dose of Fab fragments depends on its affinity and the amount of antibody administered relative to the dose of PCP. Since the affinity of the Fab fragments in the present study was so high

relative to other binding sites in the body, we felt that an amount of Fab fragments that was equimolar to the dose of PCP administered would be sufficient to bring about a favorable redistribution of PCP. Obviously, to attain the same level of binding with a lower or higher affinity antibody, one would need to administer more or less antibody, respectively.

The magnitude of drug clearance from the peripheral to the central compartment (figure 1) will govern the rate of drug redistribution from the peripheral compartment and, therefore, the rapidity with which a toxic response is reversed (assuming that the site of toxicity is within the peripheral compartment and that the effect is reversible). Unfortunately, there are too few experimental systems upon which to judge the relative importance of the rate of redistribution of drugs, in the presence of Fab, in terminating a toxic response. One such example is digoxin, whose peripheral to central clearance is relatively slow; yet Fab fragments produce a rapid and dramatic reversal of toxicity. It is difficult to judge the significance of that finding within the context of this discussion, as the toxic effects are probably mediated by action in both the central and peripheral compartment. However, intravenous administration of a sufficient amount of Fab fragments, relative to the dose of PCP, should produce a favorable shift in the equilibrium between the compartment containing the Fab fragments and the compartments containing PCP. The pharmacokinetic result of this shift in equilibrium is a significantly smaller volume of distribution for PCP. In addition, this should lead to rapid reversal of concentration-dependent, receptor-mediated, pharmacological effects through depletion of drug at the receptor binding site.

PRODUCTION OF ANTI-PCP ANTIBODY FRAGMENTS

A PCP antigen was produced by coupling the hapten 4-[(1-piperidinyl)cyclohexyl]benzoic acid sulfate 1/4 M hydrate (figure 2) to bovine serum albumin using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide HCl in aqueous dimethylsulfoxide at pH 4.0 to 4.5. The antibodies produced against this antigen have been shown to be fairly specific for PCP versus PCP metabolites (Owens et al. 1982). Two goats were immunized three times during the first 2 weeks with 1 mg of the antigen emulsified in 1 ml of Freund's complete adjuvant at several subcutaneous sites near regional lymph centers. Booster injections of 3 mg of antigen were administered at monthly intervals. The animals were bled 7 days after each boost. After several months of immunization, the titer and affinity of the antibody response was judged sufficient for use.

The immunoglobulin fraction from each bleed was purified by use of a recirculating isoelectric focusing (RIEF) technique (Bier et al. 1979). The whole serum was diluted 1:3 with urea, to yield a final urea concentration of 3 M, and then desalted by electrodialysis. The urea was added to prevent precipitation under hypotonic conditions. Ampholine (1 percent w/v, pH 3.5 to 10, LKB

Instruments, Inc., Rockville, MD) was added, and the proteins were fractionated using a 10-channel RIEF apparatus. The proteins in each of the 10 fractions were then dialyzed against large volumes of phosphate-buffered saline (PBS, pH 7.4). Immunoelectrophoresis and a radioimmunoassay (RIA) for PCP were used to determine the RIEF fractions with the greatest purity and anti-PCP activity.

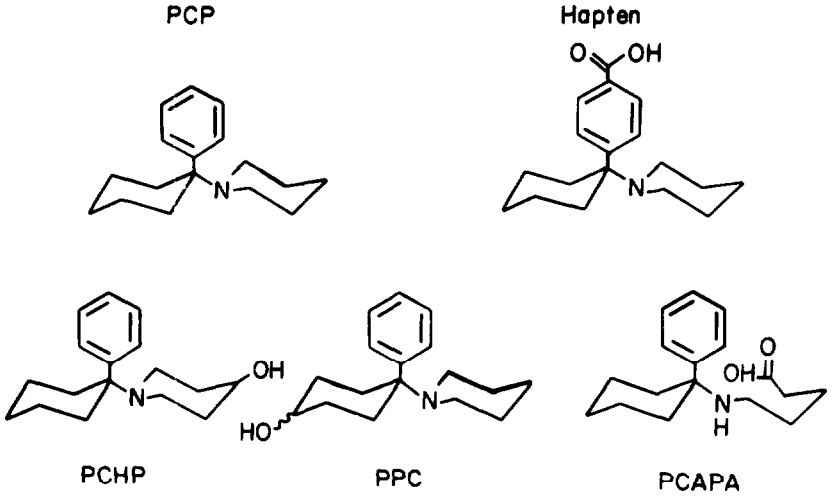

FIGURE 2. *Structures of PCP, the hapten used for antigen production, and come important PCP metabolites*

NOTE: The carboxylic acid group of the hapten was coupled to bovine serum albumin by using a water-soluble carbodiimide reaction.

The active imnunoglobulin fractions from the RIEF separation were affinity purified using a column containing the hapten covalently bound to a sepharose bead. After isolation on the affinity column, the antibody was eluted using glycine HCl and 6 M guanidine HCl. The antibody was concentrated and again tested for activity and purity using the RIA and immunoelectrophoresis. The IgG-containing samples were then digested with papain by the method of Porter (1959)) and the Fab fragments were purified by anion exchange chromatography using DEAE-sephacel (Pharmacia Inc., Piscataway, NJ). Based on the results from immunoelectrophoresis, only Fab fragments were found in the final product.

The affinity and cross-reactivity of the whole serum and Fab fragments were determined using equilibrium dialysis for the affinity determination and RIA for the cross-reactivity studies. The average intrinsic affinity constant (Ko) of the antibody (Nisonoff and Pressman 1958) changed very little throughout the

entire purification procedure, The average value was about $3x10^9$ M^{-1}. The cross-reactivity of the whole serum and the Fab fragments was tested against three important PCP metabolites: 1-(1-phenylcyclohexyl)-4-hydroxypiperidine (PCHP), 1-(1-phenyl-4-hydroxycyclohexyl)piperidine (PPC, a cis/trans mixture), and 5-[N-(1'-phenylcyclohexyl)amino]pentanoic acid (PCAPA) (figure 2). The aminopentanoic acid metabolite PCAPA showed no cross-reactivity with the antibody. The two monohydroxylated PCP metabolites PCHP and PPC showed approximately 1 to 7 percent cross-reactivity (depending on the bleed) before purification and about 13 percent cross-reactivity after digestion and purification to Fab fragments. This meant that the highest affinity binding of the Fab fragments was directed at the PCP molecule, which is known to be the most toxic form of the drug. However, the binding affinity for the two metabolites was still fairly high. Since both PCHP and PPC have been shown to have some pharmacological activity in animal models (Shannon 1981), this cross-reactivity was not considered a problem.

ADMINISTRATION OF ANTI-PCP FAB FRAGMENTS TO DOGS

Three male mongrel dogs were used for the Fab experiments. Each dog was administered a trace dose of ^{3}H-PCP (from 2.42 to 4.86 µg), and 2 hours later they were given a dose of Fab fragments (0.5 to 1.0 mg), equimolar to the dose of ^{3}H-PCP. The 2-hour delay period was chosen to allow for the distribution phase of PCP to be essentially complete (figure 2). We believe that this procedure provided the most critical test of the ability of the antibody fragments to modulate the disposition kinetics of PCP. Earlier or concurrent administration of Fab would not have provided as useful an indication of the real-life situation in which a patient comes to the emergency room after taking the drug.

Blood and urine samples were collected from each dog for about 100 hours. Several analytical assays for PCP and total drug were performed to allow a thorough characterization of the pharmacokinetic profile in each animal. Serum samples were extracted for PCP with hexane, after adjusting the pH of each sample to greater than 11.5 with 2 N NaOH. The radioactivity in the hexane extract was then measured by liquid scintillation spectrometry. Each value was corrected for extraction efficiency and converted to PCP concentration in serum based on the specific activity of the ^{3}H-PCP (specific activity was approximately 7 Ci/mM). These PCP concentrations were used to determine the pharmacokinetics of the parent drug. An aliquot of serum was analyzed directly for total radioactivity (PCP plus metabolites) to determine the pharmacokinetics of the total drug administered. An aliquot of serum was also used for determination of the change in free fraction before and after administration of the antibody. This value was determined by equilibrium dialysis, followed by extraction of each sample after dialysis (bound and free fractions) with hexane, for determination of the unchanged PCP concentration. The blood to plasma ratio of selected samples before and after Fab administration was also

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determined by the method of Owens et al. (1983). The amount of PCP present in the urine was determined after hexane extraction of each sample. The amount of total drug (parent plus metabolites) was determined by direct counting of an aliquot of urine. From these determinations we were able to calculate numerous pharmacokinetic parameters.

EFFECT OF FAB FRAGMENTS ON PCP DISPOSITION IN DOGS

Immediately after administering the anti-PCP Fab fragments, the PCP concentration in serum increased approximately 17- to 56-fold within a period of a few minutes (figure 3). The percent unbound

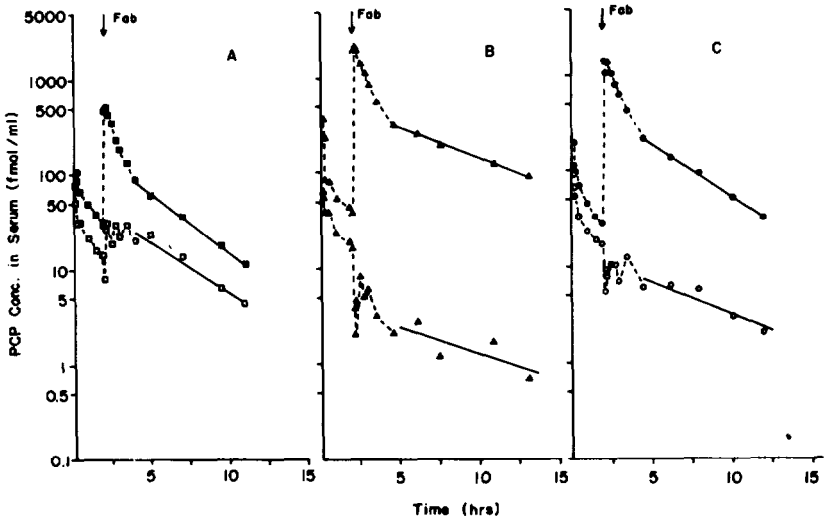

FIGURE 3. *Total unchanged PCP concentration (closed symbols and unbound PCP concentration (open symbols) before and* after *anti-PCP Fab fragment administration*

NOTE: The dotted Iines at-e used to connect sequential time points. The solid line is a ilnear regression fit of the log-linear terminal elimination phase. The unbound PCP concentration was calculated by multiplylng the total unchanged PCP concentration In serum by the unbound fraction in serum at each time point. The harmonic means for the terminal elimination half-life for unchanged total PCP and unbound PCP were virtually the same (3.5 and 3.3 hours, respectively). The arrows indicate the time of Fab administration.

PCP changed from about 50 percent before administration of the Fab, to less than 1 percent unbound PCP immediately after administration of the antibody fragments. By about 10 to 11 hours after administration of the Fab fragments, the unbound PCP was 37.7 percent, 1.4 percent, and 5.8 percent in dogs A, B,and C,

respectively. Based upon the sensitivity of the analytical methods and the relatively short half-life of PCP, the unbound fraction could not be measured accurately beyond those times. The higher than predicted unbound fraction in dog A at the late time point was not consistent with the blood to plasma ratio at the same time point. The blood to plasma ratio indicated that the drug was still highly bound to the antibody. We suspected that this might be due to a low molecular-weight breakdown product from the anti-PCP Fab fragments. Therefore, in subsequent experiments, we used a 3,500 molecular-weight cutoff (MWCO) membrane, instead of the 12,000-14,000 MWCO membrane.

We did not measure the terminal elimination half-life of the goat Fab fragments. However, the terminal half-life of sheep Fab fragments in dogs is 16.4 hours (Lloyd and Smith 1978) (recalculated as the harmonic mean). Assuming the same half-life for the goat Fab fragments in this study, after 10 hours, 66 percent of the intact Fab fragments should have remained in the body. By comparison, after 10 hours, only about 14 percent of intact PCP would remain in the body, based on the average half-life of PCP in the three dogs (i.e., 3.5 hours). Therefore, the binding capacity of the Fab fragments should have been in excess of the amount of PCP.

The total radioactivity in serum (PCP and metabolites) increased significantly after Fab administration (figure 4). This increase was mostly due to the dramatic increase in unchanged PCP concentration and not due to an increase in metabolite concentration.

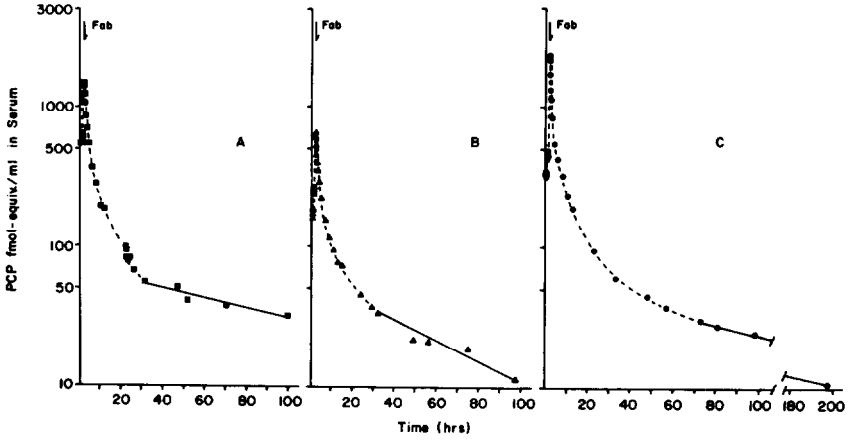

FIGURE 4. *Total PCP equivalents in serum (PCP plus metabolites) before and after Fab administration in three dogs*

NOTE: The dotted line connects sequential time points. The solid line is a linear regression fit of the log-linear terminal elimination phase.

In fact, the PCP metabolite concentration actually decreased for 1 to 2 hours after Fab administration. The PCP metabolite concentrations were determined by subtracting the total PCP equivalents in serum (PCP plus metabolites) from the PCP concentration in serum at each time point. The most likely explanation for the temporary decrease in metabolite concentration was that the high affinity binding of PCP to the Fab fragments temporarily reduced metabolism, and/or some of the metabolites also bound to the antibody and were prevented from further metabolic changes. The terminal elimination half-life for the total metabolites in the three dogs was very long (harmonic mean = 62.4 hours). Since the serum concentration of PCP was near or below our detection limit by 24 hours after the administration of PCP, this very long terminal half-life was undoubtedly due to one or more PCP metabolites.

Another interesting and important change in the disposition of PCP was the blood to plasma ratio. This ratio in the dog is normally about 1.25, and in man is about 0.94 (Owens et al. 1983). This indicates that there is an approximately equal distribution of PCP between plasma and red blood cells. From preliminary experiments, we knew that the Fab fragments were not found in the red blood cells. Therefore, the degree of success in modifying the pharmacokinetics of a drug should also be predictable from the change in the blood to plasma ratio before and after antibody administration. The blood to plasma ratio after Fab administration was approximately equal to one minus the hematocrit. This indicated that the PCP in the vascular compartment was confined to the plasma space and was prevented from distributing into red blood cells as it does in the absence of antibody.

The major route of PCP elimination in dogs is through metabolism (greater than 95 percent) (Woodworth et al., in press). Because Fab fragments have been shown to be eliminated primarily by the kidney (Wochner et al. 1967), and since PCP was highly bound to the Fab in plasma, we expected that the percentage of the dose eliminated as PCP might increase after Fab administration. This was not the case. The amount of PCP eliminated in the urine was 1.91 ± 0.45 percent of the total dose, whereas in control studies the amount was 4.8 ± 3.3 percent (Woodworth et al., in press). However, the PCP excretion rate did show a temporal increase for a period of time after the administration of Fab (figure 5). Ochs and Smith (1977) also found an increase in the percentage of digitoxin excreted in urine during the first 96 hours after administration of Fab fragments. They concluded that the antibody fragments increased the amount of digitoxin appearing in the urine. Since they collected urine for less than one half-life of the drug (half-life of digitoxin $\geq$140 hours), they cannot reach that conclusion. A more complete urine collection (of at least four half-lives of the drug) might have revealed a similar finding to ours (we collected urine for greater than seven half-lives). Our finding is also verified by Butler et al. (1977). Their initial premise was that, since Fab fragments are cleared primarily by the kidney, and antibody binding to digoxin can be detected

in urine, the Fab should increase the amount of drug eliminated by the kidney. However, their data show that the percentage of the dose appearing in the urine is not different from control values. Apparently, digoxin and PCP cannot be eliminated bound to the Fab fragments. Future studies are planned to clarify this aspect of the influence of Fab on elimination.

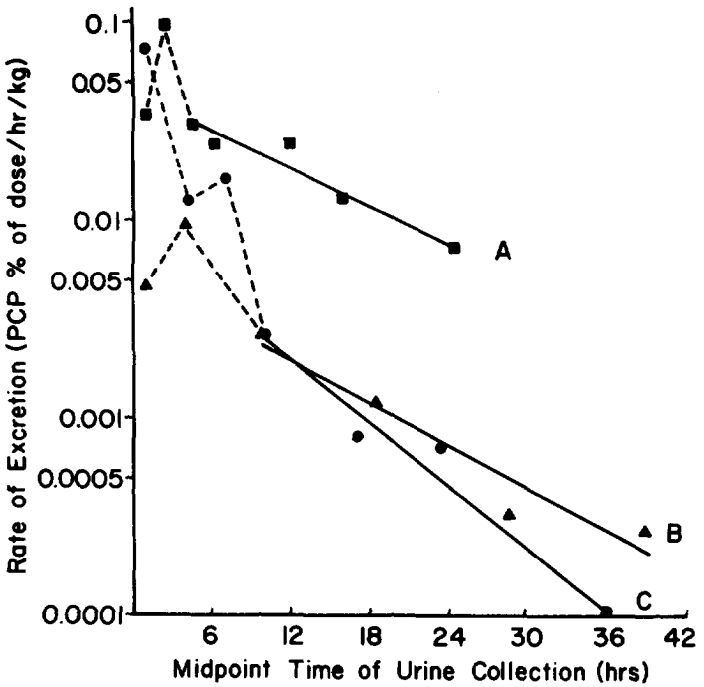

FIGURE 5. *PCP urinary excretion rate versus the midpoint* of *the urine collection time in three dogs*

NOTE: Anti-PCP Fab fragments were administered 2 hours after the start of the experiment.

RELATIVE CHANGES IN PCP PHARMACOKINETICS IN THE PRESENCE OF FAB

Figure 6 summarizes the relative changes in the disposition parameters of PCP after administration of anti-PCP Fab fragments. These data were calculated by the model-independent methods described in the text by Gibaldi and Perrier (1982). Since we were interested in calculating the effect of anti-PCP Fab fragments on

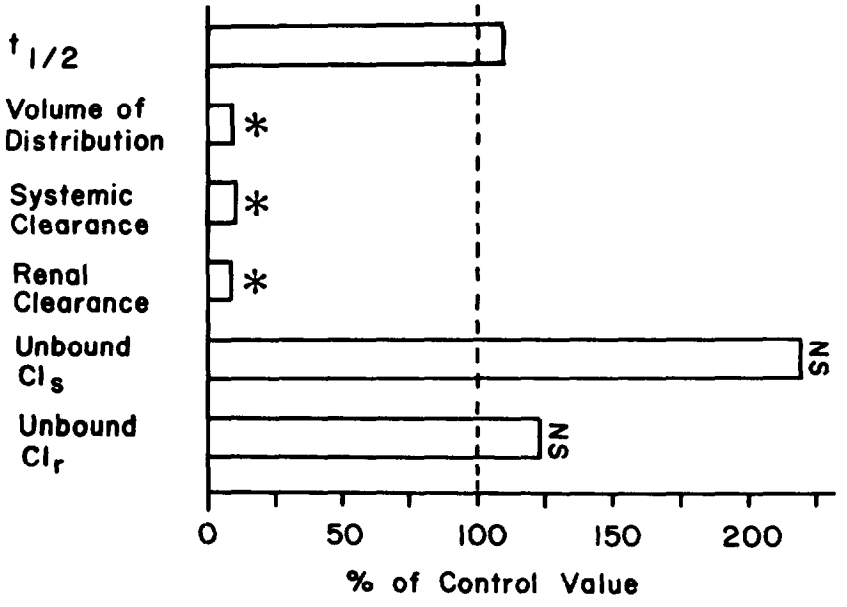

FIGURE 6. *Relative change in PCP pharmacokinetic parameters*

NOTE: The control values (dotted line) are from the data of Woodworth et al. (in press). Both studies were conducted in our laboratory. The * indicates that the values are significantly different ($p<0.05$) from control animals ($n=4$). NS indicates that the values were not significantly different ($p>0.05$). Even though the unbound Cl for the Fab-treated group was over twice the control value. It was not significantly different due to a large variability in this parameter, especially in one dog.

PCP pharmacokinetics, we calculated the changes in the pharmacokinetic parameters based on concentration-time data occurring after the administration of the antibody fragment. For these calculations, we had to estimate the amount of PCP remaining at the time of antibody administration (i.e., 2 hours after PCP administration). The amount of PCP remaining at 2 hours was estimated by calculating first the total area under the concentration-time curve in the absence of PCP and then the volume of distribution in the absence of PCP. The volume of distribution times the serum concentration just before antibody administration provided an estimate of the amount of PCP remaining at 2 hours. When we tested the validity of this calculation with data from the control animals (Woodworth et al., in press), the pharmacokinetic values for both clearance and volume of distribution were within 5 percent of the values calculated using the complete set of data.

The area under the PCP concentration-time curve (AUC) from the time of antibody administration to the last measured concentration (Cn) was determined by the trapezoidal rule. The remaining area from Cn to time infinity was calculated by dividing Cn by the terminal elimination rate constant. By using dose, AUC, and the terminal elimination rate constant, we were able to calculate the terminal elimination half-life, systemic clearance, and the volume of distribution. Renal clearance was determined from the total amount of PCP appearing in the urine, divided by AUC. Unbound clearances were calculated based on unbound concentrations of PCP. The control values are from studies performed in our laboratory on dogs administered similar radioactive doses (i.e., 2.4 to 6.5 µg of PCP) (Woodworth et al., in press). Only one of the dogs (dog C) was used in both studies.

The terminal half-life of PCP did not change significantly, relative to control studies. This reflects the fact that half-life depends on systemic clearance (Cl_s) and volume of distribution (half-life=0.693xV/Cl_s), and these two independent parameters changed approximately by the same order of magnitude, thereby producing no net change in half-life. The apparent volume of distribution, systemic clearance, and renal clearance (Cl_r) decreased to about one-tenth that of controls. This means that PCP was confined to a much smaller compartment after Fab administration, but was also cleared at a much slower rate. Both changes can be explained by the high-affinity binding of PCP to the antibody fragments.

When we calculated systemic and renal clearance based on the area under the unbound PCP concentration-time curve, we found essentially no change in these parameters compared to the control studies without antibody (Woodworth et al., in press) (figure 6). Since the values for PCP clearance in the presence of Fab were consistent with restrictive clearance, a change in free fraction at steady-state would be expected to result in a change in total drug concentration, without a change in free concentration. Nevertheless, we cannot predict from these data what is happening to total and free concentrations at the PCP site of action. The most accurate conclusions about drug disposition data are based on the system following first-order kinetic processes when an equilibrium is achieved. How the introduction of a high-affinity binding site into the body will affect the amount of drug at the site of action will have to be determined by physiological modeling, and ultimately by its effect on the pharmacological response.

CONCLUSIONS AND FUTURE DIRECTIONS

Based on the dramatic changes in volume of distribution and the free fraction of PCP found in serum, we predict that this form of therapy has the potential to rapidly reverse the toxicity of PCP, if sufficient Fab can be administered relative to the dose of PCP. The most practical method for making large quantities of antibodies with reproducible properties is through monoclonal

antibody production (Kohler and Milstein 1975). We are currently producing large quantities of high-affinity anti-PCP monoclonal antibody in mouse ascites fluid. In future studies, we plan to examine the reversal of PCP toxicity in dogs using anti-PCP monoclonal antibodies. A major limitation for this kind of therapy is the amount of antibody needed for treatment. As a starting point, we plan to use 2 to 4 grams of anti-PCP Fab to reverse the toxicity of a 1 mg/kg dose of PCP in dogs. This total dose of about 15 to 20 mg of PCP is also a fairly high dose for humans; therefore, the dog should be a realistic model to demonstrate the feasibility of this method. The major limitations to this procedure are the cost of the antibody and the possible antigenicity of mouse monoclonal antibodies in humans. Outside of the applied nature of this research, this approach should provide an important tool for studying fundamental concepts in the area of pharmacokinetics and pharmacology.

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Psychopharmacology of Phencyclidine

Joe Marwah and David K. Pitts

Phencyclidine, 1-(1-phenylcyclohexyl) piperidine hydrochloride (PCP) was introduced in 1957 as a dissociative anesthetic with a large margin of safety in humans (Domino 1964). Although limited respiratory depression was a major asset of this compound, certain side effects, including emergence psychosis and prolonged excitation, made PCP unsuitable for clinical use. Phencyclidine has now become a major drug of abuse in the United States (Snyder 1980) and phencyclidine-related deaths are being reported with increasing frequency (Noguchi and Nakamura 1978). Its continued availability as an animal tranquilizer and its increasing clandestine production, distribution, and use have contributed to phencyclidine's becoming a major public health concern.

PCP can cause CNS stimulation and depression, which vary markedly depending upon the dose and species employed. The response of rodents to PCP appears markedly more sympathomimetic than that of primates (Balster and Chait 1978). Intoxication in humans with low doses (5 to 20 mg) of PCP resembles an acute confusional state lasting several hours. Higher doses (greater than 20 mg) can elicit serious neurological (nystagmus, gait ataxia, muscle rigidity, EEG changes, and stereotypy), cardiovascular (hypertension), and psychotic (agitation, disorientation, delirium, auditory hallucinations, thought disorders , and paranoid delusions) reactions. Current treatment of PCP intoxication involves supportive psychological and medical measures. Similar clinical features between PCP-induced psychoses and schizophrenia have led investigators to view PCP intoxication in humans as a heuristic pharmacological model for schizophrenia. The most compelling evidence that PCP psychosis resembles schizophrenia is the fact that experienced psychiatrists have mistaken drug users for schizophrenics, before the psychiatrists obtained the history of drug use (Snyder 1980). PCP can both mimic and reactivate schizophrenic psychoses. Some PCP users have developed classic schizophrenia subsequent to experiencing PCP psychoses. This phenomenon suggests a relationship

between the pharmacology of PCP and the neurobiology of schizophrenia. PCP has diverse effects on behavior in rodents, depending on the dose administered. At low doses, PCP has a stimulant action; at high doses, it has a sedative effect (Chen et al. 1959).

Although the precise mechanism of action of PCP remains obscure, virtually all known neurotransmitters have been implicated in its action. Cholinergic (Alburquerque et al. 1980; Maayani et al. 1974), serotonergic (Martin et al. 1979), dopaminergic (Johnson and Oeffinger 1981; Fessler et al. 1979; Doherty et al 1980; Sturgeon et al. 1979), and noradrenergic (Marwah 1982; Bayorh et al. 1983) mechanisms have been implicated as predominant mediators of PCP effects. Of these, the dopaminergic and noradrenergic mechanisms have received the greatest attention.

The administration of low doses of PCP to rodents induces hyperactivity and stereotypy (Chen et al. 1959). The observation that neuroleptics such as chlorpromazine, haloperidol, and pimozide, and adrenolytics such as alpha-methyl paratyrosine antagonize these behavioral effects of PCP suggests that they are mediated by facilitation of central dopaminergic neurotransmission (Murray and Horita 1979). The actions of PCP on central dopaminergic neurotransmission may be similar to amphetamine. A dose of PCP (2.5 mg/kg) in rats, which has no effects when given alone, enhances the behavioral effects of 1 and 3 mg/kg of d-amphetamine (Balster and Chait 1978). PCP, like dopamine, has also been shown to suppress plasma prolactin (Bayorh et al. 1983). However, the firm establishment of an exclusive relationship between dopamine neurotransmission and PCP effects is difficult because of the prominent interactions of this drug with other neurotransmitter systems.

For example, in regions densely innervated by noradrenergic fibers, PCP is a very potent inhibitor of norepinephrine uptake. In rats, cocaine, PCP, and ketamine have been shown to enhance the spontaneous and electrically stimulated overflow of tritium from occipital cortex slices preincubated with ^{3}H-norepinephrine (Taube et al. 1975). Ary and Komiskey (1980) showed that PCP blocks the reuptake of ^{3}H-norepinephrine into synaptosomes. Consroe et al. (1982) reported that, in rodents, propranolol blocks the stereotypy and hyperactivity elicited by PCP. Clonidine and prazosin have also been reported to block a number of effects of PCP in various behavioral states. PCP and (+) PCMP, but not (-) PCMP, increase blood pressure and heart rate and suppress plasma prolactin (Bayorh et al. 1983). These investigators have suggested that, because of similar stereospecific effects of PCP derivatives on the cardiovascular system (noradrenergic system) and plasma prolactin (dopaminergic system), the actions of PCP on both the dopaminergic and adrenergic systems may be attributed to the same active conformation of the PCP molecule. In single unit electrophysiological studies with the noradrenergic locus coeruleus-Purkinje neuron synapse, PCP has been shown to have prominent sympathomimetic effects (Marwah, 1982). Use of lesion techniques

and receptor antagonists revealed that at this synapse PCP acts as an indirect sympathomimetic in that it causes release and/or blocks reuptake of norepinephrine. Marked noradrenergic actions of PCP have also been observed in the cat spleen (Marwah et al. unpublished)--a noradrenergically innervated tissue. In the cat spleen, PCP significantly potentiates the effects of nerve stimulation and exogenous norepinephrine on the contractile responses of smooth muscle. This potentiation to exogenous norepinephrine, although attenuated, is also observed in denervated cat spleens, suggesting that PCP in this system exerts both presynaptic and postsynaptic actions.

PCP has also been reported to possess properties that overlap with the opioid narcotics. These "opiatergic" effects of PCP are currently attributed to actions of PCP on the sigma "opiate" receptor. Activation of the sigma receptor by compounds such as PCP, SKF-10,047 and cyclazocine elicits dysphoria and other effects. PCP and SKF-10,047, like amphetamine, elicit locomotor activity through presynaptic dopaminergic mechanisms within the mesolimbic system (French and Vantini 1984). SKF-10,047 and PCP have also been shown to produce a biphasic (initial activation followed by inhibition) action on single dopaminergic neurons in the substantia nigra (Freeman and Bunney 1984). The actions of PCP and SKF-10,047 on sigma receptors are poorly antagonized by mu opiate receptor antagonists such as naloxone. Geller et al. (1981) showed that PCP, SKF-10,047, and cyclazocine block fluorothyl seizures. These effects are not antagonized by naloxone. However, Glick and Guido (1982) recently reported that PCP can interact at mu opiate receptors in brain areas controlling thermoregulatory processes.

It appears that mechanisms contributing to the psychopharmacology of PCP are indeed complex. Despite numerous studies, it is not yet apparent which, if any, of the above actions are responsible for the behavioral effects of PCP in humans. An increasing number of reports (Quirion et al. 1983; Vincent et al. 1979; Zukin and Zukin, 1978) point to the existence of an endogenous "PCP-like" (probably peptides) ligand. This ligand (angeldustin!) has been proposed to interact with sigma or "PCP" receptors (Quirion et al. 1981). Since PCP has been demonstrated to interact with numerous transmitter systems, it is conceivable that the PCP (sigma) receptor is located at critical (transmitter release modulating) sites on susceptible neurons. PCP, by virtue of its interaction with such a receptor, may subsequently affect steps necessary for transmitter release (or stimulus-secretion coupling). A candidate for such a step is the calcium channel. This may explain the rationale for the use of calcium antagonists during PCP intoxication. The modulation by PCP of calcium channel properties could be expressed as increased muscular strength (Marwah, 1980, 1982). Stimulation of the PCP "receptor" may alter fundamental excitability processes such as gk^{+}, which in turn could modulate calcium mobilization (Aguayo et al. 1984).

If PCP produces its multitude of effects by activating PCP (sigma) receptors, then chronic exposure to agonists should elicit the development of tolerance. Tolerance to plasma prolactin suppression by PCP is observed in rats following daily administration for 28 days (Quirion et al. 1982). Chronic PCP treatment has been also shown to reduce the number of PCP sites (receptors) in rodent brains (Quiriun et al. 1983). Behavioral studies have documented the development of tolerance to and dependence on PCP (Balster and Woolverton 1980; Flint and Ho 1980). A tolerance syndrome develops in humans, in which the user is compelled to increase his intake of drug (Jain et al. 1977).

Despite this wealth of information, numerous questions regarding the action of PCP still remain unanswered. These are:

(1) What is the endocrine status of chronic PCP users?

(2) Are the analgesic effects of PCP due to its local anesthetic properties or actions at sigma or perhaps mu receptors?

(3) Is the development of ultrashort-acting (less abused) PCP derivatives that are good anesthetics and analgesics with very little respiratory depression possible?

(4) Can a PCP receptor antagonist be developed?

(5) What is the action of PCC (a PCP analog without psychotomimetic effects) on the numerous synapses that PCP affects?

(6) What are the effects of PCP, SKF-10,047, and PCC on other central noradrenergically innervated synapses?

(7) How does PCP compare with cocaine and amphetamine at the various neuronal test systems , where PCP has been documented to have prominent actions?

(8) What could be the reasons for the existence of endogenous PCP reactive ligands and receptors? Do they produce a dissociated mental state following severe trauma or stress?

(9) What causes "flashback" psychosis in some individuals who abstain from further PCP consumption following the initial dose? Is it residual drug, slow metabolism to a new stable metabolite, or a "permanent" change in a defined portion of the CNS?

(10) What are the effects on the developing nervous system after chronic in utero exposure? Neurophysiological, neuropharmacological, and neuroanatomical studies should be useful.

(11) Is the development of tolerance to PCP pharmacokinetic or pharmacodynamic? Since PCP psychosis may be the result of a mixed tolerance and/or altered receptor plasticity, this phenomenon should be investigated at single monoaminergic neuron test systems.

Management of PCP intoxication would be significantly enhanced if the physiologic mechanisms of the drug's effects were better understood. Such knowledge, which could be derived from basic science studies in animals, might pave the way to the development of specific pharmacotherapeutic agents in treating acutely and chronically intoxicated patients. Additionally, such research might suggest the development of newer anesthetics and analgesics.

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Discriminative Stimulus Properties of PCP Mimetics

Ronald G. Browne

Phencyclidine (PCP), a dissociative anesthetic agent, which is subject to abuse, produces behavioral effects in man that frequently resemble schizophrenia (Luisada 1978). Manifestations of persistent psychopathology frequently remain after the acute effects of PCP have diminished. With PCP, subjects may display autistic and delusional thinking typical of schizophrenics (Luby et al. 1959). A more striking link between schizophrenia and PCP comes from observations of cases in which PCP was given to hospitalized schizophrenics (Luisada 1978). After receiving PCP, these patients showed extreme exacerbation of their psychoses; the reaction persisted for up to 6 weeks. By contrast, LSD produced no more severe effects in schizophrenics than in normal subjects.

The close resemblance between schizophrenia and PCP-induced psychosis suggests that the behavioral effects produced by PCP might be useful as a model of psychosis. On this basis, most animal studies have examined the ability of various agents to modify PCP-induced hyperactivity and stereotypy. While some studies suggest that neuroleptics such as haloperidol (Castellani and Adams 1981; Garey et al. 1980), chlorpromazine, or clozapine (Freed et al. 1980) antagonize the alterations in locomotor activity produced by PCP, Sturgeon et al. (1981) could find no consistent effects of neuroleptics on PCP-induced hyperactivity. In man, phenothiazines, butyrophenones, benzodiazepines, and cholinesterase inhibitors have been claimed to be partially effective in treating PCP-induced effects (Burns and Lerner 1976; Showalter and Thornton 1977; Stockard et al. 1976; Luisada and Brown 1976; Dorand 1977; Castellani et al. 1982). Thus, the fact that antipsychotic agents do not completely antagonize the actions produced by PCP in man or animals suggests that the psychotomimetic effects of PCP are probably mediated by as yet unelucidated neurochemical mechanisms.

In searching for an animal model specific to PCP and PCP-like agents, the drug discrimination procedure historically has been used. The use of drugs as discriminative stimuli provides a sensitive technique for establishing the similarities among

various agents, and the method is useful for elucidating the mechanism of action of psychoactive drugs (Lal 1977; Ho et al. 1978; Colpaert and Rosecrans 1978; Thompson and Pickens 1971). The paradigm requires animals to emit different behavioral responses depending upon differential drug states. For example, following injections of PCP, rats, pigeons, or monkeys have been required to press one of two manipulanda in operant conditioning chambers to receive a food reward. Following injection of the drug vehicle, the animals are required to press a different lever or button to receive reinforcement. After a varying number of sessions where reinforcement is associated with differential responding dependent upon drug state, animals learn to identify correctly the appropriate response, based on interoceptive stimuli produced by the drug. The dependent measure in such paradigms is the number of responses or number of animals "choosing" the "correct" lever in the absence of reinforcement feedback. If a drug fails to produce discriminative stimuli, then no evidence of learning is obtained, and animals respond at chance levels (50 percent of responses on both levers or 50 percent of animals choosing the correct lever). By contrast, drugs that readily produce subjective effects in man--PCP, for example--engender stimulus control in animals such that nearly 100 percent discrimination accuracy is often obtained.

The unique aspect of the drug discrimination paradigm is that the discriminative stimulus properties produced in animals by drugs tend to show a great deal of pharmacological specificity. Animals trained to discriminate one type of drug readily identify pharmacologically similar agents as producing similar interoceptive stimuli, while agents from different classifications do not result in stimulus generalization. For example, in rats trained to discriminate morphine from vehicle, other opiates and opioid peptides mimic morphine's effects, and narcotic antagonists such as naloxone block the discriminative stimulus properties of these agents (Browne and Fondren 1978). By contrast, stimulants, depressants, and anesthetics are not perceived as opiates in the discrimination paradigm.

A number of investigators have examined PCP in drug discrimination paradigms. Such studies have revealed a number of PCP analogs that mimic PCP's discriminative stimulus properties (Shannon 1981, Brady and Balster 1981). In addition, the sigma opiate agonist SKF-10,047 has been shown to produce stereoselective PCP-like discriminative effects (Holtzman 1980; Brady et al. 1982). While some studies have suggested generalization to the PCP cue by opiates such as cyclazocine and dextrorphan (Holtzman 1980, Herling et al. 1981), the PCP cue does not appear to be mediated via mu opiate receptors, since it was not blocked by narcotic antagonists (Holtzman 1980). Other attempts to block PCP's discriminative properties have not been successful, consistent with the fact that, to date, there is no established PCP antidote. This paper

will therefore review the data obtained in discrimination paradigms that have characterized compounds as PCP-mimetics or have attempted to antagonize PCP's discriminative properties.

AN EXAMPLE OF DISCRIMINATION METHODOLOGY

Adult, male, Sprague-Dawley rats obtained from Charles River Labs and weighing 200-250 gm on arrival were used. Throughout the study, the rats were housed individually, with water freely available. Purina Rat Chow was fed after each experimental session and on weekends, in quantities adjusted to maintain the rats between 270 and 350 gm throughout the experiment.

Training and testing sessions were conducted in 10 identical isolated Colbourn operant chambers equipped with two levers mounted on either side of a motor-driven dipper. Reinforcement consisted of 3-second presentations of 0.2 ml Carnation Slender, a commercial liquid diet food, diluted 1:1 with water. Reinforcement contingencies and data recording were performed using a Rockwell AIM 65 microcomputer.

The procedure used was based on the two-lever fixed ratio 10 (FR-10) drug-discrimination protocol, first described by Colpaert et al. (1975). At 30 minutes prior to the 15-minute session, phencyclidine HCl (1.0, 1.78, or 3.2 mg/kg, depending upon experimental group) or vehicle (5 percent ETOH: 95 percent water) was administered SC in a volume of 1.0 ml/kg. Each animal was required to discriminate the effects of only one dose of PCP from vehicle. Depending on whether the rat received drug or vehicle, reinforcement was programmed exclusively on either the left or right lever. Only responses on the left lever were reinforced after drug administration, and responses on the right lever were reinforced after vehicle administration. Sessions were conducted Monday through Friday under the alternating drug sequence used by Colpaert et al, 1975): drug-vehicle-vehicle-drug-drug and vehicle-drug-drug-vehicle-vehicle. To avoid the possibility that the correct lever for rats previously tested in the chambers could serve as an olfactory cue, the sequence of treatments on training days was alternated for successive groups (i.e., half the animals received vehicle and half received PCP).

For each session, the number of responses emitted before the first reinforcement was the measure of discrimination accuracy. For example, following PCP administration, if a rat made 10 responses on the left lever before making 10 or more responses on the opposite, unreinforced lever, then the animal correctly identified the training condition for that day. Most rats were clearly discriminating the effects of PCP from vehicle within about 30 training sessions, as demonstrated by the animals emitting their first 10 responses on the appropriate lever in 9 out of 10 consecutive sessions.

In order to determine stimulus generalization profiles for different doses of PCP, various other drugs, and drug interactions with PCP, twice weekly (Wednesdays and Fridays) experimental tests were interposed between PCP and vehicle maintenance sessions. Experimental treatments were given in the same ETOH:water vehicle described above in a volume of 1 ml/kg. Unless noted otherwise, all treatments were given SC 30 minutes prior to a 15-minute session. The reinforcement scheduling procedure was changed on experimental test days as follows: the first reinforcement was programmed after 10 responses were emitted on either lever. The lever on which 10 responses were first accumulated defined the animal's "choice" for that test treatment. If it was the left lever, the animal was said to have selected the drug side, indicating generalization of the treatment to the PCP training condition; if it was the right lever, the animal was said to have selected the vehicle side, indicating nongeneralization of the treatment to the training condition. Following the first reinforcement on experimental treatment days, subsequent reinforcements were given on an FR-10 schedule on either lever.

The degree of generalization of the various treatments to the PCP cue during the experimental sessions is reflected in the percentage of animals choosing the lever previously paired with PCP. Assuming 100 percent discrimination accuracy for both training conditions, probability estimates for selection of the drug or vehicle lever can be ascertained from the binomial theorem with an underlying probability of 50 percent. For example, using the most frequent test sample size of n=10, if fewer than four rats (40 percent) chose the PCP lever, then the treatment was considered to be identical with the vehicle condition. If eight or more rats selected the drug lever, then the treatment was considered identical to the training dose of PCP with $p<.05$. Drug choice in the 40 to 70 percent range was assumed to be different from both training conditions (i.e., not significantly different from 50 percent). Response rate data were evaluated using paired t-tests. Calculations of ED50 values for compounds mimicking PCP were obtained by linear regression analysis.

RESULTS WITH PCP-MIMETICS

After about 30 training sessions, most animals had acquired the PCP vs. vehicle discrimination, as evidenced by at least 9 out of 10 consecutive sessions during which the rats emitted fewer than 20 responses before the first reinforcement. Following this acquisition of the discrimination, the animals were tested in a random order with different doses of PCP. Figure 1 shows the dose-response profile for PCP discrimination in different groups of rats trained to discriminate 1.0, 1.78 or 3.2 mg/kg of PCP from vehicle. At low doses of PCP few, if any, rats chose the lever previously paired with PCP (i.e., most rats chose the vehicle-associated lever).

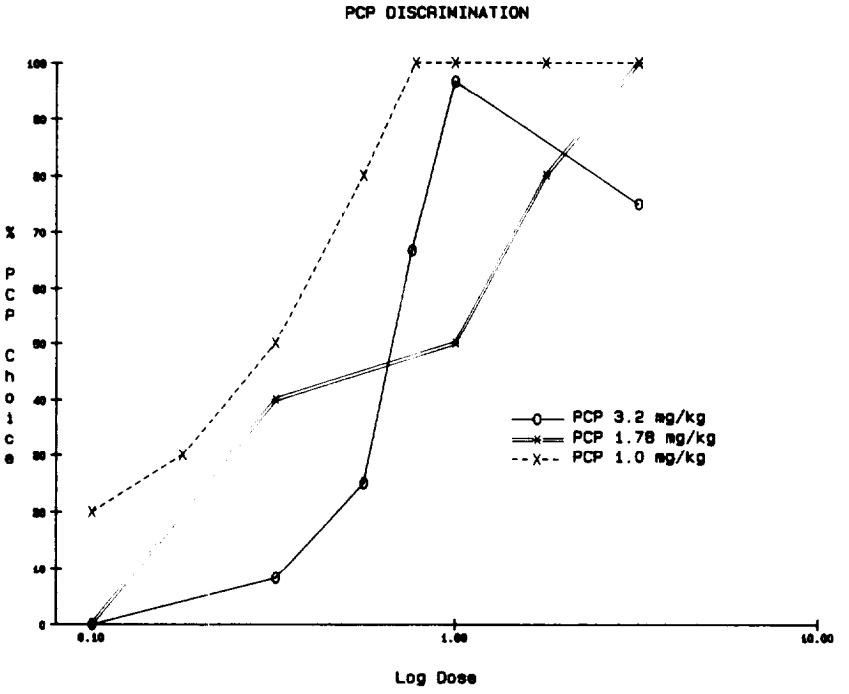


FIGURE 1. *Dose-response curve for rates trained to discriminate various doses of PCP from vehicle administered 30 minutes before the test. N=10/dos.*

As the dose of PCP was increased, more rats generalized the treatment to that produced by the training dose, so that, when tested with doses comparable to the training condition, essentially all animals completed their first 10 responses on the PCP-appropriate lever. At higher doses of PCP, a significant reduction in the number of responses emitted during the 15-minute session was observed. The rate of responding in animals trained at the lowest dose (1.0 mg/kg) appeared to be more sensitive to disruption by PCP than in those animals trained at higher doses (figure 2). However, no tolerance to this rate-disrupting effect of PCP was seen over the course of the experiments.

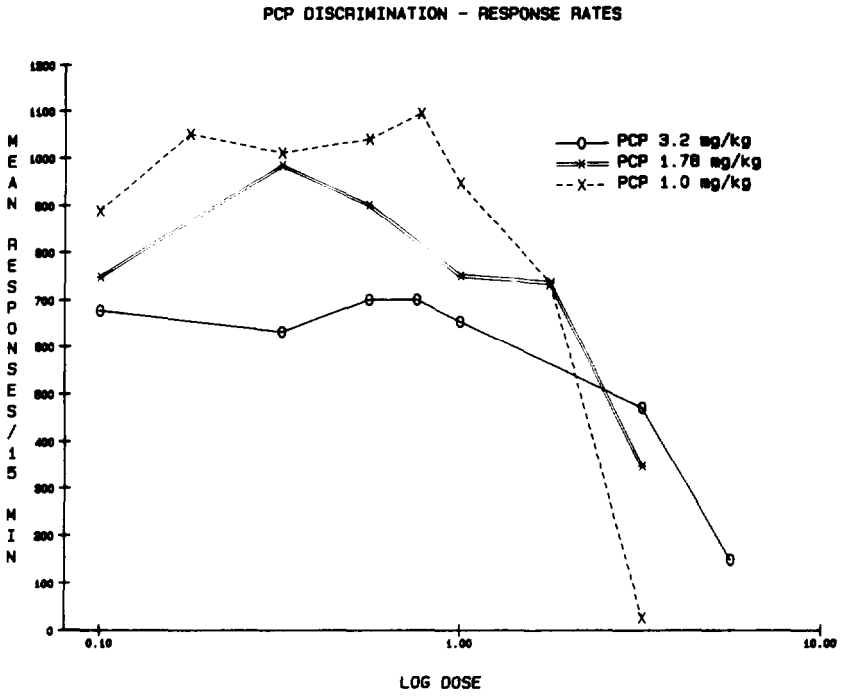
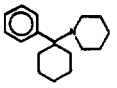
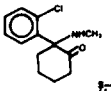
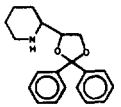
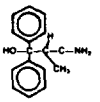
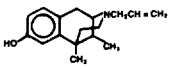


FIGURE 2. *Dose-response curve for the effects of PCP on response rates in rats trained to discriminate various doses of PCP from vehicle. N=10/dose.*

Generalization tests indicated that a number of compounds were able to substitute for PCP (table 1). Ketamine and tiletamine, which are structurally similar to PCP, produced dose-dependent effects mimicking PCP. These compounds are interesting examples of the structural requirements of molecules for PCP-mimetic activity, demonstrating that neither the piperidine nor the phenyl moieties are absolutely necessary for activity.

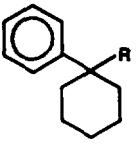
TABLE 1. *Compounds generalizing to the PCP cue*

Compound	*Structure*	*ED_{50} PCP Cueing*
PCP		0.55
(±)Ketamine		2.20
Tiletamine		0.46
Dexoxadrol Levoxadrol		1.68 >100
(-)2-MDP (+)2-MDP		2.13 >10
± SKF 10047		2.74

NOTE: All compounds were administered SC 30 minutes prior to a 15-minute test. ED50 values for compounds to mimic the effects produced by 1.78 mg/kg of PCP.

When the animals were tested with dexoxadrol, PCP-mimetic activity was found to be about one-third that of PCP. This compound is of interest because its stereoisomer, levoxadrol, was found to be completely devoid of PCP-mimetic activity at doses as high as 100 mg/kg (table 1). Another example of the stereoselectivity of the PCP cue is seen with 2-methyl-3,3-diphenyl-3-propanolamine isomers (2-MDP). Consistent with the original findings by Tang et al. (1984), the (-) isomer of 2-MDP is a stereoselective PCP mimetic, with a potency about one-fourth that of PCP (table 1). SKF-10,047, the prototypical sigma opiate receptor agonist, also engenders a dose-dependent generalization to the PCP cue. This compound has been extensively investigated for its discriminative properties (Shearman and Herz 1982; Teal and Holtzman 1980; Shannon 1983). and PCP-mimetic activity is exhibited stereo-specifically by the dextro isomer (Brady et al. 1982).

TABLE 2. *Structure-activity relationship for piperidine analogs mimicking the discriminative stimulus properties of PCP 1.78 mg/kg*



Compound	R	ED_{50} Cueing
PCP		0.55
CP-63,713-1		0.38
CP-63,986-1		<<3.2
CP-63,404-1		5.37
CP-63,631-1		1.65 racemic 0.33 R(+) >10 S(-)
CP-63,402		11.5
CP-63,774-1		0.30
CP-63,579-1		1.04

In addition to the structurally diverse compounds described above, which can serve as PCP mimetics, analogs of PCP have also been examined for their ability to support PCP cueing. The most extensive work reported to date has been done in Harlan Shannon's laboratory (Shannon 1981; Cone et al. 1984; McQuinn et al. 1981) and has demonstrated (1) that the piperidine moiety is not required since the free primary amine is active; (2) modifications to the cyclohexyl ring greatly reduce or abolish activity; and (3) increasing the chain length to the phenyl group or replacement with naphthyl abolishes activity. In addition, table 2 shows that a number of piperidine modifications can be made and still retain PCP-mimetic activity.

In contrast to the generalization observed with PCP-like compounds, a large number of agents that share similar pharmacological activities with PCP failed to mimic PCP's discriminative effects (table 3). Psychomotor stimulants, hallucinogens like THC and LSD, opiates, cholinergic and anticholinergic agents, as well as a diverse group of miscellaneous drugs, consistently produced vehicle choice.

TABLE 3. *PCP discrimination. PCP 3.2 mg/kg vs. vehicle. Compounds failing to mimic PCP.*

Compound	Dose Range	Percent PCP Choice	Response Level
Amantadine	10. - 32.	0	518
Methylphenidate	3.2 - 32.	12	530
Cocaine	3.2 - 10.	0	65
d-Amphetamine	1.0 - 1.78	0	140
Apomorphine	.32	0	400
THC	3.2 - 10.	12	455
Muscimol	1.0	0	476
LSD	.1	0	532
Yohimbine	3.2	0	721
Morphine	3.2	0	145
Ketocyclazoclne	3.2 - 56.	25	144
Cyclazocine	3.2 - 32.	12	357
Mecamylamine	1.0	0	572
QNB	1.0 - 3.2	12	419
Nicotine	1.0	0	691
Arecoline	- 3.2	12	360
Tacrine	3.2	0	602
Physostigmine	.1 - .32	12	136
Scopolamine	.32 - 1.0	0	141
Ditran	10.	0	250
Benrtropine	3.2 - 10.	12	321
Pirbuterol	10.	0	309
Cyproheptadine	3.2 - 10.	33	769
Althesin	10. - 32.	25	233
Veratridine	.001 - .32	12	83
Methaqualone	32. -100.	12	543
Navane	10. - 32.	8	544
Pentoberbital	10.	0	391
Diazepam	10.	14	634

NOTE: A number of compounds failed to generalize to PCP when administered 30 minutes prior to testing. N=at least 8 rats/treatment. Values are the highest generalization and lowest number of responses obtained over the dose-range tested.

ATTEMPTS TO ANTAGONIZE PCP DISCRIMINATION

A search for compounds that might block the PCP cue found that many drugs failed to reverse PCP discrimination to the vehicle level. Table 4 lists alphabetically the results obtained with such compounds over the dose range tested. A few agents,

TABLE 4. *PCP discrimination. PCP 3.2 mg/kg vs. vehicle. Compounds failing to block PCP.*

Compound	Dose Range	Percent PCP Choice	Response Level
Alprazolam	32.	83	322
Amantadine	10.	100	382
Apomorphine	.32	75	169
Baclofen	1. - 3.2	75	256
Caffeine	56.	87	253
Chlorpromazine	.32 - 10.	50	46
Cinanserin	3.2	100	326
Clonidine	.032	87	172
ClozaDine	1. - 3.2	100	68
Cyproheptadine	10.	83	198
Diazepam	1. - 10.	56	192
Diphenhydramine	10.	75	347
Dipyridamole	32.	92	457
Ditran	1.0	67	130
Doxapram	32. -178.	50	615
Etazolate	10.	100	381
Haloperidol	-056	100	296
	;1	57	184
	,178	56	64
	.32	67	20
Imipramine	10.	75	248
Levamisol	10. - 32.	91	252
Mecamylamine	1.0	87	318
Methysergide	32.	75	240
Mezilamine	.1	50	338
	.178	75	187
	.178	87	193
	.32	62	97
Morphine	3.2	100	74
Naloxone	10. -178.	75	85
Naltrexone	10.	62	562
Nifedipine	10.	75	78
Nimodipine	3.2	100	669
Oxolinicacid	3.2	100	413
Pentylenetetrazol	10;	100	324
Phenltrone	32.	87	290
Phenytoin	10. - 32.	100	288
Prazocine	3.2	75	336
Propranolol	10;	71	291
QNB	1.0	60	55
Scopolamine	.1	87	441
Sulpiride	32.	87	478
Traiazolate	32.	92	510
TRH	3.2	80	270
Vasopressin	.5 - 2.0	50	722
Yohimbine	10. - 32.	50	238

NOTE: Drugs which failed to reduce PCP discriminability below 50 percent. At least 8 animals/treatment were tested. However, when response level was suppressed below about 75 responses/15 minutes, a number of animals frequently failed to complete 10 responses within 15 minutes; their data were not included.

including doxapram, diazepam, haloperidol, vasopressin, and yohimbine, produced a partial antagonism to approximately the 50 percent PCP-choice level. Frequently, however, testing these agents at higher doses failed to reduce PCP discrimination further and/or resulted in complete disruption of responding. In contrast to the

absence of antagonism by these agents or by PCP analogs, we observed that potent, metabolically stable, adenosine analogs were capable of blocking completely the discriminative properties of PCP (Browne and Welch 1982). However, subsequent findings in our laboratory (Browne et al. 1983) indicated that the anti-PCP activity of adenosine analogs was most likely attributable to dispositional factors retarding PCP absorption into brain. It is of interest to note that, in contrast to reported antagonism of PCP's effects in other endpoints (e.g., locomotor activity), there has been no definitive report of an agent capable of completely reversing the discriminative properties produced by PCP. Since there is no known antidote to PCP intoxication in man, the discriminative stimulus assay may be an appropriate model for screening for such an agent.

In summary, the results presented here confirm and extend previous findings that PCP can serve as a discriminative stimulus, and that pharmacologically similar agents such as ketamine, dexoxadrol, and SKF-10,047 can mimic the PCP cue (Brady and Balster 1981; Brady et al. 1982; Herling et al. 1981; Holtzman 1980; Shannon 1981). It is known that PCP exerts a multiplicity of effects on brain monoaminergic and cholinergic systems (Ary and Kominskey 1980; Arora and Meltzer 1980; Ward and Trevor 1981). However, compounds that activate or attenuate activity of CNS noradrenergic, dopaminergic, serotonergic, cholinergic, GABAergic, opiate, or benzodiazepine systems all failed to mimic or block completely the discriminative effects of PCF. These results indicate that PCP-like agents probably exert their effects through unique neurochemical mechanisms distinctly different from other classes of agents. Indeed, it appears that PCP-like compounds may be acting on specific "PCP receptors" in brain (Vincent et al. 1979; Marwaha et al. 1981; Quirion et al. 1981; Zukin and Zukin 1979). Although good correlations between the ability of agents to support PCP cueing and their ability to displace labeled PCP from binding sites have been obtained (Zukin and Zukin 1981; Browne and Kozlowski, in preparation), it remains to be determined whether antagonists of PCP cueing and receptor binding can be eventually discovered.

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Clinical Implications of Behavioral Pharmacology Research on Phencyclidine

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As a consequence of the unanticipated epidemic of phencyclidine (PCP) abuse in the late 1960s and early 1970s, biomedical and behavioral research on this drug expanded by the late 1970s (Balster and Pross 1978). Partly because of the improved public health response resulting from this research activity, the PCP epidemic has been stopped. The major credit for this rapid growth of PCP research should go to the National Institute on Drug Abuse, NIDA supported most of these research activities, and took an active role in disseminating information on PCP (Peterson and Stillman 1978). Also exceedingly important has been NIDA's leadership in providing PCP and many critically important analogs for research use. For the last 10 years or so, NIDA has provided nearly all the PCP utilized by researchers throughout the world. NIDA has also had an active intramural research program on PCP, leading to a number of important findings.

This update of NIDA's 1978 monograph on PCP provides an opportunity to see what we have learned from this enormous expansion of PCP research over the last decade. This paper will focus on the results of behavioral studies. Since the development of PCP as an anesthetic was discontinued in the 1960s, there have been no laboratory studies of the behavioral effects of PCP in humans, presumably because of potential dangers to the subjects and probable difficulties in obtaining an IND to give behaviorally active doses. Thus, most of what we have learned about the behavioral pharmacology of phencyclidine has been from animal research. This review will highlight some of the major findings of that research. It will also examine the implications to be drawn from this research for treatment and prevention of PCP abuse. Some of these predictions for PCP abuse are consistent with clinical reports. In other cases, clinical information is incomplete. One goal of this paper is to suggest some areas where clinicians and clinical researchers might focus their attention to learn more about the implications of PCP abuse.

WHAT IS PCP?

Pharmacologists and epidemiologists have always had trouble classifying PCP. In early writings, it was classified as an anesthetic because this was its intended use; however, differences in the pharmacology of PCP and typical general anesthetics are significant, as we shall see. Initially, when PCP was abused, it was often classified as a hallucinogen; early epidemiologic studies grouped it together with classical hallucinogens such as LSD. Again, clinical experience and research have demonstrated the inappropriateness of this classification. Behavioral pharmacologists have also been very interested in classifying PCP's behavioral effects and comparing them to other drugs of abuse. Depending upon the effects being examined, PCP has many properties in common with other drugs; but, on some measures, PCP seems to represent a unique class of CNS-active drugs.

Amphetamine-Like Effects

A pioneer in studies of the pharmacology of PCP, Graham Chen, often characterized PCP as a "sympathomimetic anesthetic" (Chen 1973), a curious juxtaposition of terms. However, the two drugs to which PCP has been most often compared in behavioral research are amphetamine, or other sympathomimetic stimulants, and pentobarbital or other classical CNS depressants. PCP clearly has effects usually associated with both. PCP has many behavioral effects characteristic of indirect-acting dopaminergic agonists (Meltzer et al. 1981; Johnson 1983). Among these effects are the production of amphetamine-like stereotyped behavior (Sturgeon et al. 1979) and ipsilateral rotation in substantia nigra-lesioned rats (Kanner et al. 1975). These amphetamine-like actions are often blocked by antipsychotic drugs. PCP's effects on schedule-controlled lever pressing for food reinforcement also often appear similar to those of amphetamine, with large increases in rates of responding and rate-dependent effects (Balster and Baird 1979; Brady et al. 1980; Wenger 1976). Although amphetamine-like effects on operant behavior have been seen in mice, pigeons, and monkeys, the amphetamine-like stereotyped behavior and hyperactivity are particularly prominent in rodents. Monkeys exhibit decreased responsivity, motor incoordination, changes in visual attention, and, at high doses, a characteristic anesthesia. These species differences in overt behavioral effects of PCP lead to the speculation that dopaminergic actions are less prominent in primate species, possibly including humans.

Nonetheless, the amphetamine-like actions of PCP are of considerable interest for the following reasons. Malfunction of the dopaminergic system has been implicated as having considerable importance in schizophrenia. PCP's interactions with this system may be responsible in large measure for its schizophreniform manifestations in humans. Like amphetamines, PCP would be expected to exacerbate schizophrenia, and users with this or related disorders, or with latent psychiatric diseases, may be at

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considerable risk from taking PCP. This possible connection between the effects of acute or chronic PCP administration and schizophrenic diseases has motivated much of the research done with PCP, since it is very possible that a further understanding of this drug will provide valuable leads for study of this important psychosis (Domino and Luby 1981). Another implication of the evidence for amphetamine-like effects of PCP is that high-dose PCP toxicity may have components of amphetamine toxicity. For example, hypertensive crises have been reported in PCP overdose (Eastman and Cohen 1975), and PCP can cause convulsions at high doses. It is tempting to suggest treating PCP overdose with antipsychotic drugs; however, there is also considerable evidence for differences in the acute toxicity of PCP and amphetamine. The well-known aggregate toxicity seen with amphetamine in mice does not occur with PCP (Landauer and Balster 1982). Chlorpromazine, which antagonizes amphetamine lethality in mice, does not have a similar protective effect against PCP; indeed, it has additive toxicity (Landauer et al. 1982). Also, considering that many antipsychotic drugs lower seizure thresholds and may contribute anticholinergic effects to those of PCP, it is difficult to find a clear pharmacological rationale to use antipsychotic drugs routinely to treat PCP overdose. A final implication of PCP's stimulant properties is that there may be dangerous interactions in the combined use of PCP and sympathomimetic stimulants such as amphetamine and cocaine. PCP has been shown to enhance amphetamine stereotyped behavior in rats (Balster and Chait 1978). Further research on this possibility is needed.

Barbiturate-Like Effects

Although PCP was developed as an anesthetic, its profile as an anesthetic is very different from typical general anesthetics of the CNS-depressant class (Domino 1964). Nonetheless, PCP has a number of behavioral and pharmacological effects similar to those of depressants such as the barbiturates (Balster and Wessinger 1983). PCP has profound motor effects, as evidenced by effects on rotorod performance and similar measures (Kalir et al. 1969; Balster 1980). In this production of ataxia, PCP differs considerably from both stimulants and classical hallucinogens. Although further, more detailed study of the motor effects of PCP is needed (Ando et al. 1983), it is clear that abusers of PCP would be expected to exhibit motor signs of intoxication that might contribute significantly to PCP's behavioral toxicity. Performance of tasks requiring motor coordination, such as driving an automobile, would be expected to be significantly disrupted by PCP.

PCP, like barbiturates, also has anticonvulsant effects in various animal models (Chen et al. 1959; Geller et al. 1981; Hayes and Balster 1985). Certain convulsants, such as strychnine, are not antagonized, and PCP has some specificity for tonic rather than clonic convulsions.

Perhaps of most clinical significance, PCP very markedly enhances the effects of classical depressant drugs, including barbiturates and ethanol (Balster and Wessinger 1983). We have extensively studied this interaction. and find that quantitatively the interactions can be as large as the interactions among CNS depressants, a well-established toxic combination. This interaction has been shown in pigeons, rodents, and primates using a number of different behavioral measures (Chait and Balster 1978; Thompson and Moerschbaecher 1982a; Thompson and Moerschbaecher 1982b; Wessinger et al. 1982; Woolverton and Balster 1981). Since there is a high likelihood of combined use of PCP and depressants such as alcohol, there is a high likelihood that some of the behavioral manifestations commonly attributed to PCP may be due to combined effects. Careful histories on concurrent use of depressants such as alcohol, barbiturates, or benzodiazepines should be helpful in establishing the cause of problems encountered during acute PCP intoxication.

Classical CNS depressants, such as barbiturates and benzodiazepines, have prominent antianxiety effects. In the animal laboratory, these drugs increase responding that has been suppressed by punishment in what are often referred to as conflict procedures. Because this effect on responding-suppressed-by-punishment is relatively specific for antianxiety drugs, it is believed to be an animal model for anxiolytic activity. PCP has potent rate-increasing effects on responding-suppressed-by-punishment, at least in pigeons.(Chait et al. 1981), a widely-used species for studying these types of effects. Although it requires considerably more study, this benzodiazepine-like antipunishment activity of PCP suggests that it might have antianxiety effects in humans. These effects may contribute to PCP's attractiveness to abusers. An interaction between predisposing anxiety disorders and some forms of PCP abuse warrants further investigation.

Unique Effects of PCP

In spite of the similarities described in the behavioral effects of PCP to those of stimulants and depressants, users of PCP describe an intoxication unlike that reported for other drugs of abuse. PCP appears to have a unique spectrum of subjective effects: a spectrum that has been characterized by clinical investigators (Pollard et al. 1965; Siegel 1978). The corresponding animal behavior model for these effects utilizes a drug discrimination procedure. Animals are trained to detect whether or not they have been given a PCP injection and to indicate their condition by pressing one of two response levers. Another chapter in this volume (Browne) will consider the research using this paradigm in detail; however, a few aspects of the findings warrant mention here.

The discriminative stimulus effects of PCP differ considerably from those of other drugs of abuse (Poling et al. 1979; Shannon 1981). Animals do not generalize from PCP to other drugs of

abuse: neither to stimulants, depressants, nor hallucinogens (i.e., they do not respond as if they had detected PCP). These data are consistent with the ability of PCP to produce a unique intoxication in humans, and with its separate classification as representative of a distinct class of psychoactive drugs. The public health implications are that the PCP abuse problem would need specific treatment and prevention approaches. It would be expected that some PCP abusers would have this as their drug of choice, and not mix and match PCP with other drugs, as occurs routinely within drug classes such as opiates and hallucinogens. Patterns of PCP use and abuse would be expected to be distinctive; because of its unique effects, PCP might appeal to certain types of drug users. It is important to recognize that treatment and prevention strategies developed for other drugs of abuse may be inappropriate for problems of PCP abuse.

PCP SELF-ADMINISTRATION

Early evidence that PCP had significant abuse potential was the finding, from behavioral pharmacology research, that PCP would be self-administered by rhesus monkeys (Balster et al. 1973). In that study, monkeys with IV catheters could respond on a lever to receive injections of PCP. They readily acquired this behavior and self-administered very large doses. This finding has been replicated and expanded upon in numerous subsequent studies (e.g., Balster and Woolverton 1980; Carroll and Meisch 1980; Lukas et al. 1984; Risner 1982). Strong reinforcing properties are typically obtained only with drugs having significant potential for human recreational use. One of the interesting findings from PCP self-administration research is that, given unlimited access to the drug, monkeys will maintain nearly continuous intoxication. These results are unlike the pattern of episodic self-administration typically obtained for stimulants, and more like the patterns associated with dependence-producing drugs such as the opiates and depressants. I will have more to say on the dependence properties of PCP later. These animal results suggest that at least some segment of PCP abusers would become chronic heavy users with daily use patterns. Also, unlike the results of self-administration studies of opiates, where little overt behavioral toxicity is observed in the animals at self-administered doses, monkeys self-administer doses of PCP sufficiently high as to cause marked behavioral effects. In these respects, PCP may more closely resemble barbiturates and alcohol, with which self-administration, by animals and human users, results in severely debilitating doses. Another interesting recent development in PCP self-administration research is that the oral route is also effective (Carroll and Meisch 1980). PCP would be expected to have the potential for both IV and oral abuse, although smoking appears, currently, to be the most preferred route.

PCP-LIKE DRUGS

Although PCP has certain unique behavioral properties among drugs of abuse, behavioral pharmacology research has established that there are a number of drugs with PCP-like effects. The primary tool for classifying drugs as PCP-like has been the drug discrimination procedure, since this is presumably a model of acute subjective effects, and because this is the one behavioral measure that clearly establishes PCP's uniqueness. One group of drugs with PCP-like discriminative stimulus effects are chemical analogs of PCP, other arylcycloalkylamines. Rats or monkeys trained to detect PCP will readily respond as if they had been given PCP, when given any of a large number of PCP analogs (Shannon 1981; Brady and Balster 1981; Solomon et al. 1982). Shannon and coworkers have made considerable progress toward determining structure-activity relationships among arylcycloalkylamines and essential structural requirements for PCP-like effects (Shannon 1983; Cone et al. 1984). A number of these PCP analogs have been tested for reinforcing properties in IV self-administration studies (Risner 1982; Lukas et al. 1984). Those that are self-administered are also identified as PCP-like in drug discrimination studies; thus, there is an excellent concordance in these properties. The PCP molecule is a highly versatile one for making substantial modifications and retaining activity; therefore, many potentially abusable PCP analogs could be prepared. As of this writing, only the N-ethyl analog (TCE), the thienyl analog (TCP), and the pyrrolidine analog have been subject to much abuse, and have consequently been scheduled under the Controlled Substances Act. It would appear that many presently uncontrolled analogs have PCP-like properties. Since animal behavioral research seems capable of predicting PCP-like abuse potential, perhaps data from these procedures will be used to regulate some of these analogs before they are abused.

Ketamine is an arylcyclohexylamine analog of PCP that warrants special mention. Ketamine is currently marketed as a parenteral anesthetic for human use, and has many important clinical indications. In behavioral studies, including drug discrimination and self-administration studies, ketamine acts very much like PCP. It is generalized from PCP and is reliably self-administered. It has also been subject to some abuse, and is presently controlled. Although it is about one-tenth as potent, and is shorter acting than PCP, there are little laboratory data showing qualitatively different effects. Because ketamine is marketed, there has been more research on it than on other PCP analogs. This research literature is an important source of information with probable relevance to PCP.

Among the more important series of discoveries in behavioral research with PCP are the reports that drugs chemically distinct from PCP also have PCP-like discriminative stimulus effects. These drugs are of little immediate clinical significance because they are all research compounds not easily available to potential

abusers. On the other hand, the emergence of various classes of these PCP "biologs" has proven to be of considerable importance to basic research on PCP's neural mechanisms of action. For example, the finding that the opioid derivative, N-allylnormetazocine (also known as SKF-10,047), which was found to have PCP-like discriminative effects (Shannon 1981), also had affinity for the PCP binding site (Zukin and Zukin 1979), was very important in establishing a possible functional significance for this site. Subsequent research has considerably advanced our understanding of the behavioral and biochemical effects of this and other PCP-like opioids (Brady et al. 1982a; Holtzman 1980; Shannon 1983; Slifer and Balster 1983; Zukin et al. 1984). Remarkably, a general concordance shows that diverse drugs with PCP-like behavioral effects are active at the PCP receptor. It would appear that at least one of the major effects of PCP mediated by this newly-discovered receptor mechanism is its discriminative effect. It is unclear how many other effects of PCP are mediated through this receptor. One way to study this is to examine these PCP biologs to determine the extent of overlap with PCP in their behavioral and pharmacological properties. It is beyond the scope of this paper to review the relatively large research literature relating the pharmacology of certain opioids with unusual "psychotomimetic" effects to the pharmacology of PCP. Other papers in this volume document the considerable progress being made in identifying the neural bases for many of the important behavioral actions of PCP. This basic research may lead to novel approaches to treatment of PCP abuse and will contribute substantially to our understanding of brain-behavior relationships.

In addition to opioid derivatives, drugs from other chemical classes have been found to have PCP-like discriminative stimulus effects. The best characterized compounds are 1,3-substituted dioxolane derivatives such as dexoxadrol and etoxadrol (Brady et al. 1982b). Each has also been given to humans with evidence of PCP-like effects (Lasagna and Pearson 1965; Wilson et al. 1970). This class of compounds is of particular research interest because it shows stereospecificity of action both behaviorally (Cone et al. 1984; Slifer and Balster, in press) and in binding to the PCP receptor (Hampton et al. 1982). Stereospecificity further supports the hypothesis that PCP's discriminative stimulus effects are receptor-mediated. The finding that PCP-like effects occur in a variety of chemical classes, including the opioid and dioxolane classes described above, as well as some others (Tang et al. 1984; Zimmerman et al. 1983), suggests that the potential exists for arylcyclohexylamines to be only the first of many chemically heterogeneous classes of PCP-like compounds. New compounds may emerge with differing potential for abuse. On a more positive side, there is also the possibility that new therapeutic agents may be developed that will retain some of PCP's desirable effects but be devoid of its abuse potential (Domino 1981). The laboratory procedures to study these new compounds are already relatively well developed. This variety of PCP-like drugs also provides powerful tools for the basic study of PCP's pharmacology.

TOLERANCE

There have been a number of laboratory studies of tolerance to the behavioral effects of PCP. Some of our earlier work on this has been summarized previously (Balster and Woolverton 1981). The usual procedure for tolerance studies is to give PCP repeatedly to subjects trained to perform an operant task. We have given it daily, or up to four times a day, at behaviorally active doses, in some cases in escalating doses, to rats and squirrel monkeys. We routinely find evidence of two- to fourfold shifts in dose-effect curves, but no more. More recent studies have attempted to determine the important factors in this tolerance development. Most of it appears to be accountable for by pharmacological mechanisms, including some evidence for biodispositional changes (Woolverton and Balster 1979; Woolverton et al. 1980; Johnson and Balster 1981; Freeman et al. 1984), although, in one study (Woolverton and Balster 1979), there was some evidence that behavioral factors (learning to respond while intoxicated) play some role. Practically speaking, PCP produces relatively modest tolerance development. It would be predicted that considerable tolerance would not be a major characteristic of PCP abusers. The only evidence we have to the contrary comes, not from direct tolerance studies, but from studies of IV PCP self-administration. In one of these studies (Balster and Woolverton 1980), in which rhesus monkeys had continuous access to relatively high doses, the monkeys often self-administered over 10 mg/kg/day. These very high doses were accompanied by behavioral disruption and decreased food intake, but were tolerated for periods of weeks: food intake often recovered. Although we have not systematically studied this, I believe we could not have administered nearly as high daily doses to naive animals. It is important to keep in mind that these monkeys were, generally, keeping themselves continuously intoxicated 24 hours a day. Under conditions of unlimited access, very large tolerance often develops to other drugs as well (Balster and Woolverton 1982). Thus, this condition--unlimited access--probably reflects the extreme circumstances favoring tolerance. It is difficult to imagine human PCP abusers self-administering this much drug.

DEPENDENCE

In the study described (Balster and Woolverton 1980), of unlimited-access self-administration of PCP, in which monkeys' very large daily doses of PCP resulted in blood levels of 100 to 300 ng/ml during periods of over a month, dramatic withdrawal signs were observed when PCP access was terminated. Signs included vocalizations, bruxism, oculomotor hyperactivity, diarrhea, piloerection, difficulty remaining awake, tremors, and, in one case, convulsions. These signs appeared within 8 hours of abstinence and were most severe at about 24 hours, corresponding to the rapid decline in plasma PCP levels. To examine this evidence of dependence more fully, high daily doses by continuous IV infusion were attempted, but, as stated earlier, could not be done without

difficulty in maintaining the animals in good health. When lower doses were infused, the observable withdrawal signs were more subtle and variable.

To study the possibility of dependence upon lower, more reasonable doses of PCP, a different approach was used (Slifer et al. 1984). Again, rhesus monkeys were used, but these subjects were first trained to lever press for their daily ration of food utilizing an intermittent schedule of reinforcement (FR100). Behavioral measurements were made during four equally-spaced, 30-minute sessions each day. After the animals were well trained, continuous IV PCP infusions began through an implanted catheter. The initial dose was 0.05 mg/kg/hr (1.2 mg/kg/day). As seen in figure 1, this dose had little effect upon responding for food. The animals appeared only very mildly intoxicated. When PCP was withdrawn after 10 days, behavior was markedly affected. By 8 hours after the infusion was terminated (response period A on day 11), some animals completely ceased responding (see figure 1) and behavior recovered slowly over the next 7 to 9 days. Some mild withdrawal signs were occasionally observed during the first 24 hours of abstinence, but the animals appeared normal by after the second day. When PCP was given to animals in withdrawal, the animals recovered responding, but were disrupted again as the acute effects wore off.

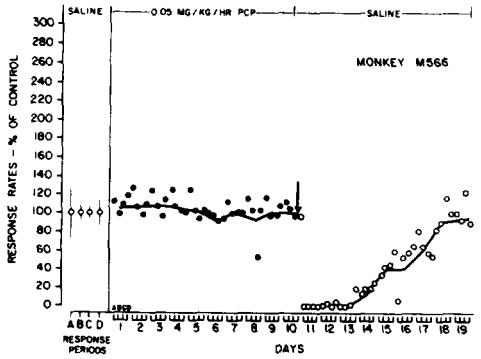

FIGURE 1. *Effects of continuous PCP infusion and withdrawal on rates of responding for food reinforcement in a rhesus monkey*

NOTE: Response rates in each of tour daily response periods are shown before (open circles), during (closed circles), and after (open circles) lnfusion of 0.05 mg/kg/hr PCP for 10 days. PCP was wlthdrawn at the arrow, 2 hours before the next session where there was no effect. The first session on day 11 was 8 hours after PCP was withdrawn. The results with this monkey are similar to the other tour monkeys studied (modified from Slifer et al. 1984). Copyright 1984 Williams and WiIkins.

We have viewed these withdrawal effects on behavior as evidence of behavioral dependence on PCP. Behavioral signs have also been reported in human users of PCP during withdrawal (Tennant et al. 1981); however, these instances appear to be relatively rare. Nonetheless, the relative ease with which a dependence phenomenon can be produced in monkeys suggests that PCP has a potential for producing dependence in PCP users, particularly those who use the drug very frequently. Behavioral sequelae seen in chronic PCP abusers might be examined as possible manifestations of dependence as well as of cumulative toxicity.

SUMMARY

This discussion has highlighted only some of the areas of behavioral, pharmacology research with PCP, focusing largely on studies in our laboratories. Some of the areas touched upon lightly have been much more extensively investigated (e.g., PCP-like properties of psychotomimetic opioids). Some areas, such as the search for a PCP antagonist, have been studied with relatively little success so far. Two other areas, among many that are worthy of mention, are the extensive series of studies of the effects of PCP on complex learning procedures, starting with the studies by Moerschbaecher and Thompson (1980a, Moerschbaecher and Thompson 1980b), and an elegant series of studies on the determinants of oral PCP self-administration, beginning with the study by Carroll and Meisch (1980).

Much progress has been made on the clinical implications of behavioral research with PCP, and we are in a much better position to respond effectively to this public health problem than we were when it emerged, only a little over 10 years ago. The impetus behind PCP research has come from two directions--from the emergence of PCP as a drug of abuse with the pressing practical questions raised by this epidemic, and from the potential that PCP research has for a fuller understanding of the brain and behavior. Although this discussion has focused on the former, progress toward the latter goal has been equally, if not more, substantial, and may have long-term health implications far beyond those presented by problems of PCP abuse.

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Phencyclidine: Changing Abuse Patterns

Raquel Crider

GENERAL TRENDS 1973 TO 1984

Phencyclidine (PCP), one of the arylcyclohexylamines. was developed and originally used as a general anesthetic for humans. Due to psychotic and hallucinogenic reactions, use of the drug for humans was discontinued. It is now used legally only in veterinary medicine as an animal immobilizing agent.

Currently, trends in PCP abuse are monitored through emergency room visits, deaths, initiates entering drug abuse treatment programs, and surveys, as shown in table 1 and figures 1 and 2. The years between 1973 and 1984 have been divided into three periods: during the years between 1973 and 1978/1979, the indicators of PCP use increased; the period 1978/1979 through 1981 marked a decline in the PCP indicators; 1981 to the present time are years in which PCP indicators have shown resurgence.

Indicators of PCP abuse, i.e., emergencies, deaths, and the number of initiates entering treatment, increased between 1973 and 1978/1979. Between 1973 and 1975, the rate of initiates, based on treatment year-of-first-use records, increased more rapidly than the number of emergencies. This phenomenon may be explained, in part, by a change in the route of administration. Beginning about 1972, PCP users changed from administering the drug orally in tablet or capsule form to smoking the drug on leaf material, such as marijuana, tobacco, or parsley. By smoking, PCP users were able to control the dosage more effectively, thus decreasing the chance of overdose.

By 1978/1979, indicators of PCP abuse leveled off and started to decline. This trend is thought to be related to a variety of activities initiated by health and law enforcement officials, including a nationwide education campaign in which 18,000 letters

were mailed to treatment programs, emergency rooms, health agencies, and medical examiner/coroner offices describing the typical reactions to PCP, and treatment procedures. In addition, PCP was rescheduled from Schedule III to Schedule II of the Controlled Substance Act, a highly restrictive category reserved for substances with limited legitimate use and/or significant abuse potential. The PCP analogues, PCE, PHP, and TCP were placed in Schedule I. Required reporting of production of the precursor, piperidine, began in 1979. Penalties for possession of PCP with intent to sell were increased at about the same time. As a result of these and other efforts, the number of emergencies, deaths, and PCP initiates entering treatment began to decline.

TABLE 1. *PCP indicators*

PCP Related Deaths	PCP Emergencies		PCP Initiate Treated[4]	Number "Ever Use" in Households[5]	Percent 30-Day Use In High School	Percent Age 12-17 "Ever Use" Households[7]
	National[2]	In Panel[3]				
1973	1.400		3.42			
1974	1.934		4.24			
1975	1.768		5.49			
1976	2.799		6.32			3.0
1977 8.1	4.993		7.16	6.98		5.8
1970 12.3	9.877		9.13			
1979 10.5	10.288		5.67	7.01	2.4	3.9
1980 8.5	7.154	3.781	2.88		1.4	
1981 9.4	5.840	2.722	1.27		1.4	
1982 16.4	8.067	3.383		8.28	1.0	2.2
1983 23.8	9.782	4.376			1.3	
1984 21.7		4.526			1.0	

1. Number of PCP related deaths x 10^{-1} reported to DAWN. Newark and New York excluded after 1981. The 1984 data are preliminary (National lnstitute on Drug Abuse 1985c).

2. Number of PCP related emergencies x 10^{-3} reported to DAWN projected to the Nation (Hinkley and Greenwood 1982).

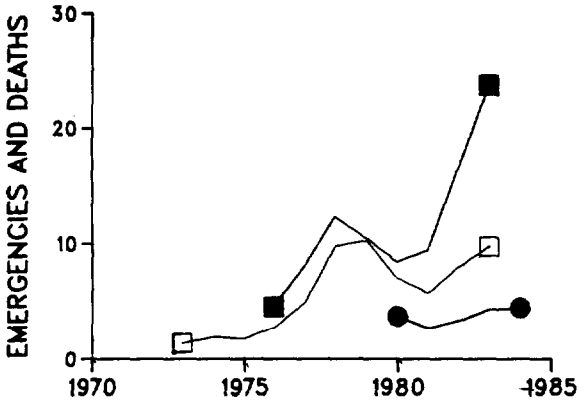
3. Number of imputed PCP related emergencies x 10^{-3} reported to a consistent panel of hospitals In DAWN (National lnstitute on Drug Abuse 1985a).

4. Number of PCP lnitiates x 10^{-2} starting use 1973-1983 admitted to a consistent panel of 402 treatment programs In 1977 through 1981.

5. Number of persons in households x 10^{-6} having ever used PCP 1970, 1979, and 1982 (Miller et al. 1983).

6. Percent of high school seniors using PCP In the 30 days prior to the survey (Johnston et al. 1985).

7. Percent ages 12 to 17 years In households reporting ever having used PCP (Miller et al. 1983).

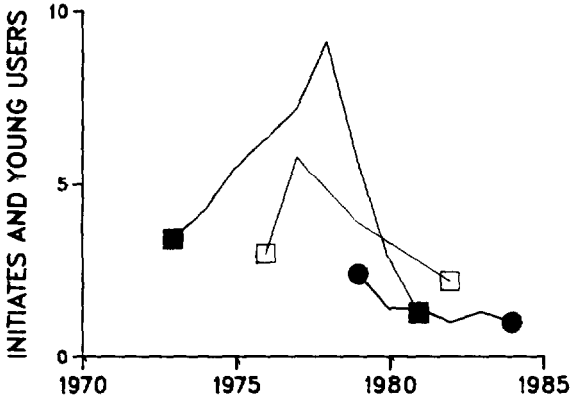


KEY: ■ = PCP ralated mortalities (NY and Newark excluded) x 10^{-1}; □ = PCP emergencies projected to nation x 10^{-3}; ● = PCP emergencies reported to consistent panel x 10^{-3}.

FIGURE 1. *The number of PCP-retated emergencies projected to the Nation, and the number of PCP-related deaths, peaked in 1978/1979, declined through 1980/1981, then increased in 1981 through 1984*

By 1981, some of the indicators of PCP abuse began to increase again. The number of PCP-related emergencies projected to the Nation from the Drug Abuse Warning Network (DAWN) data showed an increase from 5,840 in 1981 to 9,782 in 1983 (Hinkley and Greenwood 1984). Data from a consistent panel of reporting hospitals indicate that the number of emergencies continued to increase through 1983. The number of PCP-related deaths reported to DAWN increased from 96 in 1981, to 154 in 1983 (National Institute on Drug Abuse 1984). The estimated number of persons reporting ever having used PCP increased from 7.01 million in 1979 to 8.28 million in 1982 (Miller et al. 1983).

The recent increase, however, appears to be concentrated primarily in the metropolitan areas of Los Angeles, Washington, D.C., and New York City. These three areas accounted for 76.0 percent of the emergencies reported to DAWN in 1983, while Los Angeles and Washington, D.C. accounted for 81.8 percent of the PCP-related deaths[2]. Rates of PCP emergencies per 100,000 total emergencies are available for 26 major metropolitan areas in 1983, based on DAWN data (National Institute on Drug Abuse 1985d). The areas of Los Angeles, Washington, D.C., and New York City show the highest rates at 2.52, 2.03 and 0.53 per 100,000 emergencies, respectively, in 1984.



KEY: ◘ = Percent of household residents ages 12 to 17 years reporting "ever use" of PCP; ● = Percent of high school seniors using PCP In past 30 days; ■ = PCP Initiates In treatment x 10^{-2}, corrected for lag between first use and treatment.

FIGURE 2. *The increase in PCP indicators starting in 1981 does not reflect an increase for new or young users. The number of PCP initiates first admitted to treatment, the percent of high school seniors using the drug in the 30 days prior to the survey, and the percent of persons ages 12 to 17 years in households reporting ever having used PCP declined in the late 1970s and remained at low levels since the early 1980s.*

Table 2 shows the number of PCP-related emergencies for the period of 1982 to 1984 by quarter for New York, Los Angeles, and Washington, D.C. For New York and Washington, D.C., the average number of mentions increased significantly between 1983 and 1984.

The decline in Los Angeles between 1983 and 1984 cannot immediately be interpreted as a decline in PCP use for that city. In 1981, during an investigation of PCP trends in Los Angeles, it was discovered that many PCP emergencies were diverted to psychiatric units, better equipped to handle the violent behavior sometimes accompanying PCP reactions. These psychiatric units were not participating in the DAWN network at that time (Kozel and Husson 1981). It is possible that similar systemic problems may have occurred in 1984.

TABLE 2. *Number of PCP-related emergencies from a consistent panel of emergency rooms in New York, Washington, D.C., and Los Angeles, 1982-1984*

Time Frame		New York	Washington, D.C.	Los Angeles
1982	Q1	93	49	567
	Q2	147	68	660
	Q3	147	68	660
	Q4	125	96	589
1983	Q1	142	104	568
	Q2	173	97	807
	Q3	214	130	910
	Q4	303	179	910
1984	Q1	267	190	641
	Q2	217	285	635
	Q3	237	285	635
	Q4	239	229	493
Mean	1982	121.6	70.0	600.6
Mean	1983	207.9	127.6	751.8
Mean	1984	240.0	241.4	621.0

SOURCE: National institute on Drug Abuse 1985b.

Potential problems in PCP abuse were also reported in New Orleans and St. Louis (National Institute on Drug Abuse, in preparation), although the quarterly frequencies of emergency room mentions in those SMSAs were small compared to New York, Washington, D.C., and Los Angeles.

NEW OR YOUNG USERS

Based on data from national surveillance systems, the increase between 1981 and 1983 does not appear to reflect substantial increased use among new or young users, as occurred during the early and mid-1970s, although there may be regional variations. In general, the number of initiates declined sharply after 1977 and remained at low levels through 1981. Table 1 and figure 2 show that there were 913 initiates starting use in 1978, first treated in a panel of 402 consistently reporting treatment programs. The

number of initiates in treatment declined to 127 by 1981. Preliminary data from 1982 and 1983, corrected for the lag time between first use of the drug and first entry into treatment, do not show an increase. In addition, the percent of high school seniors using PCP in the 30 days prior to an annually conducted survey declined from 2.4 percent in 1979 to 1.0 percent in 1984 (Johnston et al. 1985). There was also a smaller percent of emergency cases ages 6 to 19 years in 1983 compared to 1979: 34 percent vs. 18 percent (National Institute on Drug Abuse 1984; Drug Enforcement Administration 1981).

Consistent with the decline in use among youth in these indicators is the decline in self-reported PCP use among youth and young adults in the household population. The National Survey on Drug Abuse showed a significant decline between 1979 and 1982 in the percent of 12- to 17-year-olds and the percent of 18- to 25-year-olds reporting ever having used PCP, from 3.9 percent to 2.2 percent, and from 14.5 percent to 10.5 percent, respectively (Miller et al. 1983).

One exception was noted to the declining trend among youthful users relative to other age groups. The number of 6- to 19-year-old black and Hispanic PCP emergency patients increased in one Harlem hospital from 14 in 1981, to 297 in 1984. However, since 90 percent of all PCP-related emergencies in that hospital in 1984 were ages 6 to 19 years, indicating a bias or specialized program, the hospital was eliminated from all subsequent analysis.

CHARACTERISTICS OF USERS

According to data from emergency rooms reporting to the Drug Abuse Warning Network (table 3), most users were male, black, and between the ages of 20 and 29. Table 3 shows the distribution by gender, showing 71.8 percent were male. Table 4, giving the characteristics of emergency room patients over time, shows little change in the gender of PCP emergency patients between 1976/1977 and 1983.

In contrast to the stable trends in gender, the age of emergency room patients increased. As table 3 shows, in 1983 18.1 percent were ages 6 to 19 years, 61.8 percent were ages 20 to 29 years, and 19.6 percent were ages 30 years and older. Table 4 shows the decline in the proportion of young users ages 6 to 19 years with an emergency, from 51 percent in 1976/1977, to 18 percent in 1983. This change in age can also be seen by SMSA, where New York and Los Angeles both show significant change in the age distributions between 1981 and 1984 toward older users (NY X^2 =17.35, df=3, $p < .001$; LA X^2 =44.72, df=3, $p < .001$). No significant change in age was noted for Washington, D.C.

TABLE 3. *Distribution of PCP-related emergency room visits by age, race and 8ex, 1983*

Age (Years)	Percent	Race	Percent	Sex	Percent
10-19	18.1	Black	53.9	Male	71.8
20-29	61.8	White	29.3	Female	28.1
30 and older	19.6	Hispanic	13.7	Unknown	0.1
		Other or			
Unknown	0.5	Unknown	3.1		
Total	100.0	Total	100.0	Total	100.0

SOURCE: National Institute on Drug Abuse 1984.

TABLE 4. *Distribution of PCP-related emergency room visits by selected characteristics, May 1976 to December 1983*

Period	Percent Ages 10-19 Years	Percent Black	Percent Male
May 1976-Apr 1977[a]	51	24	70
May 1977-Apr 1978[b]	47	28	72
Jan 1979-Dec 1979[c]	34	40	71
Jan 1980-Dec 1980[d]	32	37	71
Jan 1981-Dec 1981[e]	28	39	72
Jan 1982-Dec 1982[f]	22	48	71
Jan 1983-Dec 1983[g]	18	54	72

SOURCES: [a]Drug enforcement Administration 1977; [b]Drug Enforcement Administration 1978; Drug Enforcement Administration 1979; Drug Enforcement Administration 1981; National Institute on Drug Abuse 1982; National lnstitute on Drug Abuse 1983; [g]National Institute on Drug Abuse 1984.

The race distribution of emergency patients is also changing over time in the direction of a larger proportion of black and Hispanic patients. In 1983 (table 3), 53.9 percent of emergency room patients were black, 29.3 percent were white, and 13.7 percent were Hispanic. Trends over time (table 4) indicate a change from 24 percent black in 1976/1977, to 54 percent by 1983. Within SMSA, all three SMSAs showed significant changes between 1981 and 1984 toward a higher proportion of black and Hispanic patients in New York and Los Angeles, and a higher proportion of black patients in Washington, D.C. (NY X^2=33.23, df=2, $p < .001$; DC X^2=116.68, df=2, $p < .001$; LA X^2 =29.32, df=2, $p < .001$).

While most PCP emergencies involve patients ages 20 years and older, the problem among 6- to 19-year-olds is nonetheless important. Among young patients ages 6 to 19 years, PCP is more popular than any other drug of abuse. In New York, 50.7 percent of young black emergency room patients reported use of PCP, as did 19.9 percent of the young Hispanic patients. In Washington, D.C., 35.4 percent of the young black patients reported PCP abuse; in Los Angeles, 22.3 percent of the young black and 30.0 percent of the young Hispanic patients did so.

PCP-RELATED DEATHS

More than 66 percent of PCP-related deaths reported to DAWN in 1983 involved at least one other drug. Table 5 shows a statistically significant relationship for alcohol combined with PCP and heroin combined with PCP (alcohol X^2=12.41, df=1, $p < .001$; heroin X^2 =29.13, df=1, $p < .001$).

The number of deaths associated with alcohol combined with PCP, and for heroin combined with PCP has been increasing. Nationally, the number of alcohol:PCP-related deaths was 21, 50, and 59, respectively, for the three years 1981, 1982, and 1983, according to the DAWN annual reports. The number of heroin:PCP-related deaths increased from 11 in 1981, to 24 in 1982, and 58 in 1983.

TABLE 5. *PCP-related deaths in combination with alcohol or heroin, 1983*

	PCP	No PCP		PCP	No PCP
Alcohol	59	988	Heroin	58	761
No Alcohol	144	4,189	No Heroin	145	4,416

SOURCE: National Institute on Drug Abuse 1984.

The higher than expected frequency of alcohol:PCP-, and heroin:PCP-related deaths may be the result of an interaction of the combined substances. Balster (this volume) anticipated an interaction of the combined substances when he reported "PCP very markedly enhances the effects of classical depressant drugs, including barbiturates and ethanol."

The higher than expected frequencies of alcohol:PCP- and heroin:PCP-related deaths also would have occurred if the combinations were preferred by the users. The motivation may involve the injection of heroin to moderate the adverse effects of PCP, or the use of PCP to ease the pain of heroin withdrawal. Another explanation assumes a stimulant effect of PCP. The use of stimulants, especially cocaine, with heroin is increasingly popular among heroin users (Kozel et al. 1982).

Many of the PCP-related deaths were not the result of overdose or drug interaction or reaction, but the direct result of some external event. The percent of cases involving a manner of death of "drug and external event" increased from 31.3 percent in 1976 to 43.4 percent in 1983 (National Institute on Drug Abuse 1984). According to Kozel and Husson (1981), in a report on a series of 104 PCP-related deaths in Los Angeles, 54 were homicides, 29 were accidents, and 14 were accidental drug overdoses; the remainder were reported as suicides. The 54 homicides were not deaths resulting from PCP, but were the result of some event, such as a gunshot wound or strangling, in which the victim was found to have been using PCP. Of the 29 accidents, 18 were drownings and 5 were automobile accidents, while other accidents were the result of various other causes, such as, a fall or cut. The various manners of death reported in PCP-related deaths are consistent with observed symptoms of disorientation and violent aggressive behavior.

CONCLUSION

In general, PCP indicators increased between 1973 and 1978/1979, declined between 1978/1979 and 1981, then increased again through 1984. The increase is predominantly among older, over age 20 years, former users, rather than among young and new users. Nonetheless, PCP is the most popular drug of abuse among 6- to 19-year-old black and Hispanic youth with an emergency, in some cities. The age of emergency room patients presenting for PCP-related problems increased between 1976 and 1983, and there was an increasing proportion of emergencies occurring among blacks during the same period. Certain cities, such as Los Angeles, Washington, D.C., and New York, have more PCP-related emergencies per 100,000 total emergencies than other metropolitan areas of the country.

The number of alcohol:PCP- and heroin:PCP-related deaths was higher than expected. Users may prefer taking these drugs in combination, or there may be an interaction in the effect of the combinations. Many of the PCP-related deaths are the consequence of some external event rather than a direct consequence of the drug itself.

FOOTNOTES

1. DAWN is a morbidity and mortality information system, funded by the National Institute on Drug Abuse, in which data are collected from a sample of more than 800 hospitals located in 27 major metropolitan areas in the continental United States, from a National panel of hospitals outside of these areas, and from medical examiners/coroners located in 26 major metropolitan areas.

2. Medical examiner data from New York City are not included because of incomplete reporting.

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PCP and Crime: Just Another Illicit Drug?

Eric D. Wish

AVAILABLE LITERATURE

The scientific literature on PCP use and crime is sparse and consists mainly of case studies of persons who have committed violent, often bizarre acts after ingesting the drug (Siegel 1978; Siegel 1980; Fauman and Fauman 1982). Death from drowning, often in small amounts of water, has been a frequent cause of PCP-related death in California, and the media's emphasis on such extreme events has helped to increase the drug's notoriety.

PCP is easily synthesized and inexpensive. One should therefore not expect to find the need for funds to purchase PCP to be the strong motive for committing income-generating crimes that exists for users of more expensive drugs like heroin and cocaine. A potential link between PCP use and violent, impulsive crimes against persons is often hypothesized, because some users appear to become so disoriented from the drug that they commit extraordinary aggressive acts. One study of drug use and crime, in 112 boys (mean age of 15 years) committed to a training school, reported that abusers of PCP had a greater number of offenses against persons (e.g. rape, assault, robbery) than did abusers of any other drugs (Simonds and Kashani 1980). Level of PCP use was not significantly related to rates of property offenses. However, because many of these boys abused multiple drugs, and only 17 percent of the offenses against persons were preceded by use of any drug within the prior 24 hours, it is not possible to attribute the violent acts directly to the use of any of these drugs, including PCP.

The potential link between PCP use and violent crime is reflected in the legal debate regarding the defense of diminished capacity for crimes committed by persons intoxicated with PCP (Baxley 1980). It is argued that persons who have committed violent crimes under the influence of PCP are not legally responsible for their acts because they have an inability to have criminal intent. One reviewer concluded:

> The PCP-intoxicated user's orientation toward the immediate present and disregard for long range consequences of his/her behavior would make it difficult for him/her to premeditate criminal acts. But the tendency to react strongly to sensory stimuli in the immediate environment, the inclination to refer everything to oneself that often develops into paranoia, and the need to do something due to intense psychomotor stimulation can all produce an aggression-prone individual. Once again it must be emphasized that emotionally stable people under the influence of low doses of PCP probably will not act in a way very differently from their normal behavior. (Siegel 1978, p. 285, emphasis added)

The percentage of all PCP users who become intoxicated and commit violent acts is unknown. As the statement above implies, however, one would suspect that only a small minority of disturbed users reach such a stage, In a recent review of the literature concerning PCP use and crime, the authors concluded that:

> PCP is used by persons who tend to be multiple drug users. PCP is one of the more common drugs found in arrestee populations, although its prevalence varies considerably by jurisdiction. An unknown, but probably very small percentage of users suffer extreme PCP-induced intoxication and disorientation and commit bizarre, often violent acts. Much more research is needed to identify the extent of these problems in users, and to learn how personality, other drug use, and the quality and quantity of PCP ingested contribute to the occurrence of violent behavior. (Wish and Johnson, in press)

PROBLEMS IN THE STUDY OF PCP AND CRIME

A principal reason for the paucity of rigorous studies of the association between PCP use and crime is the quantity of methodological problems that must be surmounted. Researchers may not be able to depend upon the accuracy of self-reported PCP use. First, PCP is often sold under a variety of names and may be misrepresented as other drugs. Thus, users may be unable to report accurately whether they have taken the drug. Second, because marijuana is sometimes laced with PCP, users may be unaware that they have consumed the drug. Third, users of PCP may concurrently use other illicit drugs. Disentangling the effects of each drug on behavior is therefore difficult, if not impossible. Finally, to assess the impact of the drug on individual criminal behavior, one must have some idea whether PCP was present (or biologically active) in the body near the time of the crime. In view of these methodologic problems, the most basic questions regarding the prevalence of PCP use in offender populations, the characteristics of arrestees with the greatest risk of PCP use, and the types of crimes they are charged with, have gone unanswered.

Our current study of drug use and crime in arrestees in Manhattan overcame some of these measurement problems and enabled us to address some of these basic questions regarding PCP use and crime. The recent use of PCP (as well as other drugs) in male arrestees was measured by a urinalysis of a specimen obtained within hours after arrest. We therefore did not have to rely on each person's accurate report that he had taken PCP. We shall use the urinalysis test results, with information from interviews with the arrestees, and from their criminal records, to describe the prevalence of PCP use in arrestees, the demographic characteristics of users and the types of offenses for which they are arrested. The next section describes our study of drug use and crime in arrestees in Manhattan.

STUDY OF ARRESTEES IN NEW YORK CITY

Since 1971, the District of Columbia has routinely used urinalysis tests to detect recent drug use in all arrestees held in the D.C. Superior Court lock-up prior to arraignment. This program has been a valuable source of epidemiologic data regarding drug abuse trends, and drugs and crime associations (Wish et al. 1980; Forst and Wish 1983; Toborg 1984). Our current study was designed to determine whether a similar program of urine testing of arrestees could be established in New York City, and whether arrestees identified by urine tests to be current users of hard drugs are at greater risk for pretrial rearrest and/or failure-to-appear (for scheduled court appearances) than are arrestees not detected to be using drugs. We approached 6,406 male arrestees processed in the Manhattan Central Booking facility between March and October, 1984, and asked each to participate in the voluntary research.

All persons arrested anywhere in Manhattan for more than the most minor crimes are brought to Central Booking for fingerprinting and processing before they are arraigned in court. We did not have the resources to approach all persons who appeared in Central Booking during the study period. Because this research was intended to focus on serious offenders who would have substantial pretrial periods, priority was given to approaching persons charged with Felony offenses. We also excluded persons charged with offenses that were so minor that they were not detained in Central Booking prior to their arraignment.

For these reasons, about three-quarters (77 percent) of the persons in our sample were charged with felony offenses. A drug-related offense (sale or possession) was the top charge at arrest for 20 percent of the sample. Comparisons of the characteristics of our sample members with those of all males processed in Central Booking during the months that we collected data indicates that 58 percent of all males were charged with a felony, and 32 percent with a drug-related offense. Thus, our findings apply to all male arrestees processed in the Manhattan Central Booking facility, overweighted for felony offenses and underweighted for drug-related offenses.

Response rates for this voluntary, confidential research were high. Approximately 95 percent of the eligible persons approached answered the interview questions regarding their drug use and treatment experiences. Of those interviewed, 84 percent agreed to provide a urine specimen for analysis. The specimens were sent to the New York State Division of Substance Abuse Services laboratory in Brooklyn for analysis. Each specimen was tested using thin layer chromatography (TLC), a widely used general screen for about 20 drugs. In addition, each specimen was tested for alcohol by gas chromatography, and for opiates, PCP, cocaine, and methadone using the more sensitive EMIT tests. Information regarding criminal history and recent arrests was obtained from criminal justice records. Additional information regarding the study methodology and some preliminary findings may be found in Wish and Johnson (in press).

FINDINGS

In this section we first describe some background and case characteristics of the arrestees, and the types of drugs found in their urine specimens. We next describe the persons found to have a urine test positive for PCP and compare them with arrestees having other urine test results.

Characteristics of the Sample Members

Because our subsequent analyses are based upon the urine test results, we present information here only from the subset of arrestees who provided a urine specimen (n=4,847). Other analyses (not presented here) indicate that the persons who provided a specimen were virtually identical on these characteristics to the entire group of persons approached in Central Booking (n=6,406).

As one might suspect, the modal age range of the arrestees was the twenties. Almost one-half of the men (47 percent) were age 25 or less, and only 19 percent were 36 or older. The majority of the men (54 percent) were black, with a sizable minority (33 percent) being of Hispanic descent. Ten percent of the sample members were white. Education was limited in the men. More than one half (56 percent) never completed high school or its equivalent (GED). Only 15 percent had received some education at the college level.

Larceny and robbery were the most common top arrest charges in the sample. Each of these charges accounted for 14 percent of the arrests. (Arrestees are often charged with multiple offenses, and tend to plead guilty to, or be convicted of, a lesser offense. The top charge is the crime the police officer thought the arrestee had committed.) Possession of drugs was the top charge for 13 percent of the sample, and the sale of drugs accounted for an additional 7 percent. As we noted earlier, the percentage of arrestees charged with a drug-related offense would have been much higher had we not limited their recruitment into the sample. Nine percent of the sample were charged with possession of stolen

property, 10 percent with assault, and 7 percent with burglary. The remainder of the sample (about 26 percent) consisted of a variety of charges, none of which was found in more than 5 percent of the arrests.

Urinalysis Test Results

Table 1 provides the urinalysis test results for the 4,847 arrestees. While PCP was tested for by an EMIT test only, cocaine, opiates and methadone were tested for by both EMIT and thin layer chromatography (TLC). (The EMIT test for opiates is not specific to morphine, the metabolite of heroin, and can detect the recent use of a variety of opiates. A specimen positive for opiates is most likely to indicate the use of heroin in this population, however.) Our analyses will use only the results from the EMIT tests, because we have learned that the TLC general drug screen is less sensitive for detecting recent use of these illicit street drugs (Wish et al. 1983; Wish et al. 1984).

TABLE 1. *Drugs detected in the specimens of male arrestees (n=4,847)*

Drug Detected by EMIT	Percent	
Cocaine	42	
Opiates	21	
PCP	12	
Methadone	8	
Number of Drugs Found (of Four)		
None	44	
One	33	
Two	18	56
Three or more	5	
Total	100	

A test positive for opiates, cocaine, or methadone probably indicates that the drug was used within the prior 24 to 48 hours. There is some possibility that PCP, like marijuana, may be detected in the urine days or weeks after the last use (Khajawall and Simpson 1983). Thus, a test positive for PCP indicates that the drug was present in the body at the time the specimen was obtained, but does not necessarily mean that the arrestee last used the drug near the time of the crime or the arrest. This may not be too important, however, since the presence of the drug in the body implies a potential effect upon the person.

Cocaine was the drug most likely to be found in the arrestees; 42 percent had a test positive for cocaine. The next most frequently detected drug was an opiate (21 percent), followed by PCP (12 percent). Only 8 percent of the arrestees were positive for methadone. (The urine test could not, of course indicate whether the methadone was obtained legally, by a prescription, or through illegal channels.) The prevalence of PCP in the arrestees in Manhattan contrasts with its prevalence in arrestees in Washington, D.C. In recent years, PCP has been the drug most frequently detected in arrestees in Washington (found in more than 30 percent), followed by cocaine. As-table 1 indicates, 56 percent of the tested arrestees were positive for at least one drug. (This percentage is similar to the statistics currently coming out of the D.C. testing program, in which 55 to 65 percent of all male and female arrestees were positive for a drug.) More than one drug was detected in almost one-fourth (23 percent) of the specimens.

Specimens containing PCP were somewhat less likely to contain other drugs than were specimens containing any drugs other than PCP. Forty-nine percent of the PCP-positive specimens contained another drug, compared with 52 percent of the cocaine positives, 73 percent of the opiate-positive specimens, and 73 percent of the methadone positive specimens. The drug found most frequently with PCP was cocaine; 35 percent of the PCP-positive specimens contained PCP and cocaine. The third most frequent combination found in specimens containing PCP was PCP, cocaine, and an opiate (8 percent). Opiates and methadone were rarely detected in specimens containing PCP, probably because PCP was most likely to be detected in younger arrestees, while opiates and methadone were concentrated in older arrestees. As figure 1 shows, PCP was most likely to be detected in arrestees between the ages of 16 and 25. In fact, PCP use was the only drug use that peaked for those in their early twenties. Cocaine, and especially opiates and methadone, tended to become more prevalent in arrestees above age 20, and to peak for those in their thirties.

Arrest Charges Associated With a PCP-Positive Specimen

If PCP use were associated with a greater risk of violent, unpremeditated crimes, one would expect persons charged with assault, murder, or public disorder to be most likely to be positive for PCP. As table 2 shows, however, persons charged with robbery were most likely to be detected to be PCP users. Persons charged with drug-related offenses, larceny, and fare beating were next most likely to be positive for PCP. Persons charged with assault, sexual assault, public disorder, and murder actually were below the average (12 percent) likelihood of a PCP-positive test for the entire sample. PCP users appeared to be arrested for the more goal-oriented, income-generating offenses rather than for bizarre, unpremeditated crimes.

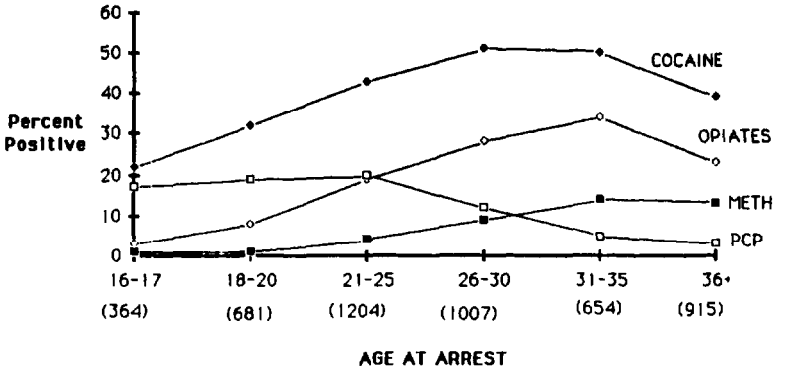

FIGURE 1. *Percent of male arrestees with a positive urine test, by age*

TABLE 2. *Percent of persons charged with each offense who had a urine teat positive for PCP (n=4,833)*

Offense Charged	Frequency	Percent Positive for PCP
Robbery	676	18
Possession of drugs	615	16
Sale of drugs	355	15
Larceny	667	14
Fare beating	98	14
Weapons	157	11
Poss. of stolen property	474	11
Burglary	348	10
Sexual assault	79	10
Public disorder	108	10
Assault	506	10
Stolen credit card	56	9
Forgery	56	6
Murder/manslaughter	64	5
Gambling	147	5
Fraud	54	4
Criminal mischief	66	4
Other offenses	269	8

We found that PCP use is concentrated in the younger arrestees and that almost one-half of the PCP-positive arrestees were also positive for another drug. It is, therefore, possible that the PCP-crime associations in table 2 could have been partially confounded by the youthful ages and multiple drug use of PCP users. (For example, PCP users, being predominantly young, may be more likely to commit robbery merely because youths tend to specialize in this crime.) The analyses in the remainder of this paper examine PCP use and crime, taking into account these possible confounding variables.

We divided our sample into four groups: (1) persons negative for all drugs (D- , n=2,153); (2) persons positive for PCP only (PCP only, n=309); (3) persons positive for PCP and another drug (PCP + other, n=295); and (4) persons negative for PCP but positive for another drug (D+, no PCP, n=2,090). As table 3 shows, both groups of PCP-positive arrestees were younger than the other arrestees.

TABLE 3. *Age at arrest in the four groups of arrestees (n=4,821)*

	Urine Test Results			
Age	D- (n=2,141) (In Percent)	PCP Only (n=307) (In Percent)	PCP + Other (n=294) (In Percent)	D+, No PCP (n=2,079) (In Percent)
16-20	27	28	25	13
21-25	22	37	42	24
26-30	17	17	22	25
31+	34	8	11	38
	100	100	100	100
Mean age (years)	28.4	22.9	24.3	29.2

Even the PCP-positive arrestees who were also positive for another drug were rarely over age 30 (11 percent). The PCP-positive arrestees had average ages in their early twenties, while the other arrestees had average ages in their late twenties. Age will therefore continue to be a possible confounding factor to be allowed for in comparisons of drug use and crime in the four groups of arrestees. The remaining section of this paper examines the drug use and crime patterns for these four groups of arrestees. We will especially be looking at whether the two PCP-positive groups of arrestees tend *to* resemble the D- arrestees or the other hard drug users.

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Self-Reported Drug Use in the Four Groups of Arrestees

During the brief interview at Central Booking, we asked each arrestee several questions about his prior use of drugs and his treatment needs. Table 4 presents these results.

TABLE 4. *Self-reported drug use and treatment, by urine test result (n=4,847*)*

	Urine Test Results			
	D-	PCP Only	PCP + Other	D+, No PCP
Ever used (percent)**				
Marijuana	56	79	80	76
Cocaine	22	34	48	60
PCP	8	36	33	8
Heroin	10	11	24	48
Used PCP within 24 to 48 hours before arrest (percent)	1	14	18	1
Mean age first felt dependent on PCP	18.3	19.5	19.1	17.8
(Base N)	(18)	(26)	(27)	(9)
Needs any drug abuse treatment now (percent)	10	8	24	35

*Group n's vary slightly because of missing information.

**Percentages may add to more than 100 because of multiple drug use.

Lifetime use of illicit drugs varied considerably in the four groups, but the nature of the differences depended on the drug. For example, more than three-fourths of the arrestees in the three drug positive (D+) groups reported having used marijuana, compared with only about half (56 percent) of the D- arrestees. Cocaine use was relatively rare in the D- arrestees (22 percent), more prevalent in the two PCP-positive groups (34 to 48 percent), and most prevalent (60 percent) in arrestees detected to be using drugs other than PCP. The high level of reported cocaine use in the latter group is probably related to our finding that these persons were older; many had a urine test that was positive for cocaine.

The two groups of PCP-positive arrestees were four times more likely to admit using PCP at least once than were persons who were D- or positive for drugs other than PCP. Still, only about one-third of the PCP-positive arrestees admitted to using PCP. One reason for this discrepancy is intentional underreporting of PCP use by the arrestees. (Underreporting of illicit drug use and other deviant behaviors is common in persons interviewed in the potentially threatening criminal justice environment. In contrast to research conducted in relatively neutral research settings, it is difficult to convince apprehended persons to disclose sensitive information about themselves in Central Booking, even in a confidential and independent research project such as ours.) The fact that many persons are unaware that they have been given PCP is another possible reason for this lack of concordance. Self-reported heroin use was rare in the D- and PCP-only groups. Consistent with the urine test results, heroin use was most frequently reported in the other two groups of arrestees.

Both groups of arrestees who were positive for PCP were more likely to report using the drug in the 24 to 48 hours prior to arrest than were arrestees in the other two groups (14 percent and 18 percent vs. 1 percent). Again, however, only a small minority of the PCP positives reported recently using the drug. (Arrestees are even more likely to underreport illicit behaviors that occurred in the very recent past.) Fewer than 10 percent of the arrestees in the four groups who reported using PCP at any time in their lives reported *ever* feeling dependent on the drug. However, of those who did report such feelings, it is clear that the average age of onset for feelings of dependency was in the late teens.

Few arrestees said that they currently needed drug abuse treatment. There was a clear difference here between the two PCP-positive groups. The PCP-only arrestees were as unlikely to indicate a need for treatment as were the D- arrestees. The PCP + other arrestees were three times more likely to report that they needed treatment (24 percent vs. 8 percent). This was still less than we found among the persons positive for drugs other than PCP (35 percent). These findings are consistent with the fact that drug dependence and treatment were more common in older persons abusing cocaine and/or heroin, drugs that were detected in the urine of the latter two groups of arrestees.

Our findings suggest that the arrestee who is detected by urinalysis to be using only PCP is more involved with drugs than the arrestee who is negative for all drugs, but is less seriously involved than the arrestee detected to be using PCP and other hard drugs. The arrestee who is detected by urinalysis to be using only PCP is typically younger than hard drug use arrestees, and may be an especially good candidate for interventions that may prevent his progression to more serious drug abuse.

Criminal Behavior in the Four Groups

Table 5 presents the top charge at arrest and other criminal background information (obtained from criminal justice records) for the four groups of arrestees.

TABLE 5. *Arrest charge and criminal history, by urine test result (n=4,847*)*

	Urine Test Results (Percent)			
	D-	PCP Only	PCP + Other	D+, No PCP
Top charge at arrest**				
Robbery	14	22	19	12
Larceny	14	14	17	14
Poss. of drugs	7	13	20	18
Assault	15	11	5	7
Stolen property	9	8	9	11
Burglary	7	6	5	8
Drug sale	5	6	12	10
Other	29	20	13	20
	100	100	100	100
Prior felony conviction	15	28	27	29
Prior misdemeanor conviction	34	47	59	55
Had 2+ arrests within 3 years***	35	60	70	55

*Group n's vary slightly because of missing information.

**Specifies all charges applied to at least 5 percent of either PCP group.

***Counts arrests In a J-year period that extends before and after the index arrest: excludes the index arrest at which the person was interviewed.

We found that the group of arrestees who were positive for PCP only were most likely to be charged with robbery (22 percent). While assault was the most common charge for D- arrestees, it was the fourth most frequent charge for the PCP-only arrestees, and was even less common in the arrestees detected to be using hard drugs.

Table 5 also presents information about PCP-positive arrestees' involvement with the criminal justice system. The D- arrestees were least likely to have had a prior felony or misdemeanor conviction, or two or more other arrests within 3 years of their current arrest. The criminal records of the three drug-positive groups tended to be quite similar, however, and indicated a greater level of prior criminal justice contacts. More than one-fourth of these groups of D+ arrestees had a prior felony conviction, one-half had a prior misdemeanor conviction, and over half had multiple arrests within 3 years of their current arrest. Most important, the criminal backgrounds of the arrestees positive for PCP alone were similar to those of persons found positive for the harder drugs (opiates, cocaine, or methadone).

We were most interested in the PCP-using arrestees' apparent affinity for robbery. It occurred to us that there were two competing hypotheses that could explain this association: (1) our findings could simply reflect the fact that youths tended to be charged with robbery and that many of the PCP-positive arrestees were younger; (2) perhaps many of the persons positive for PCP had last used the drug weeks before the arrest (or crime). Would robbery still be the most prevalent crime in persons known to have used PCP in the day or two prior to arrest? To test for these possibilities we first looked at the proportion of arrestees, by age, in each group, who were charged with robbery. Figure 2 presents these findings (n varies from 38 to 790).

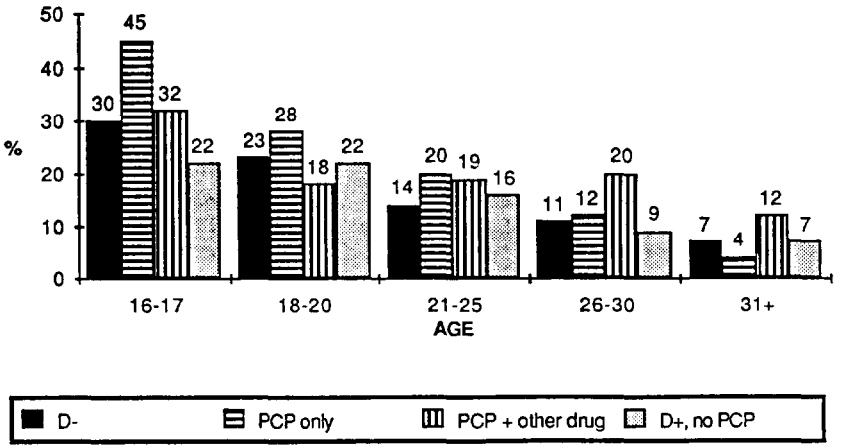

FIGURE 2. *Percent of arrestees charged with robbery, by urine test result and age*

Within each age group, at least one of the groups positive for PCP was the most likely to be charged with robbery. On the other hand, the size of the differences depended on age. Arrestees 16 to 17 years of age and positive for PCP only were more likely to be charged with robbery than any other group of arrestees at any age level. With increasing age, the PCP-only arrestees' higher likelihood of robbery decreased. At the higher age levels, the arrestees positive for PCP plus other hard drugs were those most likely to be charged with robbery. Thus, although PCP users had more arrests for robbery at all age levels, in the younger ages, when PCP is most likely to be found in an arrestee, persons positive for PCP only are the most likely to be charged with robbery.

To examine the possibility that our findings might change if we knew that the person had taken PCP within hours of the arrest, we isolated the 96 persons who reported using PCP in the 24 to 48 hours prior to arrest and were positive for PCP by the urine test. We found that robbery was still the most frequent offense charged. Twenty-three percent of these persons were charged with robbery; the percentage was identical for persons positive for PCP only, and those positive for PCP plus other hard drugs. The next most frequent offense charged was the possession of drugs (20 percent), followed by larceny (14 percent). A charge of assault was found for 12 percent. Thus, even in a group of PCP-positive persons who admitted to using PCP shortly before arrest, we found that robbery was the most frequent offense charged.

This information suggests that the PCP-positive arrestee in Manhattan looks much like other drug-using arrestees. Far from being charged with assaults or bizarre types of offenses, PCP-positive arrestees are most likely to be charged with robbery, larceny, and other drug offenses.

DISCUSSION

This section presents some of the implications of our findings. Where possible, we will discuss comparable information from the urine testing program in Washington, D.C., in order to provide a larger context for our findings.

Perhaps of most significance, we have found that PCP use is relatively common in an arrestee population. Twelve percent of the male arrestees in Manhattan and about 30 percent of arrestees in Washington, D.C. have a urine test positive for PCP. In New York, this would translate into approximately 12,000 PCP-positive persons arrested and processed in Manhattan Central booking each year. Furthermore, these are probably minimum estimates of the number of users, since the urine tests failed to detect the many users who had not taken the drug soon before arrest.

The fact that PCP is the drug most frequently detected in the urines of arrestees in Washington, D.C., but only the third most frequently detected drug in Manhattan, implies that there may be

considerable differences in the use of this drug in different regions of the country. We cannot say whether these differences are the result of fads in drug use, accessibility of the drug, or some other factor.

Another implication of the large numbers of arrestees who use PCP is that only a small percentage of users probably experience the bizarre, violent behavior that is often attributed to PCP. If more than one or two percent of the arrestees in New York City and Washington, D.C. were to experience violent psychotic-like behavior when they use PCP, the police and treatment resources in these cities would be overburdened by the problem. Furthermore, these estimates do not include the many users of PCP who are never arrested.

PCP use is concentrated in young offenders under age 25. Since opiates and methadone are largely found in older arrestees, it would appear that PCP may be an excellent marker for identifying the drug-involved offender before he progresses to other hard drugs. Our findings indicate that the PCP-positive arrestee in New York City is no stranger to the criminal justice system. He is likely to have a history of prior arrests and convictions. By identifying the young PCP-using arrestee at entry to the criminal justice system and by applying suitable constructive interventions, it may be possible to deter him from progressing to the more serious hard drug habits found in older arrestees.

Far from finding a preponderance of charges for bizarre, violent offenses in PCP-positive arrestees, we unexpectedly found that their most frequent offense was robbery. This affinity for robbery remained at all age levels, and was found even when we selected out the few persons in our sample who were positive for PCP and admitted taking the drug within hours of arrest. One possible explanation for this association between robbery and PCP use is that both behaviors require a willingness of the person to risk his/her physical and/or mental well-being. If this is the case, the PCP-using robber may be an especially dangerous offender. A top charge of robbery accounted for only a minority of the PCP-positive arrestees. Following the robbery charge, larceny, drug offenses, and assault were the most frequent charges for PCP-positive arrestees. Comparable analyses of information from the testing program in Washington, D.C. confirm these findings. Drug offenses, robbery, possession of stolen property, and assault were the most frequent offenses charged for persons positive for PCP only, in that city.

Our findings indicate that many PCP users are apprehended for goal-oriented, income-generating crimes. We did not find a preponderance of the types of offenses one might expect from persons commiting the bizarre, irrational acts ascribed to PCP users. One possible explanation for these findings is that PCP use in these offenders is so light that PCP intoxication is rare. It is probably true, as Siegel (1978) suggested, that emotionally stable

persons taking low doses of PCP will behave the way they would normally act. Because the criminal backgrounds and the drug abuse histories of many PCP-positive arrestees were similar to those of other drug-positive offenders in our sample, we suspect that the detection of PCP use in an arrestee is the same indicator of intense criminal activity that the presence of cocaine and heroin is (Wish and Johnson, in press).

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Neuropsychological Assessment of Phencyclidine Abusers

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The behavioral testing of phencyclidine (PCP) abusers by means of neuropsychological (NP) assessment serves as a bridge between neuroscience research into brain effects of PCP and the treatment and rehabilitation of the drug abuser in the community. The systematic individual NP case study includes: (1) a critical review of historical/developmental antecedents to an individual's drug use; (2) observations pertaining to a mental status evaluation, performance on full-scale intelligence, NP, and screening achievement tests; and (3) a diagnostic interview focusing on educational ,occupational, and legal implications of the evaluation.

Due to the subtle and gross effects found in brain functioning of the PCP abuser, assessment information can be critical to developing rehabilitation plans, successful psychotherapy and/or behavioral treatment programs, and total treatment objectives. The development of briefer screening assessment techniques, in lieu of the 6- to 8-hour full NP evaluation, has been recommended for particular clinical populations, to provide a cost-effective service while still obtaining important clinical information. Nevertheless, a significant amount of professional time and effort continues to be spent providing treatment to PCP and other polydrug abusers: time and effort that prove unsuccessful, possibly due to the lack of any form of objective assessment.

PURPOSES OF THE REVIEW

The purposes of this review are twofold: (1) to describe the contents and rationale of an abbreviated (2- to 4-hour) NP evaluation of PCP abusers; and (2) to explain the usefulness of this evaluation in relating critical information concerning an individual's pattern of higher cortical strengths and weaknesses to the therapist's treatment and rehabilitation decisions. Specifically, we discuss the nature of NP tests and their value in assessing PCP abusers, and the relevance of history-taking of certain premorbid developmental variables or factors pertinent to a drug abuse lifestyle, e.g., toxicity-related transient organic brain syndromes,

closed head injuries (CHI), etc. Further, this paper summarizes patterns and trends in the predrug histories and NP test data obtained in a pilot sample of PCP-polydrug abusers. Finally, four case studies are presented to illustrate the diversity of effects that PCP abuse may have on persons with varied predrug-use characteristics and with varied patterns of drug abuse.

HISTORY OF THE NP EVALUATION IN CHEMICAL DEPENDENCY

In the early stages of clinical neuropsychology, Reitan (1955) and others demonstrated the utility of NP tests as instruments sensitive to subtle forms of brain dysfunction. Medical specialists, particularly in neurology, have acknowledged the need to quantify and elaborate on "soft signs" of brain dysfunction. Despite rapid advances in radiological (e.g., computed tomography) and EEG technologies, the medical model approach alone has been insufficient for full evaluation of impairment of higher cortical functions, especially complex sensory, cognitive, and coordinated motor behavior. Parsons and Farr (1981), in their review of research on alcohol and polydrug abuse, illustrated that a careful NP evaluation can provide valuable information on an abuser's verbal and nonverbal intelligence, complex motor and sensory functions, and adaptive "everyday functioning" skills (Heaton and Pendleton 1981). From these NP data, both subtle and gross impairment of higher cortical functions can be inferred.

At this time, the most thorough and widespread use of NP tests, in the field of chemical dependency, has been to evaluate effects of alcohol abuse on higher cortical functions. Though similarities exist between alcohol abusers and other drug abusers, there are many ways in which these two groups differ. Grant et al. (1979), Mider and Lewis (1981), and Parsons and Farr (1981) have applied knowledge gained from research and clinical use of NP test results obtained from evaluation of alcohol abusers, to the study of more complex polydrug and PCP abusers.

COMPLICATIONS IN THE EVALUATION OF THE PCP ABUSER

Kolarik and Vayhinger (1983) implied that any neurological investigation into PCP abuse must begin by addressing drug identity and purity problems inherent in the "street supply" of PCP. Analysis of street samples of PCP reveal significant chemical differences, with indications that one-third to one-half of all sampled PCP illegally distributed is contaminated with chemical agents that differ significantly from pharmaceutically manufactured PCP. The issue of the chemical nature of the drug presumably ingested as PCP is further complicated by street sales of chemicals that often have little or no chemical resemblance to PCP, but may grossly mimic PCP's physiological and psychological effects. Thus, NP deficits identified in individual PCP abusers may be due to other unknown substances that are toxic to the brain and central nervous system (CNS). In addition to these pharmacologic issues, the vast differences in patterns (frequency, amount, and types) of drugs

used by PCP abusers further complicates the evaluation of suspected PCP-induced toxic organic brain syndromes.

To date, nearly all published studies of human PCP use have shown that most PCP abusers are not single-substance abusers. Specifically, PCP abuse is more often part of a larger pattern of polydrug abuse, which may include the abuse of alcohol, marijuana, and cocaine. Other drugs of abuse, reported less frequently by PCP abusers, are amphetamines, barbiturates, sedative/hypnotics, opiates, and inhalants. Thus, clinical NP research on the CNS effects of PCP is complicated not only by differing characteristics of the drug itself, but also by prior and concurrent patterns of PCP and other drug use. This polydrug abuse produces indeterminable, though suspected, potentiating and addictive effects.

Although many PCP abusers have histories of normal (before-drug use) physical and psychological development, recognition of relevant historical and developmental antecedents to PCP and polydrug abuse are especially important in light of NP models that underlie the interpretation of NP test results. Adolescence, in terms of NP functioning, represents the "meeting point" of interpretive models used to understand child versus adult brain dysfunction. The child NP model presumes a developing, maturing brain in which complex cognitive and perceptual skills are being acquired and mastered. Childhood brain dysfunction is hypothesized as delaying or impairing acquisition of verbal and nonverbal skills as well as of psychological coping strategies used to deal with normal life stresses. In contrast, the NP model of adult brain dysfunction presumes a developed, mature brain, in which most skills have "peaked" in terms of acquisition and mastery. Insult to the adult brain may involve loss or impairment of previously acquired and mastered cognitive and perceptual skills as well as loss or impairment of other psychological mechanisms and coping strategies. By the onset of puberty, many basic academic (and other) skills and abilities have been acquired and mastered, but there continues to be some "fine tuning" of complex psychological functions mediated by the higher cortex.

Recent research (Mider and Lewis 1981) suggests the existence of a large subsample of PCP abusers who have premorbid histories of moderate to severe learning disabilities (LD). The genesis of LD is often associated with prenatal, birth, and early childhood factors that are postulated to have influenced or delayed the development of various higher cortical functions related to the acquisition and mastery of specific academic skills. The General Accounting Office Report to the Congress (1977) suggests a further correlation between developmental LD and juvenile delinquency (JD), a term often associated with drug abuse. The LD-JD hypothesis derives from the observation that LD is estimated to be present in 50 percent to 80 percent of the JD population, compared to estimates of LD's presence in 8 percent to 12 percent of the normal-IQ school-age population at large.

The interpretation of NP test results, in adolescents and young adults suspected of drug-induced brain dysfunction, can be a difficult task, since most NP and psychological evaluations represent a first testing, or "baseline" situation. Inferences of predrug-use levels of brain functioning often must be made using existing educational data and/or by making a premorbid optimal estimate of functioning from "best subtest" IQ scores. Thus, it becomes a complex diagnostic issue to determine (1) whether observed deficits on complex cognitive, sensory, and motor tasks represent a pattern of loss or impairment of previously acquired functions due to PCP and other associated drug abuse effects, or (2) whether the observed deficits represent poorly developed learning and performance skills that were impaired prior to PCP and other drug abuse. These complex diagnostic issues have important prognostic and treatment implications. For example, an individual PCP abuser may have no history of developmental learning or performance disorders; however, the toxic effects of PCP on higher cortical functions may contribute to the onset of learning disabilities "acquired" as part of a toxic organic brain syndrome. Thus, PCP-induced brain toxicity will impair skills involved in new learning and directly influence academic and vocational success.

The examination of individual NP case studies by other investigators, as well as summary results of our pilot research, suggest at least two clinically distinct populations. One subsample of PCP abusers has a developmental history of prenatal and birth complications, e.g., prematurity, anoxia at birth, or low APGAR scores, and of early childhood factors, e.g., CHI with loss of consciousness, febrile illnesses with or without convulsions, or chronic ear infections. These histories contribute to developmental learning and performance disorders. In this group, LD causes academic failure and frustrations, which in turn contribute to the development of psychological and interpersonal problems. The second subsample has little or no evidence of LD or impairment of cognitive skills necessary for academic success, prior to PCP abuse. However, this group does show evidence of impairment in skills involved in new learning, following PCP and other drug abuse. Socially, these adolescents have little or no history of associating with a JD peer group but engage in experimental or "recreational" drug use only. PCP-induced changes in personality and behavior in these adolescents are anathema to their parents and families, and sometimes even to the individual abuser.

RECOVERY OF FUNCTION

In working with PCP and polydrug abusers who have impaired everyday functioning, counselors must be ultimately concerned with the individual's ability to recover. Objective prediction of recovery of function, using NP tests, involves a baseline evaluation and at least one repeated assessment. Patterns of NP strengths and deficits in the two or more assessments may then be compared. Clinical inferences can be made, describing skills that show relative permanence of deficit (with no change on repeated measurement), or

skills that show relative recovery of function (with NP test score improvement).

After drug abstinence has been established, the subgroup of PCP abusers with no premorbid history of brain dysfunction or LD would be expected to show the least impairment on NP tests and have the best prognosis for recovery of lost or impaired functions. However, case study reports utilizing NP assessment in evaluating PCP abusers find highly idiosyncratic effects of PCP, as measured on higher cortical functions. Specifically, NP case studies have shown moderate to severe impairment on NP tests in individuals with histories of minimal use. Conversely, there is another group of PCP abusers who show only borderline to mildly impaired NP functioning subsequent to 1 or more years of chronic, moderate to heavy PCP abuse.

Similar findings have been noted in NP case studies of PCP abusers after 6 months or more of abstinence from all drugs of abuse. The less frequent the PCP use, the better the prognosis usually is for lost or impaired higher cortical functions to recover, following a period of drug abstinence. However, there are instances of individual PCP abusers who show moderately to severely impaired performances on NP tasks after months of abstinence, following light or "experimental" PCP use. As indicated above, these mixed findings may be due to the actual chemical nature of what is presumed to be PCP, as well as to additive and potentiating effects from using PCP and other drugs. Other idiosyncratic differences in the body's ability to metabolize PCP and related chemical contaminants occur among individual PCP abusers. Human and animal neuroscience research of PCP effects on neurotransmission may enhance the understanding and interpretation of NP test results.

An analogue to drug-induced CNS dysfunction suggested by Parsons and Farr (1981) is the dysfunction seen in aging. Reitan (1973) first conceptualized the "brain age quotient" (BAQ), a combination of Wechsler Adult Intelligence Scale-Revised (WAIS-R) and Halstead-Reitan Battery (HRB) subtests as representing behavioral manifestations of impaired brain functioning that occur as a normal consequence of aging. The BAQ pattern appears surprisingly similar to deficits resulting from alcohol and polydrug abuse. Because they reflect impairment in adaptive abilities necessary to cope successfully with everyday functioning, BAQ test deficits may be good prognostic indicators of diminished potential for completing treatment and/or of drug and alcohol recidivism. Serious clinical and research consideration of this hypothesis may lead to more revealing NP interpretations, especially since PCP abuse may be far more devastating to NP functions than are alcohol and other polydrug abuse.

RATIONALE FOR BRIEF NP ASSESSMENT WITH PCP ABUSERS

Due to drug treatment program budgetary constraints and the relative unavailability of clinicians having expertise in the use of

NP assessment techniques, little or no psychological or NP evaluation is currently employed. It is believed that the lack of knowledge of the PCP abuser's pattern of higher cortical strengths and deficits is responsible for a vast majority of current treatment and program failures. This supposition is in marked contrast to blaming the individual abuser or drug counselor for treatment failures and recidivism. For an individualized treatment and rehabilitation plan to be effective, both the PCP abuser and the counselor should have a thorough understanding of that individual's pattern of higher cortical strengths and deficits. The following sequence of events is not uncommon. First, many counselors and therapists are predominantly trained in counseling techniques that rely heavily on use of verbal concept formation. However, results of NP case studies, as well as research into "group" differences among PCP abusers, suggest that it is not uncommon for verbal abstraction skills to be moderately to severely impaired as a result of PCP abuse. Regardless, the PCP abuser is unwittingly placed into a treatment program where success in the therapy or counseling session depends implicitly on reliance on an impaired or defective skill. The subsequent treatment failure and return of the PCP user to a drug-use lifestyle, away from achieving and maintaining abstinence, is frequently attributed to client "resistance" or the therapist's lack of skills.

Historically, the HRB NP test, the most widely used and well-validated of all NP test batteries, takes from 6 to 8 hours for complete administration. Reducing an established test battery to a 2- to 3-hour structured assessment procedure requires the use of selected subtests: those most sensitive to PCP-induced brain dysfunction. The development and validation of briefer screening batteries, which represent a reduction in the total number of subtests used, professional time, and expense is an emergent trend (Hartlage and Mains 1982, Reynolds et al. 1983). Based on our literature review and results of a pilot sample study of 30 PCP and polydrug abusers, the following subtests are recommended for inclusion in a brief NP assessment battery.

Wechsler Intelligence Scales

Depending on the drug abuser's age, either the Wechsler Intelligence Scale for Children-Revised (WISC-R) or WAIS-R should be used to assess Verbal and Performance (nonverbal) IQ. These intelliaence scales contain subtests that have been documented. over a 20- to 30-year history of research, as being sensitive to discrete types of brain dysfunction. The NP research with adults suggests that WAIS-R Verbal IQ may estimate the efficiency of functioning of the left cerebral hemisphere. Among the Verbal portions of the WAIS-R, the Similarities subtest gives important information regarding the client's ability for verbal abstract reasoning, an important skill that underlies success in most forms of counseling and psychotherapy. The Comprehension subtest estimates the individual's knowledge of social conventions and expectations. This subtest has specific treatment implications, and relates to an

individual's capacity for understanding relationships between the components and consequences of socially acceptable behavior.

Revised Wechsler Memory Scale (RWMS)

The RWMS is included to assess the PCP abuser when specific evidence regarding verbal and nonverbal memory functions are necessary for treatment and rehabilitation planning, or when other HRB and WAIS-R performances suggest impairment of discrete memory functions. Originally, age norms for this test were generally inadequate, but Russell (1975, 1984) has developed scoring techniques and criteria that improve the clinical utility of this test.

Category Test

The Category Test involves nonverbal problem solving with complex and novel stimuli where the skills of flexibility of thinking, incidental memory, and nonverbal concept formation are implicit. Since adequate performance on this test requires the brain to function efficiently as a unified whole, the test tends to be sensitive to any impairment of higher cortical functioning. The research history of this subtest established it as the single best indicator of comprehensive brain dysfunction when compared to all other psychological and NP tests. Specific damage or impairment to frontal lobe functions is inferred when performance on the Category Test is impaired, but performances on other HRB subtests are in the average range.

Speech-Sounds Perception (SSP) and Seashore Rhythm Test (SRT)

Presented in a recorded tape format, these HRB subtests give evidence of efficiency of left and right temporal lobe functioning, respectively. Individuals with specific LD impairment in acquiring language-related academic skills, such as reading and spelling, often perform poorly on SSP. Notably, SSP deficits among PCP abusers may be due to developmentally-related as well as to PCP-induced impairments. The SRT shows impairment when there is damage or dysfunction associated with the right anterior temporal lobe. Also, this subtest contains rather significant attention and concentration components, skills often impaired as a result of PCP-induced brain toxicity, especially when the NP assessment test results are obtained with fewer than 30 days of PCP abstinence.

Trail-Making Test

Trails A is a timed task which requires graphomotor performance with a random visual presentation of a numerical sequence. Trails B, also a timed task, requires the individual to perform a similar visual-motor task, but with an additional cognitive component of alternating between a numerical and alphabetical sequence. The presence of above-average times as well as number of errors gives important information about the brain's capacity to function as a

unified whole. Left, rather than right, hemisphere dysfunction is suggested when performance on Trails B (alphabetic sequence) is much more impaired than Trails A.

Hand Dynamometer and Finger Oscillation Tasks

These tasks provide reliable information and measurement of gross and fine motor functions, respectively. It is important to realize that psychomotor functions are the basis, and therein the foundation, of all behavior. The measurement of intensity of gross voluntary motor activity (grip strength in kilograms) has been associated with the total functional efficiency of cerebral hemisphere activity. Skills of finger oscillation have been associated more specifically with the functional efficiency of the primary motor cortex. In addition to comparing functional efficiency of both sides of the body, the presence of below-average performances on these tasks may indicate gross CNS disturbances rather than specific and/or subtle functional deficits.

Test of Finger Agnosia

This subtest was included because it indicates the relative functional efficiency of somatosensory-mediated brain functions. Furthermore, difficulty with either the left or right hand on this tactile finger recognition task has been associated with disturbances of the angular gyrus, and associated with developmental dyslexia. Significant differences between the preferred and non-preferred hand also gives important lateralizing information regarding differential PCP-induced toxic effects on left versus right hemisphere parietal functions.

Wide Range Achievement Test (WRAT)

The WRAT (Jastak and Jastak 1978) provides grade equivalents and standard scores on subtests of reading (word recognition), written spelling, and written arithmetic calculations, and is included in this brief assessment battery for several reasons. An objective screening measure of academic achievement is needed to compare with an individual's self-report of highest grade completed and average report card grades. Further, functional illiteracy may suggest evidence of either developmental or "acquired" LD. And, finally, specific information on academic achievement in reading, spelling, and arithmetic are critical for rehabilitation plans for adolescent and young adult abusers, prior to recommending tutorial (remedial) academic assistance and/or enrollment in General Education Diploma (GED) classes.

SUMMARY OF PILOT FINDINGS

The above-described subtests were administered in part or in whole to 30 adolescents and young adults referred either on a voluntary or court-ordered basis for drug abuse counseling. Psychodiagnostic and developmental histories were taken--additional information

was obtained through family members when needed. These individuals ranged in age from 18 to 32 with a mean age of 24.3 years. Males outnumbered females in this sample by 3 to 1 (24 to 6). Highest grade completed in school ranged from seventh grade to college level work with a mean of 10.9 grades completed. Approximately 25 percent of this sample reported having been identified within the school system as LD and having been placed in special education classes. Nearly 90 percent of the sample reported predrug-use histories of one or more of the following: prematurity either by weight or by term, anoxia or low APGAR scores at birth, febrile illnesses, early childhood seizures or convulsions with no subsequent adolescent or adult seizure occurrences, chronic ear infections, and CHI with or without loss of consciousness. Subsequent to drug use, nearly 80 percent of the sample reported histories of at least one of the following: CHI with or without loss of consciousness, episodes of fainting and/or dizziness, blackouts, seizures, and complaints of headaches or memory difficulties.

Verbal, Performance, and Full-Scale IQ scores ranged from 67 (mentally deficient range) to 111 (bright normal range) with a mean Full-Scale IQ score of 92.5, a mean Verbal IQ of 91.7, and a mean Performance IQ of 96.2. On the whole, these results are similar to past research findings (Mider and Lewis 1981), which suggest that adolescents and young adults with histories of JD have slightly higher Performance (nonverbal) IQ than Verbal IQ. The extreme variation from individual to individual, in light of the obtained prenatal and early childhood histories, suggests that there have been impaired intellectual functions prior to drug use, as well as loss of previously acquired intellectual capacity, subsequent to PCP and other drug abuse. Furthermore, about 30 percent of the sample showed above brain-damage cutoff scores on Trails B while fewer than 10 percent showed above brain-damage cutoff scores on Trails A. This may be due either to the fact that Trails B is a much more sensitive indicator than Trails A to impairment of the brain's functioning as a unified whole, or that left hemisphere-mediated language dysfunction may occur somewhat more among PCP abusers, a finding consistent with the lower Verbal IQ than Performance IQ scores reported above.

Among the HRB subtests, the Category Test showed the most impairment in terms of total number of individuals in the sample who scored above the brain-damage cutoff score (50 errors) as recommended by Reitan (1973). More than 70 percent of the sample were in the mild, moderate, or severe impaired range on the Category Test, a finding that suggests that PCP predominantly affects the brain's capacity to function as an intact unified whole. These findings suggest significant difficulty with flexibility of thinking, incidental memory, and the ability to formulate simple and complex abstractions. These observed difficulties with changing mental set and perseverating errors despite constructive feedback form a pattern typically found with organic brain syndromes.

Compared to the Category Test, SSP and SRT results show a relatively mixed performance profile. This profile is indicative of temporal lobe impairment and may explain the idiosyncratic character of PCP-induced brain dysfunction. Other HRB subtest data suggest that parietal lobe-mediated functions are less influenced by PCP abuse, since approximately 30 percent of this sample had error-free performances on a test sensitive to finger agnosia. When finger agnosia was present, there were more errors with the nonpreferred hand (2.05 mean errors) than with the preferred hand (1.88 mean errors). Fewer than 10 percent of the sample showed performances on the hand dynamometer below the normative standards. Conversely, nearly 60 percent of the sample showed below normal performances on the finger oscillation test, a finding that suggests that fine motor dysfunction is more prevalent as a result of PCP and other drug abuse than gross motor dysfunction.

The net results of our pilot study suggest that PCP-induced brain dysfunction cannot be understood solely on the basis of the pharmacological characteristics of PCP itself. There appear to be as many individuals with histories of intermittent, light use as there are chronic, moderate to heavy abusers of PCP who show significant impairment on the NP tests.

CASE STUDIES

Case Study #1

This was a 31-year-old white married male with a 14-year history of chronic, light to heavy PCP abuse and a late adolescent history of heroin, cocaine, LSD, and marijuana abuse. Also, he drank beer in moderate to heavy amounts, at times, to enhance the effects of PCP. His wife also had a significant PCP abuse problem. Originally, both were self-referred with presenting concerns about the obsessive-compulsive nature of their involvement with PCP, financial problems, an unproductive lifestyle, and a general deterioration of physical and mental health. The couple had recently had a baby and were concerned for the child's welfare. Little progress was made in reducing the amount of PCP abuse, and, after 2 weeks and four marital counseling sessions, they did not return for additional treatment. However, due to a criminal drug-related charge, the court ordered him to obtain treatment. Child custody and other marital/familial problems were additional reasons for his compliance with drug counseling requirements and his rehabilitation plan.

The NP assessment was completed after 6 months of drug abstinence. Assessment of developmental (predrug-use history), orientation, lateral preference, and sensory-perceptual examination provided significant evidence of mixed dominance. For example, since age 5, he had played the guitar and was ambidextrous on many tasks requiring the coordination of fine motor movements. This strongly suggested that, prior to drug abuse, higher cortical functions were bilaterally mediated. Though he

reported having great difficulty with mathematics in high school, he graduated, and continued to be an avid reader. His history of employment was primarily as an adept tradesman. He was a socially uninhibited person and at times a very assertive communicator. Diagnostic interview information revealed an inherent high energy level with strong libido interests. He remembered sustaining two CHI at age 17 and 24. Further, 1 month prior to our examination, he sustained a broken jaw in a barroom altercation. Although there was no indication of concussion-like symptoms, the shear/strain effects of the injury may have caused an additional CHI.

	Preferred	Non-Pref
Signature Speed	LH:7sec	RH:15sec
Tactile Recognition	0 errors	0 errors
Sensory Suppression	0 errors	0 errors
Finger Agnosia	0 errors	0 errors
Strength of Grip	56.5 Kgs	59 Kgs
Finger Oscillation	48.5	49.0

Trails-Making A: 30 seconds 0 errors
Trails-Making B: 35 seconds 3 errors

Category Test: 67 total errors
Speech-Sounds Perception: 3 errors
Seashore Rhythm: 30 raw 1 ranked score
Revised Wechsler Memory Test:
Verbal Short-term 15. 1/2 hour 12.5
Figural Short-term 11. 1/2 hour 11.

Wechsler Adult Intelligence Scale-Revised:	
Verbal IQ	101
Performance IQ	99
Full-Scale IQ	100
Subtest Scaled Scores	
Information	10
Digit Span	10
Vocabulary	11
Arithmetic	11
Comprehension	13
Similarities	9
Picture Completion	11
Picture Arrangement	10
Block Design	12
Object Assembly	8
Digit Symbol	9

Measures of intellectual functioning were in the average range and showed little variability, except for poor performance on a test designed to measure visual and inductive reasoning skills. However, this exception was incidental , as other Performance subtest measures of visual-motor and perceptual skills requiring nonverbal abstract reasoning were at or above his age group mean. The NP tests designed to assess the brain's ability to discriminate auditory speech and rhythmic-sound information were also in the average to above-average range. Actually, these latter test scores may reflect in part avocational interests and practice in reading and music. Scores on the memory and intelligence subtest as well as a subtest of the Category Test (measuring incidental memory) indicated a full range of at least average memory functions. In contrast, his poorer performances on other NP tests and WAIS-R visual-spatial tasks, considered the most sensitive general indicators of brain impairment, suggested a mild diffuse organic brain syndrome, probably transient in nature.

Though a recent facial impact injury may have caused additional diffuse cerebral damage, the total performance seemed more indicative of chronic PCP and alcohol abuse. Specifically, the NP profile was characteristic of deficits in frontal lobe-mediated adaptive abilities. While the severity of these deficits seemed slight as compared with the mental status of others of similar

histories of abuse, many higher cortical functions may have been spared due to the premorbid bilateral representation of higher cortical functions.

Case Study 12

This was a 23-year-old black male with a 5-year history of chronic, moderate marijuana use and a 5-month history of moderate PCP abuse ending 1 month prior to the NP assessment, as certified by urinalysis reports. Further, he reported multiple personal and legal problems as a result of PCP abuse, and complained of chronic bilateral headaches, several times weekly during the last 5 years. He described these headaches as caused by an undiagnosed "brain tumor or brain cancer." Birth and prenatal history suggested that he was the victim of Fetal Alcohol Syndrome (FAS). He was reared by relatives and had minimal contact with his parents through adolescence. He withdrew from vocational high school in the 12th grade, then worked for 5 years as an attendant cashier in fast food franchises, with dependable performance, until he began to use PCP. His ambitions were to reestablish permanent employment or to join the military to receive job skill training. Further, he was ordered by the court to be on a 3-year probation with special requirements to obtain a GED and to maintain full-time employment, as contingencies in lieu of incarceration.

All NP and intelligence testing was accomplished in 1 day. The client sustained good attention throughout the examination, but was anxious about his failure to complete the more difficult sections of particular subtests. He showed a strong preference for lefthanded and ocular activity and mixed preference foot-leg coordinated motor movement. His aggregate gross and fine motor and perceptual-motor functions were characteristic of borderline-normal intact performance. There were signs of mild impairment on right-hand tactile-perceptual functions and diminished right-hand motor speed. These deficits on the right side of the body suggested some (contralateral) left cerebral hemisphere dysfunction, possibly involving more primary motor and somatosensory cortex dysfunction. Additionally, he showed test-taking behaviors often associated with organicity, such as rotations of paper and difficulty with organization of space on writing and copying tasks. However, testing of all other left and right hemisphere-mediated functions failed to identify any significant localized NP deficits. Generally, the performance on other tests designed to measure the integrity of coordinated brain functioning was in the borderline impaired range. The "borderline range" interpretation was based on a comparison of his test scores with those of standard scores of an adult normal population; his status was better than average when these test scores were compared with standard scores of an adult drug-abusing population. These NP deficits may best be characterized as diffuse in nature and the result of both developmental (predrug use) and PCP/polydrug abuse influences.

	Preferred	Non-Pref
Signature Speed	LH: 7sec	RH: 15sec
Tactile Recognition	0 errors	0 errors
Sensory Suppression	0 errors	1 error
Finger Agnosia	0 errors	2 errors
Strength of Grip	50.5 Kgs	49. Kgs
Finger Oscillation	47.0	44.0

Trails-Making A: 27 seconds 0 errors
Trails-Making B: 80 seconds 1 error

Category Test: 53 total errors
Speech-Sounds Perception: 4 errors
Seashore Rhythm: 26 raw 5 ranked score

Wide Range Achv. Test: grade equivalent
Reading 8.7 Spelling 7.9 Arith 4.3

Wechsler Adult Intelligence Scale-Revised:

Verbal IQ	79
Performance IQ	80
Full-Scale IQ	78

Subtest Scaled Scores

Information	5
Digit Span	8
Vocabulary	6
Arithmetic	7
Comprehension	6
Similarities	6
Picture Completion	9
Picture Arrangement	6
Block Design	7
Object Assembly	9
Digit Symbol	6

Mastery level skills in WRAT Arithmetic revealed errors of subtraction, division, and multiplication, and little or no understanding of fractions, decimals, or percentiles. Fatigue was assessed not to be a limiting factor in his performance because this testing was performed early in the examination. The WAIS-R yielded Verbal, Performance, and Full-Scale IQ scores in the low dull to normal range. There were outstandingly low scores on tests measuring verbal abstract reasoning and general knowledge gained from experience (long-term attention and memory). However, he scored better on tests measuring immediate recall (working memory) of nonverbal and verbal information, and on tasks requiring the application of basic mathematic processes (simple mental addition). These intellectual strengths provided examples of well-learned crystallized functions and were probably the direct result of 5 years of skill development as an attendant cashier with fast food franchises.

It was recommended that special attention be given to complaints of headaches and a much delayed medical/neurological evaluation. The NP test results suggested that observed deficits were probably more likely to be residual deficits from congenital (prenatal or neonatal) insulting factors, aggravated by developmental problems and recent drug abuse, than attributable solely to a current or degenerative organic brain condition. However, his belief that his headaches were caused by a "tumor or cancer" suggested a diseased self-concept and other basic self-assessment issues. Depending on the final diagnostic outcome, these headaches may need concurrent medical (pharmacologic) and psychological treatment through counseling.

Diagnostic interview information revealed that a portion of his interest in PCP was an attempt to self-medicate headache pain. Notwithstanding the negative neurological test results, the conceptualization of the presenting problems based on NP test results helped formulate the direction and development of treatment goals and subsequent counseling efforts. Over the next several months,

his cognitive functioning showed improvement and drug counseling centered more on preventing recidivism to marijuana abuse.

Concerning his ability to fulfill the court-ordered probationary requirement to obtain a GED and literacy level academic skills, he was an excellent candidate for individual and/or group tutorial services. His reading and spelling skills were well established and it was predicted that arithmetic skills would advance quickly. His attitude toward treatment was positive, and he was motivated to pursue educational study as a prerequisite to other vocational goal developments. Therefore, formal vocational interest testing and counseling was also strongly recommended. This additional counseling attention reinforced other treatment objectives commensurate with his potential, and helped establish values and goals appropriate to his physical and mental health status.

Case Study #3

This was a 19-year-old white single female with a 5-year history of chronic, moderate PCP use and heavy marijuana/alcohol abuse. She also had experimented with LSD and cocaine freebasing numerous times within the past 2 years. Throughout her history of substance abuse she experienced an increasing frequency of periods of dazed consciousness and blackouts multiple times yearly, while under the influence of alcohol. Further, she reported that other family members had chemical dependency problems, though her parents never abused drugs/alcohol.

This young woman had 13 years of education with computer skills training, and had just obtained an entrance level position in the programming field. However, her job performance and her ability to maintain satisfactory interpersonal relationships had deteriorated. Recently, she had been jilted by her boyfriend. She was self-referred for treatment with additional complaints of anxiety, paranoid thinking and behavior, problems with memory, headaches, dizziness, and intermittent "after-image" visual hallucinations. Though she failed to attend a formal psychiatric assessment interview, she responded well to supportive psychotherapy with progress in her mental status and general level of competency. Except for several episodes of binge drinking, for the next 4 months she remained drug abstinent while enhancing her performance at work, sociability, and insight into her own behavioral and emotional lifestyle. At this time, the purpose of the assessment was to ascertain the presence, despite her response to treatment, of any residual NP deficits.

All measures of gross and fine psychomotor coordinated activity, as well as sensory-perceptual functions, were in the normal range, with the exception of moderate left-handed finger agnosia. This latter finding suggested inefficient contralateral (right) parieta1 functioning. Subtest scores on Performance IQ tasks and results of the figural memory section of the RWMS revealed intact performance. Complex auditory verbal versus rhythm discrimination

!test results further suggested anterior right cerebral hemisphere dysfunction. This profile was characteristic of the early signs and symptoms of an alcohol-related organic brain syndrome. However, based on the above mixed findings, recent psychotherapy results, and her recently reduced drug/alcohol consumption, it seemed likely that the mild but significant NP impairments reflected residual NP deficits, while the intact performances suggested the beginnings of recovery of function.

	Preferred	Non-Pref
Signature Speed	RH: 5sec	LH:9sec
Tactile Recognition	0 errors	0 errors
Sensory Suppression	0 errors	0 errors
Finger Agnosia	0 errors	3 errors
Strength of Grip	33.5 Kgs	30. Kgs
Finger Oscillation	50.0	46.5

Trails-Making A: 22 seconds 0 errors
Trails-Making B: 45 seconds 0 errors

Category Test: 23 total errors
Speech-Sounds Perception: 1 error
Seashore Rhythm: 25 raw 6 ranked score
Revised Wechsler Memory Test:
Verbal Short-term 13.5 1/2 hour 12.5
Figural Short-term 14. 1/2 hour 14.

Wechsler Adult Intelligence Scale-Revised:	
Verbal IQ	103
Performance IQ	105
Full Scale IQ	104
Subtest Scaled Scores	
Information	9
Digit Span	10
Vocabulary	9
Arithmetic	11
Comprehension	7
Similarities	11
Picture Completion	9
Picture Arrangement	11
Block Design	10
Object Assembly	10
Digit Symbol	12

Diagnostic interview information confirmed WAIS-R Comprehension subtest weaknesses in the use of practical judgment and common sense in social situations. As such, the recommendation was for future treatment sessions to focus on issues of reality testing, decision making, interpersonal relations, and other expressive psychological processes. The majority of IQ and NP performances suggested a positive prognosis and good to excellent ability to recover, assuming continuance of drug and alcohol abstinence.

Case Study #4

This was a 25-year-old black inner-city male with a history of chronic, moderate levels of PCP abuse for 7 years, and intermittent, moderate levels of whiskey drinking for several years. All PCP and alcohol abuse ended 3 months prior to the NP assessment, as determined by self-report and urinalysis results. He was motivated to comply with all drug counseling requirements because of an outstanding drug-related criminal charge. The major reason for referral was to assess his current educational level, and his memory and other neuropsychological functions. The drug counselor also questioned whether complaints of recent memory problems were symptomatic of a temporary (transient and reversible) condition, or characteristic of a progressive or more permanent organic brain dysfunction.

During the examination he was quite cooperative, and concerned about his performance. He used a cautious approach to the various tasks and sustained good attention throughout the examination. He reported receiving some minimal special education assistance in junior high school, but he dropped out in his senior year owing to scholastic problems, though he subsequently earned a GED. He reported earlier, limited involvement in amateur boxing, which he quit because of being "punched dizzy" on numerous occasions. This suggested a history of CHI. Though at the time unemployed, he participated in classroom study of the bricklaying trade, but had difficulty maintaining good vocational school grades due to problems in sustaining attention and recalling learned material.

	Preferred	Non-Pref
Signature Speed	RH:10sec	LH:25sec
Tactile Recognition	0 errors	0 errors
Sensory Suppression	0 errors	0 errors
Finger Agnosia	0 errors	0 errors
Strength of Grip	49.5 Kgs	45.5 Kgs
Finger Oscillation	48.0	45.5

Trails-Making A: 40 seconds 0 errors
Trails-Making B: 85 seconds 0 errors

Category Test: 42 total errors
Speech-Sounds Perception: 4 errors
Seashore Rhythm: 29 raw 1 ranked score

Wide Range Achv. Test: grade equivalent
Reading 6.9 Spelling 3.9 Arith 5.1

Wechsler Adult Intelligence Scale-Revised:	
Verbal IQ	84
Performance IQ	96
Full-Scale IQ	87
Subtest Scaled Scores	
Information	12
Digit Span	11
Vocabulary	4
Arithmetic	7
Comprehension	3
Similarities	8
Picture Completion	9
Picture Arrangement	11
Block Design	11
Object Assembly	11
Digit Symbol	6

On NP tests of gross motor activity and fine motor speed, he was mildly impaired in comparison to adult norms. However, he was able to attain normal performance levels with practice and direct encouragement. It is important to note that all other NP tests of sensory, perceptual, and conceptual functions were in the normal range; his minimal errors are often made by normal, nonimpaired individuals.

Measures of academic achievement showed mastery skills just above functional literacy levels, but well below the ninth grade-level skill development often required to successfully complete a GED examination, which had been obtained several years ago. Measures of intellectual functioning showed problems with tasks requiring expressive language and use of practical judgment and common sense in social situations. These findings, in part, may be attributable to cultural bias, lack of educational opportunity, and limited interpersonal or social experience. His major strengths were his ability to analyze and synthesize abstract nonverbal information, and to attend to a task under conditions designed to create frustration and stress. Further, he scored well on tests requiring inductive reasoning skills: both on the intelligence subtests and on the NP measures.

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Considering the chronic history of PCP and alcohol abuse, the anticipated finding was for more pronounced impairment of psychological functions. However, the NP and IQ scores reflected good potential for recovery of function with sustained drug abstinence, since there was little evidence of permanent deficit. An average premorbid optimal estimate of intelligence was established, using educational history, WAIS-R "best subtest" score, measures of recent and remote cognitive-memory functions, and abstract reasoning skills. Further, diagnostic interview information suggested intact mental status prior to drug abuse. Collectively, these findings supported a diagnosis of a transient (toxic) organic brain syndrome in early stages of recovery. Therefore, the complaints of memory loss and associative concerns seemed to be symptomatic of a temporary disorder. The prognosis was good to excellent, assuming continued drug and alcohol abstinence. Consequently, it was recommended that he continue to receive probationary supervision and mandatory drug counseling, in conjunction with a random schedule for urinalysis surveillance to ensure drug abstinence. A 6- to 9-month period of drug abstinence was estimated to be necessary for more significant recovery of NP, IQ, and complex psychomotor functions. It was further recommended that he accept a more active role in his own rehabilitation, to encourage the development of psychological mechanisms and interpersonal skills complementary to the objectives of the treatment plan and personal goals.

TREATMENT AND RESEARCH IMPLICATIONS

The clinical information obtained from NP assessment and structured history taking provides a basis for understanding the multifaceted nature of brain functions and their relation to human behavior. The use of NP results, in conjunction with other diagnostic information, to develop rehabilitation plans for PCP abusers can be invaluable in suggesting a prognosis. Thus, individual treatment goals and expectations can better complement the cognitive-behavioral strengths and weaknesses of an individual in need of drug abuse consultation.

For many PCP abusers, a thorough NP examination, followed by a review of assessment results with the PCP abuser, should be a treatment policy. This debriefing strategy, when used as a planned intervention. can have powerful therapeutic implications. Foremost, discrepancies between-the clinical findings and an individual's own assessment of level and pattern of functioning can be addressed. This provides an opportunity for the PCP abuser to receive objective feedback on mental status and can enhance the therapeutic alliance and commitment to treatment. Due to the behavioral nature of many of the tasks comprising the NP assessment, individuals frequently have an intuitive understanding of their own performance prior to a formal debriefing. In practice, this process of active participation and self-assessment reduces psychological defensiveness and the tendency for denial.

Estimates suggest that PCP abusers sustain a greater frequency and severity of NP deficits than other drug and/or alcohol abusers. These deficits are probably related to a combination of developmental, toxicity, and idiosyncratic factors which differentially affect CNS function. The complexity of NP diagnostic interpretation is further compounded in developing a prognosis and predicting the ability to recover. Issues of brain plasticity and recovery of function need extensive research in direct relation to specific treatment objectives.

Forensic Use of NP Assessments

The PCP abuser poses unique problems for law enforcement agencies and the judicial system. McCarron et al. (1981), in reviewing medical and behavioral characteristics of 1,000 PCP episodes observed in medical emergency rooms, have noted the extremely high incidence (35 percent) of violence and rage reactions. Possibly because of anesthetic effects, and/or PCP uptake in limbic-mediated emotional centers, PCP abusers can sometimes behave with superhuman strength, causing harm to self, others, and property. Thus, it is not surprising that PCP abusers often incur criminal charges ranging from simple possession and distribution to homicide.

The NP evaluation of the PCP abuser may be useful in pretrial investigation in a number of ways. In general, objective estimates of intellectual functioning and NP status at the time of criminal incident (projected from later assessment) can suggest limited versus intact capacity of the PCP abusers for appreciating the criminality of their actions or indicate similar capacity for conforming their behavior to the requirements of the law. Perhaps more important, from a standpoint of ultimate outcome, NP screening techniques can suggest a prognosis for rehabilitation versus a risk for recidivism, and aid judicial decision making by providing an objective basis for sentencing that is equitable to both society and the PCP abuser.

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Phencyclidine Intoxication

Margaret M. McCarron

BACKGROUND

At the Los Angeles County/University of Southern California (LAC/USC) Medical Center, phencyclidine (PCP) intoxication accounts for more emergency department visits and hospitalizations than any other drug of abuse. Most of the areas of the hospital are called upon to treat PCP intoxication and related problems. Emergency physicians, internists, and psychiatrists treat the majority of cases, but orthopedists, neurosurgeons, and general surgeons are well acquainted with the traumatic events often accompanying PCP use. Pregnant women smoke PCP before entering the hospital for delivery; babies are born with PCP intoxication. Small children become intoxicated with PCP in the home, and older children use the drug for "kicks." Since 1979, an average of five patients per day have been arrested and brought to the Prison Service because of illegal acts performed under the influence of PCP.

PCP is usually smoked on "Sherman" or "More" cigarettes that have thick brown wrappers that absorb PCP liquid and still allow the cigarette to be smoked. Ingestion of partially smoked PCP cigarettes can result in severe toxicity. About one hour from ingestion of such a cigarette, seizures may suddenly occur, followed by coma, apnea, and hyperthermia.

Sometimes liquid PCP is ingested, often mixed with lemonade or some alcoholic beverage. One man had eaten clams laced with PCP. Solutions of PCP are also injected intravenously. Some patients inject PCP two or three times a day for long periods of time.

Liquid PCP often contains volatile solvents that impart an "ether-like" odor to the patient, although PCP itself is odorless. PCP is nonvolatile at room temperatures, but ether is highly volatile. Undoubtedly, some of the acute reactions that occur after exposure to street "PCP fumes"' are due to the effects of the ether and not to PCP. Several reactions of this type have been observed, such

as a woman who became dizzy and nauseated and felt as if she were about to faint when "PCP" fumes entered her apartment from a "PCP laboratory" next door.

Another type of reaction that occurs when a person is inadvertently exposed to "PCP fumes" is acute anxiety. An example of this was a policeman who smelled "PCP fumes" in the squad car while transporting a person with PCP intoxication. The policeman was examined and found to have a severe anxiety reaction with marked hyperventilation and carpopedal spasms.

PCP can apparently be inhaled by a person working in a PCP laboratory when the laboratory catches fire. Eight acutely intoxicated people were admitted to the LAC/USC Medical Center prison wards with PCP toxicity and thermal burns incurred during explosions of volatile chemicals in makeshift PCP laboratories (McCarron et al. 1981a).

PCP is also ingested in pill form, each tablet containing about 2 to 6 mg of PCP (Lundberg et al. 1976). PCP powder may be sniffed or snorted, or incorporated into marijuana cigarettes.

TABLE 1. *Routes of PCP use (1,000 patients)*

Route	Percent Using
Smoked	72.6
Sniffed/snorted	13.3
Ingested	12.3
Intravenous	1.8
Two or more routes	1.0

SOURCE: McCarron et al. 1981a.

In 42 percent of cases, PCP was used with another drug, usually alcohol, marijuana, a barbiturate, or a narcotic.

Several analogues of PCP with similar pharmacological effects are available on the streets. These include PCE (cyclohexamine), PHP (phenyl-cyclohexyl-pyrrolidine, PCPP (phenyl-cyclo-pentyl-piperidine), and TCP (thienyl-cyclohexyl-piperidine) (Baselt 1982).

DIAGNOSIS

In a series of 1,000 cases of PCP intoxication (McCarron et al. 1981a), 87 percent of patients were male: 45 percent were black, 36 percent Caucasian, and 19 percent Hispanic. The youngest patient was 13 years old and the oldest was 65, with a median age

of 23 years; however, 65 percent of patients were 18 to 25 years old. One patient had seven episodes of PCP intoxication.

Unlike other drugs of abuse, the diagnosis of PCP intoxication is often difficult because of the wide spectrum of clinical findings that occurs with this drug. PCP toxicity sometimes can be mistaken for delirium tremens, acute psychiatric illness, sedative/hypnotic overdosage, amphetamine intoxication, or sedative/hypnotic withdrawal syndromes.

History

A description of the patient's actions before admission to the hospital often provides valuable clues to the diagnosis. Since PCP seems to diminish the user's ability to integrate sensory input into meaningful behavior (Pender 1971), symptoms and findings suggesting this problem should be sought. A demonstration of sensory deprivation was provided by a patient who was found head down in a dumpster filled with garbage. He was nude and the weather was cold, but he didn't seem to be uncomfortable. He also didn't mind the smell of garbage, or the discomfort of the upside-down position. In one reported case, loss of pain sensation resulted in an act of self-injury by biting of the forearms almost to the bone (Grove 1979). Irrational acts, such as driving too slowly on the freeway, or bizarre behavior, such as strolling down the street nude or "standing in the park like a statue," may be manifestations of PCP toxicity. Other general characteristics include waxing and waning of the mental status or behavior and evidence of increased strength.

Physical Findings

PCP affects the sensorium, behavior, and vital signs, and it may affect motor and autonomic functions. Hypertension and nystagmus are hallmarks of PCP intoxication. Nystagmus occurs in about 57 percent of patients, and hypertension occurs in about 48 percent. Nystagmus may be horizontal, vertical, or rotary. The presence of nystagmus, while helpful, does not provide the diagnosis because all types of nystagmus may accompany other kinds of drug overdosage, such as sedative/hypnotic intoxication. The usual level of blood pressure in patients with hypertension is 140-160/95-105 mm Hg (McCarron et al. 1981a) However, hypertensive crises may occur with blood pressures as high as 200-300+/140+ nun Hg. Severe hypertension may be accompanied by intracranial bleeding.

Sensorium. Patients with PCP intoxication can have a clear sensorium, or they can be disoriented, confused, stuporous, lethargic, or comatose. Signs of cerebral stimulation, such as pressured speech, verbigerations, and echolalia, may also occur. Frank psychotic symptoms, including hallucinations, delusions, and paranoid ideation, are not unusual.

Behavior. Some patients with PCP toxicity display inappropriate behavior. Behavioral effects include muteness, staring, violence, and agitation. Violent behavior occurred in 35 percent of people with PCP intoxication who were examined on the prison wards of the LAC/USC Medical Center (McCarron et al. 1981a).

Motor Signs. PCP causes grimacing, localized dystonic reactions, generalized rigidity, catalepsy, athetosis, tremors, twitching, coarse jerky movements, and grand ma1 seizures. Status epilepticus may occur. Deep tendon reflexes may range from hyperactive to absent.

Autonomic Signs. The most common autonomic signs are profuse diaphoresis, hypersalivation, bronchorrhea, and urinary retention. Wheezing and severe bronchospasm occur occasionally. Pupils may be any size.

Vital Signs. Although hypertension is common and may be severe, hypotension can also occur. Tachycardia occurs in about 30 percent of cases. Severe tachypnea with respiratory rates as high as 88/min or respiratory depression with rates of 10/min or less may be seen. Respiratory arrest and cardiac arrest may occur. Hyperthermia with temperatures as high as 108.0 °F is a life-threatening event and may be associated with submassive liver necrosis (Armen et al. 1984).

Numerous deaths have been reported in people under the influence of PCP. Most of the fatalities resulted from various kinds of trauma, but some have been attributed to the direct effects of PCP (Burns and Lerner 1978; Caplan 1979; Armen et al. 1984).

PATTERNS OF INTOXICATION

In adult patients, the manifestations of PCP use can be grouped into nine clinical patterns of intoxication. Four of these are called major patterns because they may be associated with severe toxicity and often necessitate hospitalization. Patients with major patterns are usually unpredictable; symptoms wax and wane, and the patient may abruptly change from one pattern of intoxication to another. Five other symptom complexes are designated as minor patterns since toxicity is usually mild and of short duration. Major Patterns consist of: coma, catatonic syndrome, toxic psychosis, and acute brain syndrome. Minor Patterns are lethargy, bizarre behavior, violent behavior, agitation, and euphoria (McCarron et al. 1981b).

In determining the pattern of intoxication, the manifestations of toxicity obtained by history should be considered, since many patients with severe intoxication improve considerably by the time they are admitted to a hospital. Nontraumatic rhabdomyolysis occurs almost exclusively in patients who have experienced a major pattern of PCP intoxication.

Major Patterns

Coma. Patients with PCP-induced coma are unresponsive to stimuli, are nonverbal, and have closed eyes. Some patients may have no other findings. Others may have any of the motor and autonomic signs and disturbances of vital signs listed above. A triad of coma-apnea-seizures occurs in this group.

Some comatose patients are unconscious for less than 2 hours, do not show signs of severe toxicity, and have few complications. In other patients, coma lasts from 2 to 24 hours, and symptoms are more marked. Patients with severe toxicity, including status epilepticus and malignant hyperthermia, may remain in coma for 1 day to 3 weeks. These patients often have respiratory or metabolic acidosis. Comatose patients are susceptible to aspiration pneumonia and rhabdomyolysis. Head injury and intracerebral bleeding should be considered as the cause of the comatose state.

Catatonic Syndrome. The essential characteristics of the organic catatonic syndrome are (1) central nervous system excitement alternating with stupor, and (2) catalepsy. Many patients are mute and staring, and have generalized muscle rigidity or localized dystonic reactions. PCP catatonic syndrome often includes: posturing, repetitive actions, grand mal seizures, nudism, agitation, violence, hallucinations, delusions, and verbigerations. The patient may be alert and oriented, withdrawn or lethargic, or have an acute brain syndrome. There is a high incidence of rhabdomyolysis and hyperthermia in PCP-induced catatonic syndrome. Some patients have the neuroleptic malignant syndrome or develop it after administration of haloperidol.

The neuroleptic malignant syndrome is characterized by hyperthermia (temperature over 103 °F without evidence of infection), altered sensorium, muscle rigidity, and autonomic disturbances, usually profuse diaphoresis, hypersalivation, bronchorrhea, and urinary retention.

Toxic Psychosis. Any patient who is not catatonic but has hallucinations, delusions, paranoid ideation, or other psychiatric manifestations is classified as having toxic psychosis. These patients are often difficult to differentiate from those with acute agitated psychosis, and about 25 percent appear manic. Motor and autonomic disturbances are less common in this group than in any of the major patterns. Severe hypertension has been noted. Rhabdomyolysis is unusual.

Acute Brain Syndrome. Any patient with disorientation, lack of judgment, inappropriate affect, and loss of recent memory who was not comatose or catatonic and has no discernible hallucinations, delusions, or other psychiatric manifestations is included in this pattern. Acute brain syndrome is the most common pattern of PCP intoxication among patients brought to the emergency department at LAC/USC Medical Center, accounting for 25 percent of the PCP

cases. All of the manifestations and complications of PCP toxicity can occur in this group. These patients are often misdiagnosed as having delirium tremens.

Minor Patterns

Patients with the lethargy pattern of PCP toxicity may be clinically indistinguishable from patient with mild sedative/hypnotic intoxication, although hypertension and grand mal seizures which may occur with PCP intoxication, are not expected with sedative/hypnotic overdose. The remaining minor patterns are differentiated as follows.

TABLE 2. *Characteristics of minor PCP patterns*

Pattern	Sensorium	Behavior
Bizarre behavior	Alert & oriented	Bizarre, violent or agitated
Violent behavior	Alert & oriented	Bizarre, violent or agitated
Agitation	Alert & oriented	Agitated
Euphoria	Alert & oriented	No behavioral disturbance

SOURCE: McCarron et al. 1981b.

Any of the motor or autonomic signs, and hypertension and/or nystagmus may occur with any of the minor PCP patterns. Minor patterns should not be diagnosed on physical examination in an emergency department without adequate information about the patient's behavior and sensorium prior to admission. Many patients with major patterns may be alert and oriented when they reach the hospital. If no history is available, the patient is kept under observation and rhabdomyolysis is ruled out.

Toxicology Tests

Urine concentrations of PCP determined by enzyme immunoassay did not correlate with the state of intoxication at the time the urine sample was taken. The test was negative in 15 percent of 1,000 patients with clinical evidence of PCP toxicity, many of whom admitted taking PCP (McCarron et al. 1981a). Several of these negative urines were analyzed for PCP analogues; none were found.

Serum concentrations of PCP determined by enzyme immunoassay in 405 patients also did not correlate with the state of intoxication at the time the blood speciman was obtained, although the highest PCP concentrations in the study were associated with major patterns. However, some patients with major patterns had negative

tests or lower concentrations of PCP than some patients with minor patterns (Walberg et al. 1983).

A radioimmune assay for PCP in saliva and serum showed that saliva could be used as a specimen for PCP analysis (McCarron et al. 1984). Of 79 patients with acute PCP intoxication clinically, 70 had positive tests in both serum and saliva, two had positive serum tests and negative saliva tests, and seven had negative tests on both serum and saliva.

TREATMENT

The treatment of acute PCP toxicity depends on the pattern of intoxication and the physical findings. On the prison wards of the LAC/USC Medical Center, approximately 60 percent of patients are treated and released within 24 hours. Most of these patients have minor patterns of intoxication and no medical complications. Another 10 percent of patients have minor problems with medical complications, usually trauma.

Treatment of Minor PCP Patterns

For the most part, patients with minor PCP patterns are treated symptomatically. Abnormalities in the vital signs are treated with supportive care. Patients with grand mal seizures are given IV diazepam in doses of 5 to 20 mg. Bizarre, violent, and agitated patients are placed in restraints to protect themselves and others. Haloperidol 5 to 10 mg is given IM as needed. Localized dystonic reactions are treated with 50 mg diphenhydramine IV. Few of these patients require gastric lavage and none are given syrup of ipecac. Each patient has a Hemastix test performed on urine. If the test is positive, the urine is examined microscopically for red blood cells. If no red blood cells are found, a tentative diagnosis of myoglobinuria is made, serum chemistries are obtained, and the patient is held to rule out rhabdomyolysis. If the uric acid and creatinine kinase (CK) values are normal, and the patient is asymptomatic, he/she is discharged from the hospital. Routine toxicology tests include urinary PCP, serum alcohol, and hypnotic screen.

Treatment of Major PCP Patterns

All patients with major patterns of PCP intoxication are placed in restraints. If the patient is comatose or catatonic, if multiple intoxication is suspected, or if ingestion of PCP is suspected, gastric lavage with activated charcoal is performed. If the patient is severely intoxicated, a nasogastric tube is inserted and connected to suction in order to remove any PCP that is excreted in the gastric juice, and arterial blood gases are obtained. Metabolic acidosis is treated by administration of sodium bicarbonate. No attempt is made to acidify the urine. All patients are given IV fluids. To combat hypoglycemia, 50 ml of 50 percent

dextrose solution IV is routinely administered. Status epilepticus is controlled with IV diazepam; if diazepam is ineffective, the patient is treated with neuromuscular blockade in the medical intensive care unit. Severe hypertension is treated with sodium nitroprusside. Agitation or violence is controlled with chlorpromazine or haloperidol (Giannini et al. 1984), unless these drugs are contraindicated by the presence of shock or hyperthermia, in which case diazepam may be used. For temperatures above 105 °F, dantrolene sodium in doses of 1 to 1.5 mg/kg is given in addition to cooling measures.

All patients with major patterns are monitored for rhabdomyolysis and renal failure. An early sign of rhabdomyolysis is an elevated serum uric acid, associated with an increase in serum CK. Within 8 to 12 hours, the serum tests are repeated. If the uric acid falls and the CK rises, rhabdomyolysis is likely. Renal function tests may also be increased at this time. When the diagnosis of rhabdomyolysis is made, the patient is treated with 40 mg furosemide IV once, and IV fluids. Urine myoglobin concentrations are obtained. If the patient develops renal failure, hemodialysis or peritoneal dialysis may be necessary. In all cases, multiple drug intoxication, trauma, and rhabdomyolysis are ruled out or treated. All patients are kept under observation until they are asymptomatic.

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Diagnosis and Treatment of Chronic Phencyclidine (PCP) Abuse

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INTRODUCTION

Phencyclidine (PCP) abuse remains a serious public health problem in large urban areas of the United States, with recent trends suggesting increased use after a period of decline (Crider, this volume). Most clinical and research attention has focused on the psychiatric and medical manifestations of acute or subacute PCP intoxication, especially the organic mental disorders (toxic delirium, psychosis, or depression) that PCP can induce (McCarron et al. 1981; McCarron, this volume; Sioris and Krenzelok 1978). Much less attention has been paid to chronic PCP use per se, i.e., the substance use disorder itself. Such issues as the effects of chronic PCP use, and the diagnosis, clinical characterization, and treatment of chronic PCP abusers are rarely discussed in the published literature, even in detailed review articles (Davis 1982; Pearlson 1981; Pradhan 1984). This paper reviews the literature on inpatient and outpatient treatment of PCP abuse, outlines our own experience with PCP users and abusers in one large, public, urban hospital, and makes suggestions for future research based on this information and animal research findings (Balster, this volume).

We were able to find only five published studies on the inpatient or residential treatment of PCP abusers (DeAngelis and Goldstein 1978; Fauman and Fauman 1980; Khajawall and Simpson 1981; Rawson et al. 1981; Simpson et al. 1983), with a total sample size of 397 patients. Two of these studies are from the same 32-bed unit in a large urban state hospital (Khajawall and Simpson 1981; Simpson et al. 1983), and therefore may have included some of the same patients. Three are from residential therapeutic communities (RTC) (DeAngelis and Goldstein 1978; Fauman and Fauman 1980; Rawson et al. 1981). While all of these studies provide some sociodemographic and clinical data on their patients, only two give even minimal short-term (i.e., during hospitalization) treatment outcome results, and none give any long-term (i.e., after hospital discharge) outcome results. Khajawall and Simpson (1981) found

that only 6 percent of 182 consecutive adult PCP abusers completed the entire rehabilitation program (minimum stay 45 days). The average length of stay was 36 days. Most patients wanted only detoxification treatment. DeAngelis and Goldstein (1978), studying adolescent patients (mean age 16 years) in an RTC, found that the 22 "chronic PCP users" (using at least 3 to 4 times weekly) had a significantly longer length of stay than the 42 non-PCP users (108 days vs. 68 days), but not longer than the 23 occasional (once a week or less) PCP users (85 days). There was no difference between chronic and occasional PCP users in frequency of aberrant behaviors or program rule infractions. Chronic users were somewhat less likely than occasional users to show angry and belligerent behaviors (46 percent vs. 80 percent occurrence), but more likely to have sexual acting out (31 percent vs. 12 percent) and delusions (12 percent vs. 0 percent).

All five published studies dealt with a young population, with mean patient ages ranging from 16 years (DeAngelis and Goldstein 1978) to 23 years (Simpson et al. 1983). The oldest PCP patient included was 46 years old (Khajawall and Simpson 1981). The racial makeup of the study populations varied from 96 percent white (Fauman and Fauman 1980) to 25 percent white (Khajawall and Simpson 1981), presumably reflecting selection bias due to the geographic location and funding mechanisms of the various treatment programs. The majority of patients in all studies (where data were given) were male (54 to 80 percent), unmarried (79 to 87 percent), unemployed, and with less than 12 years education. The mean durations of regular PCP use (3+ times weekly) were 2.4 to 4 years.

We found only one published systematic study of outpatient treatment for PCP abusers, involving 158 patients (73 percent male) of a private clinic (Bolter et al. 1976). This study gave no treatment outcome data, but the authors did comment that treatment was difficult because of the patients' strong psychological dependence on PCP.

METHODS

Our own studies were conducted at the Brentwood Division of the West Los Angeles Veterans Administration Medical Center. Brentwood is the 450-bed psychiatric division of the Medical Center, which serves a large catchment area in the central and western Los Angeles basin and includes general psychiatry programs (230 beds), substance abuse inpatient (80 beds) and outpatient programs, an involuntary locked ward (15 beds), and several other specialty programs. The substance abuse wards on which studies were done are voluntary rehabilitation programs with scheduled admissions and 4- to 6-week lengths of stay. They do not accept acutely psychotic, violent, or suicidal patients, nor patients requiring specialized medical attention (e.g., IV therapy or cardiac monitoring).

PCP assays were performed in the hospital's Clinical Psychopharmacology Unit, using gas chromatography with nitrogen/phosphorus detection after PCP was extracted from the raw samples by column chromatography. The authenticity of PCP samples was occasionally verified with gas chromatography/mass spectrography. (Assay parameters had been adjusted to avoid false positive results from substances known to be potentially interfering.) Assay sensitivity was 0.1 ng/ml, intraassay variability was 3 percent, and interassay variability was 5 percent. Urine samples were refrigerated within 4 hours of collection and assayed within 4 days. Sociodemographic and clinical data were collected by social worker interview with the patient, usually within 2 days of admission. It was rarely possible to confirm this data by contacting collateral sources of information or reviewing old records (if any).

RESULTS

General Psychiatry Inpatients

All inpatients admitted through the hospital emergency room over a 15-month period (June 1982 through August 1983) had urine samples collected in the emergency room for later PCP assay. This represented 1,550 admissions of 1,384 individual patients, but did not include all hospital inpatients (i.e., excluded those who were admitted from outpatient status). PCP was detected in the urine of 16.5 percent (255) of the total admissions and 15.5 percent (215) of individual patients. In the vast majority of cases, the PCP levels were low (less than 30 ng/ml in 85.0 percent).

Clinical data on 1,454 admissions (1,128 individual patients) was obtained from hospital records. The most common primary discharge diagnosis among the PCP-positive patients was alcohol dependence (27.5 percent), followed by drug dependence (26.6 percent), schizophrenia (20.0 percent), and drug-induced psychosis (7.8 percent). In terms of the proportion of patients with positive PCP assays, the diagnoses ranked as follows: drug-induced psychosis (63.0 percent), followed by drug dependence (33.3 percent), alcoholic psychosis (23.1 percent), and schizophrenia (13.7 percent). Even among patients with primary discharge diagnoses of affective disorder, personality disorder, and neurosis, 8 to 12 percent had PCP-positive urine on admission. The PCP-using patients (as reflected by PCP-positive urine on admission) were admitted throughout the hospital. The proportion of discharges that had PCP-posltive urine varied from 23.8 percent from a mixed substance abuse ward (20 beds) and 22.5 percent from the involuntary ward, to 17.6 percent from general psychiatry wards and 13.1 percent from the alcohol treatment ward (40 beds), There was no significant trend towards PCP-positive patients having a longer length of stay in the hospital or more frequent admissions during the study period.

A small pilot study was done to determine the clinical impact of routine screening of urine for PCP on admission. Forty-one

inpatients on three different types of wards had their charts reviewed 5 to 10 days after their admission to see whether the result of their PCP urine assay, done on admission, was reflected in their treatment plan (laboratory reports were sent to the wards 2 to 3 days after admission). In only 34 percent of cases was the PCP assay result mentioned in the treatment plan. The substance abuse wards did best, with 60 percent mention, followed by the involuntary ward (21 percent), and general psychiatry wards (17 percent).

Substance Abuse Inpatients

Admission urine PCP assays were done on 155 consecutive males admitted over a g-month period (December 1982 to August 1983) to a mixed abuse ward (20 beds). Forty-two patients (27 percent) had PCP detected in their urine; another 14 (9 percent) gave a history of PCP use. Of these, 14 (9 percent of the total sample) initially denied any PCP use, and 9 continued to deny use after they were confronted with the laboratory results.

Patients were classified into PCP abusers or users by applying DSM-III criteria to the history obtained from the admission interview. The 42 PCP-positive patients broke down into 20 PCP abusers and 22 PCP users. All 14 patients who gave a history of PCP use, but had negative urine assays, were considered nonabusers. The PCP abusers were significantly younger (32 vs. 40 years) and had more prior arrests (2 vs. 1) than the users, but did not differ in race, education level, marital status, or employment status. Abusers differed from users in having much higher urine PCP levels and more recent PCP use, but did not differ significantly from users in number of prior drug abuse treatments, time since last treatment, or abuse of other drugs. There was also no difference between abusers and users in immediate treatment outcome, as reflected by length of stay in the program or reason for discharge.

A high proportion of both groups reported abuse of other drugs, including alcohol (61 percent), opiates (38 percent), and marijuana (29 percent). All the PCP abusers in the sample had used PCP for at least 2 years (55 percent more than 5 years); 35 percent used it at least daily. All but one abuser smoked his PCP; the exception used it by insufflation.

The immediate treatment outcome resulted in less than half (47 percent) of the PCP abusers completing the treatment program. The mean length of stay was just under 4 weeks.

There was a significant negative correlation between (log) admission urinary PCP level and self-reported time since last PCP use ($r=-0.53$, $p<0.001$). Visual inspection of a graph of these two variables suggested a possible biphasic elimination curve, with the initial phase having a half-life of 5 to 7 days, and the later phase a half-life of about 30 days. However, formal curve fitting of these data to standard pharmacokinetic models (using BMDP

computer programs) showed the data to be equally consistent with a monophasic elimination curve (i.e., with a one-compartment pharmacokinetic model). The 42 patients with PCP-positive admission urines had weekly urine assays done thereafter, until a negative urine assay was obtained. No urine acidification treatment was given to increase elimination. Thirty-seven patients showed a monotonic decline in urine PCP levels, with negative assays by the fourth or fifth week. The remaining five patients showed a significant increase in PCP levels at one or more measurement points, but PCP reuse was suspected on clinical grounds. When analyzed by computer curve fitting, these data were also equally consistent with either a one- or two-compartment pharmacokinetic model.

Substance Abuse Outpatients

The Substance Abuse Service at the hospital includes a weekly outpatient therapy group for PCP abusers, run by psychiatric social workers. The approach used is supportive, behavioral, and educational, with the goal of decreasing or eliminating drug-seeking and drug-taking behavior, and increasing problem-solving skills. Weekly urine samples for PCP assay and drug screen are required for group membership, but patients are not automatically discharged from the group because of a positive urine test. The results presented here are based on 24 patients who attended at least one group session after the group was formed in February, 1984. The majority of patients (54 percent) were self-referred to the clinic; 16 percent attended only because of probation or parole conditions.

Outpatient group members were very similar to the inpatient PCP abusers in most sociodemographic and drug-use characteristics. Their mean age was 29 years, educational level 12.6 years, and number of prior arrests 1.5. The majority of outpatients were black (83 percent), unmarried (67 percent), and unemployed (67 percent). Their mean duration of PCP use was almost 8 years, with, usually, no prior or recent substance abuse treatment. Thirty-seven percent used PCP at least daily, always by smoking. Like the inpatient PCP abusers, outpatients frequently (87 percent) reported abuse of other drugs: alcohol (46 percent), marijuana (46 percent), and cocaine (37 percent). Several outpatients for whom cocaine was the preferred drug of abuse used PCP as a "cheaper high" when cocaine was not affordable.

There was frequent group consensus on the psychological effects of PCP and motivations for its use. The two main psychological effects often cited as maintaining PCP use were the feelings of strength, power, and invulnerability it engendered; and a psychic numbing that was used to self-medicate dysphoric affects, especially anger and rage ("I use PCP because I want to forget"). Some patients were attracted by the challenge of the risk in using PCP, i.e., not knowing what would happen. Three types of acute intoxication responses were described: stimulation, depression, and hallucinogenic. Many patients reported being able to predict

which response they would have by the concentration of the PCP that they used. Almost all patients had had religious experiences while intoxicated: feelings of meeting God, impending death, etc. Whatever the experience, all patients reported liking PCP use and having great psychological difficulty in giving it up. This was despite common adverse effects such as legal problems, difficulty in working regularly, transient depression following cessation of use, and uncomfortably warm sensations in the extremities (sometimes prompting patients to feel like taking off their clothes).

The outcome of this specialized outpatient group therapy was mixed. Patients stayed in treatment for a mean of 14 weeks (range 2 to 60 weeks), and attended 67 percent (range 25 to 100 percent) of the scheduled group sessions. Urine samples were positive for PCP 47 percent of the time; patients reported PCP use 24 percent of the weeks they attended. Over the 14 months of the group's existence, 75 percent of members have stopped participating: 42 percent to enter treatment elsewhere (60 percent residential, 40 percent outpatient); 8 percent to go to jail; and 25 percent to drop out of treatment completely. Of those 6 patients currently, remaining in the group, only one has become completely drug free (and has returned to full-time employment).

DISCUSSION

We found that about 15 percent of patients admitted to a large, public, urban hospital had PCP present in their urine. This is a substantially lower prevalence than the 43 to 78 percent previously reported from another large, public hospital in Los Angeles (Aniline et al. 1980; Yago et al. 1981), but still suggests that PCP use is not rare among psychiatric patients. The PCP use occurred in both substance abuse and general psychiatry patients and in all diagnostic categories, not just identified substance abuse patients. Therefore, routine screening for PCP might well detect a significant number of unsuspected users in such a population. For example, even on a voluntary inpatient substance abuse program, admission urine screening detected 9 percent of newly admitted patients who initially denied PCP use. It is tempting to speculate on the clinical significance of PCP use in newly admitted psychiatric patients, i.e., what role it plays, if any, in precipitating the admission. Only future longitudinal and prospective research can address this question. In any case, our small pilot study suggests that specific training of clinical staff may be necessary before results of PCP assays are incorporated into treatment planning for patients in whom PCP use is not initially suspected.

The sociodemographic and clinical characteristics of our PCP abusers were similar to those previously reported in the literature, except for a somewhat older age range. This indicates that chronic PCP use does occur outside the adolescent/young adult age group, and suggests that future treatment and research efforts should include older age groups.

Our experience with inpatient and outpatient treatment of PCP abuse was not very successful, similar to experiences reported in the literature. A few authors have commented on the difficulties in treating PCP abusers, citing their impaired attention span and concentration, emotional lability, impulsiveness, poor group interaction, and low tolerance for confrontation (Bolter 1980; Bragg 1980). Systematic, controlled studies using appropriate comparison groups are needed to validate these anecdotal observations and to determine whether they are effects of PCP use or antecedent conditions (which perhaps might predispose to PCP use). In particular, studies of the direct neuropsychological and neurophysiological effects of chronic PCP use (over and above the short-term effects of acute intoxication) would have important treatment implications (Lewis and Hordan, this volume). Recent studies of alcoholic patients suggest that neuropsychological functioning at admission may be a significant predictor of treatment outcome (Donovan et al. 1984). There is no a priori reason why a similar phenomenon might not occur with PCP abusers.

There are currently no systematic data to guide a decision on inpatient vs. outpatient treatment. However, the cheap and easy availability of PCP reported by outpatients in their living environments, and the frequent continued use of PCP by outpatients suggest that a brief period of inpatient treatment might be useful in initiating drug abstinence. There is clearly a strong need for research on specific treatment modalities for PCP abuse.

Findings from psychopharmacological and neuropharmacological studies of PCP in animals suggest other potentially fruitful areas of clinical research (Balster, this volume). The PCP drug stimulus in animals does not generalize well to other drugs of abuse. This has led to the hypothesis that PCP has a unique psychotropic action, and that therefore PCP abusers would have a distinctive pattern of drug use and tend to avoid use of other drugs. In fact, clinical data from our own studies and the published literature show that the majority of PCP abusers regularly use other drugs, either concurrently or sequentially. A possible explanation for this lies in the variety of behavioral effects produced by PCP in animals. Both stimulant and sedative effects of PCP have been reported in various animal paradigms, analogous to the variety of intoxication responses reported by patients. This suggests that PCP may be considered at least somewhat interchangeable with other drugs of the stimulant and CNS depressant classes. Furthermore, PCP might be considered effective self-medication for a variety of psychopathologic states, e.g., the stimulant effects might be attractive to those with dysthymic symptoms, and the the sedative effects to those with anxiety symptoms. Careful psychiatric studies of representative samples of PCP abusers in the sober state (along with corroborative information about psychiatric history) are needed to test these hypotheses.

Almost all the PCP abusers we studied had a "psychological dependence" on PCP, i.e., an inability to give up drug use despite serious adverse consequences, coupled with a conscious desire to use the drug (craving). No patient described clear evidence of physical (physiological) dependence, either in terms of tolerance or a withdrawal syndrome. (However, we did not systematically evaluate patients for these phenomena.) Anecdotal reports of fourfold tolerance to PCP have been published (Burns and Lerner 1981). Animal studies have found moderate (two- to fourfold) tolerance to PCP, probably involving metabolic, pharmacodynamic, and behavioral adaptation processes (Balster and Woolverton 1981; Freeman et al. 1984). There is also some animal evidence for a PCP withdrawal syndrome. Balster and Woolverton (1980) noted a marked syndrome occurring in rhesus monkeys who self-administered very large IV doses (up to 10 mg/kg/day or more) for over a month. Bruxism, oculomotor hyperactivity, tremor, diarrhea, and piloerection appeared within 8 hours of drug cessation, and peaked at 24 hours. Slifer et al. (1984) found a much milder syndrome in monkeys who received a continuous IV infusion of PCP (1.2 mg/kg/day) for 10 days. The principal withdrawal effect was a disruption of conditioned lever pressing for food, which appeared within 8 hours of drug cessation and resolved over the next week. An acute PCP dose temporarily reversed the behavioral disruption, supporting its interpretation as a withdrawal phenomenon. These findings suggest that, while physical dependence on PCP can exist, it probably requires long-term regular exposure to relatively high levels.

Tennant and colleagues (Tennant et al. 1981; Ayd 1981) studied 26 long-term (at least 3 months) daily PCP abusers and described the following syndrome occurring within 1 day of drug cessation: depression, anxiety, irritability, restlessness, anergia, sleep disturbance, confused thoughts, and strong craving for PCP. It is not clear how long this syndrome lasted, since none of the eight untreated patients returned to the clinic for follow-up. The 18 patients treated with desipramine (50 to 150 mg/day open-label) reported a rapid and substantial reduction in symptoms, which helped 15 of them become drug free during a 2-week follow-up period. Given the probable role of withdrawal symptoms and drug craving in promoting continued drug use (and relapse from abstinence), further systematic, controlled research in this area, including double-blind medication trials with random assignment of subjects to treatment groups, would appear very worthwhile.

Our pharmacokinetic data indicate that detectable PCP levels may remain in the urine for 4 to 5 weeks after the last use, similar to previous reports (Khajawall and Simpson 1983). The observed elimination kinetics were equally consistent with a one- or two-compartment model, but methodological problems with our data make

any conclusions highly tentative. The time variable was based on patient self-report, making its accuracy uncertain. Although the PCP level itself was measured accurately, the PCP dose yielding that level varied among patients in an unknown fashion (since no data on dose could be collected).

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Legal Issues Associated With PCP Abuse—The Role of the Forensic Expert

Steven E. Lerner and Richard S. Burns

It is not uncommon for individuals under the influence of phencyclidine to come to the attention of the criminal justice system. Increasingly, there is a need for forensic experts to advise and testify in cases involving PCP and other psychoactive drugs. With the publication of a paper on acute intoxication and fatalities from PCP use, we began to receive requests from attorneys to evaluate PCP-related cases (Burns et al. 1975). We have now consulted in over 400 civil and criminal cases and have testified in municipal, superior, and Federal courts from Hawaii to Washington, D.C. In this chapter, we will examine some of the issues that are frequently raised in both criminal and civil PCP-related litigation.

Most jurors and many courts have limited knowledge about psychoactive drugs, including PCP. From our experience, it is not uncommon for the average juror to believe that the effects produced by PCP are no different from those produced by other drugs. For this reason, jurors must be educated if they are to be expected to make informed decisions about complex issues with which they have little or no familiarity. It is possible, in a limited amount of time, using visual aids, to provide a jury with a basic understanding of PCP, through expert testimony. We have found that a general discussion, prior to testimony, of the specifics of a case, covering PCP's history, street pharmacology including modes of administration, patterns of use, duration of effects, signs and symptoms of intoxication, toxicological screening, and effects on brain functioning provide an adequate foundation for many issues that jurors must consider (Lerner and Burns 1978). The following case histories illustrate some of the issues faced by PCP abusers, law enforcement personnel, and the courts.

CRIMINAL LITIGATION

Case 1. Determination of Implied Malice Associated With Driving While Intoxicated

Prior to 1981, in California, the most serious charge possible for death occurring as a result of alcohol- or drug-related vehicular homicide was the crime of vehicular manslaughter with gross negligence. That year, the California Supreme Court decided that second degree murder could be charged when the facts surrounding a vehicular homicide supported a finding of "implied malice." Under California law, implied malice exists where the killing results from an intentional act, the natural consequences of which are dangerous to life, which act was deliberately performed by a person who knows that his conduct endangers the life of another, and who acts with conscious disregard for life. Under this definition, it is not necessary to prove that a defendant intended to kill another. Proof of the subjective state of mind of the intoxicated driver is critical in the determination of whether the driver was acting with implied malice and therefore guilty of murder. Elements of knowledge and cognitive thinking ability must be proven.

In People vs. Ernesto Rangle Juarez[1], the issue of PCP and its effects upon a person's state of mind became the focal point of the trial. The prosecution sought to prove that Juarez intentionally used PCP, was aware that using PCP and driving an automobile was dangerous to human life, and acted with conscious disregard for human life. The defense sought to prove that Juarez's use of PCP was unintentional, and that the effect of the PCP was to render him incapable of being aware of the consequences of his conduct and unable to control his conduct; therefore, Juarez was not guilty of murder.

Summary of facts. The factual situation was important in the trial, for the resolution of the PCP issue, Evidence produced at the trial revealed that around noon on March 6, 1982, Juarez was driving his automobile in the City of South San Francisco, with three of his friends as passengers. The men smoked what Juarez claimed to be a joint of marijuana in his automobile, while parked in a store parking lot. Juarez claimed that he took only one or two inhalations from the joint. He then drove from the parking lot and became involved in two minor traffic accidents within a span of 30 seconds. Accelerating rapidly, he fled the scene. A South San Francisco police officer on patrol in the area saw Juarez's automobile and gave chase. Juarez took evasive action when the officer activated his emergency lights and siren, and Juarez's automobile reached speeds of 65 to 70 miles per hour. As the automobile approached a curve in the roadway, Juarez failed to control the automobile, which went into oncoming traffic lanes and hit the victim's car head-on, killing the victim instantly. A great deal of evidence was produced concerning Juarez's conduct and action after the accident. Juarez was not significantly

injured in the collision, although paramedics found him somewhat dazed. Police officers and medical personnel testified that he answered questions appropriately. His speech was slurred, and he appeared to be extremely intoxicated or under the influence of drugs. Approximately 1 hour after the accident, blood and urine samples were obtained for toxicological screening. The analysis revealed a PCP blood level of 30 ng/ml and a PCP urine level of 2.1 µg/ml. No alcohol was detected.

Prior to the collision, Juarez had been on probation for sales of narcotics and had been reporting to an adult probation officer. The officer testified concerning a 2-year period of probation during which Juarez continually used PCP, as evidenced by toxicological screening, a condition of probation. This information was introduced by the prosecution to show Juarez's awareness of PCP and its effect upon him.

Expert Testimony. Drug abuse experts testified on both sides. The prosecution's expert used slides and a motion picture to inform the jury of the effects of PCP. He testified that a person with a PCP blood level of 30 ng/ml would be considered under the influence of this drug, and should display nystagmus and have difficulty with coordination. A person with this blood level would be classified as being in an acute confusional state (Burns and Lerner 1981). This level would not necessarily mean that an individual would not be conscious of what he was doing, nor would he be unable to control his conduct. Emphasis was placed on Juarez's behavior on the day of the collision. Important factors presented to the jury were his history of PCP abuse, his driving ability throughout the entire incident, and his conduct and behavior after the collision. In addition, testimony was given regarding the substantial evidence of what was referred to as reality-oriented, goal-directed behavior exhibited by Juarez both before and after the collision. This testimony enabled the prosecution to argue that, despite PCP intoxication, Juarez was aware of his conduct and had the ability to make conscious decisions regarding his conduct. Under the prosecution's theory, this reality-oriented, goal-directed behavior was evidence of Juarez's state of mind of implied malice.

On this issue, the defense called a drug abuse expert who testified to Juarez's state of mind. The defense expert testified that for a person to be aware that his conduct is dangerous to another and in order for him to make a conscious decision to refrain from such activity, or to act without regard to such known danger, he must be able to engage in abstract thinking. A PCP blood level of 30 ng/ml would result in a high likelihood that there would be gross impairment of the ability of the defendant to think abstractly.

Outcome. After consideration by the jury, defense testimony was rejected and Juarez was found guilty of second degree murder. This was the first time in the history of the State that an individual was convicted of murder based upon an automobile collision while under the influence of PCP.

Case 2. Diminished Capacity Associated With PCP Intoxication

The diminished capacity defense associated with PCP intoxication has frequently been used as an explanation of an individual's conduct. In 1981, this explanation was the sentral issue in the case of People vs. Richard Cavesuella et al. that became known as the Mt. Madonna murders.

Summary of facts. In Watsonville, California, a town located near the City of Santa Cruz, two youth gangs became embroiled in a turf war that ended with the brother of Cavesuella receiving a shotgun wound to the head, which resulted in a severe, permanent brain injury. Gang and family pride led Cavesuella to seek to avenge his brother's injury. With a friend, he ventured into so-called neutral territory, to a party at a fairgrounds. There, they encountered two young males (15 and 16 years of age) associated with the rival gang. After drinking to the point of intoxication, the youths were invited out for more beer.

During a ride to a nearby park called Mt. Madonna, the youths were terrorized and one was stabbed. Very quickly, it became clear that Cavesuella was interested in revenge for his brother's shooting. Both youths protested that they were not in the other gang, nor had they been involved in the shooting. Their protests were to no avail. They were subsequently harrassed, interrogated, and stabbed repeatedly. There were approximately 140 stab wounds to the two bocies that were deposited by the side of a road.

Trial strategies. The defense described the killings as "frenzied," so that they could attempt to use the manslaughter instruction. In essence, a killing committed in the heat of passion, or upon a sudden quarrel, that is not premeditated or deliberated is manslaughter at most. The defense strategy was to make the drug be the culprit in the case. PCP had been given wide media attention and had been highlighted as causing indiscriminate fits of rage and/or violence. Toxicological screening had not been conducted at the time of Cavesuella's arrest. Nevertheless, the defense attempted to prove that Cavesuella had taken PCP and was under the influence of the drug at the time of the killings.

The prosecution's main trial issue was to counteract or show the jury that, even assuming Cavesuella ingested PCP, his acts were reality-oriented; goal-directed in such a way that the drug did not prevent him from meditating, deliberating, or harboring malice. This was accomplished by cross-examination of the defense's drug expert and presentation of testimony by the prosecution's drug expert. The defense expert was questioned repeatedly

about different facts in the case that showed the presence of reality-oriented, goal-directed behavior on the part of Cavesuella. In those areas, he indicated the presence of an intellectual capacity to premeditate and deliberate. While the expert still stuck with his opinion that Cavesuella was diminished because of the use of PCP, he conceded that he had not read the crime reports or much of the information that was utilized in cross-examination of his testimony.

Testimony by the prosecution's expert was that it was possible Cavesuella had taken PCP at some time. Whether or not he did on the night of the killings could not be determined. However, Cavesuella's actions were inconsistent with someone who, under the influence of PCP, is significantly impaired.

Outcome. The jury deliberated for 2 weeks before deciding that Cavesuella was guilty of first-degree murder with special circumstances. He was sentenced to life imprisonment without the possibility of parole.

CIVIL LITIGATION

Case 3. Death Associated With Law Enforcement Intervention

It is not uncommon for civil actions to be brought against law enforcement personnel who have come into contact with individuals under the influence of PCP. Helen A. Burns vs. City and County of Honolulu et al. represents an issue that is being brought before the courts with increasing frequency.

Summary of facts. On the night of May 10, 1979, officers from the Honolulu Police Department responded to a call that a disturbance was taking place at a night club frequented by sailors as well as by "locals." The first officers to arrive observed a group of sailors in the parking lot. A shirtless young man in this group was asked for some identification and gave one officer a card that identified him as Richard Burns. One officer went into the club to find out what had happened.

As the other officer approached, Burns yelled "Watch your back!" causing the officer to turn around, but no one was there. Burns's skin appeared to be covered with perspiration, and he appeared to have been involved in a fight. He would occasionally spit on the sidewalk and try to wipe it up with a handkerchief or rag. Once in a while he would yell "Watch your back!" and/or "Is it over?" The officer suspected that Burns was on drugs. Once Burns attempted to run past the officer, who was just barely able to restrain him. Although the officer was much larger, Burns pulled away with such ease that the officer knew if he had to hold him there was going to be a problem.

Additional officers arrived as the crowd grew, and Burns continued his bizarre behavior. A decision was made to remove Burns and

defuse the situation that seemed to be building; the supervising officer ordered him arrested for disorderly conduct. Burns backed into an officer who applied what was described as a neck hold as the officers struggled to handcuff him. There was disagreement as to whether Burns actually lost consciousness after this first hold, although he did go limp, and handcuffs were placed on his wrists. Burns was immediately back up on his feet, kicking wildly in all directions. This time an officer managed to apply a carotid restraint hold. In addition, a belt was placed around his feet. This hold was applied for not more than a fraction of a minute by all accounts.

All three officers got up from Burns at the same time. The supervising officer stated that Burns looked like anybody who was unconscious; he saw nothing out of the ordinary. Several minutes had passed after application of the second hold (there was a dispute about how many holds had been applied), at which time the officers discovered that Burns was not breathing and applied cardiopulmonary resuscitation. Burns, however, was dead.

It was later learned that Burns had accosted two female employees in a restroom. A struggle had ensued, during which a bouncer applied a neck hold; he had been kicked in the head by someone wearing a hard shoe; he was either bounced against or bounced himself against a wall, and had slipped from the grasp of five or six well-built men.

Issues at trial. The decedent's mother and his estate brought an action that came to trial in Federal court against the City and County of Honolulu for intentionally, recklessly, or negligently causing his death. The propriety of the arrest was never questioned by the plaintiff, only the manner in which it had been handled. Much of the plaintiff's case focused on attempting to prove an alleged third choke hold. The third hold was supposedly witnessed by a security guard, from a rooftop parking lot, who observed one officer come back after the second hold and "strangle" Burns for up to 14 seconds. No one else observed this, and testimony from other witnesses was that this officer had gone back into the bar after the second hold.

The medical examiner for the City and County of Honolulu ruled that the cause of Burns's death was asphyxiation. Laboratory analysis confirmed the presence of PCP in his body. However, it was the medical examiner's opinion that PCP did not play a role in the death. It was later learned that the medical examiner's knowledge of PCP was limited to articles he had read that were written by experts subsequently retained by the City and County of Honolulu.

These experts had been requested to determine the cause of death and to evaluate the officers' conduct in this matter. At trial, they testified that the medical examiner was in error regarding the cause of death. There were no statements made that anyone had

cut off the decedent's air supply for the minimum time required for asphyxiation. It was their opinion that Burns had died from an idiosyncratic reaction from a combination of control hold(s) and PCP (Burns and Lerner 1978). Testimony was also offered that, under the circumstances, and with the absence of any knowledge by police of the effects of PCP, the conduct of the officers was appropriate. It was stressed that traditional control holds may be ineffective in controlling someone under the influence of PCP. For this reason, law enforcement training in signs and symptoms of PCP intoxication and appropriate methods of control was extremely important. However, in this case, it would not be reasonable to expect officers to have this specialized training, since PCP had not been recognized as a problem in Hawaii.

Outcome. After a week of deliberation, the jury returned a finding of no improper conduct by the police in effecting the arrest. They did find the City and County of Honolulu 20 percent negligent in failing to discover sooner that Burns was not breathing, and negligent in administering CPR. However, under Hawaii law, negligence must be more than 51 percent for a cash award.

SUMMARY

These cases illustrate some of the complex issues associated with PCP-related litigation. The concept that malice is implied when an experienced drug user commits a crime while under the influence of the drug is not held in most states, at the present time.

The authors have now reviewed in detail four cases of unexpected death following the use of neck holds in PCP-intoxicated individuals. In all of the cases, multiple carotid compression holds had been attempted, according to the history. Skin abrasions, hemorrhage into the soft tissues of the neck, and fractures of the hyoid bone and thyroid cartilage provide structural evidence of the application of substantial force to the neck. On autopsy, there has been no evidence of lethal injuries to the bronchial tree, brain, or heart.

Drugs related to PCP are known to alter the carotid sinus reflex. Mechanical stimulation of the carotid sinus in the neck normally results in a slowing of heart rate and a decrease in blood pressure. Carotid sinus stimulation, coupled with the effects of PCP on blood vessels, might result in a marked fall in the blood pressure that could lead, ultimately, to death. Individuals intoxicated with PCP may be at a higher risk to complications of carotid compression neck holds. Hence, additional cases would be expected to become medicolegal issues.

FOOTNOTES

1. Charles J. Smith, Deputy District Attorney, County of San Mateo, contributed case information.

2. Arthur Danner III, District Attorney, County of Santa Cruz, contributed case information.
3. Adrienne Sepaniak King, former Deputy Corporation Counsel, City and County of Honolulu, contributed case information.

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The Long-Term Effects on Neurodevelopment in Infants Exposed Prenatally to PCP

Judy Howard, Vickie Kropenske, and Rachelle Tyler

Abuse of phencyclidine hydrochloride (PCP) is a national problem that has reached epidemic proportions in urban areas of the United States. The drug is inexpensive, readily obtainable, and is usually used in combination with other drugs such as marijuana, heroin, cocaine, and alcohol (Golden et al. 1982). The routes of PCP use include inhalation, ingestion and parenteral administration. In Los Angeles County, the number of PCP abusers seen in emergency rooms rose from 1,567 in 1980 to 3,001 in 1983, an increase of 92 percent. In addition, approximately 30 percent of these individuals were women of child-bearing age, who reported that their first use of PCP was at the age of 20 years (Husson 1984).

With the increased use of PCP by young women, pediatricians have begun to identify the newborn's neurobehavioral symptoms after in utero exposure. In 1980, Golden et al. were the first to document the placental transfer of PCP in humans and to describe the resulting neurobehavioral symptoms. They reported on one infant whose mother had smoked an average of six joints per day of marijuana dusted with PCP. The behaviors emerging shortly after birth included extreme jitteriness , coarse flapping movements in response to slight auditory or tactile stimuli, nystagmus, poor visual tracking, and hypertonicity. At 2 months of age, the infant continued to have coarse tremors, roving eye movements, and hypertonicity. Furthermore, the infant had dysmorphic features. Subsequent to this report, Strauss et al. (1981) described two other infants who had been exposed prenatally to PCP. These infants also displayed signs of irritability, tremulousness, and increased muscle tone. However, no congenital anomalies were noted.

More recently, Chasnoff et al. (1983) have described the behavior of seven infants whose mothers used PCP daily throughout their pregnancies as well as using various other drugs intermittently. As compared to a control group of 27 infants, the PCP-exposed newborns had rapid changes in their levels of consciousness, with lethargy alternating with irritability. Furthermore, these

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infants were very sensitive to auditory stimuli and had tremors and facial grimacing.

The effects of PCP in its purest form, as a single drug, have been studied in animals. In 1977, Cooper et al. noted the placental transfer of PCP in pigs. In fact, they found that plasma levels in the piglet were 10 times higher than in the sow. Other animal studies support marked neurobehavioral changes in the newborn, but have yet to incriminate PCP as a teratogen (Goodwin et al. 1980; Tonge 1973; Tenor 1974). A more specific description of the behavior of monkeys that had received PCP was given by Balster and Chait in 1976. The monkeys had nystagmus and rhythmical limb movements, and were unable to track visually.

While the aforementioned studies have described the manifestations of *in utero* exposure to PCP by human and animal fetuses as well as behaviors adult monkeys who had received only PCP, the long-term consequences of prenatal abuse have not been described. Therefore, this report will elaborate upon our observations of the effects of PCP upon the growth and development of 12 neonates between 2 and 18 months of age, whom we have followed from August 1983 to March 1985.

DESCRIPTION OF INFANTS

During an 18-month period the growth and development of eight male and four female infants exposed prenatally to phencyclidine was observed.

The Ballard Screening System (Ballard et al. 1977) was used to determine the gestational ages for the five preterm and five full-term neonates born at UCLA. Maternal dates and physical exam established the gestational ages for the two full-term infants born at community hospitals. The average gestational age for all infants was 37.75 weeks with a range of 33 to 42 weeks. The five preterm infants had a mean gestational age of 34.6 weeks with a range of 33 to 36 weeks. The average gestational age for the seven full-term infants was 40 weeks with a range of 38-42 weeks.

The 12 neonates included in this study had a mean birth weight of 2,481 grams (10 percent), a mean frontal-occipital head circumference of 31.5 cm (10 percent), and a mean crown-to-heel length of 47 cm (25 percent). Among preterm infants the respective mean weight, head circumference, and length were 1,804 grams [referent to the norms established by Lubchenco et al. (1966). this weight fell at the 10th percentile], 29 cm (10th percentile), and 42 cm (25th percentile). Full-term infants averaged a birth weight of 2,964 grams (25 percent), head circumference of 33 cm (10 percent), and length of 49 cm (25 percent). Two of the preterm neonates were small for gestational age. All infants were normocephalic and no congenital anomalies were apparent.

Urine toxicology screens from the mothers and infants were obtained during the labor and delivery and/or postnatal periods.

All specimens were analyzed by EMIT (Enzyme Immunoassay Technique), an enzyme method based upon the competitive bonding of an enzyme and an antibody. This method yields a positive result with concentrations of 75 ng of PCP/ml or greater (Rubenstein et al. 1972).

For all 12 mother-infant pairs, either the mother or the infant's toxicology report was subsequently positive for PCP. In nine cases, the screens for both mother and infant were positive. In two cases, the mother's results were positive and the infant's were negative. In one case, the infant had a positive result while the mother's test was negative. Test sensitivity, specimen handling procedures, and delays in obtaining specimens undoubtedly contributed to the inconsistency in paired results. Cocaine, codeine, and glutethemide, in addition to phencyclidine, were identified in the urine toxicology screens of two mothers and their neonates.

All infants developed deviant neurobehavioral symptoms within the first 24 hours of life. Most commonly, the neonates were found to have symptoms of irritability, tremors, and hypertonicity. Bizarre eye movements and staring spells were seen in 25 percent of infants. Poor sucking, lethargy, diarrhea, and facial twitching, symptoms commonly associated with prenatal opiate exposure, were seen infrequently in these PCP-addicted infants.

In addition, the temperature, pulse, and respiratory rates for 10 infants were reviewed for evidence of drug effects on autonomic nervous system function. However, no abnormal patterns were noted during the course of hospitalization.

In 58 percent of cases, symptomatic treatment with Valium, phenobarbital, or paregoric, for a period ranging from 2 to 14 days, was required to control drug effects. However, in 42 percent of the cases, symptoms were successfully managed with more conservative measures such as swaddling, use of a pacifier, decreased environmental stimulation and excessive handling, and modification of feeding schedules and techniques. Although all infants remained symptomatic, only two neonates continued to require medication at the time of discharge.

In addition to normal neurobehavioral symptoms, 67 percent of infants were also noted to have one or more medical problems during the perinatal period including respiratory distress, meconium-stained amniotic fluid, hyperbilirubinemia, anemia, syphilis, omphalitis, and electrolyte imbalances. Meconium staining and respiratory distress were the most commonly observed problems for both preterm and full-term infants. However, among preterm neonates, respiratory problems were noted with much greater frequency, and the severity of the preterms' early respiratory problems

continued to lower 1-minute Apgar scores. Eighty percent of preterm Infants had Apgar scores below 7 at 1 minute, compared to 14 percent of full-term infants with low 1-minute scores. Among 43 percent of full-term infants, the sole identified medical problem was abnormal neurobehavioral signs. In contrast, during the perinatal period, 80 percent of preterm infants experienced three or more medical problems in addition to withdrawal symptoms.

TABLE 1. *Incidence of neonatal medical problems*

Medical Problem	Preterm n=5 n(%)	Term n=7 n(%)	Combined Groups n=12 n(%)
Withdrawal symptoms			
Jittery	5 (100)	7 (100)	12 (100)
Irritable	1 (20)	4 (57)	5 (42)
Hyperreflexia/hypertonic	2 (40)	3 (43)	5 (42)
Hypertonic	2 (40)	1 (14)	3 (25)
Abnormal eye movements	1 (20)	2 (29)	3 (25)
Poor suck	2 (40)	-	2 (17)
Lethargic	2 (40)	-	2 (17)
Diarrhea	1 (20)	-	1 (8)
Prematurity	5 (100)	-	5 (42)
Meconium	2 (40)	3 (43)	5 (42)
Respiratory distress	3 (60)	2 (29)	5 (42)
Hyperbilirubinemia	2 (40)	1 (14)	3 (25)
Anemia	1 (20)	1 (14)	2 (17)
SGA	2 (40)	-	2 (17)
Syphilis	1 (20)	1 (14)	2 (17)
Electrolyte imbalances	2 (40)	-	2 (17)
Omphalitis	1 (20)	-	1 (8)

The medical problems and slow weight gain of the preterm infants contributed to their prolonged hospitalization. The five preterm infants remained in the hospital an average of 24 days with a range of 10 to 37 days. At UCLA, infants between 33 and 37 weeks' gestational age routinely require 10 days of hospitalization. The seven full-term infants had a mean hospital stay of 8 days with a range of 4 to 14 days. While the average length of hospitalization at UCLA is routinely 2 1/2 days for full-term infants, the stay for these essentially healthy infants was extended to monitor their neurological status, and to taper or stabilize medications.

At the time of discharge , all infants were placed in the homes of relatives or foster parents. In the State of California, a child born withdrawing from drugs or alcohol is considered to be abused and must be reported to child protection agencies (Los Angeles County 1982). Therefore, all the infants reported in this paper

were identified as having been abused, were referred for court supervision, and were placed in foster homes or with extended-family members during the period of follow-up observation.

TABLE 2. *Summary of neonatal data*

Data	Preterm n=5 n(%)	Term n=7 n(%)	Combined Groups n=12 n(%)
Sex			
Male	5(100)	3(43)	8(67)
Female	-	4(57)	4(33)
Gestational age	34.6 ± 1.5	40 ± 1.3	37.75 ± 3.1
Birth weight (grams)	1,804 ± 170	2,964 ± 366	2,481 ± 664
Head circumference	29 ± 0.7	33 ± 0.6	31.5 ± 2.2
Birth length	42 ± 2.8	49 ± 2.2	47 ± 4.3
Apgar scores			
1 minute	4.4 ± 2.9	7 ± 2.7	5.9 ± 2.9
5 minutes	6.8 ± 2.9	8.4 ± 1.2	7.6 ± 2.1
6 at 1 minute	4(80)	1(14)	5(42)
Withdrawal			
Mild (no meds.)	2(40)	3(43)	5(42)
Moderate (meds. 2 weeks)	3(60)	4(57)	7(58)
Length of hospitalization	24.6 ± 9.7	8.7 ± 3.1	15.3 ± 10.3

GROUTH PARAMETERS

The physical growth scales used are those published by the National Center for Health Statistics: percentiles which are based upon the work of Lubchenco et al. in 1966. The infant's weight, height, and head circumference were adjusted for sex and corrected for prematurity.

At an age of 35 weeks, the mean weight and head circumference were at the 10th percentile and height was at the 25th percentile. By 18 months of age, five infants had a mean weight between the 25th and 50th percentile, and a mean height at the 75th percentile. The mean head circumference of the four males was at the 10th percentile. The one female's head circumference was at the 50th percentile.

DESCRIPTION OF MOTHERS

Maternal data were obtained during interviews with the mothers following delivery and by review of the maternal and infant medical records.

The mean maternal age for the 12 mothers included in this study was 25.8 years, with a range of 20 to 31 years. Mother's race was: 75 percent black, 17 percent white, and 8 percent Hispanic. All were low income. Eighty-three percent of the women were multiparas with an average of 5.2 previous pregnancies and 2.7 live births.

TABLE 3. *Summary of maternal demographic data*

Maternal Status	Preterm n=5 n(%)	Term n=7 n(%)	Combined Groups n=12 n(%)
Age	27.6 ± 3	24.6 ± 3.7	25.8 ± 3.5
Race			
Black	4(80)	5(71)	9(75)
Hispanic	1(20)	1(14)	2(17)
White		1(14)	1(8)
Gravida	4.1 ± 1.3	5 ± 3.5	4.8 ± 2.7
Para	2.2 ± 1.7	4 ± 2.8	3.3 ± 2.4
Marital status			
Single	4(80)	5(71)	9(75)
Married	-	1(14)	
Separated	1(20)		1(8)
Divorced	-	1(14)	1(8)

Criteria developed in the National Institute of Medicine Study (Gortmaker 1979) was used to establish the adequacy of prenatal care. In 67 percent of our 12 cases, prenatal care during pregnancy was inadequate. However, among mothers of preterm infants, care was inadequate in all cases. Thirty-three percent of all mothers received no prenatal care.

TABLE 4. *Characteristics of prenatal care*

Level of Care	Preterm n=5 n(%)	Term n=7 n(%)	Combined Groups n=12 n(%)
Adequate	-	2(29)	2(17)
Intermediate	-	2(29)	2(17)
Inadequate	5(100)	3(43)	8(67)

Mothers of preterm infants were also more likely than mothers of full-term infants to have obstetrical complications at the time of delivery. Eighty percent of mothers of preterm infants had three or more obstetrical complications. Possible complications included premature labor. oremature rupture of membranes, prolonged rupture of membranes', Caesarean section, chorioamnionitis, and marginal placenta abruption. In contrast, only one mother of a full-term infant developed obstetrical complications during the perinatal period.

However, the pregnancies of 67 percent of all mothers were complicated by a variety of medical problems including anemia, hepatitis B, syphilis, and psychiatric emergencies. At the time of delivery, 57 percent of mothers of full-term infants and 80 percent of mothers of preterm infants were noted to have had one or more medical problems during the pregnancy. Seventy-five percent of all mothers smoked.

TABLE 5. *Incidence* of *maternal perinatal obstetrical and medical complications*

Complications	Preterm n=5 n(%)	Term n=7 n(%)	Combined Groups n=12 n(%)
Premature labor	5(100)	-	5(42)
Premature rupture of membranes	5(100)	-	5(42)
Prolonged rupture of membranes	3(60)	-	3(25)
Caesarean section	2(40)	1(14)	3(25)
Marginal placental abruption	1(20)	-	1(8)
Chorioamnionitis	2(40)	-	2(17)
Anemia	2(40)	1(14)	3(25)
Hepatitis B	1(20)	1(14)	2(17)
Syphilis	1(20)	1(14)	2(17)
Psychiatric hospitalization	1(20)	1(14)	2(17)
Smoking	4(80)	5(71)	9(75)

Maternal reports of drug use during pregnancies reflected a pattern of polydrug exposure during the gestational period. In only two cases was phencyclidine the sole reported drug of abuse. Alcohol, marijuana, and cocaine were commonly used in varying combinations with PCP. The extent of reported maternal use of phencyclidine ranged from daily smoking of PCP-laced cigarettes to "one-time" use 3 months prior to delivery. Fifty-eight percent of women reported smoking as the primary route of ingestion. percent of cases, the method of use is unknown.

Information regarding the long-term history of drug abuse was available for eight mothers: four who delivered full-term infants and four mothers of preterm infants. The average number of years of drug use for this group of mothers was 7.4 years, with a range of 3 to 15 years.

TABLE 6. *Incidence of reported maternal drug use during pregnancy*

Drug Used	Preterm n=5 n(%)	Term n=7 n(%)	Combined Groups n=12 n(%)
PCP	5(100)	7(100)	12(100)
Alcohol	4(80)	2(29)	6(50)
Marijuana	3(60)	2(29)	5(42)
Cocaine	2(40)	1(14)	3(25)
Valium	1(20)	-	1(8)
Doriden	1(20)	-	1(8)
Heroin	-	1(14)	1(8)

Of the 10 mothers who delivered at UCLA Medical Center, one returned for the scheduled 6-week follow-up appointment. Twenty-five percent of all mothers have had repeat pregnancies.

DESCRIPTION OF THE INFANTS' POSTDISCHARGE ENVIRONMENT

Following their hospitalization, all infants were placed with foster parents or in the care of extended-family members. Four infants were discharged to relatives and eight infants were placed in foster care. Later, two of the foster children were also placed with extended families.

During the follow-up period, no infant was returned to the care of the mother. In 25 percent of cases, the child was essentially abandoned after delivery. While, in the remaining 75 percent of cases, the mothers expressed a strong desire to care for their infants, none of the parents was able to complete a drug rehabilitation program and/or successfully sustain a drug-free life style, conditions stipulated by the court as the basis for reunification. Furthermore, there was evidence from previous childrearing patterns that the mothers who already had children would have difficulty managing the caretaking responsibility for the new infant, if the parents' drug use continued.

Of mothers who had older children (58 percent), 85 percent already had one or more of their offspring in foster placement or in the care of extended-family members. In addition, physical and

developmental evaluations of six children who were living with two of the mothers at the time of this delivery revealed significant developmental delays in two of the children, and emotional and school problems among the four siblings. Medical neglect was also evident in all six children.

After discharge, all infants were followed by a team composed of a pediatrician with subspecialty training in Child Development, a public health nurse, and a social worker. In order to maintain contact with the foster families and relatives who had responsibility for the care of the infant, team members made regular home visits and had frequent telephone contact with the infants' caretakers. During the first 3 months of placement, infants were seen (an average of twice per month) for follow-up visits at home or in the UCLA Child Development Clinic. Phone conferences with caretakers were held on a biweekly basis. During the following 3 months, clinic and home visits were tapered to once per month and phone contacts were made biweekly.

Team members provided and coordinated referrals to a variety of community agencies, and supported caretakers in learning about normal infant development, sleep-wake patterns, and feeding schedules and appropriate foods. Caretakers were also helped to understand the infants' developmental strengths, what would effectively soothe him/her, and what play activities were appropriate at certain ages.

The team also assisted the infants' caretakers with obtaining appropriate medical care and treatment. The primary health care of 58 percent of the infants was received from physicians who lived within the foster family's community; 42 percent of infants returned to the UCLA Pediatric Clinic for routine pediatric follow-up. In order to promote optimal medical care for all infants, team members provided the primary physician with summaries of the child's birth history, developmental progress, and information regarding the medical treatment and management of the PCP-exposed infant.

The intent of these specialized follow-up services to families was to provide education, support, and anticipatory guidance in order to maintain a nurturing and stable environment for the high-risk infant. In 67 percent of the 12 cases, the infant did remain in the same home environment throughout the follow-up period. There were, however, four infants who had multiple changes in placement following discharge. Among these four cases, three infants were placed in two different homes within the first 2 months of life. Thereafter their placements were stable. The fourth infant experienced four placements during the first 9 months, two placements being with foster parents and two with relatives.

DEVELOPMENTAL OUTCOME OF INFANTS

In order to determine the infants' behaviors in the areas of gross motor, fine motor, adaptive, language, and personal-social development, the standardized Gesell Developmental Evaluation (Gesell & Amatruda 1954) was administered to them. This examination provides a developmental age (DA) and developmental quotient (DQ) (ascertained by dividing the chronological age into the developmental age) in each of the five areas of behavior, and an aggregate DA and DQ. For those infants born preterm, correction for their gestational age was made. The average DQ is 100.

The DQ's of eight infants who had a mean age of 34.5 weeks are described in table 7. The DQ's of five infants who had a mean age of 17.75 months are described in table 8.

TABLE 7. *Gesell developmental evaluation of 8 infants at 34.5 weeks (±4.6)*

Developmental Area	Developmental Quotient
Gross motor	106 ± 32.9
Fine motor	81 ± 18.7
Adaptive	90 ± 20.1
Language	96 ± 14
Personal-social	103 ± 19
Aggregate score	96 ± 18

TABLE 8. *Gesell developmental evaluation of 5 infants at 17.75 months (±1.1)*

Developmental Area	Developmental Quotient
Gross motor	114 ± 14
Fine motor	86 ± 12.9
Adaptive	93 ± 17.5
Language	86 ± 11.1
Personal-social	90 ± 8.4
Aggregate score	94 ± 11.3

The evaluation results are mildly worrisome; however, the quality of the infants' behaviors are very worrisome. In the area of fine motor development, the infants performed in the low normal range. Furthermore, the items used to score fine motor behaviors do not identify deviant movements required for the fine motor act. For instance, each of these infants displayed abnormal movement

patterns when attempting to grasp small objects. The movements of the arms were awkward and the positioning of the hands was peculiar in that the fingers were held in an extended, splayed position. There was a palmar approach to the cube, with overextension of the mark and an overhand approach. When the infants attempted to retrieve a small pellet, they would bat at the pellet with their palms, and seemed to have difficulty flexing their extended fingers. Some infants were very persistent in their attempts to grab the objects, other were easily frustrated. Paralyses and weaknesses were not seen. Tactile and/or proprioceptive dysfunction are possible causes for these peculiar movements of the arms and hands.

The infants' gross motor milestones were obtained well within the normal range. However, observations of their early attempts to walk independently revealed awkward leg movements and placement of their feet. These movements improved over time as did the total arm movements.

Eye movements were noted to be deviant in 25 percent of the infants during the neonatal period. Nystagmus and darting eye movements were seen. Also, a glazed stare associated with total body stillness was frequently seen during the first 6 weeks.

The infants' adaptive or playing behaviors with the test objects showed the infants to be spontaneous in their approach to the toys and to demonstrate an interest in manipulating them. Some infants were easily frustrated by their inability to manipulate the objects due to their fine motor difficulties. However, there was no evidence of gross retardation in the emerging cognitive areas.

Language skills were more difficult to evaluate. The infants' caretakers reported age-appropriate vocalizations. However, at clinic and home visits, we found the infants to be less vocal during the 1-hour session than we would have anticipated.

A further area of concern is the infants' personal-social development. During the latter half of the first year, we noted seemingly appropriate eye contact with their primary caretakers as well as joyful expressions. However, during the first half of the second year, the primary caretakers expressed concern about the infants' emerging interactive and affective behaviors. These infants seem more prone to oppositional behavior demonstrated by temper tantrums, and less enjoyment of social interaction with the adults in their environment.

DISCUSSION

The clinical characteristics of newborns exposed prenatally to PCP are similar to behavior patterns of infants born addicted to heroin and/or methadone. In 1973, Wilson et al. described the early development of infants of heroin-addicted mothers. The neurobehavioral symptoms of the newborn included tremors, irritability,

and hypertonia. Following discharge from the hospital, these infants continued to be agitated and restless. By the second half of the first year, the infants slept for longer periods of time and became less irritable. However, between 1 and 2 years of age, the authors noted increased activity levels and impaired attention span.

Clinical experience with the infants exposed primarily to PCP prenatally is remarkably close to Wilson et al. These neonates are difficult to console, have alternating periods of lethargy and irritability, and are unable to control the tremors of their extremities when unswaddled. Vasomotor instability, diarrhea, and voracious sucking movements are infrequently seen in the PCP-exposed infants who were followed. Chasnoff et al. (1983) compared these behaviors in infants exposed prenatally to PCP to those of adults who have acute intoxication.

McCarron's paper (this volume) describes the behaviors of 1,000 adults admitted to an inpatient service with acute symptoms of PCP intoxication. She states that some of the patients have appropriate behavior while many have mute and staring episodes, bizarre facial grimacing, localized dystonic reactions, rigidity, tremors, coarse jerky movements, and nystagmus. Thus, there is similarity between the acutely intoxicated adult's behavior and that of the newborn with a positive urine toxic screen for PCP.

Following the initial period of observation, the infants frequently continued to be highly irritable and sensitive to tactile and auditory stimuli during the first half of the year. They were also unable to adjust to a sleep-wake cycle that contained extended periods of sleep during the night (Parmelee 1977). In addition, some infants continued to demonstrate sudden changes in motor tone, ranging from hypotonia during sleep to rigidity that would awaken them and cause intense crying. By 9 months of age, most infants had become easier to manage because of increasing sleep periods and lessening of irritability.

As the infants were emerging into a more predictable pattern of behavior, the deviant fine motor movements became apparent. Central nervous system maturation progresses in a cephalo-caudal manner, allowing for differentiation of fine motor movements, as those seen in the pincer grasp by 9 months (Gesell et al. 1954). Fair evaluation of the fine motor system was not possible until the last quarter of the first year.

The observations of fine motor problems in infants born to heroin addicts has also been described by Wilson et al., in 1973. She notes the discrepancy between the gross motor skills of the infants and fine motor abilities during the first year. Furthermore, in 1979, Wilson et al, described the development of preschool children between 3 and 6 years of age, born to heroin-addicted mothers. They performed poorer on measures of visual, tactile, and auditory perception, were more active, and had

greater difficulties in the process of organization than the children born to mothers who did not use drugs. The poor fine motor abilities of these preschoolers were attributed to their poor attention span and persistence rather than to a central nervous system dysfunction. Unfortunately, these preschoolers' fine motor movements were not described.

The most recent studies addressing the outcome of infants exposed to drugs prenatally tend to stress the importance of the perinatal problems and the poor environment. Lifschitz et al. (1985) studied the effects of prenatal exposure to heroin and methadone on head growth and neurodevelopmental performance in preschool children. They found that the factors associated with postnatal head growth were birth weight, interpartum risk, and race. Furthermore, the increased incidence of low-average and mildly retarded intellectual performance in the drug-exposed children was related to the amount of prenatal care, prenatal risk, and the home environment. The amount of narcotics used by the mother during her pregnancy was not a significant factor. The narcotic index used in their data analysis was solely based upon the mothers' report of drugs taken during their pregnancies. Experience indicates that these reports are not reliable and, in addition, the quality of the street drugs is notoriously uneven.

Chasnoff et al. (1984) have reported on the developmental outcome of three groups of children, from birth until 2 years of age. The methadone, polydrug, and control groups demonstrated a downward trend in scores in the Bayley Scales of Infant Development. Their interpretation is that the infants' environment and subsequent lack of stimulation has a more direct influence on long-term development than does maternal use of drugs during pregnancy.

These findings are in contrast to the developmental outcome of the PCP infants reported in this paper. In spite of the consistent, nurturing environments, these infants have consistently demonstrated borderline abilities in fine motor, adaptive, language and personal-social development.

The effects of PCP, heroin, and methadone upon the developing fetus may indeed be different. We have found that the PCP infants are more deviant in their development than the reported development of the heroin and methadone infants. Our concerns about stating that drug use by the mothers during pregnancy does not affect developmental outcome are great.

Information from well-controlled animal studies that focus on the effects of prenatal exposure to single and polydrug use will be of great value. Further evaluation of the fine motor movements that appear to be clearly neurologically deviant in the PCP-exposed infants is essential. The emerging socialization skills during the second year of life also need more detailed evaluations.

Future effort:; in this area of study must be collaborative. Psychopharmacologists, biochemists, neurologists, psychiatrists, pediatricians, psychologists, and other health care providers need to share their observations about the effects of drugs upon the various organ systems as well as upon the behavior of the species studied. Clinically, we recognize that drug levels in most instances cannot be detected in the urine for more than 3 days after last use (Baumgartner et al., in press). Furthermore, within this 3-day period, we cannot determine when or how much of the drug(s) was taken. Thus, we have a difficult time defining the groups we are to study. Attrition of subjects is another problem. However, it has been our experience that an intensive service program incorporated in the research design lessens this problem. By combining the knowledge gained about drugs from animal studies, quantifying the drugs in the system, carefully assessing the neurobehavioral activities of the developing infant through videotape analysis, and stabilizing the infants' environments, we will learn about the effects of the drugs upon the developing fetus.

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Clinical Observations in the Treatment of Adolescent and Young Adult PCP Abusers

David H. Fram and Nancy Stone

INTRODUCTION

Over the past 20 to 25 years, drug abuse has become a major public health issue in this country. An "epidemic" of abuse commenced in the sixties that had not been seen before (Wilford 1981). Drug abuse has, however, always been pandemic. People have always sought out psychoactive substances for their euphoriant properties. Individuals impaired by the excessive use of such substances have always been a concern. Our society has taken both therapeutic and law enforcement approaches to dealing with the problems of drug abuse. Our country's unsuccessful experiment with Prohibition in the twenties and early thirties demonstrated the difficulties of legislatively attempting to change culturally accepted ways of handling psychoactive substances. More recently, the disregard for laws regulating the use of marijuana and other substances have demonstrated the continuing difficulty of legislating contraculturally.

The concern over most substances of abuse arises from the effect of the drug use on the individual's health or social functioning. Negative attitudes toward the use of substances may be founded upon a desire to limit the damage done to individuals, or to limit the burden on society of supporting chronically intoxicated individuals, who have diminished ability to care for themselves. Antisocial activities engaged in during illegal procurement of drugs, or behavior resulting from impaired judgment while intoxicated may present a hazard to persons other than the drug abuser. The illegal distribution system for drugs provides, of course, a significant danger to the community from both individual and organized illegal activities that such a system fosters. It is generally accepted that the primary impetus for antisocial activity is the procurement of drugs, rather than the effect of drugs.

The problem of phencyclidine (PCP) abuse has an added dimension. In addition to the antisocial activities involved in procurement, PCP has effects on the user that may evoke dangerous, bizarre, or

deviant behavior. These effects may be considered undesirable by the user, or may be sought after. Our understanding of this drug needs to take into account not only the PCP user's desire for euphoria, but also the user's acceptance of, often seeking of, the behavioral effects.

The work of the Psychiatric Institute of Washington and the Metropolitan Psychiatric Group provides considerable opportunity for clinical observations of PCP users. Much of the author's professional time and nearly all of mine is spent evaluating and treating disturbed individuals with severe drug dependence problems, or supervising the work of our staff members, who collaborate with us. Our programs and practices treat about 150 patients, of whom approximately 20 are PCP abusers. There are about 500 admissions per year including approximately 75 who use PCP. Psychiatric Institute of Washington is a private psychiatric hospital in Washington, D.C., which has clinical services for both adolescent and adult substance abusers. Metropolitan Psychiatric Group is the group practice that conducts much of the treatment at Psychiatric Institute. While the Psychiatric Institute has maintained drug treatment services for more than 10 years (Capodonno et al. 1984), recently it became necessary to organize a special admissions service to treat PCP users, because of the particular difficulties in engaging these patients in treatment.

PCP has been a drug of abuse in Washington, D.C. for the entire 15 years that this author have been working with drug abusers. Until the past few years, it tended to be used either unknowingly, as an adulterant of other drugs, or as one of many drugs used by polydrug users. A few disturbed young people may have used it as the drug of preference to enhance their disturbances. It was, initially, a drug primarily used by young, white, middle-class users. Recently there has been a marked change in the patterns of its use in the District of Columbia. PCP has become the drug of choice for many users. Its use has become more widespread, and it is now used in the black community, where it had not been seen much before.

CLINICAL OBSERVATIONS--YOUNG ADULTS

When asked why they use PCP, young people frequently answer, "to get high." Drug users want "to get high" for the easily obtainable pleasure that is, for the young, worth the adverse effects and other costs. Young people also use drugs to be part of the group. The term "peer pressure" is often used to describe this phenomenon. I think that "peer example" or "following the crowd" describes the phenomenon better. I have rarely heard of anyone being forced or pressured to use drugs. Rather, being a member of the drug culture is highly valued, and the use of drugs, including PCP, comes as a result.

We need to understand better why being a member of the drug culture became so highly valued. Until the sixties, drug abuse

was mostly the domain of the "inner city" and the criminal subculture. At that time, however, a major social change commenced, in which the recreational use of illicit substances, especially marijuana and cocaine, eventually became a part of the dominant culture. In addition, we saw the development of the subculture of heavy drug users, made up of individuals often exhibiting markedly deviant behavior. Both of these developments had their roots in the disaffection of the sixties, with its widespread rejection of traditional "establishment" values by youth, often focused around a rejection of our country's involvement in the Vietnam War.

I think that it is important to attempt to understand these sociocultural aspects of drug abuse. Perhaps we can then better understand why a drug like PCP, after being around for a time, suddenly becomes fashionable. Perhaps also, as we understand these phenomena of social change better, we can develop more effective means of primary prevention, and perhaps foster social change that might discourage the use of such drugs.

Another important problem is why some drug users prefer PCP, while others avoid it. The answers are probably found in biological and psychological variations in individuals, and also in the constituents of different mixtures of PCP available on the street. I have found it instructive to discuss this point with drug abusers who avoid PCP. Some have never used it because of the horror stories they have heard. I have worked with several dozen young drug abusers who tried PCP and did not like it. Some reported experiencing paranoia, frightening hallucinations, or dysphoria, which they did not want to repeat. Others described an intense loss of control, far in excess of what they could tolerate. They felt that they would be dominated by the use of PCP, if they continued to use it.

Other drug abusers, however, who continued to use PCP, described experiences that they intentionally sought. For many, the experience appears to be a relatively mild one, in which the user has a pleasant intoxication that lasts several hours and then wears off. Such users, although often aware of the bizarre or violence-producing experiences of others, have never experienced such episodes themselves. Some report having used PCP repeatedly, for many years, without experiencing any effects other than a simple high. Clinical observation of these people, furthermore, does not demonstrate deterioration of intellectual functioning or obvious personality change. For these users, PCP offers an inexpensive, pleasant high. It is often the discovery of their use of substances by someone else, such as an employer in the case of an adult, or a parent in the case of an adolescent, that brings such individuals into treatment.

Another group of users appears to seek the bizarreness and lack of control that PCP offers. These individuals, who are likely to manifest much psychopathology apart from the drug abuse, are often threatening and violent. They perceive the actions of others as

being threatening, and deny the significance of their own actions. Two cases are instructive. Both were PCP users in late adolescence who came for treatment after getting in trouble with the law. One had wrecked his truck after hearing PCP-induced voices commanding him to do so. He spoke of how much he loved to be violent and hurt others. He did have some inhibitions about expressing violence, so found PCP the optimal drug for "putting him in the mood" to be violent.

The second patient, a 19-year-old, was, upon entering my office, immediately suspicious, irritable, irrational, and showed characteristic decreased psychomotor activity and intense staring expression. As the person who does most of the outpatient intake evaluations for the adult drug program, I have become very wary of new patients who enter with characteristics of PCP use. When the patient casually mentioned, early in the interview, that he had just been released from jail on a charge of assaulting a police officer, I wondered to myself if he had a weapon in the umbrella he was carrying--on a warm, sunny day. He became agitated and threatening in the course of the interview, and eventually had to be escorted from my office by the police. The following morning he called, apologetic, but not comprehending why I and my staff responded to him the way we had. He remembered everything, but lacked an appreciation of the emotional impact of his actions. Later the same day, intoxicated again, he called to scream threats and profanity over the phone.

Both of these young men appeared to use PCP to enhance a desired loss of control. PCP-induced loss of control also raises forensic considerations. A few years ago, I received a call from a lawyer defending a young man accused of assault during a robbery. At issue was the question of possible diminished criminal responsibility, as the defendant acknowledged using PCP before the alleged incident. He had been noted to be more brutal in his treatment of the victims of the assault than his nonintoxicated cohorts. The lawyer was trying to build an insanity defense. I declined to become involved in the case, as I believe that individuals should be held responsible for actions committed while intoxicated. I have been pleased to note the legal trend away from considering the altered states of mind induced by drugs as grounds for diminished criminal responsibility for acts committed while in a drug-induced condition.

Another important area for consideration is that of the addiction- and dependence-producing potential of PCP. Our observations are that PCP does not produce classical physical addiction in the sense of the development of tolerance and withdrawal symptoms. It does, however, produce drug craving, although to a lesser degree than does heroin. Users apparently develop a compulsion to repeat the PCP experience, but do not seem to organize their lives around drug-seeking behavior as do heroin users.

CLINICAL OBSERVATIONS--ADOLESCENTS

Some of the same factors that apply to all adolescents with chemical abuse dependency problems contribute to the use of PCP. A principal developmental task of adolescence is that of separating from parents and consolidating one's identity as a separate person, who will be able to cope with independence. Adolescents will often engage in activities of which parents disapprove, to assert their independence and protect themselves from a felt need to return to emotional dependency. Furthermore, adolescents rely on peers, who may also be using street drugs, for information about the world as well as for support for their self-esteem. The capacity for denial and for risk-taking, and the need for excitement, all make experimentation with illicit drugs attractive to adolescents. Adolescents have a remarkable capacity for denial. The argument often goes that "drugs won't hurt me," "I know lots of people that use drugs all the time and make good grades, play on the football team," and so forth. Adolescent drug users will frequently maintain that the real problem is that adults are trying to scare them, that parents are gullible and believe everything they hear about drugs. Thus, the early adolescent's egocentric and immature sense of the world, the initial pleasurable effects of drug use, and the possible biological vulnerability to chemical dependence implement the use of street drugs as an attempt to solve some of the problems of adolescence. Biological vulnerability to chemical dependence, which may account for the progression in some adolescents from experimentation to dependence, is an area for further research.

A personality type that leads to a preference for PCP as the drug of choice has not been identified. Experience has shown that disturbed adolescents for whom PCP is a drug of choice have histories indicating significant depression, feelings of hopelessness, powerlessness, and dysphoria, prior to the use of PCP. The feelings of power and invulnerability obtained from PCP use seem to be sought by some, while others appear to seek the feeling of "numbness" that this drug provides. Many adolescents with PCP psychosis who have been admitted to Psychiatric Institute have characteristics like those described in PCP users admitted to psychiatric facilities elsewhere (DeAngelis and Goldstein 1978). They exhibit minimal coping skills, including lack of employable skills, limited academic skills, and minimal meaningful interpersonal relationships. Depression, and a sense of alienation and hopelessness about themselves and the future are also observed. This profile, however, does not distinguish PCP-using adolescents from many other adolescents seen, who do not use PCP. As yet, there is no satisfactory explanation for why some adolescents with this profile abuse PCP and others do not.

TREATMENT CONSIDERATIONS

The literature regarding treatment of PCP users is not encouraging (Graeven and Sharp 1981; Russ and Wang 1979). Our experience has

been similar to others in that the percentage of patients who remain only for detoxification, then leave the hospital against medical advice, is discouragingly high. This pattern is particularly seen in patients over 17, who are legally adults and make their own decisions about treatment.

Treatment of the Intoxicated Patient

An initial evaluation of the intoxicated patient is needed to determine the level of care indicated. Some patients, although frequent users, may have sufficient ego strength, behavioral control, and capacity to form a treatment alliance to commence treatment in an outpatient setting. Their repeated PCP intoxications may continue for a time, but the intoxication picture is sufficiently benign to allow an outpatient program to be conducted safely, and with a reasonable chance of success.

Other patients require hospitalization. Some present with a psychotic picture: paranoia, irritability, agitation, and a tendency to violent behavior. The diagnosis of this condition is often not too difficult to make. Patients tend to readily acknowledge their use of PCP. Moreover, the irritable, easily angered, suspiciously staring, rigid person with impaired reasoning is not hard to spot. Urine testing for drugs can be done to verify the diagnosis when there is doubt.

Psychoses, when they occur, appear to be due to drug effect interacting with a vulnerable personality organization (Luisada 1978). Our experience has been that some adolescents with borderline personality disorders, as well as adolescents at risk of schizophrenic decompensation, may have this vulnerability. Although we do not have hard data to support the hypothesis that patients with PCP psychoses that are most resistant to treatment have the poorest long-term prognosis (Erard et al. 1980), our observations have been that persistence of symptoms of psychosis after the first 2 to 3 weeks of treatment often correlates with extended periods of impairment.

When hospital treatment is indicated, we have found that a closed, highly structured, intensely staffed setting is required. Until recently, when we started getting greater numbers of referrals of PCP abusers, we treated those who came on our general drug-dependence services. The PCP abusers were very difficult to manage, resistant to treatment, and frequently left treatment early. We established, on our locked intensive care unit, a separate admissions service with therapy sessions and educational sessions focused on PCP problems. Following this 2-week program of evaluation and acute treatment, the patient is then sent to continuing treatment, either in a residential/hospital setting for general drug patients or to our outpatient PCP-specialized program.

Pharmacotherapy for PCP-intoxicated patients is delayed. For the first 48 hours of admission we avoid all psychotropic medication,

if possible, and try to manage the patient by placing him in a quiet, secure environment with a few people to relate to. After this period, we encourage the patient to take haloperidol in order to ameliorate the psychotic process as much as possible.

Although it has not been proven that acidification of the urine to increase PCP excretion alters the duration of the symptoms of psychosis, it appears appropriate to facilitate excretion of PCP from the adipose tissue in which it is stored in any PCP user (Done 1980). Maintaining the urine pH at an acid level for several weeks, even though the mental status is normal, is advised. It is important to test the pH of the urine to ensure compliance with the acidification. We have found that PCP becomes detectable in acidified urine for a time, even after being undetectable in alkaline urine, in previously intoxicated individuals. We have not found a change in mental status to result from such acidification treatment and resultant enhanced PCP excretion.

Finding ways to enhance the treatment alliance and decrease denial are major tasks of the hospital phase of treatment. One method used to engage the patient is to engage the family actively. Staff spend a lot of their time talking with families, educating them, increasing their understanding of what has happened to their ill family members, and also helping the family to change habitual ways of relating to the patient, patterns that have facilitated or "enabled" rather than discouraged drug use. Often a change in family interaction can make the difference in success or failure of treatment. For example, families are often very tolerant of deviation or irresponsible behavior. Members will continue to support or cover for their family members, fearing that patients will be hurt if held accountable for their actions. In fact, the family members' tolerance has often reinforced the deviant behavior. The family sessions help the family members understand this and also provide support for behavioral change.

Narcotics Anonymous (NA)

Another important focus in developing a workable treatment plan for these patients is promoting their involvement with Narcotics Anonymous, or NA. The phenomenal growth of NA in the Washington, D.C. area over the past 2 to 3 years may be the most hopeful thing that has happened with regard to the drug problem in recent years. Good hospital programs, good detoxification techniques, talented therapists and counselors are weak forces, compared to the pressures that reinforce drug use in the outside community. In our experience, Alcoholics Anonymous has been useful in the past for only a limited number of drug abusers, as many drug-dependent individuals do not identify sufficiently with the dominant alcoholic group, therefore do not remain involved in Alcoholics Anonymous. Narcotics Anonymous is an organization of people who have experienced the drug-use lifestyle, rejected that lifestyle, and are developing another. NA provides a drug-free model for the recovering person, a social milieu, and a value system that

promotes continued abstinence. NA members state their beliefs loudly and publicly, and provide needed support for each other, especially at times of weakness. Membership in and identification with NA provides, for many, the counterforce needed to withstand the lure of the drug-abusing peer group. Consequently, a major thrust in the PCP admissions service, as well as the other components of the drug-dependence services, is to acquaint the patient with NA and persuade him of the importance of membership and participation.

Aftercare Treatment

The outpatient aftercare phase of the program is where the difficult long-term changes in the individual's relation to drugs take place. Changes commenced in the protective inpatient environment are tested in the outside environment. We recommend that our patients attend a group therapy program for recovering PCP abusers, which meets twice weekly and includes regular monitored urine testing and family involvement. We recommend this program be attended for no less than 6 months. We further recommend daily attendance at NA initially, and continued involvement with NA indefinitely.

Even with the intense involvement of the inpatient program and a carefully devised treatment plan, many drop out of outpatient treatment and return to drug use. Nevertheless, we have found various psychotherapeutic strategies and methods worthwhile.

An educational, behavior modification approach should be taken with the patient. Education about chemical dependency is most important. Expected behavioral changes must be clearly conceived and communicated to the patient. Evaluation of vocational status and skill development require attention.

The patient can be taught to recognize the impulsiveness and sense of powerlessness that leads to the return of use of this drug. The patient can be introduced to alternatives to a chemically-induced sense of invulnerability, and encouraged to practice these alternatives.

The treatment staff must be aware of countertransference issues, and anticipate relapses and failures. For both patient and staff, it helps to define and accept limited goals. Appropriate security measures are necessary, so that staff can feel safe; also, staff need to be educated about not taking unnecessary risks in handling these patients. Staff frustration has to be recognized and managed.

CONCLUSION

Treating the PCP abuser remains a dangerous and frustrating business. To date, our therapeutic measures have less effect than they do with abusers of other drugs. Part of the solution to the

problem of PCP abuse may be an understanding of why drug abuse has become acceptable in our society. It may then be possible to devise appropriate primary prevention measures, so that the abuse of other drugs will not develop as has that of PCP.

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