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Neurobiological Models for Evaluating Mechanisms Underlying Cocaine Addiction

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Contents

Role for the Mesocortical Dopamine System in the Motivating Effects of Cocaine

George F. Koob, Barak Caine, Athina Markou, Luigi Pulvirenti, and Freidbert Weiss

The search for a neurobiological substrate for the stimulant and reinforcing properties of cocaine has focused for some time on a particular part of the forebrain, the mesocorticolimbic dopamine (DA) system. This mesocorticolimbic DA system innervates the region of the nucleus accumbens (NACC) (ventral striatum) in the anterior part of the basal forebrain and appears to play a critical role in mediating the acute reinforcing effects of cocaine and amphetamine.

This chapter reviews the role of mesocorticolimbic DA in the reinforcing properties of psychomotor stimulants as measured by intravenous (IV) drug self-administration in rats. In addition, the primary neuropharmacological mechanism for cocaine reinforcement provides a rich substrate for studying nondopaminergic modulation of the reinforcing actions of cocaine.

NEUROPHARMACOLOGICAL MECHANISM OF ACTION OF COCAINE AND OTHER PSYCHOMOTOR STIMULANTS

Psychomotor stimulant drugs such as cocaine have important effects on monoamine metabolism. Cocaine blocks noradrenaline, 5-hydroxytryptamine (serotonin), and DA reuptake and increases monoamine turnover (Groppetti et al. 1973). Amphetamine has similar effects on monoamine reuptake but also increases monoamine release and blocks monoamine oxidase activity (Groppetti et al. 1973). The local anesthetic properties of cocaine (for which it is still used clinically) are not thought to be critical for the production of its acute reinforcing effects in humans, since similar subjective effects cannot be observed with other local anesthetics such as procaine (Fischman et al. 1983). However, procaine is self-administered IV ‘in animal studies (Johanson 1980).

Dopamine and the Activating Effects of Psychomotor Stimulants

In animals, cocaine and amphetamine acutely increase motor activity (Groppetti et al. 1973), decrease food intake (Groppetti et al. 1973), have psychomotor stimulant actions on operant behavior (Spealman et al. 1977), enhance conditioned responding for a variety of reinforcers (Spealman et al. 1977), decrease thresholds for reinforcing brain stimulation (Kornetsky and Esposito 1981), and are readily self-administered IV (Koob et al. 1987*a*). As a psychomotor stimulant, cocaine is shorter acting and less potent than amphetamine (Simon 1973). Nevertheless, higher doses of cocaine produce the intensely stereotyped behavior associated with amphetamine or apomorphine, although cocaine may be less effective in provoking a maximal response (Simon 1973).

A critical role for mesocorticolimbic DA in the psychomotor-activating effects of amphetamine was identified by the observation that micro-injections of the DA receptor antagonist haloperidol into the NACC blocked amphetamine-induced locomotor activity (Pijnenburg et al. 1975). Also, the locomotor activation produced by amphetamine or cocaine was blocked by 6-hydroxydopamine (6-OHDA) lesions of the NACC (Kelly and Iversen 1976; Kelly et al. 1975). This lesion effect was thought to be largely due to DA depletion since a norepinephrine-sparing lesion (6-OHDA plus pretreatment with the norepinephrine reuptake blocker desmethylimipramine) remained effective in blocking the effects of amphetamine and cocaine (Kelly and Iversen 1976; Kelly et al. 1975). Furthermore, similar 6-OHDA lesions of the NACC blocked the locomotor stimulant effects of d-amphetamine but not of caffeine or scopolamine (Joyce and Koob 1981), heroin, or corticotropin-releasing factor (Swerdlow and Koob 1985).

A Role for Dopamine in the Acute Reinforcing Effects of Psychomotor Stimulants-Intracranial Self-Stimulation

Experimental situations implicating a role for DA in reward processes have included studies of the effects of DA-releasing drugs on reward thresholds (Kornetsky et al., this volume), measures of preference for the environment paired with drug administration (Van der Kooy 1987), and IV or intracerebral self-administration of the drug. Reward thresholds have been measured using the procedure of intracranial self-stimulation (ICSS) (Olds and Milner 1954). In this procedure, an animal self-administers electrical stimulation to certain brain regions, effectively

short-circuiting the reinforcement process (Kornetsky et al., this volume). Amphetamine and cocaine reduce ICSS reward thresholds using a rate-independent procedure (Kornetsky and Esposito 1979, 1981), and systemic injections of DA receptor antagonists such as pimozide produce both reward and performance effects on ICSS using rate-intensity methods, rate-frequency methods, and discrete-trial threshold procedures (Kornetsky et al., this volume; Stellar and Rice 1989). The reward-decreasing effect of amphetamine and cocaine on brain stimulation reward (BSR) has been shown to be counteracted by DA receptor antagonist treatment (Gallistel and Karras 1984; Kometsky et al., this volume).

A limited amount of work has explored site-specific effects for the facilitation of brain stimulation by psychomotor stimulants (Stellar and Rice 1989). A study on rats used a choice procedure where the same animals had continuous access to brain stimulation from three separate electrodes via three concurrently available levers (Koob et al. 1977). Current levels for ICSS were adjusted to produce equal rates of responding for self-stimulation at each electrode. The rats, when injected with d-amphetamine, selected a single lever for responding for different lengths of time depending on the dose. The lever selected when the animals were given moderate or high doses of d-amphetamine corresponded to an electrode location that paralleled the course of the mesocorticolimbic DA system. Taken together, these results suggest that DA in the mesocorticolimbic DA system has a role in ICSS reward and may mediate the facilitation of ICSS produced by psychomotor stimulants.

A Role for Dopamine in the Acute Reinforcing Effects of Drugs

DA has been strongly implicated in the reinforcing effects of cocaine and amphetamine by studies employing IV self-administration of drugs. Rats implanted with IV catheters and trained to self-administer cocaine with limited access (3 hours/day) show a stable and regular drug intake over each daily session. Rats are generally maintained on a low-requirement, fixed-ratio (FR) schedule for IV infusion of the drug, such as an FR-1 or FR-5. A special aspect of using these FR schedules and doses is that the rats appear to regulate the amount of drug self-administered, showing an inverse dose-effect function. Lowering the dose from the training level of 0.75 mg/kg per injection increases the number of self-administered infusions and vice versa.

Low doses of DA receptor antagonists, when injected systemically, reliably increase cocaine and amphetamine self-administration in rats (Ettenberg et al. 1982; Yokel and Wise 1975). The animals seem to compensate for decreases in the magnitude of reinforcement with an increase in cocaine self-administration or a decrease in the interinjection interval (ITI), a response similar to that produced by lowering the dose of cocaine. This suggests that a partial blockade of DA receptors produces a partial blockade of the reinforcing actions of cocaine.

In general, experiments investigating the effects of antagonists selective for DA type 1 (D_1) (Koob et al, 1987*a*) or DA type 2 (D_2) (Bergman et al. 1990; Woolverton and Virus 1989) receptors on cocaine self-administration suggest that both can decrease the reinforcing properties of cocaine in rats and primates (Bergman et al., this volume) (figure 1). Studies with intracranial microinjection of the D_1 antagonist SCH 23390 have shown that the NACC (Maldonado et al. 1993) and subregions of the NACC and the amygdala (Caine et al. 1993) may be particularly sensitive to the D_1 antagonist blockade of the reinforcing effects of cocaine.

DA agonists typically have the opposite effect, decreasing cocaine self-administration or increasing the ITI using these same parameters, an effect similar to that produced by increasing the dose of cocaine (Hubner and Koob 1990; Pulvirenti and Koob 1993). Recent results using a selective DA type 3 (D_3) agonist, 7-OHDPAT, show that this compound potently decreases cocaine self-administration, suggesting a role for D_3 receptors in cocaine reward (Caine and Koob 1993) (figure 2). This is particularly intriguing, given the selective distribution of these D_3 receptors in the terminal areas of the mesocorticolimbic DA system (Levesque et al. 1992). These results suggest that D_1 and D_3 receptors in the NACC may be particularly important for the reinforcing properties of cocaine.

A role for mesocorticolimbic DA in the reinforcing properties of cocaine and amphetamine was extended by the observation that 6-OHDA lesions of the NACC produce extinction-like responding and a significant and long-lasting decrease in self-administration of cocaine and amphetamine over days (Lyness et al. 1979; Roberts et al. 1980). Not all animals showed a clear extinction-like pattern of responding, suggesting that factors other than the motivational aspects of cocaine reinforcement might be altered.

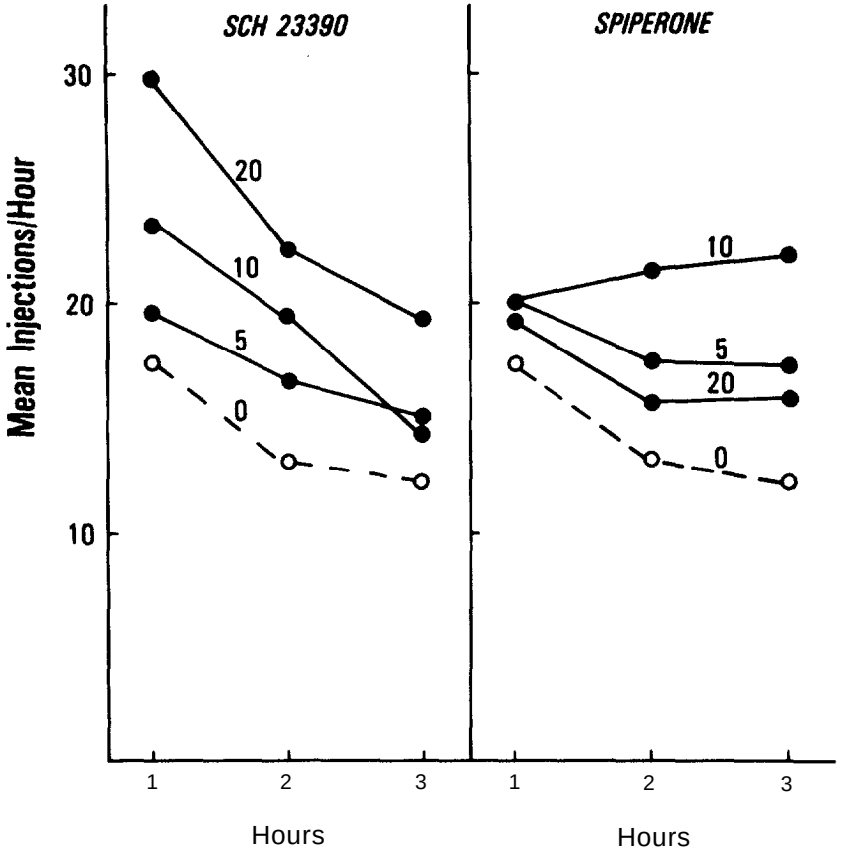

FIGURE 1. *Effects of subcutaneous injection of D, receptor antagonist SCH 23390 (left side) and the D_2 receptor antagonist spiperone (right side) on cocaine self-administration. Each point represents the average hourly intake of cocaine by injection (n = 5). Doses are in µg/kg. For SCH 23390, doses of 5, 10, and 20 µg/kg significantly increased cocaine self-administration ($p < 0.05$, Newman-Keuls test following analysis of variance [ANOVA]). For spiperone, the dose of 10 µg/kg significantly increased cocaine self-administration ($p < 0.05$, paired t-test; overall ANOVA, $p > 0.05$).*

SOURCE: Taken with permission from Koob et al. (1987*a*)

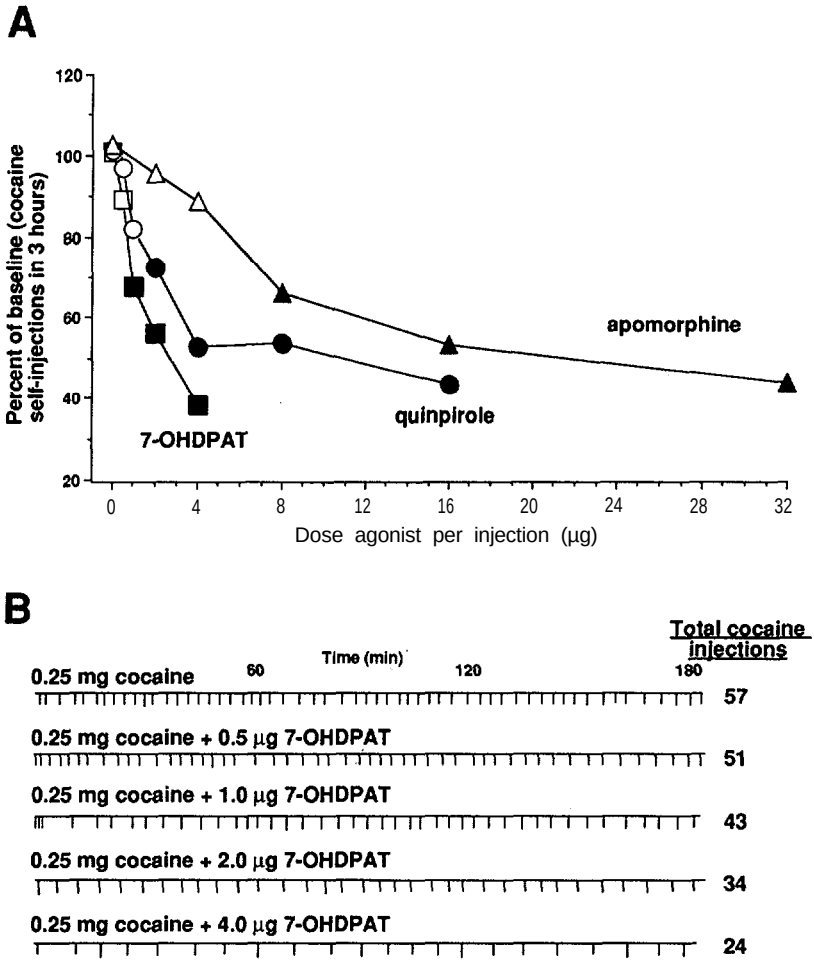

FIGURE 2. *(Panel a): Effects of D_3 agonists on cocaine self-administration in rats. Solid symbols indicate doses significantly different from zero by independent comparison ($p < 0.05$, Dunnett's t-test following ANOVA). (Panel b): The self-administration records for a single animal. Each mark indicates delivery of a cocaine infusion (0.25 mg of cocaine with 0-4 µg of 7-OHDPAT) after completion of five lever presses.*

SOURCE: Taken with permission from Caine and Koob (1993)

To address this issue and to examine the anatomical specificity of this effect, rats were trained to self-administer cocaine on a progressive ratio schedule. In this procedure, the response requirement is increased after each self-injection until each animal stops responding. This breakpoint provides a reliable measure of the relative reinforcing value of a self-administered drug. In rats with 6-OHDA lesions of the NACC, there was a dramatic decrease in the FR value for which they continue to work for cocaine (Koob et al. 1987*b*) (figure 3). Rats received continuous reinforcement data averaged for the first 3 days postlesion (mean±SEM). Rats received 8 µg 6-OHDA in 2 µL vehicle injected into the caudate nucleus or NACC. Sham: vehicle (0.1 mg/mL ascorbic acid in saline) injected controls. The middle dose (m) was 0.75 mg/kg 6-OHDA per injection; M, twice this dose; L, half of this dose. These results show that animals with the DA removed from the NACC (but not the corpus striatum) fail to continue to work for cocaine, particularly when the work requirements (e.g., cost in effort) are increased. Similar DA-depleting lesions of the caudate nucleus failed to significantly alter performance on the progressive ratio test, indicating the specificity of the effect to the NACC. These results suggest that DA denervation of the region of the NACC can significantly blunt the motivation to respond for cocaine reward. In a further study of the behavioral specificity of this effect, rats were trained on a multiple schedule for food and cocaine, with FR-15 components for food and cocaine alternating every 30 minutes for 2 hours. DA denervation of the NACC decreased responding for cocaine but not food in this paradigm (Caine and Koob 1994).

A Role for Dopamine in the Motivational Aspects of Withdrawal Associated With Psychomotor Stimulants

Cocaine withdrawal in dependent subjects is not characterized by the obvious physical signs like those observed with opiates or sedative-hypnotics. Evidence exists in humans, however, to show that following a cocaine binge, abstinence produces severe depressive symptoms combined with irritability and anxiety (Gawin and Kleber 1986). These symptoms last several hours to several days and form the state described as a “crash” associated with the cocaine dependence cycle.

Anhedonia, or the inability to derive pleasure from normally pleasurable stimuli, is one of the more salient symptoms of the crash stage and may be one of the major motivating factors in the etiology and maintenance of the cocaine dependence cycle. An animal model for anhedonia is an increase in reward thresholds as measured with the ICSS procedure. As

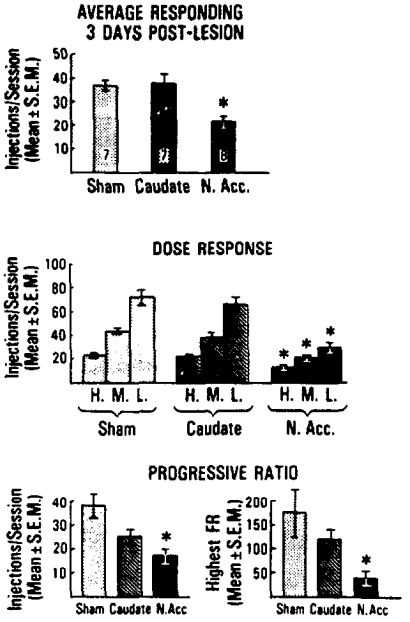

FIGURE 3. *Effects of 6-OHDA lesions to the NACC and caudate nucleus (caudate) on responding in rats self-administering cocaine. (Top) continuous reinforcement; (middle) dose-effect functions for each group; and (bottom) mean rewards and mean highest ratio obtained by each group on the progressive ratio probe.*

KEY: *Significantly different from sham group, $p < 0.05$ Newman-Keuls test.

SOURCE: Taken with permission from Koob et al. (1987*b*)

discussed above, cocaine, injected acutely, lowers self-stimulation thresholds in rats (Kornetsky and Esposito 1981); this enhancement of reward is likely to involve the mesocorticolimbic DA system.

One hypothesis is that the withdrawal from chronic self-administration of cocaine may result in the opposite effect, that is, an increase in brain stimulation thresholds. To test this hypothesis, rats were allowed to self-administer cocaine IV for long periods, and reward thresholds were monitored during the course of cocaine withdrawal (Markou and Koob 1991*a*). The animals were allowed to self-administer cocaine for different time periods (3, 6, 12, 24, and 48 hours using a within-subject design). Brain stimulation thresholds were determined at varying times after the termination of the self-administration session (0, 1, 3, 6, 12, 24, 48, and 72 hours). Withdrawal from prolonged cocaine self-stimulation resulted in elevated BSR thresholds, compared to predrug baseline levels and compared to thresholds of control animals. The magnitude and duration of the elevation in reward thresholds was proportional to the amount of cocaine self-administered, that is, the duration of the self-administration session (figure 4). The results are expressed as percent change from baseline threshold levels: for the experimental group, 37.4±2.5 µA, and for the control group, 35.9±3.1 µA (mean±SEM). This elevation in reward threshold may reflect the state of the brain's motivational systems and, as such, may be homologous to the anhedonia reported by human cocaine users (Gawin and Kleber 1986).

The effect of cocaine withdrawal on ICSS thresholds was opposite to the effect of acute cocaine (Kornetsky and Esposito 1981), suggesting that during the course of a cocaine self-administration bout and withdrawal the drug can dramatically alter the substrates in the medial forebrain bundle that mediate BSR. Similar elevations in reward thresholds have been observed during withdrawal following chronic amphetamine administration (Kokkinidis et al. 1980).

The neurochemical basis for the elevation in reward thresholds may, at least in part, involve mesocorticolimbic DA. This would involve a within-system adaptation; that is, an adaptation where the primary molecular or cellular response responsible for the positive hedonic effects of the drug would itself adapt to neutralize the effects of the drug, and subsequent removal of the drug would produce the withdrawal effect. The withdrawal effect in this case is reflected in an increase in reward thresholds. Consistent with this hypothesis, recent data from microdialysis studies using the same experimental design as that for

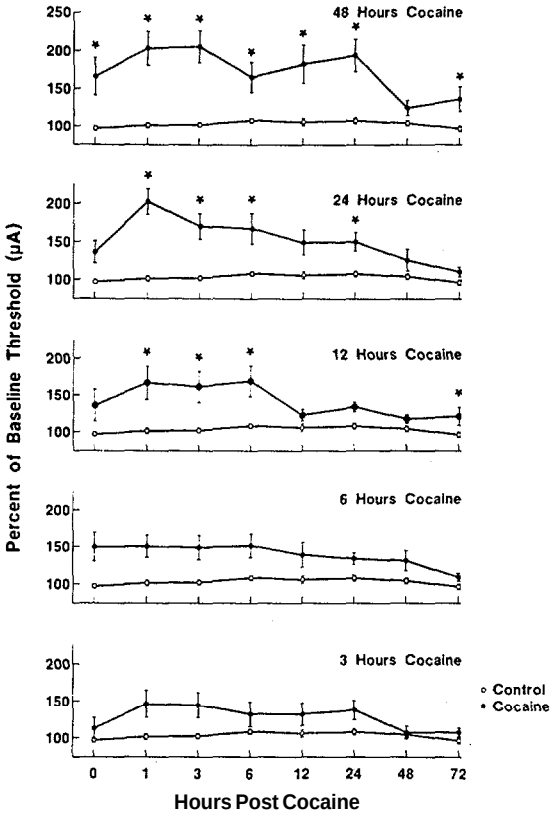

FIGURE 4. *Intracranial self-stimulation thresholds at several time points after cocaine withdrawal following the self-administration of cocaine for periods of 3 to 48 hours. The asterisks indicate statistically significant differences ($p < 0.05$) between control and experimental groups (Dunnett's test), following a significant group x hours interaction in an ANOVA. These results show that prolonged chronic IV self-administration of cocaine produces a dose-related increase in reward thresholds (anhedonia) that can persist for several days after the highest dose.*

SOURCE: Taken with permission from Markou and Koob (1991*a*)

chronic cocaine reward threshold studies showed that chronic self-administration of cocaine produces a decrease in DA release in the NACC at the time points associated with the greatest increases in reward thresholds (Weiss et al. 1992) (figure 5). As can be seen in figure 5, DA release was significantly suppressed below basal levels between 2 to 6 hours postcocaine. Although DA levels tended to increase between 8 and 12 hours after onset of the withdrawal period, DA overflow remained significantly below presession basal values for the cocaine group. The dotted line represents mean presession basal DA levels for cocaine self-administering rats. Control data in panels 5(b) and 5(c) correspond to the mean duration of approximately 14 hours of self-administration for the cocaine rats. Note also that precocaine basal DA levels in trained, cocaine self-administering rats were significantly higher than in drug-naive control rats (panel a). Control rats (n = 3) were drug-naive animals placed in the self-administration chambers for 30 hours without access to cocaine. Importantly, this decrease may account for the observation that bromocriptine can reverse cocaine-induced increases in reward threshold during cocaine withdrawal (Markou and Koob 1991*b*).

This decrease in extracellular DA, however, is not of great magnitude (approximately 50 percent). Other neurochemical systems may be involved as a between-system adaptation; a different neurotransmitter pathway and separate molecular and cellular apparatus would be triggered by the changes in the primary system responsible for the positive hedonic effects of the drug. Removal of the drug would then unmask the activity of this system to produce the anhedonia of withdrawal. Such a between-system interaction may ultimately interface with the mesocorticolimbic DA system to effect motivational changes.

Nondopaminergic Interactions With the Mesocorticolimbic Dopamine System

The neurobiological interfaces of the mesocorticolimbic DA system with the limbic system and the extrapyramidal motor system provide a rich substrate for potential nondopaminergic interactions in cocaine dependence. The region of the NACC (ventral striatum) receives important limbic system (e.g., amygdala, hippocampus, and frontal cortex) afferents that may be critically involved in reward. These afferents appear to be glutamatergic, and they may modulate the function of DA in the NACC. In fact, local intracerebral injection of glutamate receptor antagonists into the NACC attenuates the locomotor-activating

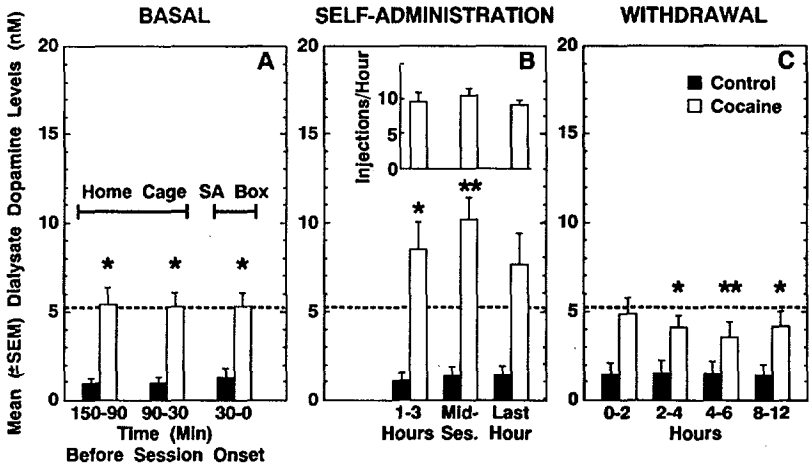

FIGURE 5. *Mean±SEM DA levels in microdialysate fractions collected from the NACC of rats (n = 5) before, during, and after an unlimited access cocaine self-administration session. (Panel a): Basal DA levels during two 1-hour periods in the home cage and 30 minutes in the self-administration chamber prior to cocaine access. (Panel b): Response rates for cocaine (inset) and DA levels during cocaine self-administration averaged over the first 3 hours, midsession (total self-administration session time minus the first 3 hours and the last 1 hour), and the final 1 hour of self-administration. (Panel c): Dialysate DA concentrations during cocaine withdrawal.*

KEY: *p < 0.05, **p < 0.01; significantly different from presession basal levels (Newman-Keuls posthoc tests following a significant ANOVA).

*p < 0.02; significantly different from controls.

SOURCE: Taken with permission from Weiss et al. (1992)

The efferent connections from the NACC to the region of the substantia innomiuat/ventral pallidum may be an important site in the subsequent processing of the reinforcing effects of cocaine. Cell body lesions (kainic acid) of the NACC block cocaine self-administration (Dworkin et al. 1988; Zito et al. 1985), and ventral pallidal/substantia innominata cell

properties of cocaine and cocaine reinforcement as measured by IV self-administration (Pulvirenti and Koob 1993; Pulvirenti et al. 1991).

The efferent connections from the NACC to the region of the substantia innominata/ventral pallidum may be an important site in the subsequent processing of the reinforcing effects of cocaine. Cell body lesions (kainic acid) of the NACC block cocaine self-administration (Dworkin et al. 1988; Zito et al. 1985), and ventral pallidal/substantia innominata cell body lesions (ibotenic acid) have similar effects (Hubner and Koob 1987). Subsections of this region that appear to be critical for this functional output of the NACC involve the medial parts of the ventral pallidum/substantia innominata, also called the sublenticular extended amygdala (Robledo and Koob 1993). Together these studies suggest that certain subsets of neurons in the region of the NACC may be critical for mediating the acute reinforcing properties of psychomotor stimulants and that this NACC/sublenticular extended amygdala circuit (connection) may be a second-order link for stimulant reinforcement.

Recent studies suggest that there are common neurochemical, cytoarchitectural, and circuit connections between subparts of the NACC (the shell), the bed nucleus of the stria terminalis, and the central nucleus of the amygdala (Alheid and Heimer 1988; Koob et al. 1993). This has led to the hypothesis that the extended amygdala may be of functional importance for motivation in general and motivation for cocaine self-administration in particular (Koob et al. 1993).

The afferents and efferents to the NACC DA system provide a rich substrate for the development of means by which to modulate the reinforcing actions of cocaine without directly acting on the meso-corticolimbic DA system. This may provide a key to understanding the relationship of the behavioral properties of rewarding stimuli to the subjective feelings of pleasure or emotion in humans. Such knowledge may provide clues for the development of novel pharmacotherapies for the treatment of cocaine dependence and the treatment of the psycho-pathology associated with cocaine intoxication and dependence.

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Dopamine, a Common Substrate for the Rewarding Effects of Brain Stimulation Reward, Cocaine, and Morphine

Conan Kornetsky and Christine Duvauchelle

INTRODUCTION

Brain stimulation reward (BSR) is among the animal models used for studying the neurobiology and neurochemistry of the rewarding effects of abused substances. There have been numerous papers and reviews demonstrating and attesting to the validity of BSR as a model for the study of neuronal bases for the rewarding effects of abused substances (Izenwasser and Kornetsky 1992; Phillips and Fibiger 1989; Steller and Rice 1989; Unterwald and Kornetsky 1993). Cocaine, as well as most other abused substances, increases the rate of response for intracranial rewarding stimulation and lowers the threshold for the stimulation. The most common sites for stimulation in these experiments were the medial forebrain bundle (MFB) and the ventral tegmental area (VTA). The thesis of this chapter is that BSR itself is a model for the rewarding effects of cocaine and the abused opioids and that the underlying mechanisms involved in BSR are similar to those of these abused substances.

The first description of the effects of cocaine on BSR was published by Crow (1970). Figure 1 is a tracing from the Crow paper of a cumulative record of a rat's rate of response after receiving 5.0 mg/kg of cocaine, showing a marked increase in the rate of response caused by cocaine. However, there are earlier reports of the facilitative effects of amphetamine, a psychomotor stimulant with many of the same effects as cocaine, on BSR (Killam et al. 1957; Stein 1964). The effect of cocaine on BSR was replicated by Wauquier and Niemegeers (1974) using rate of response (as in the Crow experiment) as the dependent variable. Since these early papers, a number of investigators have shown that cocaine (Esposito et al. 1978; Frank et al. 1988; Kornetsky and Esposito 1981; Moody and Frank 1990) and other dopamine (DA) agonists (Cassens and Mills 1973; Esposito et al. 1980; Izenwasser and Kornetsky 1989; Leith and Barrett 1976) increase the rate of response or lower the threshold for

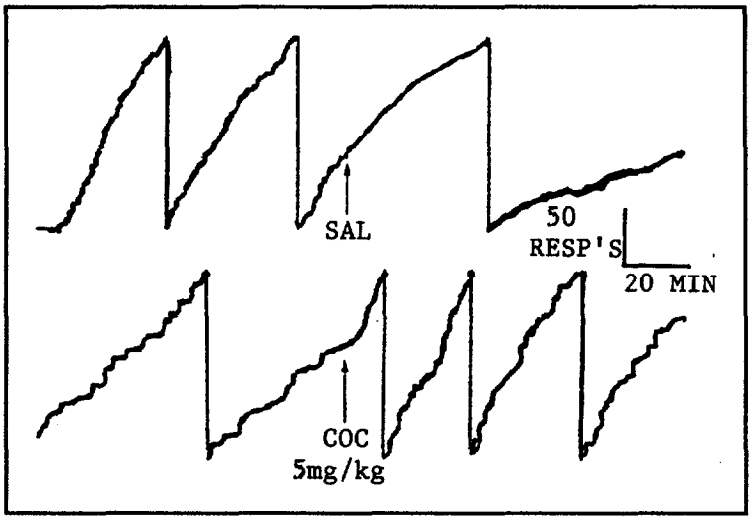

FIGURE 1. *A tracing of the first published figure of the effects of cocaine on BSR. Shown is the cumulative record, continuous reinforcement schedule, of 5 mg/kg of cocaine in a single rat on rate of response*

SOURCE: Crow (1970)

for rewarding brain stimulation. Figure 2 illustrates the threshold-lowering effects of cocaine on the BSR threshold.

The threshold-lowering effect of abused substances on BSR is a useful predictive model for the abuse liability of various substances. The more important questions, however, are why these abused substances increase the sensitivity of an animal to this very artificial rewarding stimulation, and whether there is similar activation of the same neuronal systems.

The threshold-lowering effects of cocaine or other abused substances are clearly not the result of a general central nervous system (CNS)-stimulating effect. The discrete trial psychophysical threshold method is independent of motor effects (Esposito and Kornetsky 1977; Kornetsky and Bain 1990; Markou and Koob 1992.) The abused opioids that have marked dose-dependent depressant motor effects robustly lower the threshold for rewarding brain stimulation (Hubner and Kornetsky 1992;

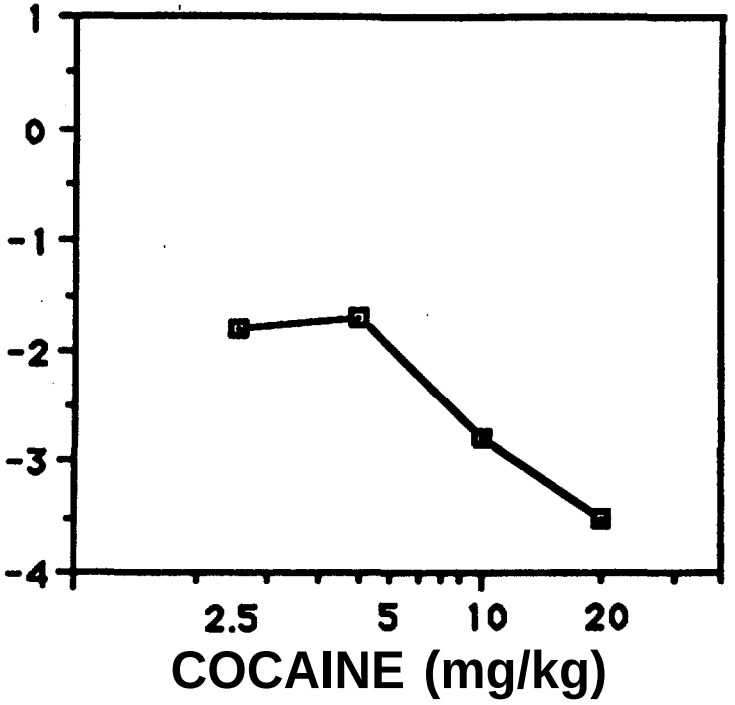

FIGURE 2. *Mean effects of various doses of cocaine on the threshold for BSR. Saline levels are indicated by z = 2.0, and a z-score of ±2.0 indicates the 95 percent confidence limits for individual animals. Scores in the negative direction indicate a lowering of the threshold,*

SOURCE: Kornetsky and Esposito (1981)

Marcus and Kornetsky 1974). Furthermore, cocaine lowers the threshold for rewarding brain stimulation at doses that raise the threshold for the detection of nonrewarding intracranial stimulation (Kornetsky and Esposito 198 1).

Although the facilitating effects of the psychomotor stimulants on BSR were demonstrated relatively easily, the earliest experiment on the effects of opioids on BSR yielded ambivalent results (Olds and Travis 1960). The first published report demonstrating that an abused opioid increases responding for rewarding brain stimulation was by Lorens and Mitchell (1973). This was followed by a paper showing that morphine lowered the threshold for BSR using a rate-independent procedure (Marcus and

Kornetsky 1974). A number of subsequent experiments confirmed these early findings. Figure 3 illustrates the threshold-lowering effects of heroin and its two metabolites, morphine and 6-acetylmorphine, on BSR (Hubner and Kornetsky 1992).

Sensitization of the Effects of Cocaine and Morphine

A common effect of repeated doses of cocaine and other drugs with known indirect DA agonist effects is sensitization to the motor effects (Kalivas et al. 1988; Post and Weiss 1989). There are a number of reports that argue for a role for DA in the cocaine-induced stereotypy (Akimoto et al. 1989; Kalivas and Duffy 1990, 1993; Pettit et al. 1990). However, there is some evidence indicating that behavioral sensitization can occur without concomitant changes in extracellular DA. Kalivas and Duffy (1993) concluded that the expression of increases in extracellular DA was a function of both the dose of chronic cocaine administration and the length of time between the end of chronic treatment and the cocaine challenge. Although DA antagonists block the development of the cocaine sensitization, they do not block the expression of previously developed sensitization (Post et al. 1992).

Less well known is the sensitization to morphine-induced stereotypy resulting from chronic high doses (Pollock and Kornetsky 1989). Three high doses of morphine (10, 20, and 20 mg/kg) administered within a 24-hour period result in repetitive oral stereotypy characterized by self-biting or biting of the cage floor. There have been reports of this oral stereotypy in the literature at least since 1963 (Martin et al. 1963). Evidence of sensitization is seen in the reexpression of the biting behavior caused by a 4 mg/kg dose of morphine as long as 6 months after the initial three high-dose treatments with morphine (Pollock et al. 1990). The results of this experiment are shown in table 1.

This sensitization to the stereotypic effects of morphine can be blocked by the DA type 1 (D_1) antagonist SCH 23390 (Pollock and Kornetsky 199 1). More recent experiments have demonstrated that the N-methyl-d-aspartate (NMDA) antagonist MK 801 blocks not only the development of the sensitization but the expression of it, and suggests that DA's role in the etiology of this opiate-induced sensitization is mediated by action of glutamate on the DA system (Livezey et al. 1993).

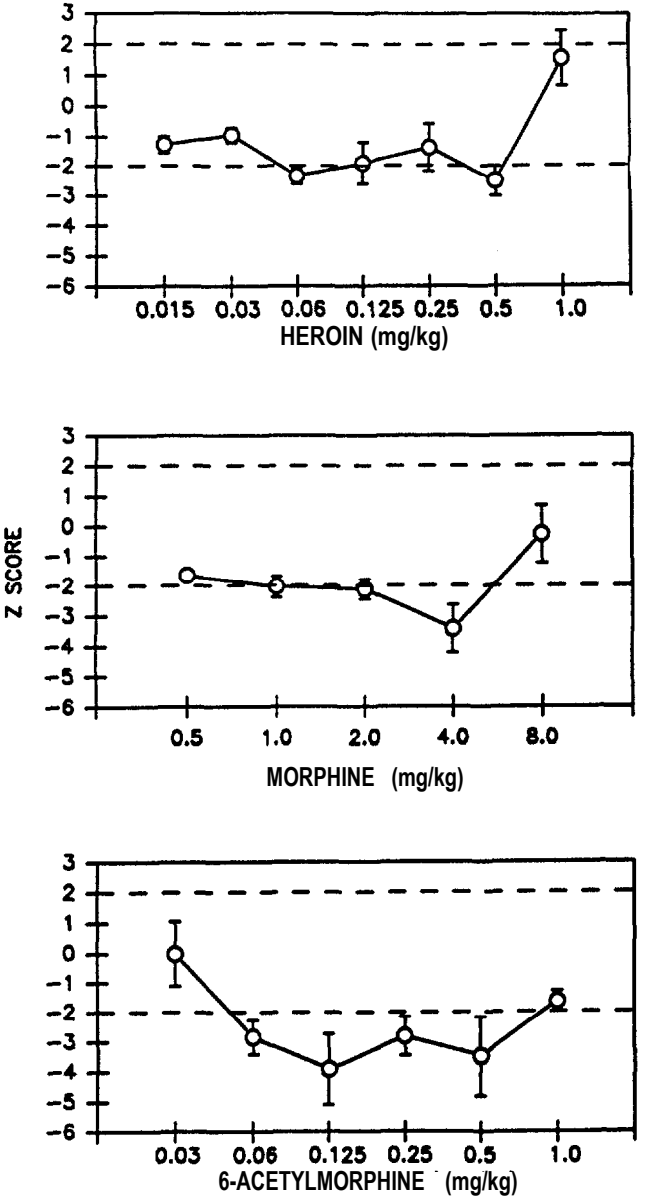

FIGURE 3. *Mean±SEM standard score (z-score) changes in the threshold for BSR for heroin, morphine, and 6-acetylmorphine.*

SOURCE: Hubner and Kornetsky (1992)

TABLE 1. *Incidence (# of rats in each group) of morphine-induced oral stereotypy independent groups*

Initial Rx	30 days	90 days	180 days	183 days
MS (N = 4)	4*	-	-	-
SAL (N = 4)	0	-	-	-
MS (N = 4)	-	4*	-	-
SAL (N = 4)	-	0	-	-
MS (N = 4)	-	-	4*	4*
SAL (N = 4)	-	-	0**	0

KEY: * p = 0.03

** Although stereotypy was observed in 2 of the animals, it did not meet the criterion of 5 consecutive minutes.

MS = morphine sulfate

SAL = saline

Although sensitization to the motor and stereotypic effects of both cocaine and morphine has been demonstrated, there is less evidence of sensitization to the effects of these drugs on BSR. Frank and colleagues (1988) reported that cocaine administered for 18 consecutive days to rats consistently lowered the BSR threshold but did not result in tolerance or sensitization. Kokkinidis and McCarter (1990), however, found evidence of sensitization that was dependent on the dosing schedule. The difference in findings also could be the result of differences in the time of testing after chronic cocaine administration.

Figure 4 illustrates the dose-response curves (Kornetsky and Bain 1982) of the effects of morphine determined prior to chronic administration and after 14 to 38 days of daily doses up to 30 mg/kg. The original purpose of the figure was to illustrate the lack of tolerance to the threshold-lowering effects of morphine on BSR. Not only does the figure indicate that there is no tolerance, but also that there is evidence of sensitization. The dose-effect curve was displaced to the left, and the maximum lowering of the threshold was greater after chronic administration.

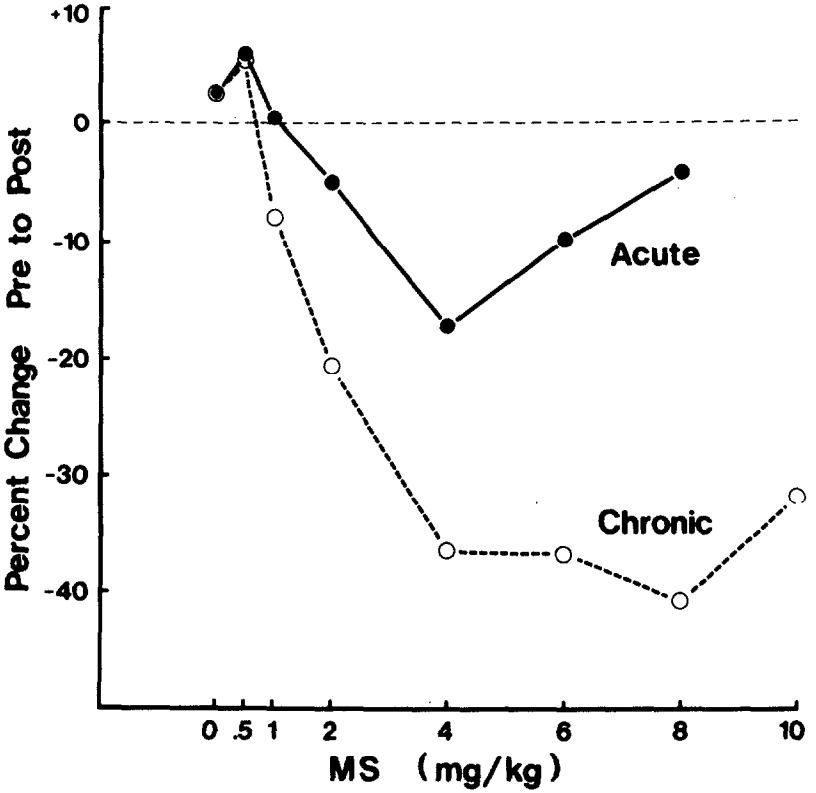

FIGURE 4. *Percent change in threshold (pre to post) from that of saline before and after chronic morphine treatment (14 to 38 days) in the same animals (N = 9).*

SOURCE: Kornetsky and Bain (1982)

Blocking of Opioid Effects by DA Antagonists and Psychomotor Stimulant Effects by Opioid Antagonist on BSR

The threshold-lowering effect of morphine on BSR can be blocked by the DA type 2 (D_2) antagonist pimozide (Kornetsky and Porrino 1992; Sarkar et al. 1992). The mu receptor agonist tyr-d-ala-gly-nme-phe-gly-ol (DAMGO), applied directly to the nucleus accumbens (NACC) or the olfactory tubercle (OT), lowers the BSR threshold (Duvauchelle et al. 1993) as robustly as subcutaneously administered morphine. Evidence that this effect is DA-mediated was suggested by the blockade of this effect by the D_1-D_2 blocker cis-flupenthixol. This effect is illustrated in figure 5.

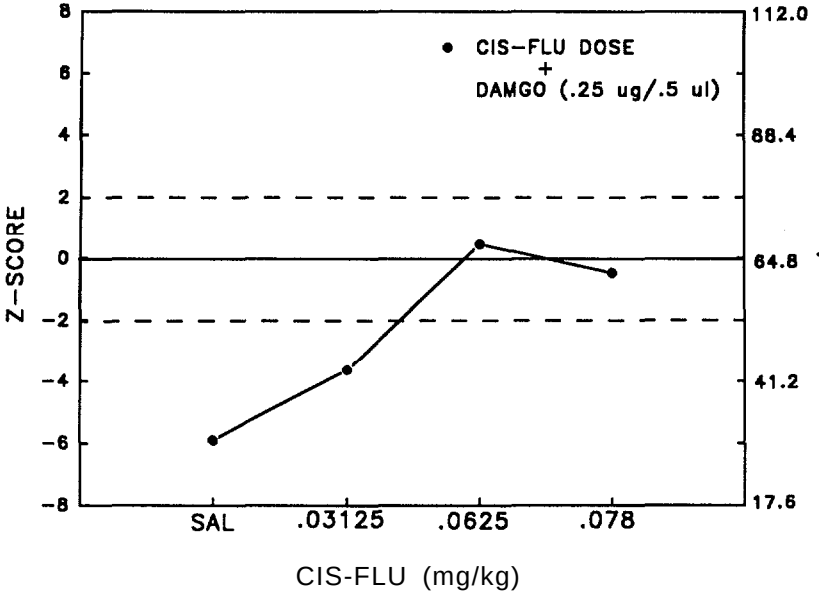

FIGURE 5. *The reversal of the effects on the BSR threshold of intra accumbens DAMGO by various doses of intraperitoneal cis-flupenthixol (CIS-FLU) in a single animal. A z-score of 0 indicates the saline threshold level. On the right are given the equivalent stimulation levels in microamperes. Only the 0.78 mg/kg dose of CIS-FLU, by itself; significantly raised the threshold.*

SOURCE: Duvauchelle and Kornetsky (1993)

The corollary to the finding that DA antagonists block the BSR threshold-lowering effects of opioids is seen in experiments showing that a number of the psychomotor stimulants can be blocked by opiate antagonists (Bain and Kornetsky 1987; Esposito et al. 1980; Knapp and Kornetsky 1989; Kornetsky and Bain 1990).

Self-Administration of Cocaine or Morphine, Common Mechanism?

Using the self-administration paradigm, experimental evidence suggesting similar mechanisms for the reinforcing effects of the psychomotor stimulants and the abused opioids is less convincing than the evidence derived from BSR experiments. Ettenberg and coworkers (1982) were unable to alter cocaine self-administration by the

administration of an opiate antagonist, and a DA antagonist had little effect on the self-administration of heroin. Pettit and colleagues (1984) found that 6-hydroxydopamine (6-OHDA) lesions of the NACC had a relatively greater effect than heroin in blocking self-administration of cocaine. Zito and colleagues (1985) found that kainic acid lesions of the NACC, which destroy cell bodies but leave fibers of passage intact, blocked both cocaine and heroin self-administration. Koob and Goeders (1989), in reviewing these experiments, suggest "that neurons in the region of the nucleus accumbens-ventral pallidum circuit (connection) may be a common second-order link for both stimulants and opiate reward" (p. 232).

Most of the conflicting evidence suggesting that DA does not play a role in the rewarding effects of opioids has used the drug self-administration model. There has been a great deal of variability in results using the self-administration model, despite the fact that it is probably the most homologous model of human drug-taking behavior. Among the reasons for this variability is the extent to which this behavior is schedule-dependent. Changes in the reinforcement schedule can result in major differences in drug intake (e.g., fixed-ratio [FR] 5 versus a progressive ratio schedule).

The Role of Dopamine in BSR

Using in vivo microdialysis and in vivo voltometry, researchers have found considerable evidence that rewarding brain stimulation to the VTA results in an increase in DA release in the NACC (Blaha and Phillips 1990; Fibiger et al. 1987; Phillips et al. 1987). Further evidence for DA's importance in BSR is seen in lesion studies. Ipsilateral lesions, but not contralateral 6-OHDA lesions, of the DA pathways in the lateral hypothalamus blocked rewarding stimulation to the VTA but had little effect on responding for stimulation to the NACC (Phillips and Fibiger 1989). The direct application of a DA agonist into projection sites of the mesocorticolimbic system causes facilitation of BSR. Olds (1990) induced DA receptor activation by intracerebral injections of DA, d-amphetamine, and pargyline into the NACC and measured the self-stimulation rate of response from electrodes implanted in the MFB. This intracerebral treatment resulted in facilitation of rates of response for rewarding brain stimulation. There have been two preliminary reports of increased sensitivity to amphetamine when applied directly into the accumbens, as determined by the curve-shift method of determining BSR

changes. The stimulating electrodes were in the VTA (Colle and Wise 1986; Spencer and Steller 1986).

If DA is mediating BSR, then DA antagonists should decrease the rate of response or raise the threshold for rewarding brain stimulation. Although it is much easier to conclude that a lowering of the BSR threshold is the result of increased sensitivity to the rewarding stimulation, it is more difficult to prove that drugs that raise the threshold are not doing so because of an effect on motor function. A number of experiments, both rate-independent and rate-dependent, show that DA antagonists decrease the sensitivity of animals to rewarding brain stimulation. A summary of much of this work is found in the review by Steller and Rice (1989). Using the rate-independent threshold method, the D_2 antagonist pimozide raises the threshold for BSR at doses that have no effect on the animal's ability to recognize the presence or absence of nonrewarding stimuli via the same stimulating electrode (Bird and Kornetsky 1990). This effect is shown in figure 6. The D_1-D_2 antagonist cis-flupenthixol has been found to raise the BSR threshold in a dose-dependent manner (Duvauchelle et al. 1993).

Although all of these experiments implicate DA in BSR, they do not rule out a role for other neurotransmitters either acting independently or altering the DA system. For example, the absolute threshold for BSR from the ventral tegmental nuclei of Gudden (VTG) was only slightly higher than that obtained from the MFB (Sarkar et al. 1991). Although it was believed that this site was primarily serotonergic, recent immunocytochemistry studies indicate that the VTG does not contain DA, serotonin, or noradrenergic cell bodies (Sarkar et al., unpublished data). Figure 7 shows the lack of significant difference between threshold levels obtained from both the MFB and the VTG.

Effects of BSR, Cocaine, and Morphine on Metabolic Rates of Glucose Utilization

Further evidence that BSR, cocaine, and morphine have rewarding effects that may be mediated by similar mechanisms was obtained in experiments employing the quantitative 2-deoxyglucose method for determining metabolic rates in specific brain structures. These experiments determined the effects of BSR, cocaine alone, and morphine alone, as well as the effects of BSR in the presence of each of these drugs in the rat (Kornetsky et al. 1991; Porrino et al. 1990).

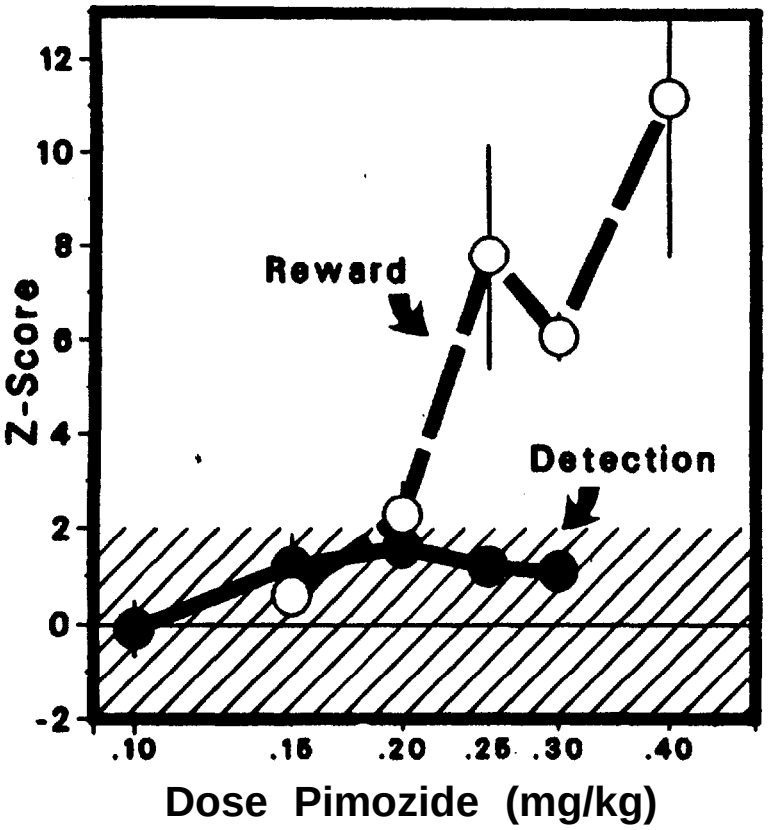

FIGURE 6. *Mean z-score changes in the threshold for detection of nonrewarding and rewarding intracranial stimulation. Note that at doses that significantly raise the BSR threshold, the detection threshold is not significantly altered.*

SOURCE: Bird and Kornetsky (1990)

Local cerebral metabolic rates of glucose utilization ($LCMR_{glu}$) in rats were determined under four conditions: control (saline), cocaine, morphine, and BSR. A comparison of the metabolic rates under these conditions yielded both similarities and differences. There was a strong trend for BSR to increase metabolic rates throughout the brain, with a similar but lesser trend after the administration of cocaine. This trend for increases in $LCMR_{glu}$ was not seen after morphine. Morphine tended to decrease metabolic activity throughout the brain with the exception of the

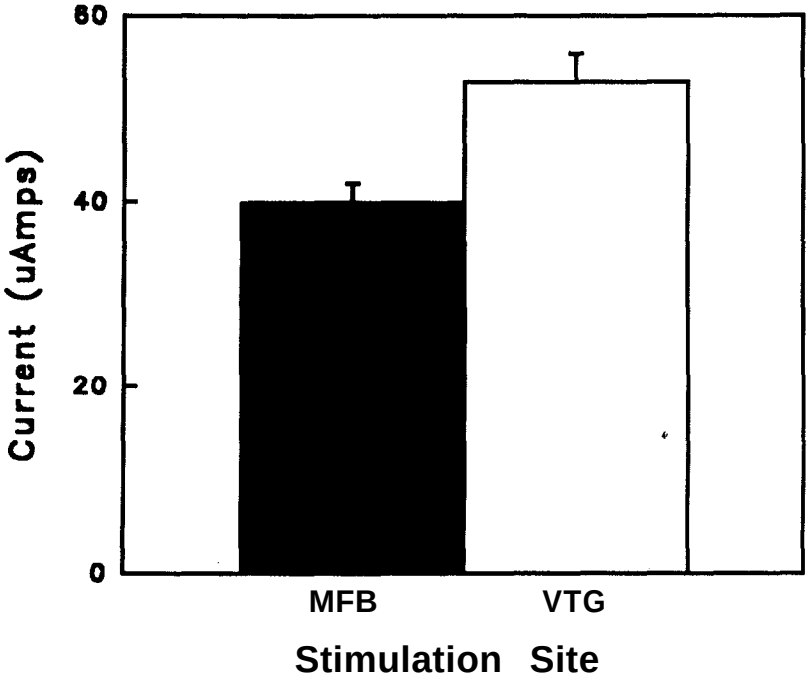

FIGURE 7. *A comparison of the BSR threshold obtained from stimulation of the medial forebrain bundle (MFB) and ventral tegmental nuclei of Gudden (VTG) in the same animals. Although the VTG threshold was significantly higher than that obtained from the MFB, acquisition of the BSR behavior was acquired as easily as that for MFB stimulation.*

SOURCE: Sarkar et al. (1992)

OT, a finding not dissimilar to that of other investigators (Ito et al. 1983; London et al. 1987). The OT was the only structure in which there was a significant increase in metabolic activity caused by all three treatments. The mesocorticolimbic structures, in which there were significant changes from control levels, are illustrated in figure 8. Although the increase in metabolic rate in the NACC did not reach a significant statistical level ($P < .05$), it is included in the figure because of the interest in the NACC as a major site implicated in rewarding effects of abused substances. The distribution of the effects of BSR on metabolic rates are not dissimilar to those seen in other reports of the effects of

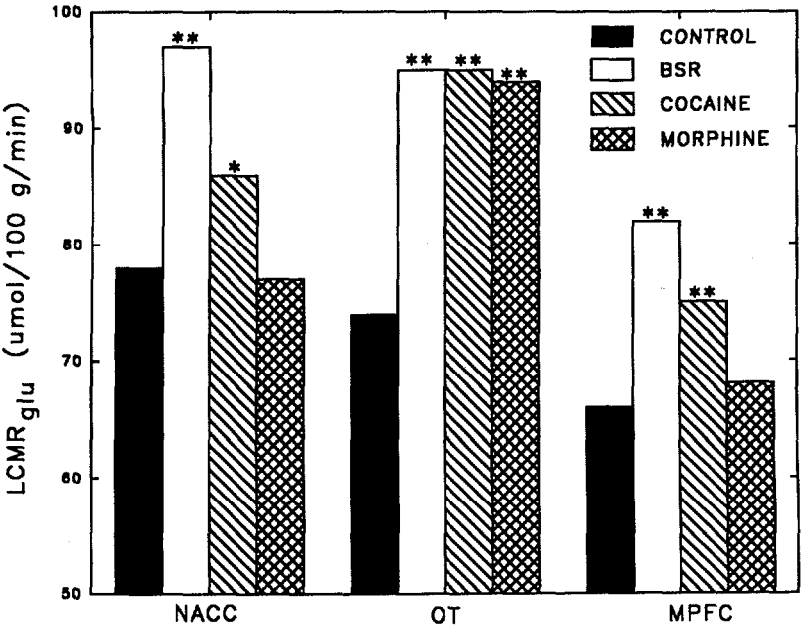

FIGURE 8. *A comparison of the $LCMR_{glu}$ rates for animals treated with saline, morphine (4mg/kg, SC), cocaine (10 mg/kg, ip), and lever-pressing for rewarding brain stimulation. Data are presented for the nucleus accumbens (NACC), the olfactory tubercle (OT), and the medial prefrontal cortex (MFC)*

SOURCE: Data from Porrino et al. (1990) and Kornetsky et al. (1991)

cocaine (Porrino 1992) or in which BSR was obtained from other brain reward sites (Esposito et al. 1984; Porrino et al. 1984).

Is BSR Itself a Model for the Rewarding Effects of Drugs?

If brain stimulation, cocaine (or other psychomotor stimulants), or morphine (or other abused opioids) are affecting similar systems, are there similarities in the subjective effects of the experiences? Theoretically, the question could be answered using the drug discrimination (DD) procedure. Is there generalization between rewarding electrical stimulation and cocaine? Because of the marked differences between the physical characteristics of brain stimulation (e.g., duration of stimulation and the pharmacokinetics of cocaine), it is highly

unlikely that generalization from one to the other could be established. Lepore and Franklin (1992), however, modeled the kinetics of drug effects with frequency-modulated trains of brain stimulation. These trains of stimulation had a time course that resembled the time course of drugs in the brain. Thus, there would be an increment in frequency of stimulation to model the gradual increase in drug brain levels after drug administration, followed by a delay in frequency that modeled the elimination half-life of a drug. Under these conditions, as opposed to a fixed frequency, increasing the increment in the stimulation train (dose) resulted in a decrease in response rate. This is illustrated in figure 9.

Is Electrical Stimulation to Humans Rewarding, and Does It Mimic Drug Effects?

A more direct validation of the reinforcing effects of BSR and its similarity to the rewarding effects of drugs is found in the reports of human subjects who have received electrical stimulation to the brain. The use of electrical stimulation to discrete brain sites has been carried out in human subjects for the control of intractable pain and in the belief that such brain stimulation might have a palliative effect on the symptoms associated with schizophrenia, These studies were carried out in the early 1950s (Heath and Mickle 1960; Sem-Jacobsen and Torkildsen 1960). Many of the patients in these clinical experiments reported positive feeling from such stimulation, with some of them alluding to its feeling like sexual stimulation. Sem-Jacobsen and Torkildsen (1960), in reviewing their finding with depth intracerebral electrical stimulation in human subjects, stated that subjects reported pleasant as well as unpleasant sensations. These sensations were dependent on the placement of the electrodes. “In some regions they like to keep the stimulus on for a prolonged period, only interrupted by short breaks. In other areas; they seem to get the most pleasure by frequently starting and stopping the stimulus” (p. 284). They also reported a patient in whom the stimulation “evoked a fluttering in a muscle group in the pelvis which tickled the patient and she responded with joy and laughter” (p. 284).

Whether these feelings are similar to those elicited by cocaine could only be determined if a subject had experienced both the drug and electrical stimulation. Certainly cocaine elicits feelings of well-being and a rush that has been described by some as sexual in nature. Freud (1974), in his treatise on cocaine, *Uber Coca,* did not let this effect escape him. He wrote, “Among the persons to whom I have-given coca, three reported violent sexual excitement which they unhesitatingly attributed to coca”

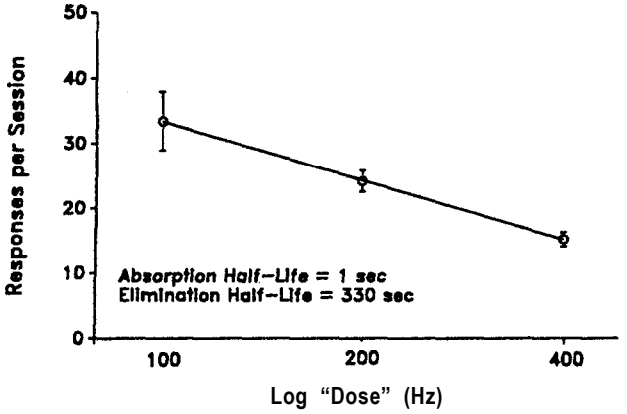

FIGURE 9. *Relationship between the size of the increment in frequency of the BSR ("dose") and the self-administration response rate.*

SOURCE: Lepore and Franklin (1992)

(p. 73). Although opioids tend to cause relaxation in abusers, they often report that the rush after an intravenous (IV) injection is similar to that of an orgasm (Chessick 1960), a report not dissimilar to that of the cocaine/crack user.

SUMMARY AND CONCLUSIONS

These experiments suggest that the neuronal mechanisms involved in the rewarding effects of BSR are similar to those for cocaine and, to a significant degree, those of morphine. Although there is considerable evidence that DA plays a significant role in the mechanisms involved in these reinforcing effects of abused substances and BSR, it is highly unlikely that the reinforcing effects can be explained by DA alone. Although many studies suggest that DA is at least necessary but not sufficient, there is other evidence discussed in this monograph suggesting a major role for other neuronal systems.

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Neurobehavioral Pharmacology of Cocaine: Role for Serotonin in Its Locomotor and Discriminative Stimulus Effects

Kathryn A. Cunningham and Patrick M. Callahan

INTRODUCTION

The highly abused psychostimulant cocaine elicits psychological manifestations in humans (e.g., mood elevation, euphoria) that have been well described and are similar to those of the amphetamines (Fischman et al. 1976). With continued use or high doses of cocaine, psychiatric disorders such as anxiety, panic attacks, depression, and paranoid psychosis, as well as toxic physiological reactions, have been reported (Lowenstein et al. 1987; Post 1975). In rodents, cocaine stimulates locomotor activity at low doses and stereotypy and convulsions at higher doses (Kilbey and Ellinwood 1976; Post and Comel 1983; Robinson and Becker 1986; Scheel-Kruger et al. 1976). Repeated treatment with cocaine results in the development of either tolerance or a progressive enhancement of these behaviors (i.e., sensitization) (Post and Contel 1983; Robinson and Becker 1986). In addition to these effects on motor activity, cocaine is also a highly efficacious reinforcer that maintains operant responding (de Wit and Wise 1977; Pettit et al. 1984; Roberts et al. 1980) and produces interoceptive stimulus effects easily discriminable from saline (Callahan and Cunningham 1993*a*; Callahan et al. 1991; Colpaert et al. 1979; Witkin et al. 1991).

The behavioral effects of acute and chronic cocaine administration clearly depend upon intact dopamine (DA) function, particularly within mesolimbic pathways that originate in the DA somata of the ventral tegmental area (VTA) and terminate in limbic forebrain nuclei, including the nucleus accumbens (NACC) (Fallon and Moore 1978; Swanson 1982). Cocaine binds to the DA transporter (Ritz et al. 1987) and inhibits DA reuptake from the synapse (Koe 1976), prolonging the normal stimulation of DA receptors. The potentiation of mesolimbic DA transmission appears to mediate the locomotor stimulatory (Delfs et al. 1990; Kelly and Iversen 1976; Kilbey and Ellinwood 1976; Scheel-Kruger et al. 1976), rewarding (de Wit and Wise 1977; Pettit et al.

1984; Roberts et al. 1980), and discriminative effects of cocaine (Callahan et al. 1991, 1994; Colpaert et al. 1979; Dworkin and Smith 1988; Witkin et al. 1991; Wood and Emmett-Oglesby 1989), as well as play a critical role in the development of cocaine sensitization (Henry and White 1991; Kalivas and Duffy 1990; Pettit et al. 1990; Post and Contel 1983; Robinson and Becker 1986).

While both presynaptic DA somata and terminals, as well as postsynaptic DA receptors located on non-DA neurons, are vital targets for its indirect DA agonist actions, cocaine is not a selective DA reuptake inhibitor and does not share an identical behavioral profile with such compounds, particularly with regard to abuse liability (Bergman et al. 1989; Lamb and Griffiths 1990).

The differentiation between cocaine and selective DA reuptake inhibitors could be related to other pharmacological actions of cocaine. This psychostimulant is a local anesthetic (Ritchie and Greengard 1966) and inhibits the reuptake of serotonin (5-hydroxytryptamine [5-HT]) and norepinephrine (NE) (Koe 1976) with at least equal potency and efficacy as that of DA reuptake. In addition, cocaine has affinity for the 5-HT_3 receptor (Kilpatrick et al. 1989), M_1 and M_2 muscarinic receptors (Sharkey et al. 1988*a*), and u-receptors (Sharkey et al. 1988*b*). Thus, the actions of cocaine on each of these non-DA systems probably contribute to cocaine's overall behavioral profile.

The purpose of this chapter is to review evidence to support the contribution of 5-HT to two well-characterized behavioral effects of cocaine in rodents: its hypermotive and discriminative stimulus effects. It is the authors' intent to address this question in light of available data and to indicate gaps in the current knowledge of this topic.

ROLE FOR 5-HT IN THE MOTOR STIMULATORY EFFECTS OF ACUTE COCAINE

Of the behavioral effects of cocaine, modifications in motor behavior have been studied extensively over the last 15 years. Cocaine dose-dependently increases horizontal and vertical (rearing) motor activity and induces stereotypies (e.g., sniffing, head weaves, forepaw treading) at high doses or upon chronic administration (Berman et al. 1982; Post and Contel 1983; Robinson and Becker 1986; Scheel-Kruger et al. 1976). The ability of cocaine and its structural analogs to induce hyperactivity

correlates with its actions as a DA reuptake blocker (Heikkila et al. 1979), while 6-hydroxydopamine (6-OHDA) lesions (Kelly and Iversen 1976) and DA antagonists (Spealman et al. 1992) block this behavioral effect. Thus, DA is clearly a prominent mediator of motor activation elicited by cocaine.

Appraisal of cocaine-induced hyperactivity following administration of 5-HT agonists and antagonists or depletion of 5-HT comprises the chief pharmacological approach to studying the involvement of 5-HT in this behavior (table 1). In early studies, the 5-HT precursor 5-hydroxy-tryptophan (5-HTP) was reported to reduce cocaine-evoked hyper-locomotion and stereotypies (Pradhan et al. 1978; Scheel-Kruger et al. 1976; Taylor and Ho 1979). The nonselective 5-HT antagonist metergoline potentiated cocaine-induced hyperactivity and converted the mild stereotypy observed following cocaine administration to the more intense forms typically seen upon amphetamine administration (gnawing, biting) (Scheel-Kruger et al. 1976), although another ergot derivative, methysergide, had no effect on cocaine-induced hyperactivity in mice (Reith 1990).

Induction of biting and licking was also seen following pretreatment with the nonselective 5-HT antagonist cyproheptadine (Berman et al. 1982). These authors suggested that cyproheptadine unmasked behaviors that are putatively mediated by DA (intense gnawing, grooming), suggesting that the expression of these DA stereotypies is inhibited by a serotonergic action of cocaine (Berman et al. 1982; Taylor and Ho 1979). Following pretreatment with *p*-chlorophenylalanine (PCPA), which depletes 5-HT through inhibition of 5-HT synthesis, cocaine hypermotility was also enhanced (Scheel-Kruger et al. 1976).

In sum, the decrease in cocaine-evoked hyperactivity induced by 5-HTP and the increases elicited by blockade of 5-HT release or 5-HT depletion are in keeping with the hypothesis that inhibitory 5-HT mechanisms may influence cocaine-induced hyperactivity, as appears to be the case for amphetamine. For example, global destruction of the raphe increases spontaneous activity (Geyer et al. 1976; Lorens 1978) and levels of DA metabolites in forebrain (Herve et al. 1979, 1981), raising the possibility that both locomotion and DA mesolimbic function are under the control of raphe neurons. These lesion-induced effects are in part related to a loss of 5-HT neurons as psychostimulant-induced hyperactivity and stereotypy are increased following selective 5-HT depletion (Gately et al. 1985; Geyer et al. 1976; Lorens 1978; Scheel-Kruger et al. 1976),

TABLE 1. *Effect of 5-HT compounds on motor activity elicited by cocaine**

5-HT Compound	Effect on Cocaine-Induced Motor Activity
Reuptake inhibitor	
Fluoxetine	NC hyperactivity[16]
Fluvoxamine	⇑ hyperactivity[16]
Paroxetine	NC hyperactivity[16]
Sertraline	NC hyperactivity[16]
Synthesis inhibitor	
PCPA	⇑ hyperactivity[17,18]
Precursor	
5-HTP	⇓ hyperactivity[14,17,19] ⇓ stereotypy[14]
5-HT_{1A} agonists	
Gepirone (partial)	⇑ hyperactivity[13]
NAN 190 (partial)	⇓ hyperactivity[7]
5-HT_3 antagonists	
ICS 205,930	⇓ hyperactivity [rats[18]; mice[15]]
MDL 72222	⇓ hyperactivity[18]
Ondansetron	NC hyperactivity[8]
Zacopride	⇓ hyperactivity [rats[18]; mice[15]] NC hyperactivity[6]
Nonselective antagonists	
Cyproheptadine	induced gnawing, biting[2†]
Metergoline	⇑ hyperactivity[17] induced biting, licking[17†]
Methysergide	NC hyperactivity (mice)[15]

NOTE: * In most cases, a single dose of the 5-HT cormpound was administered prior to assessment of motor behavior induced by one acute injection of cocaine. All studies were conducted in rats unless otherwise noted: ⇑, ⇓ and NC indicate increase, decrease, and no change, respectively. Superscript numbers refer to citations found in table 3.

KEY: † These stereotypies are not typically observed following injection of cocaine alone.

although specific loss of raphe 5-HT neurons does not yield consistent alterations in spontaneous locomotion (Geyer et al. 1976; Lorens 1978). Serotonin neurons may, therefore, exert an inhibitory effect upon cocaine-induced, DA-dependent hyperactivity and stereotypy.

Until recently, only nonselective 5-HT compounds had been assessed for their effects on cocaine-elicited motor behavior, so the extent to which the 5-HT transporter and specific 5-HT receptors might contribute to the observed effects of 5-HT compounds on cocaine-induced behavior was impossible to determine. In addition to the 5-HT transporter, approximately 14 5-HT receptors have been identified, many of which have been localized to the brain (5-HT_1 [5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}], 5-HT_2 [5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}], 5-HT_3, 5-HT_4, 5-HT_5 [5-HT_{5A}, 5-HT_{5B}], 5-HT_6, 5-HT_7) (Branchek 1993). Selective agonists and antagonists that allow differentiation among these receptor subtypes are unavailable in many cases, although selective 5-HT reuptake inhibitors have been developed. Several recent attempts have been made to characterize cocaine-induced motor activity following pharmacological manipulations of the 5-HT system, using such compounds as the 5-HT_{1A} partial agonist gepirone, 5-HT reuptake inhibitors (e.g., fluoxetine), and 5-HT_3 antagonists (e.g., zacopride).

The 5-HT_{1A} receptor is found in abundance on 5-HT somata and dendrites in the raphe nuclei; stimulation of this receptor by 5-HT_{1A} agonists results in a suppression of impulse activity of 5-HT neurons (Sprouse and Aghajanian 1986) and a significant and reversible reduction of 5-HT release in terminal areas (Adell et al. 1993; Sharp et al. 1989). While most other compounds with affinity at this site are described as partial agonists (e.g., gepirone, ipsapirone, NAN 190), 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OHDAPAT) is a reasonably selective agonist for 5-HT_{1A}receptors.

Analogous to the case with PCPA, which depletes 5-HT preferentially in terminal regions, 5-HT_{1A} agonists might be expected to increase cocaine-induced behaviors based upon somatodendritic autoreceptor activation and consequent reduction in 5-HT terminal release (Adell et al. 1993; Sharp et al. 1989). To test this hypothesis, the partial 5-HT_{1A} agonist gepirone (7.5 mg/kg intraperitoneally [IP]) was administered 15 minutes prior to a dose of cocaine (10 mg/kg, IP); this dose of gepirone did not alter activity levels alone but did enhance acute cocaine-stimulated hyperactivity (figure 1) (Paris et al. 1992).

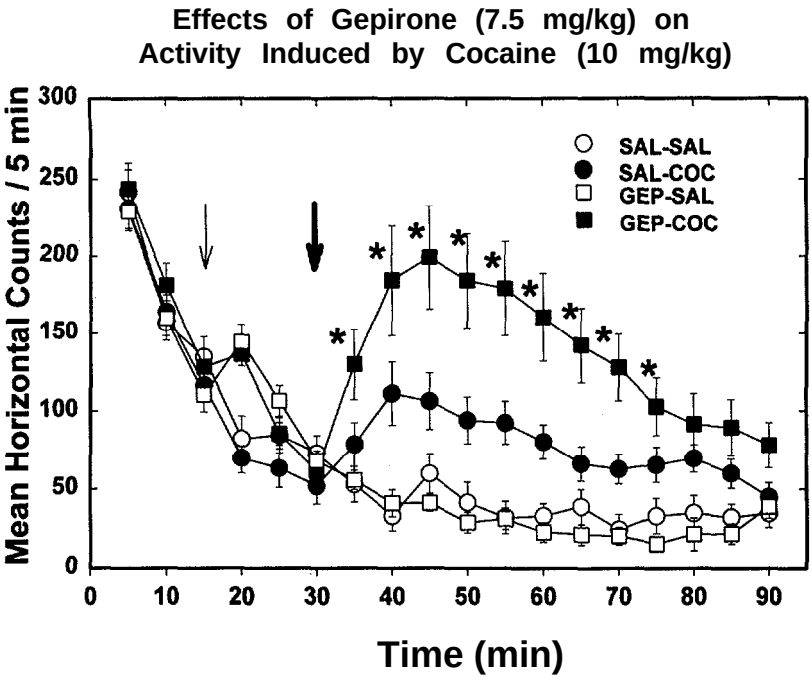

FIGURE 1. *The effects of the partial 5-HT_{1A} agonist gepirone on the activity induced by cocaine. Rats habituated to the locomotor chamber were injected (thin arrow) with saline (SAL) or gepirone (GEP; 7.5 mg/kg, IP), followed 15 minutes later (thick arrow) by SAL or cocaine (COC; 10 mg/kg, IP). Data are presented as means of horizontal activity (±S.E.M.) measured in the center and periphery of an open field chamber equipped with a 4x4 photobeam matrix. Cocaine (SAL-COC) elicited an increase in activity over saline (SAL-SAL) or gepirone-treated rats (GEP-SAL), while gepirone pretreatment (GEP-COC) significantly enhanced the activity elicited by cocaine (* $p < 0.05$ versus SAL-COC). Gepirone (GEP-SAL) at this dose did not alter activity from saline controls (SAL-SAL).*

SOURCE: Adapted from Paris et al. (1992)

These data support the concept that the action of cocaine to enhance 5-HT availability normally counteracts the maximal output of the DA system and, hence, maximal increase in motor activity. When the impulse activity of 5-HT neurons is halted and 5-HT release diminished due to pretreatment with 5-HT_{1A} agonists, this normally dampening effect of 5-HT is not apparent, and the locomotor stimulatory actions of cocaine are enhanced.

In support of this hypothesis, King and colleagues have recently shown that pretreatment with the putative 5-HT_{1A} antagonist NAN 190 reduced cocaine-induced hyperactivity (King et al. 1993). However, because both gepirone and NAN 190 arc partial agonists, it is difficult to attribute their stimulatory and antagonistic effects, respectively, to either agonism (presynaptic) or antagonism (postsynaptic) at the 5-HT_{1A} receptor. For this reason, it will be necessary to reassess the effects of cocaine following pretreatment with the full 5-HT_{1A} agonist 8-OHDAPAT versus a full antagonist (e.g., Way 100135) (Cliffe et al. 1993) to help establish whether the relevant action of the partial agonist gepirone to enhance cocaine hyperactivity is as a presynaptic agonist or postsynaptic antagonist.

In a comprehensive study in mice, Reith and colleagues (Reith et al. 1991) investigated the hypothesis that selective 5-HT reuptake inhibitors might antagonize the acute motor-activating effects of cocaine due to the increased 5-HT available to activate 5-HT postsynaptic receptors (similar to 5-HTP) (Pradhan et al. 1978; Taylor and Ho 1979). However, with the exception of a high dose of fluvoxamine that enhanced this behavior, cocaine-induced locomotion in mice was unaffected by several doses of fluoxetine, paroxetine, or sertraline (Reith et al. 1991). These compounds are selective and efficacious 5-HT reuptake inhibitors that increase extracellular 5-HT levels in terminal regions. However, in comparison to precursors (Rivot et al. 1983) and the 5-HT releaser fenfluramine (Sarkissian et al. 1990; Schwartz et al. 1989), the magnitude of the enhancement is more modest following administration of the 5-HT reuptake inhibitors (Caccia et al. 1993; Perry and Fuller 1992; Rutter and Auerbach 1993). This finding may be related to the preferential action of selective 5-HT reuptake inhibitors to indirectly stimulate 5-HT_{1A} somatodendritic autoreceptors and concurrently and significantly reduce 5-HT neural firing (Chaput et al. 1986; Clemens et al. 1977; Cunningham and Lakoski 1990); synthesis (Bohmaker et al. 1992), and release (Wilkinson and Middlemiss 1992). Thus, the enhancement of 5-HT transmission in 5-HT terminal regions that is elicited by selective 5-HT

reuptake inhibitors is self-limiting (Hjorth 1993; Reith et al. 1991), which may explain why these drugs did not consistently decrease cocaine-induced activity as predicted by the findings with 5-HTP.

A systematic comparative study of cocaine with and without 5-HT precursors (e.g., 5-HTP), releasers (e.g., fenfluramine), and reuptake inhibitors in intact and 5-HT-depleted rats may help to determine which aspects of motor activity are related to DA versus 5-HT reuptake inhibition induced by cocaine. Because some behaviors elicited by high doses and chronic administration of cocaine (Berman et al. 1982; Taylor and Ho 1979) are similar to those seen upon administration of some 5-HT agonists (i.e., forepaw treading, head weaves) (Glennon et al. 1991), particular attention must be given to a separation of horizontal activity (locomotion, ambulation), vertical activity (rearing), and stereotypies (which can be expressed as stereotyped locomotion or rearing as well as sniffing, head weaves, and forepaw treading). This microanalysis is necessary to establish whether the effects of 5-HT compounds on the generation of cocaine-induced behaviors are related to neural mediation by 5-HT or competition among expressed behaviors.

The 5-HT antagonists cyproheptadine and metergoline were reported to increase cocaine-induced hyperactivity or to unmask more intense DA stereotypies such as gnawing and biting in rats (Berman et al. 1982; Scheel-Kruger et al. 1976), although methysergide did not alter cocaine behaviors in mice (Reith 1990). The nonselectivity of these antagonists makes determination of the 5-HT receptor subtype(s) involved in the overall enhancement of cocaine-evoked behaviors difficult; to date, very few attempts to do so have been made. Of note, an interest in the potential role of 5-HT_3 receptors in locomotor hyperactivity induced by cocaine has been generated by a number of findings. First, cocaine has affinity at the 5-HT_3 receptor (Kilpatrick et al. 1987) and was found to inhibit 5-HT-induced stimulation of adrenergic and cholinergic autonomic neurons via competition at the 5-HT_3 receptor (Fozard et al. 1979). Yet, while these data support an antagonistic effect of cocaine on 5-HT_3 receptors, several 5-HT_3 antagonists including ICS 205-930, MDL 72222, and zacopride have recently been found to reduce cocaine hyperactivity (Reith 1990; Svingos and Hitzemann 1992).

One proposed mechanism of action for 5-HT_3 antagonists to block motor activity induced by cocaine is via a reduction in the 5-HT-mediated stimulation of DA release in forebrain areas thought to mediate the stimulatory actions of cocaine, such as NACC (Chen et al. 1991;

McNeish et al. 1993). The fact that depletion of 5-HT with PCPA blocked the ability of zacopride to reverse cocaine-induced hyperactivity demonstrates the dependence of this antagonism on endogenous 5-HT stores (Svingos and Hitzemann 1992). However, the reliance of this phenomenon specifically on modulation of DA release via 5-HT_3 receptors is less clear. At a dose of zacopride (0.1 mg/kg, IP) that completely abolished cocaine hyperactivity, only a modest (27 percent) reduction in cocaine-elicited increases in extracellular DA in NACC was observed (McNeish et al. 1993).

Because PCPA pretreatment blocked the ability of zacopride to antagonize cocaine, actions of 5-HT at 5-HT receptors other than the 5-HT_3 subtype probably contribute to the observed effects of zacopride. However, the generality and reproducibility of the 5-HT antagonist blockade of cocaine hyperactivity is in doubt, given that both zacopride (De La Garza and Cunningham 1993) and ondansetron (King et al. 1994) failed to alter cocaine-induced hyperactivity in other studies. The reasons for discrepancies among studies are not clear, although the type of activity measured (horizontal and vertical versus stereotypy), species, route of administration, doses of cocaine, and doses and receptor affinity profiles of different 5-HT_3 antagonists are suspect. *If* 5-HT_3 antagonists can be shown to block cocaine hyperactivity in a reproducible and consistent fashion, further neurochemical studies will be necessary to identify the contribution of 5-HT_3 receptor modulation of DA release to the antagonistic actions of 5-HT_3 antagonists.

Because of the complexity of the 5-HT system and the relatively obscure manner(s) in which 5-HT and DA systems interact, the specific mechanisms by which 5-HT contributes to motor activation elicited by cocaine are difficult to pinpoint. Cocaine inhibits reuptake of both DA and 5-HT (as well as NH), and its actions to increase synaptic availability of 5-HT may actually dampen the maximal responsivity of the DA system to cocaine. The ability of 5-HT depletion to enhance cocaine-induced hyperactivity and the ability of nonselective 5-HT antagonists to unmask more intense forms of DA-mediated stereotypies support this contention. Similar processes are presumably involved in the psychostimulant actions of amphetamine, although these may not be identical because of the manner in which cocaine and amphetamine act: While the actions of cocaine to enhance extracellular levels of monoamines are impulse dependent, those of amphetamine are impulse independent (Carboni et al. 1989). Manipulations that can be viewed as reducing 5-HT function, such as decreased 5-HT content (e.g., PCPA),

terminal release (e.g., gepirone), or blockade of 5-HT receptors (e.g., cyproheptadine) enhance the acute motor-activating effects of cocaine. Several 5-HT receptors are most likely to be involved, including the 5-HT_{1A} and 5-HT_3 receptors, while others remain to be studied.

ROLE FOR 5-HT IN THE DISCRIMINATIVE STIMULUS EFFECTS OF COCAINE

Serotonin and DA interactions may also underlie other behavioral effects of cocaine in addition to its locomotor stimulatory effects. Humans experience subjective effects that include euphoria, mood elevation, increased confidence, and a heightened sense of awareness as well as anxiety, dysphoria, and nervousness following administration of cocaine (Fischmari and Schuster 1982; Post 1975). If the interoceptive effects of cocaine are perceived as pleasurable, this state can initiate and help to maintain a pattern of drug-seeking behavior (Childress et al. 1988).

Drug discrimination (DD) procedures have been used to model the subjective effects of psychoactive drugs in animals for the last 20 years. In these tasks, the drug serves as a stimulus (cue) that signals the availability of reinforcement conditional upon the occurrence of some operant response (Appel et al. 1982). After acquiring such a discrimination, various pharmacological manipulations can be conducted in an effort to discern the mechanism(s) that underlie the discriminative stimulus properties of the psychoactive compound.

The DD procedure has several positive aspects that make this assay attractive, and these techniques have gained wide acceptance and some measure of popularity. Its primary value for neuropharmacology is derived from its specificity within a given drug class; drugs do not substitute solely on the basis of psychoactive effects, nor do randomly selected compounds mask the stimulus effects of a drug (Appel et al. 1982). However, two notes of caution are in order. In some instances, a test compound only partially mimics or antagonizes a cue; these partial substitutions and antagonisms are difficult to interpret. Furthermore, as is the case with all pharmacological procedures, DD specificity often depends upon the selectivity of agents that act on particular neurotransmitter systems or at specific receptor subtypes.

One possible drawback to DD studies is the necessity of maintaining trained animals for many months with drug(s) and vehicle(s)

administered frequently. In general, tolerance to the discriminative effects of drugs develops only under chronic regimens of drug treatment in the absence of continued training (Wood et al. 1984). Nonetheless, these procedures have provided significant information concerning psychostimulant mechanisms in vivo.

With regard to cocaine, substitution and antagonism tests have revealed that both dopamine type 1 (D_1) and dopamine type 2 (D_2) receptors are important mediators of the interoceptive effects of cocaine. Agonists for the D_2 receptor (e.g., quinpirole) and selective DA reuptake inhibitors (e.g., GBR 12909) substitute fully for the cocaine stimulus, while D_1 agonists (e.g., SKF 38393) partially substitute; both D_1 (e.g., SCH 23390) and D_2 antagonists (e.g., haloperidol) attenuate the stimulus effects of cocaine in rats (Callahan and Cunningham 1993*a*; Callahan et al. 1991; Colpaert et al. 1979; McKenna and Ho 1980; Witkin et al. 1991). Microinjection of cocaine into NACC fully mimics the stimulus effects of systemic cocaine (Callahan et al. 1994; Wood and Emmett-Oglesby 1989), while both 6-OHDA lesion of NACC (Dworkin and Smith 1988) and intra-NACC microinjection of the D_1 antagonist SCH 23390 block the discriminability of cocaine (Callahan et al. 1994). Thus, the neuropharmacological profile supports the overall importance of DA systems, specifically mesoaccumbens, in elicitation of the interoceptive effects of cocaine.

Few systematic studies of 5-HT agonists and antagonists have been undertaken in rats trained to discriminate cocaine from saline (tables 2 and 3). In early research, neither direct (mescaline, d-lysergic acid diethylamide [LSD]) (Colpaert et al. 1979) nor indirect 5-HT agonists (e.g., fenfluramine) (McKenna and Ho 1980; Wood and Emmett-Oglesby 1988) mimicked cocaine. Several nonselective 5-HT antagonists (cinanserin, cyproheptadine, methysergide) did not block the cue (Colpaert et al. 1979). These data suggested the lack of importance of 5-HT in this behavioral effect of cocaine. However, these studies in general failed to assess the hypothesis that pharmacological enhancement (e.g., 5-HTP) and reduction (e.g., PCPA, 5-HT antagonists) of 5-HT neurotransmission might block and enhance, respectively, the discriminability of cocaine as suggested by studies of cocaine-evoked hyperactivity (above).

TABLE 2. *Effect of 5-HT compounds on the stimulus effects of cocaine**

5-HT Compounds	Substitutes	Enhances	Antagonizes
5-HT reuptake inhibitor			
Citalopram	X[1]	?	?
Fluoxetine	X[1,5]	√[5]	X[3]
Imipramine	X[9]	?	?
5-HT releaser			
Fenfluramine	X[3,11,20]	?	?
5-HT$_{1A}$ agonists			
8-OHDPAT	X[3]	X[3]	X[3]
Gepirone	X[3]	X[3]	X[3]
Other 5-HT agonists			
LSD (5-HT$_{2A/2C}$)	X[4]	?	?
Mescaline (5-HT$_{2A/2C}$)	√[11]	?	?
MCPP (5-HT$_{1B/2C}$)	X[3]	X[3]	√[3]
MK 212 (5-HT$_{1B/2C}$)	X[3]	X[3]	√[3]
TFMPP (5-HT$_{1B/2C}$)	√[3]	√[3]	X[3]
5-HT$_3$ antagonists			
ICS 205-930 (5-HT$_3$)	X[12]	?	X[12]
MDL 72222	X[12]	?	X[12]
Ondansetron	?	?	X[10]
Nonselective 5-HT antagonists			
Cinanserin	?	?	X[11]
Cyproheptadine	?	?	X[4]
Metergoline	?	?	X[1]
Methysergide	?	?	X[4]

NOTE: * Complete (√√) and partial (√) substitutions (SUBSTITUTES) are defined as >80 percent and 60-79 percent cocaine-lever responses, respectively. An enhancement (√; ENHANCES) is defined as a significant increase in the percentage of cocaine-lever responses upon coadministration of the compound with cocaine. A complete (√√) and partial (√) antagonism are defined as < 30 percent and 31-60 percent cocaine-lever responses following the combination of the 5-HT compound and cocaine. An X and ? indicate that the drug had no effect or was not tested, respectively. Superscript numbers refer to citations found in table 3.

TABLE 3. *Effects of 5-HT compounds on the stimulus effects of cocaine citations*

No.	Reference
1	Baker et al. (1993)
2	Berman et al. (1982)
3	Callahan and Cunningham (1993*b*)
4	Colpaert et al. (1979)
5	Cunningham and Callahan (1991)
6	De La Garza and Cunningham (1993)
7	King et al. (1993)
8	King et al. (1994)
9	Lamb and Griffiths (1990)
10	Lane et al. (1992)
11	McKenna and Ho (1980)
12	Paris and Cunningham (1991)
13	Paris et al. (1992)
14	Pradhan et al. (1978)
15	Reith (1990)
16	Reith et al. (1991)
17	Scheel-Kruger et al. (1976)
18	Svingos and Hitzemann (1992)
19	Taylor and Ho (1979)
20	Wood and Emmett-Oglesby (1988)

Substitution tests with selective 5-HT reuptake inhibitors indicated that citalopram (Baker et al. 1993), fluoxetine (Baker et al. 1993; Cunningham and Callahan 1991), and imipramine (Baker et al. 1993) did not mimic cocaine. In contrast, fluoxetine pretreatment did potentiate the cocaine cue, shifting the dose-effect curve for cocaine to the left (Cunningham and Callahan 1991). Other selective 5-HT reuptake inhibitors, such as sertraline and fluvoxamine, share this ability (Callahan et al., unpublished observation). Perhaps specific 5-HT receptors activated by the increased synaptic 5-HT account for the enhancement afforded by 5-HT reuptake inhibitors.

The manner in which 5-HT might control the interoceptive effects of cocaine appears to differ from the serotonergic contribution to its locomotor stimulating effects, since fluoxetine and other 5-HT reuptake

inhibitors in general failed to alter locomotor activity induced by cocaine in mice (Keith et al. 1991). Note that the NE reuptake inhibitor desipramine also effectively enhanced the cocaine cue (Cunningham and Callahan 1991), and nonspecific pharmacokinetic processes cannot be ruled out (e.g., increased brain cocaine levels induced by reuptake inhibitors, possibly as a result of inhibition of cocaine metabolism [(Misra et al. 1986; Tella and Goldberg 1993]).

The potentiation of the cocaine cue with 5-HT reuptake inhibitors prompted a further pharmacological analysis to test the hypothesis that other 5-HT agonists may mimic, potentiate, or antagonize the cocaine cue. The full 5-HT_{1A} agonist 8-OHDPAT and the partial 5-HT_{1A} agonist gepirone were without effect, despite evidence that gepirone effectively enhanced the locomotor stimulatory actions of cocaine (Paris et al. 1992), once again suggesting a differentiation in the manner in which 5-HT modulates the locomotor versus discriminative effects of cocaine. The 5-HT agonists m-chlorophenylpiperazine (MCPP), MK 212, and 1 -(*m*-trifhroromethylphenyl) piperazine (TFMPP) were not perceived as similar to cocaine, although TFMPP did elicit persistent 30 to 60 percent drug-lever responding (Callahan and Cunningham 19933). Like fluoxetine, TFMPP enhanced the discriminability of low doses of cocaine (figure 2) (Callahan and Cunningham 1993*b*). On the other hand, MCPP and MK 212 neither mimicked nor potentiated cocaine, but dose-dependently blocked the stimulus effects of cocaine (figure 3) (Callahan and Cunningham 1993*b*). Surprisingly, the efficacy of MCPP and MK 212 was similar to that of many DA antagonists (Callahan et al. 1991). Of note, these compounds do not have appreciable affinity for DA receptors (Hamik and Peroutka 1989; Neale et al. 1987). Thus, two groups of piperazine derivatives can be distinguished: One group (TFMPP) that serves to potentiate, and a second group (MCPP, MK 212) that blocks the cocaine cue.

The piperazines MCPP, MK 212, and TFMPP are considered 5-HT agonists; however, each differs with regard to its profile of interactions with the 5-HT transporter and various 5-HT receptors. While the structurally similar compounds MCPP and TFMPP have similar affinity for 5-HT_{1B} and 5-HT_{2C} receptors (Curzon and Kennett 1990; Sills et al. 1985), TFMPP has a greater affinity for the 5-HT transporter than does MCPP (Curzon and Kennett 1990; Sills et al. 1985). Therefore, TFMPP (like fluoxetine) may potentiate the effects of cocaine via 5-HT reuptake inhibition.

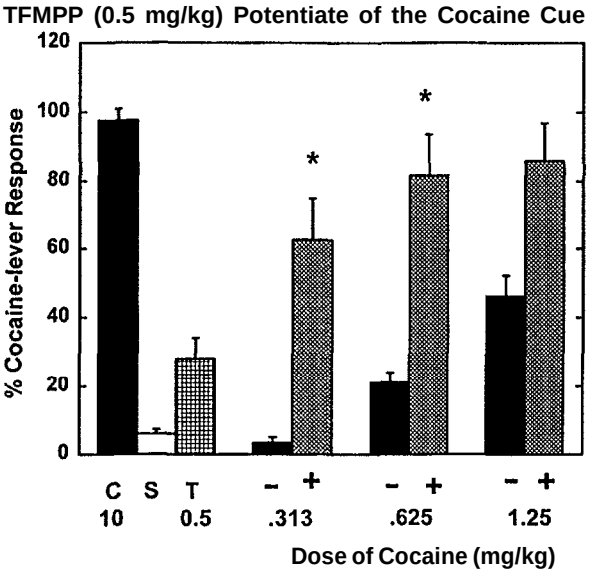

FIGURE 2. *The effects of the 5-HT agonist TFMPP on the stimulus properties of cocaine. Rats were trained to discriminate cocaine (10 mg/kg, IP) from saline in a two-lever, water-reinforced drug discrimination task (Callahan and Cunningham 1993b). During combination tests, rats were pretreated with TFMPP (0.5 mg/kg, IP) 15 minutes prior to an injection of cocaine (0.313, 0.625, or 1.25 mg/kg) and were placed in operant chambers 15 minutes later. Bars denote the mean percentage of cocaine-appropriate responses (±SEM) observed following a dose of cocaine given in the absence (-; filled bars) or presence (+; hatched bars) of TFMPP pretreatment. Data points are the mean of 8/8 rats [n/N: number of subjects (n) completing at least 20 responses out of the number of subjects tested (N)]. Asterisks denote values significantly different than the indicated dose of cocaine alone ($p < 0.05$). Control points are found on the left side of graph and show the degree of stimulus control engendered by 10 mg/kg of cocaine. (C 10; filled bar), saline (S; open bar), and 0.5 mg/kg of TFMPP (T 0.5; plaid bar).*

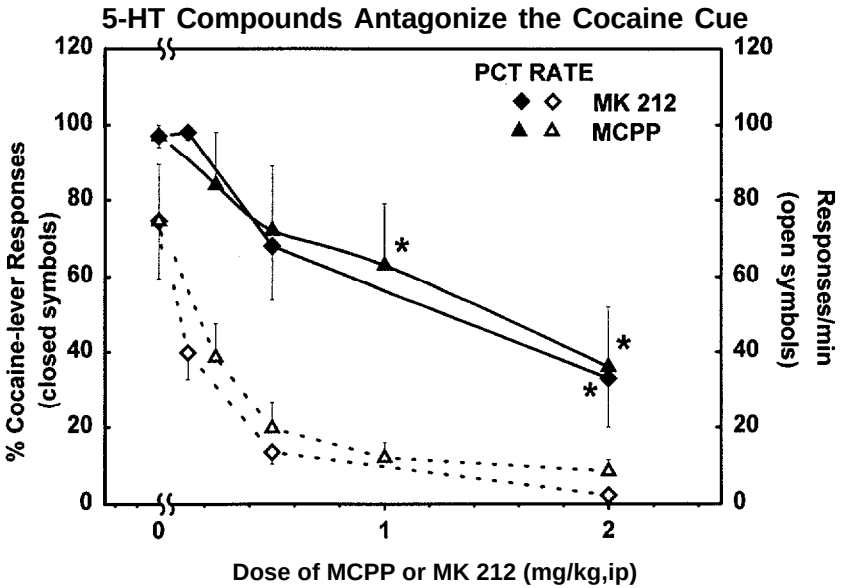

FIGURE 3. *The effects of the 5-HT agonists MCPP and MK 212 on the stimulus properties of cocaine. Rats were trained to discriminate cocaine (IO mg/kg, IP) from saline in a two-lever, water-reinforced drug discrimination task (Callahan and Cunningham 1993b). During combination tests, rats were pretreated with MCPP or MK 212 (0.25-2 mg/kg, IP) 15 minutes prior to an injection of cocaine (5 mg/kg) and were placed in operant chambers 15 minutes later. Closed symbols denote the mean percentage of cocaine-appropriate responses (±SEM; left ordinate); open symbols denote the mean response rate/minute (±SEM; right ordinate). Data points are the mean of 5-7/7 rats. Asterisks denote values significantly different than cocaine (5 mg/kg) alone $p < 0.05$). At a dose of 0 mg/kg, the degree of stimulus control engendered by 5 mg/kg of cocaine is shown.*

Further evidence that the in vivo actions of TFMPP can be distinguished from those of MCPP is suggested by the finding that, in rats trained to discriminate MK 212 from saline, MCPP (but not TFMPP) produces a full substitution (Cunningham et al. 1986). While it is difficult to propose one neural mechanism to account for these potentiations based upon 5-HT reuptake inhibition, one possibility might be an enhancement

of DA release; in fact, intra-VTA injection of TFMPP has been shown to increase release of NACC DA, an action that would be expected to enhance the behavioral effects of cocaine (Guan and McBride 1989).

The compounds MCPP and MK 212, which blocked the cocaine cue, share affinity at a number of 5-HT receptors including the 5-HT_{1B} and 5-HT_{2C} receptors. Since the 5-$HT_{2A/2C}$ antagonist LY 53857 does not alter the cocaine cue (Callahan and Cunningham, unpublished observation), 5-HT1B receptors may be involved in the antagonistic effects of these compounds. These 5-HT_{1B} receptors are found in DA cell body areas and accumbens and are thought to modulate 5-HT release at terminals (Bobker and Williams 1989; Pazos and Palacios 1985). An action 'of these compounds to modulate DA release at the level of the raphe, VTA, or limbic sites may be possible. Furthermore, a potential role for NE in mediating these antagonistic actions of MCPP and MK 212 requires investigation. However, the potency order for antagonism of the cocaine cue does not correlate with the affinity of these compounds for either α_1- or α_2-adrenoceptors (Hamik and Peroutka 1989; Neale et al. 1987).

Few 5-HT antagonists with selectivity at 5-HT receptors have been assessed for substitution, potentiation, or antagonism of cocaine (tables 2 and 3). Because of the affinity of cocaine for the 5-HT_3 receptor (Kilpatrick et al. 1987) and the interest in the role of 5-HT_3 receptors in controlling DA function (Costall et al. 1987), several 5-HT_3 antagonists have been assessed in rats trained to discriminate cocaine from saline. Neither MDL 72222, ICS 205-930 (Paris and Cunningham 1991) nor ondansetron (Lane et al. 1992) substituted or blocked cocaine; the ability of such compounds to potentiate the cocaine stimulus has not yet been studied. Although 5-HT_3 antagonists inhibit a variety of DA-mediated events, including (in some studies) cocaine-evoked hyperactivity (Reith 1990; Svingos and Hitzemann 1992), the stimulus effects of cocaine appear to be resistant, thus providing further evidence that the 5-HT modulation of cocaine behaviors is not identical for its locomotor stimulatory and discriminative stimulus effects.

CONCLUSION

While the bidirectional modulatory effects of 5-HT agonists on the stimulus effects of cocaine probably reflect the fact that these 5-HT agonists have distinctive profiles with regard to affinity and action at

multiple 5-HT receptors, it appears that the locomotor and discriminative effects of cocaine can be augmented or reduced by manipulations of 5-HT tone. In general, these behavioral studies support the hypothesis that 5-HT may modulate DA output at the level of the 5-HT soma (raphe), DA soma (VTA), or the terminals of mesolimbic DA circuits that are critical to these behaviors. Unfortunately, assimilation of these studies into one conceptual framework is difficult because of the relative lack of a concrete understanding of how and where 5-HT and DA interact in the brain to control behavior, and an incomplete knowledge of the complexity of the 5-HT system, including the large number of 5-HT receptors and the relative lack of specific and selective ligands for each site.

One long-held hypothesis is that 5-HT, under normal conditions, tonically inhibits DA systems; many of the research findings discussed in this chapter support this hypothesis. However, alternate hypotheses (e.g., 5-HT tonically excites DA activity) appear to explain other behavioral findings (Nader and Barrett 1990; Paris et al. 1992). Nevertheless, it is apparent that a full appreciation of how cocaine produces its behavioral effects is dependent upon a better understanding of the mechanisms and loci at which 5-HT modulates DA mesolimbic systems and how cocaine biases this balance.

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A Review of the Effects of Dopaminergic Agents in Humans: Implications for Medication Development

Richard B. Rothman

INTRODUCTION

The purpose of this chapter is to expand on issues related to the mechanism or mechanisms of cocaine's addictive and euphorogenic effects that were discussed in previous papers (Rothman 1990; Rothman et al. 1989).

THE DOPAMINE HYPOTHESIS OF COCAINE'S REINFORCING EFFECTS

The hypothesis that mesolimbic dopamine (DA) plays a critical role in mediating the reinforcing effects of cocaine is well supported by a wide variety of data. An article by Johanson and Fischman (1989) comprehensively reviews much of the data. There is a high degree of correlation between the potency of cocaine-like drugs as inhibitors of DA reuptake and their potency in tests of self-administration (Madras et al. 1989; Ritz et al. 1987; Spealman et al. 1989) and observations that lesions of the mesolimbic DA system disrupt cocaine self-administration (Dworkin et al. 1988; Koob et al. 1987*a*; Roberts and Koob 1982; Roberts et al. 1977).

Further support for the DA hypothesis comes from observations that DA antagonists disrupt cocaine self-administration in a predictable manner (De La Garza and Johanson 1982; Ettenburg et al. 1982; Johanson et al. 1976; Koob et al. 1987*b*; Roberts and Vickers 1984; Wilson and Schuster 1972; Woods et al. 1978) and that DA agonists such as apomorphine, bromocriptine, and piribedil are self-administered (Baxter et al. 1974; Woolverton et al 1984; Yokel and Wise 1978), as are the DA reuptake blockers bupropion (Woods et al. 1983), mazindol (Wilson and Schuster 1976), and nomifensine (Spyaki and Fibiger 1981). It should be noted, however, that some investigators suggest that disruption of cocaine

self-administration by DA antagonists results from a nonspecific rate-reducing effect (Johanson and Fischman 1989; Woods et al. 1987; Woolverton and Balster 1981; Woolverton and Virus 1989).

EFFECT OF DOPAMINERGIC AGENTS IN HUMANS

Although these data are convincing, they are puzzling. There are apparent incompatibilities between the animal data and clinical experience with regard to medicines that increase DA or block its actions. These drugs can be informally classified as DA reuptake inhibitors, direct DA agonists, DA increasers, and DA antagonists. Although DA-releasing agents such as amphetamine produce euphoria in humans, these are not discussed in this chapter.

The exact relationship between reinforcement, as measured in animal studies, and the subjective and addictive effects of cocaine in humans is not completely understood. It is reasonable to suppose that the ability of cocaine to produce euphoria in humans is probably related to its addictive effects. After all, most people take cocaine, at least initially, because it makes them feel good. Cocaine produces euphoria in humans after intravenous (IV), oral, and inhalational administration (Johanson and Fischman 1989). Moreover, cocaine produces euphoria in the great majority of people who take it (Johanson and Fischman 1989).

A direct prediction of the DA hypothesis is that dopaminergic agents that produce cocaine-like effects in animals should produce cocaine-like effects in humans. Cocaine produces a number of subjective and objective effects in humans, but it is not clear which cocaine-like effects one would want to see successfully predicted by animal studies. This chapter focuses on euphoria, or a feeling of well-being; as mentioned earlier, this is an effect of cocaine that is likely to be related to its addictive properties. However, the relationship between euphoria and reinforcement is not necessarily straightforward, since drugs can exert reinforcing effects in the apparent absence of euphoria. Indeed, it could be argued that an alternative relevant measurement of a drug's reinforcing effect is its actual abuse by humans. Although dopaminergic agents do produce some cocaine-like effects, these effects do not include euphoria, and they do not occur in the majority of patients who are administered these drugs. Moreover, these dopaminergic agents are not known to be drugs of abuse.

DA Reuptake Inhibitors

There are four DA reuptake blockers that are, or have been, marketed in the United States: bupropion, nomifensine, mazindol, and benztropine. As noted in table 1, bupropion is an antidepressant. Nomifensine, an antidepressant, was taken off the market because it produced severe allergic reactions in some patients. Mazindol is used for the treatment of obesity. Benztropine is commonly prescribed for the treatment of movement disorders (Bianchine 1980).

As shown in table 2, all four of these medications are more potent than cocaine in inhibiting [^{3}H]dopamine ([^{3}H]DA) reuptake into striatal synaptosomes (Andersen 1987). Setting aside pharmacokinetic considerations, one would predict that these agents, like cocaine, would produce euphoria in humans. However, the prescribing literature for these drugs do not mention the occurrence of euphoria as either a primary effect or as a side effect (Bianchine 1980; Chait et al, 1987; Hadler 1972; Rickels et al. 1982; Stem et al. 1982; Yakabow et al. 1984). Moreover, with the exception of mazindol, these agents are all Schedule V drugs, indicating a very low abuse liability. Since mazindol is dysphoric in humans (Chait et al. 1987), it is surprising that it is classified as a Schedule IV drug. If these drugs could produce euphoria, one would

TABLE 1. *DA reuptake inhibitors marketed for use in humans*

Agent	Indication	Euphoria/Addiction?
Bupropion	Antidepressant	None reported'
Nomifensine	Antidepressant	None reported[2]
Benztropine	Movement disorders	None reported[3]
Mazindol	Anorectic	None reported[4]

1 Stern et al. (1982)
2 Rickels et al. (1982)
3 Bianchine (1980)
4 Chait et al. (1987); Hadler (1972)

think this would have been readily observed, since these medicines have been collectively prescribed to millions of people.

This common-sense notion has stood up to scientific scrutiny. As summarized in table 3, when the subjective effects of bupropion and nomifensine were specifically examined, there was no mention of drug-induced euphoria (Hamilton et al. 1983; Miller and Griffith 1983; Parrott et al. 1982; Peck and Hamilton 1983; Shekim et al. 1989; Yakabow et al. 1984). The studies of Peck and Hamilton (1983) showed that oral administration of 200 mg of bupropion or 100 mg of nomifensine did not produce amphetamine-like central nervous system stimulant activity in normal volunteers. Supporting these results were studies (Griffith et al. 1983; Miller and Griffith 1983) demonstrating that at oral doses up to 400 mg, bupropion did not produce amphetamine-like subjective effects in experienced amphetamine abusers.

Direct DA Agonists

DA agonists available for use in humans include pergolide and bromocriptine, which act equally at DA type 1 (D_1) and type 2 (D_2) receptors. Their primary therapeutic use is in the treatment of Parkinson's disease, acromegaly, and hyperprolactinemia. Since they are

TABLE 2. *IC_{50} values for drugs as inhibitors of [^{3}H]DA reupake in vitro*

Drug	IC_{50} (nM)
Cocaine	690
Bupropion	***648***
Benztropine	175
Nomifensine	134
Mazindol	29

NOTE: IC_{50} values for inhibition of [^{3}H]DA reuptake into striatal synaptosomes (Andersen 1987).

TABLE 3. *Studies that reported on the subjective effects of DA reuptake inhibitors in humans*

Drug	Citations
Bupropion and nomifensine	1
Benztropine	2
Mazindol	3

[1] Hamilton et al. (1983); Miller and Griffith (1983); Parrott et al. (1982); Peck and Hamilton (1983); Shekim et al. (1989); Yakabow et al. (1984)
[2] Bianchine (1980)
[3] Chait et al. (1987)

self-administered by animals (Woolverton et al. 1984), one might expect them to produce cocaine-like effects in humans. Although these agents do produce a variety of psychiatric side effects, as shown in table 4, euphoria is not among them.

DA Increasers

The DA increasers include the monoamine oxidase (MAO) inhibitors and levodopa. The MAO inhibitors commonly used in the United States are phenelzine, tranylcypromine, and selegiline. Whereas phenelzine and tranylcypromine inhibit both MAO types A and B, selegiline is a selective inhibitor of MAO type B (Murphy 1978; Murphy and Kalin 1980; Murphy et al. 1984). Phenelzine and tranylcypromine are effective antidepressants (Baldessarini 1990). Selegilme is approved by the Food and Drug Administration only for the treatment of Parkinson's disease (Cedarbaum and Schleifer 1990). Preliminary data suggest it might also have antianxiety and antidepressant properties (Tariot et al. 1987).

Selegiline's mechanism of action in the treatment of Parkinson's disease is thought to result from inhibition of MAO type B, which metabolizes DA and results in an increase in the synaptic concentration of DA (Cedarbaum and Schleifer 1990). In support of this hypothesis, in vivo

TABLE 4. *Neuropsychiatric (plus some general) side effects of pergolide and bromocriptine*

Pergolide	Bromocrintine
Dyskinesia	Nausea
Dizziness	Headache
Hallucinations	Dizziness
Dystonia	Fatigue
Confusion	Lightheadedness
Somnolence	Vomiting
Insomnia	Abdominal cramps
Anxiety	Nasal congestion
Tremor	Constipation
Depression	Diarrhea
Abnormal dreams	Drowsiness
Personality disorder	
Psychosis	
Abnormal gait	
Akathisia	
Extrapyramidal syndrome	
Incoordination	
Paresthesia	
Akinesia	
Hypertonia	
Neuralgia	
Speech disorder	

microdialysis studies in rats have shown that MAO inhibitors increase the concentration of extracellular DA (Colzi et al. 1990; Imperato and Di Chiara 1984; Miller and Gold 1988). Moreover, studies of Alzheimer's disease patients (Sunderland et al. 1987) demonstrated that administration of selegiline decreased the cerebrospinal fluid (CSF) levels of the DA metabolite homovanillic acid (HVA), presumably as a result of MAO inhibition. Similar results were observed in the CSF of monkeys treated chronically with the selective MAO type A inhibitor clorgyline (Cox et al. 1991).

Since MAO inhibitors increase synaptic concentrations of DA, the DA hypothesis would predict that they should have cocaine-like effects. Indeed, in rats trained to discriminate 5 mg/kg of cocaine from saline,

Colpaert and colleagues (1980) found that the cocaine interoceptive cue was generalized to selegiline and tranylcypromine, consistent with the notion that these agents act to increase DA. However, as indicated in table 5, the side-effect profile does not include euphoria. In fact, these drugs are quite dysphoric. Similarly, levodopa is prescribed to patients with Parkinson's disease because it increases synaptic DA, yet it does not produce euphoria (Cedarbaum and Schleifer 1990).

DA Antagonists

The DA antagonists include the relatively large number of medicines used mainly in the treatment of schizophrenia. The reader is referred to a textbook for a more thorough description of the antipsychotic drugs (Baldessarini 1990). Although the recent description of DA types 3, 4, and 5 (D_3, D_4, and D_5) receptors (Sokoloff et al. 1990; Sunahara et al. 1991; van Tol et al. 1991) complicates the task of deciding which DA receptor or receptors might mediate the reinforcing effects of cocaine in animals, the data demonstrate that antipsychotics, which are prescribed to humans, attenuate cocaine self-administration in animals as predicted by the DA hypothesis.

Evidence that antipsychotics block cocaine-induced euphoria in humans is negative, lacking, or inconclusive. As summarized in table 6, Gawin (1986) contributed a case report in which he noted that "four cocaine abusers with histories of stimulant-induced paranoid psychoses reported selective reduction in psychotic symptoms but not euphoria when treated with dopamine blockers. This provides preliminary evidence against efficacy of neuroleptics in cocaine abuse prevention, and suggests euphoria and paranoia may have discriminable neurophysiological substrates" (p. 142).

Sherer and colleagues (1989) reported that haloperidol (8 mg intramuscularly [IM]) partially reduced the high, but not the rush, induced by IV cocaine. This finding is difficult to interpret, since it is not clear if the sedating effect of haloperidol contributed to the partial amelioration of the cocaine-induced high. In an open-label study of the effectiveness of flupenthixol deconoate for treating cocaine abuse in crack addicts, Gawin and colleagues (1989) noted that "subjects treated informally before this trial at higher doses (30 to 80 mg) . . . often reported diminished intensity or duration of cocaine's euphoric effect, but not complete blockade, when cocaine smoking was resumed . . . [This]

TABLE 5. *Neuropsychiatric side effects of MAO inhibitors*

Phenelzins	Selegiline
Dizziness	Hallucinations,
Headache	Dizziness
Drowsiness	Confusion
Sleep disturbances	Anxiety
Fatigue	Depression
Weakness	Drowsiness
Tremors	Dreams/nightmares
Twitching	Tiredness, delusions
Hyperreflexia	Disorientation
Myoclonic movements	Lightheadedness
	Impaired memory*
	Increased energy*
	Transient high*
	Hollow feeling
	Lethargy/malaise
	Apathy
	Overstimulation
	Vertigo
	Personality change
	Sleep disturbance
	Restlessness
	Weakness
	Transient irritability
	Behavior/mood change

KEY: * At doses greater than the usual 10 mg/day. Rate of occurrence not specified.

may not occur in a clinically meaningful magnitude in the low doses used in this study" (p. 17).

Indirect evidence that antipsychotic medications do not attenuate the euphoric effects of cocaine comes from studies that indicate that schizophrenic patients, many of whom are taking antipsychotic medication, abuse cocaine (Brady et al. 1990; Bunt et al. 1990; Dixon et al. 1991; Schneier and Siris 1987; Sevy et al. 1990). Thus, although

TABLE 6. *Summary of studies reporting on the effects of antipsychotic drugs on cocaine-induced subjective effects in humans*

Gawin (1986)
"Four cocaine abusers with histories of stimulant-induced paranoid psychoses reported selective reduction in psychotic symptoms but not euphoria when treated with dopamine blockers. This provides preliminary evidence against efficacy of neuroleptics in cocaine abuse prevention, and suggests euphoria and paranoia may have discriminable neurophysiological substrates."
Sherer et al. (1989)
Haloperidol 8 mg IM partially reduced the "high" but not the rush induced by IV cocaine. This finding is difficult to interpret, since it is not clear if the sedating effect of haloperidol contributed to the partial amelioration of the cocaine-induced high.
Gawin et al. (1989)
In this open-label study, 10 crack addicts were given 10 or 20 mg of flupenthixol decanoate IM. Dr. Gawin noted that:
". . . subjects treated informally before this trial at higher doses (30 to 80 mg) . . . often reported diminished intensity or duration of cocaine's euphoric effect, but not complete blockade, when cocaine smoking was resumed . . . [This] may not occur in a clinically meaningful magnitude in the low doses [used in this study."
Unfortunately, this finding must be classified as anecdotal.

the hypothesis that DA antagonists block cocaine-induced subjective effects in humans has not been rigorously tested, the currently available data suggest that they do not. Clearly, this issue calls for careful study by clinical investigators.

INITIAL CONCLUSIONS

The data reviewed here raise more questions than they answer. Nevertheless, some tentative conclusions can be reached. Although animal studies demonstrate that DA is a key neurochemical mediator of the reinforcing effects of cocaine, the interpretation of the human data is less clear. With the exception of cocaine and amphetamine-like drugs, the various dopaminergic agents reviewed here do not produce euphoria in humans and are not drugs of abuse. Although factors other than the ability to produce euphoria play a role in determining abuse liability (Balster 1991), the simplest explanations for the fact that these medicines are not abused drugs is that they do not produce euphoria and are weak reinforcers.

Although various arguments can be made as to why any particular dopaminergic agent might not produce cocaine-like effects in humans, the lack of cocaine-like effects produced by this relatively broad mechanistic spectrum of dopaminergic agents is difficult to reconcile with the DA hypothesis as specifically formulated in this chapter. This interpretation suggests that the DA hypothesis may be too simple to completely explain the human subjective (euphoria) and objective (actual abuse) response to cocaine administration.

The ability of a drug to support self-administration behavior in animals using a substitution paradigm is often predictive of its abuse liability in humans (Johanson 1990; Johanson and Balster 1978; Johanson and Fischman 1989; Schuster 1991). Although behavioral pharmacologists acknowledge the limitations of the method (Johanson 1990), the simplistic notion that self-administration of a drug means the drug has significant abuse liability seems to have become almost a dogma among scientists not trained in the subtleties of behavioral pharmacology. The results of the self-administration substitution paradigm are often used to predict the abuse liability of test drugs. Like any diagnostic test, the self-administration (substitution) paradigm can be expected to have measurable rates of false positives and false negatives. Drugs such as lysergic acid diethylamide and marijuana, which are not self-administered by animals, are often used as examples of false negatives (Johanson 1990).

Table 7 lists drugs that the author feels are false positives. These data are adapted from the paper of Iwamoto and Martin (1988). These agents are self-administered by animals in the substitution paradigm, but do not produce cocaine-like effects in humans. For example, bupropion (Woods et al. 1983), mazindol (Wilson and Schuster 1976), nomifensine (Spyraki and Fibiger

TABLE 7. *Drugs that are self-administered (substitution procedure) but do not produce euphoria in humans*

Opioids	Dopaminergic agents	Misc. agents
Ketocyclazocine	Apomorphine	Procaine
Ethylketocyclazocine	Piribedil	Clonidine
	Bromocriptine	
	Mazindol	
	Bupropion	

SOURCE: With the exception of mazindol, nomifensine, and bupropion, the data are from the review of Iwamoto and Martin (1988).

1981), bromocriptine, and pergolide (Woolverton et al. 1984) all support self-administration behavior in animals yet do not produce cocaine-like effects in humans. Similarly, the alpha, agonist clonidine and the local anesthetic procaine support self-administration behavior but do not produce euphoria in humans.

In addition to the false-positive drugs, there are drugs such as the MAO inhibitors that one would expect to be self-administered by animals but which presumably are not (based on the lack of published data on this class of drugs in the self-administration literature). These agents behave consistently in animals and humans. In that both cocaine and MAO inhibitors increase synaptic levels of the biogenic amines, it is puzzling why the former produces euphoria and is a drug of abuse while the latter agents do not.

An implication of this assessment is that the self-administration substitution paradigm, as applied ***to*** cocaine-like drugs, does not always accurately predict the ability of a drug to produce euphoria or cocaine-like effects in humans. Assuming that this is true, one would also question the ability of the self-administration paradigm to predict the activity of a cocaine antagonist in humans. Indeed, as reviewed earlier, the apparent inability of DA antagonists to block the euphoric effects or abuse of cocaine in humans supports this idea.

The significance of this interpretation for efforts to develop effective pharmacotherapeutics for cocaine abuse is that preclinical drug development programs are generally structured so that the self-administration substitution paradigm is used to select candidate drugs for possible use in humans. Thus, researchers may be selecting medications that will not work or, alternatively,

ruling out medications that may work. These considerations point to the need for developing animal models that can detect the difference between dopaminergic drugs that are and are not abused by humans.

A STRATEGY FOR DRUG DEVELOPMENT

Viewed collectively, these data and their interpretations might lead one to take a pessimistic view of researchers' ability to develop effective medications for cocaine abuse. However, it is the opinion of this author that the problem lies not with the models that have been developed, but probably with the fact that there is a tendency to overinterpret the data resulting from the models.

Take, for example, the self-administration paradigms referred to earlier. As generally practiced, IV self-administration studies in animals use a substitution procedure in which the animal is first trained to self-administer cocaine, and then the ability of a drug to substitute for the cocaine is quantitated. Behavioral pharmacologists mostly agree that this rate-dependent approach is not the best one possible for measuring the reinforcing efficacy of the drug (Johanson and Fischman 1989). That is, the substitution method does not measure if a drug is less reinforcing than cocaine, but only determines whether the animal will self-administer the drug when denied access to cocaine. Indeed, it seems reasonable, though perhaps simplistic, to suggest that a cocaine-addicted monkey that is denied access to cocaine will self-administer any drug that will increase synaptic DA even if the drug is not as intrinsically reinforcing as cocaine. In other words, if the monkey cannot have cocaine, it will take the next best thing.

Thus, in the opinion of this author, the self-administration substitution paradigm functions as a pharmacological assay that detects drugs that have direct or indirect dopaminergic activity. It does not always detect the property of the drugs that produce euphoria in humans. When viewed in this context, it is not an unexpected result that dopaminergic drugs that are self-administered in substitution procedures do not produce euphoria in humans.

A hypothesis consistent with both the human and animal data is that mesolimbic DA does mediate the addictive and euphorogenic effects of cocaine, but only certain dopaminergic agents can produce euphoria in humans (Rothman 1990). Although this hypothesis creates secondary research questions as to why these differences among dopaminergic agents

exist, it also creates the possibility of pharmacotherapeutic intervention. There are several possible reasons for these differences. Limited data support the hypothesis that the rate at which an addictive drug enters the brain is important to its addictive properties (Balster and Schuster 1973; Hemingfield and Keenan 1993). On this basis, heroin is thought to be more addictive than methadone.

According to this hypothesis, dopaminergic agents in humans, which are generally taken orally, may not rapidly achieve the brain concentrations required to produce the rapid increase in mesolimbic DA that is hypothesized to be necessary for the production of euphoria. Although this hypothesis has intuitive appeal, it has not (to this author's knowledege) been rigorously tested. Nevertheless, this hypothesis does suggest that a high-affinity DA transporter ligand with slow pharmacokinetic characteristics might actually block the effects of cocaine or substitute for cocaine. Alternatively, direct agonists might not stimulate the appropriate DA receptors. Another possibility is that unpleasant side effects of these drugs in humans prevent attainment of doses that would be required to produce cocaine-like effects. Perhaps these agents have other effects in humans that somehow cancel out their effects on mesolimbic DA. It may be that, in humans, the drugs never achieve high enough brain levels to produce euphoria. Finally, perhaps cocaine is doing something that is not completely understood.

A paper focused primarily on the DA reuptake inhibitors (Rothman 1990) proposed dividing DA reuptake inhibitors into two classes. Type 1 blockers are drugs that produce addiction and euphoria in humans, such as cocaine-like drugs. Type 2 blockers are drugs such as mazindol, nomifensine, and bupropion that do not produce euphoria or addiction. Assuming that the initiating event for cocaine-induced euphoria is the binding of cocaine to the DA transporter, administration of a D_2 reuptake blocker should block the binding of cocaine to the DA transporter, and thereby attenuate cocaine-induced euphoria.

The identification of a such a competitive antagonist would undoubtedly provide an important research tool. However, it might have limited therapeutic uses as a medication. A patient could overcome the drug inhibition by self-administering more cocaine, thereby increasing the probability of increased toxic side effects that would not be blocked by the competitive antagonist.

An alternative approach is to develop a type 2 agent that binds with high affinity to the DA transporter and dissociates slowly. If the dissociation rate

were slow enough, the agent would behave as a noncompetitive inhibitor, creating insurmountable inhibition of those cocaine effects initiated by its binding to the DA transporter. A sustained increase in mesolimbic DA produced by such an agent might provide a cocaine addict with some relief from cocaine craving, which some investigators suggest is related to a relative deficiency of DA (Dackis and Gold 1985). Thus, such a drug might act as a substitute-type medication.

A key issue is how a D_2 reuptake inhibitor might be identified prior to its administration to humans. In this author's opinion, the answer may be to measure its reinforcing efficacy, relative to cocaine, in animals. This can be done by performing self-administration studies designed according to either a progressive-ratio paradigm or a choice paradigm (Johanson and Fischman 1989). One possible set of criteria for identifying a D_2 reuptake inhibitor is that it should have low reinforcing efficacy, act as a classical locomotor stimulant (i.e., stimulate locomotor activity), generalize to a cocaine-induced interoceptive cue, and be self-administered in a substitution paradigm. However, prior to the validation of these methods, good judgment and luck will probably dictate the correct choice of a putative type 2 agent.

These and additional considerations (see. below) led to investigation of the high-affinity DA reuptake inhibitor 1-[2-[bis(4-fluorophenyl) methoxy]ethyl]-4-[3-phenylpropyl]piperazine (GBR12909) and its analogs (Rothman et al. 1989, in press) as possible prototypical noncompetitive inhibitors. Published data have shown that GBR12909 is about 700-fold more potent than cocaine in inhibiting DA reuptake in vitro (IC_{50} = 1 nM) (Andersen 1989); GBR12909 is a relatively selective inhibitor of DA reuptake (Andersen 1989); the behavioral profile of GBR12909 in animals is somewhat different from that of other locomotor stimulants (Nielsen and Scheel-Kroger 1988); and after systemic administration, GBR12909 binds persistently to the DA transporter and attenuates the ability of cocaine to increase extracellular DA (Rothman et al., in press).

CONCLUSION

According to the hypothesis of D_1 and D_2 reuptake inhibitors, cocaine antagonists already exist. However, researchers have not yet fully developed and validated animal models that predict the antagonists' ability (or absence thereof) to produce euphoria in humans. With a little luck and considerable effort, work with analogs of GBR12909 will advance the understanding of

the mechanisms of cocaine-induced euphoria and also lead to successful development of pharmacotherapeutics for cocaine abuse.

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Use of Rodent Self-Administration Models to Develop Pharmacotherapies for Cocaine Abuse

Steven I. Dworkin and Raymond C. Pitts

INTRODUCTION

The search for a therapeutic agent to treat cocaine abuse has been identified as one of the major goals of the National Institute on Drug Abuse (NIDA). Although one may question the probability of discovering a "magic bullet" for cocaine abuse, this behavior has been reinforced in the past, albeit on a very lean schedule of reinforcement. The early development and growth of the field known as behavioral pharmacology has been credited to the discovery of chlorpromazine, the "magic bullet" for the treatment of severe psychotic behavior (Carlton 1983).

The demonstration that a pharmaceutical agent could be used to normalize complex psychotic behaviors resulted in a significant investment by the Federal Government and private industry in the development of behavioral pharmacology. This investment was based on the assumption that additional drugs could be developed to treat other behavioral disorders. A discipline that combined the expertise of pharmacology (founded on the idea that drugs could be developed to treat diseases) with an experimental analysis of behavior was considered ideally suited to aid in the identification and development of these compounds.

The early success in finding compounds that could be beneficial in the treatment of depression, anxiety, and schizophrenia firmly established the field of behavioral pharmacology. The acknowledgment of this field included accepting the notion that nonhuman models could be used to predict the clinical efficacy of psychoactive compounds. The development of nonhuman models of drug abuse and the discovery of compounds that are effective in the treatment of heroin addiction

(i.e., methadone, naltrexone, buprenorphine) support the notion that pharmaceuticals could be developed to treat cocaine abuse (Schuster 1986).

DRUG SELF-ADMINISTRATION

The initial impetus for determining if psychoactive compounds could maintain operant responding was to provide a behavioral approach to the analysis of physical dependence (Thompson and Schuster 1964). Early research demonstrated that the self-administration model could be used in monkeys (Thompson and Schuster 1964; Yanagita et al. 1965) and rats (Davis 1966; Weeks 1962). It was almost immediately realized that drug-maintained responding was similar to behavior maintained by other environmental events (i.e., food and water) and that drug delivery could serve as a reinforcer to engender and maintain drug-seeking and drug-taking behaviors (Kelleher and Goldberg 1977). Thus, animal studies of drug self-administration could be an important model of human drug abuse. These demonstrations and technical refinements paved the way for using the self-administration procedure for a variety of research endeavors (Brady and Lukas 1984; Young and Herling 1986).

The drug self-administration model has been shown to be an exquisite animal model of substance abuse and dependence (Goudie 1991; Hartnoll 1991; Sanger 1991). Johanson and Schuster (1981) elucidated six areas of research that were initiated as a result of the development of drug self-administration procedures. The first area of research was the determination of factors related to engendering, maintaining, and influencing the patterns of drug seeking and drug taking. A second area was to investigate pharmacologic and environmental manipulations that could decrease drug taking. The third and fourth areas were the elucidation of the mechanisms of clinical problems associated with drug abuse therapy and the determination of the biochemical correlates of drug abuse, respectively. The fifth and sixth areas were the development of screening tests for preclinical assessment of abuse potential and toxicity, respectively. Much of the research using the self-administration model can be listed under one or more of these six areas, and a significant amount of information on all of these areas has been accumulated. The self-administration model has provided a screening test to evaluate the potential abuse liability of novel compounds, a behavioral bioassay to investigate the neurobiology of reinforcement, and a simulation of a major behavior disorder.

The demonstration that drugs could serve as reinforcers in operant paradigms provides a new class of environmental events for researchers to investigate. Initial studies were directed toward determining the similarities and differences between the reinforcing effects of drug and nondrug reinforcers (i.e., food and water). These studies resulted in the realization that drug-maintained responding is influenced by the same variables that altered responding maintained by nondrug reinforcers (Johanson 1978; Johanson and Schuster 1981; Katz 1989; Kelleher and Goldberg 1977; Spealman and Goldberg 1978; Young and Herling 1986). For example, different schedules of reinforcement (Ferster and Skinner 1957) could be used to maintain schedule-appropriate rates and patterns of self-administration (see figure 1).

However, there are some important differences in behavior maintained by a drug compared to responding maintained by other environmental events. One of the major differences is the relationship between magnitude of reinforcement and increases in dose and response rates. While studies with nondrug reinforcers generally result in an increase in responding as the magnitude of reinforcement is increased, responding maintained by pharmacologic agents generally shows an inverted U-shaped function. Figure 2 shows dose-effect curves for response rates, interinjection intervals, and absolute amount of cocaine self-administered under a fixed-ratio (FR) schedule during 4-hour sessions. As the dose of cocaine increases, responding first increases and decreases while the total amount of the drug and the mean interinfusion interval increases.

At least three different mechanisms for the descending limb of the self-administration dose-effect curve have been suggested (Katz 1989). The first was that the descending limb was the result of the subject titrating the level of drug to produce a consistent drug effect. This notion followed the observation that inter-injection intervals maintained by stimulants were relatively constant and directly related to dose. Studies that attempted to predict or model drug levels at the time when drug seeking starts to occur provide some support for this hypothesis. Studies that correlated the blood levels of amphetamine (Yokel and Pickens 1974) with amphetamine self-administration or the extracellular levels of dopamine (DA) in the nucleus accumbens resulting from cocaine self-administration (Pettit and Justice 1991) indicated that rats did maintain a relatively constant level. However, the level maintained was related to the dose of the drug.

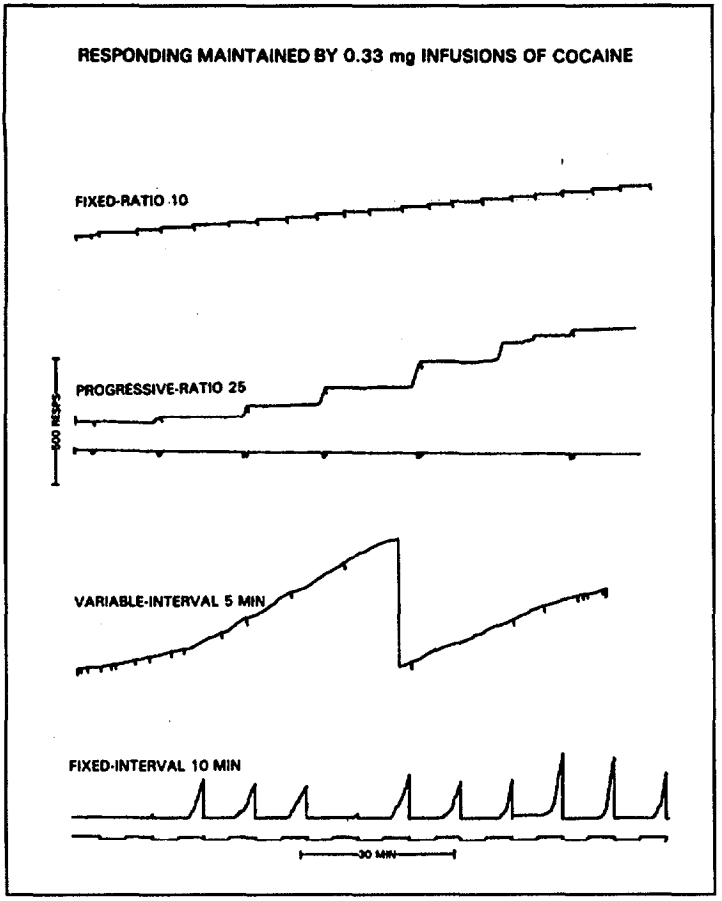

FIGURE 1. *Cocaine self-administration under different schedules of reinforcement*

A second explanation for the decreasing limb of the dose-response curve was that the self-administered drug has direct effects on subsequent responding independent of, and in addition to, its reinforcing effects. These direct effects should decrease responding maintained by other reinforcers or be attenuated with experimenter-imposed timeout periods if they are independent of the reinforcing effect of the drug. Studies that have evaluated the potential influence of the direct effects of self-administered drugs suggest that the direct effects can result in a decreased rate of responding maintained by other reinforcers (Pickens and Thompson 1968; Spealman and Kelleher 1979) or can be attenuated by using experimenter-imposed minimum interinjection intervals (Griffiths

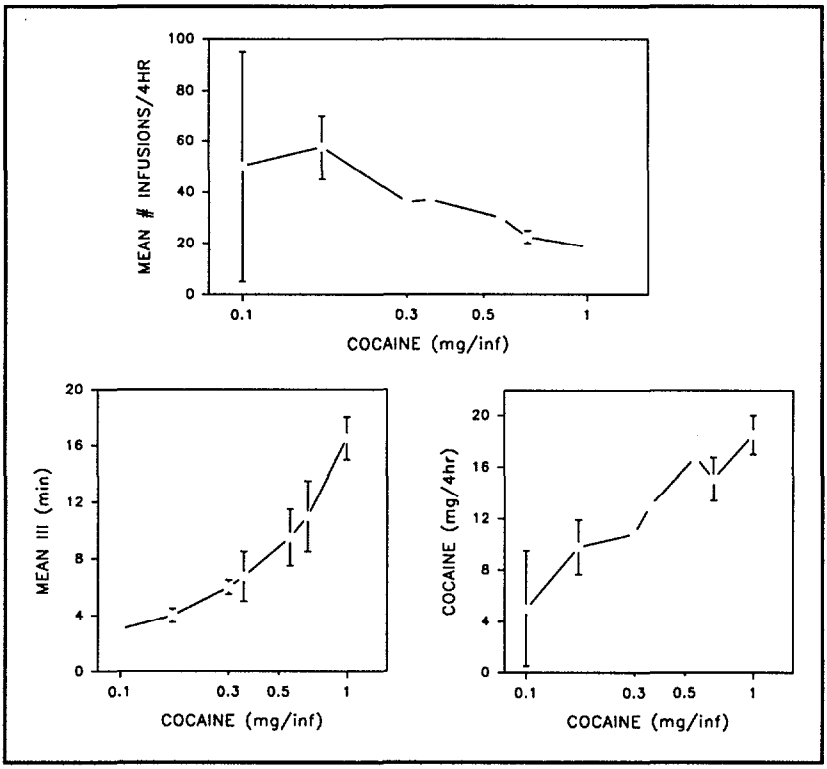

FIGURE 2. *Dose-response curves for cocaine self-administration under an FR-10 schedule*

et al. 1979). These studies are not conclusive; however, relatively large doses of a drug can increase self-administration at doses that suppress ongoing behavior maintained by other reinforcers (Balster and Schuster 1973; Spealman and Kelleher 1979). However, the patterns of self-administration (at least in rats) are consistent over several hours and do not indicate an increasing direct effect of the drug as more drug is self-administered.

The third explanation proposed was that the descending limb was a result of a change in the reinforcing effects of the self-administered compound. Larger doses are not as reinforcing as lower doses, or they may have some aversive component associated with their administration. Although extremely large doses of amphetamine (Sanger et al. 1980) and cocaine (D'Mello et al. 1981; Foltin et al. 198 1) can result in a conditioned taste aversion, these doses are typically in excess of those that are on the descending limb of the dose-effect curve for self-administration. In

addition, results from studies using a dose-choice procedure indicate that larger doses of cocaine are preferred to lower doses (Iglauer and Woods 1974; Johanson 1975). Moreover, larger doses are preferred to lower doses even when the choice of the higher doses also results in the presentation of electric shocks (Johanson 1977). Satiation has also been proposed to account for the decreasing limb of the dose-effect curve. Like food-maintained responding, after the subject has received a sufficient amount of the drug, additional injections are not as reinforcing.

It is unlikely that any single mechanism is responsible for the descending limb of the dose-response curve for all species and drugs for which it occurs. There are data that support or refute all of the hypotheses presented. However, one must appreciate the difficulty in interpreting changes in the rate of self-administration, especially following the administration of a potential treatment compound. These compounds may alter the direct effects, the bioavailability, or the reinforcing effects of the self-administered compound. The use of any single procedure is not sufficient for the screening or characterization of a potential pharmacotherapy for drug abuse.

PROCEDURES USED TO CHARACTERIZE THE THERAPEUTIC POTENTIAL OF PUTATIVE TREATMENT COMPOUNDS

One of the most commonly used procedures to evaluate the effects of putative treatment compounds on drug self-administration is to investigate the effects of these compounds on responding maintained by FR schedules of drug administration. The FR schedule does not impose significant constraints on the amount or frequency with which an animal can receive drug infusions. In fact, both rats (Bozarth and Wise 1985; Dworkin et al. 1987) and monkeys (Johanson et al. 1976) will self-administer lethal quantities of cocaine if given unlimited access to the drug under FR schedules. Therefore, most investigators limit access to the drug to only a few hours each day.

A second problem associated with the use of FR schedules, as discussed above, is the inverted "U" dose-effect curve that is obtained when appropriate doses are evaluated. This necessitates evaluating several different doses of a drug to determine if a treatment compound increases or decreases the reinforcing effects or whether it alters the unconditioned effects of the drug (Katz 1989). For example, the DA type 1 (D_1) agonist

SKF 38393 decreased responding maintained by low doses of cocaine, increased responding maintained by moderate doses, and had no effect on responding maintained by the two largest doses evaluated (Katz and Witkin 1992). Thus, the examination of a putative treatment on a range of doses of the drug of interest increases the likelihood of determining a potential therapeutic effect of the test compound.

A second procedure that has been used to evaluate the compound's efficacy in the treatment of drug abuse is the progressive-ratio (PR) schedule. This schedule is similar to the FR schedule, except that the ratio value increases after the delivery of each infusion. The ratio value at which responding does not occur for a specified period of time is termed the breakpoint, and it has been suggested to provide a measure of reinforcing efficacy (Hodos 1961). Studies investigating serotonergic involvement in the reinforcing effects of cocaine have shown that modulation of the serotonergic system alters the breakpoint and rate of responding maintained by cocaine under PR schedules.

Depletion of forebrain serotonin with 5,7-dihydroxytryptamine lesions of the amygdala or medial forebrain bundle has been reported to augment cocaine reinforcement by increasing the breakpoints under a PR schedule (Loh and Roberts 1990). Fluoxetine pretreatment decreased these breakpoints, suggesting that serotonin may inhibit the reinforcing effects of cocaine (Richardson and Roberts 1991). However, there is still some ambiguity regarding the interpretation of data from PR studies. Since responding is maintained by a ratio schedule, the unconditioned effects of a compound could influence the breakpoint independent of a change in reinforcing efficacy.

A major concern of studies that demonstrate a particular compound alters drug-maintained responding is the behavioral specificity of any changes observed. Since drug self-administration is viewed as conceptually similar to responding maintained by conventional environmental events that serve as reinforcers, food-maintained responding has been used as a control to evaluate the behavioral specificity of putative treatment compounds. For example, chlorpromazine was shown to decrease both food-maintained responding and responding maintained by small cocaine doses under a second-order schedule of reinforcement. However, responding maintained by larger doses of cocaine was increased by the same doses of chlorpromazine that decreased responding maintained by the lower doses (Herling and Woods 1980). Both the decrease in the self-administration of the lower doses and the increase in the self-

administration of larger cocaine doses was suggested to result from the drug effects on response rates and not a change in reinforcing efficacy.

A similar strategy was employed to evaluate the potential specific effects of the opiate buprenorphine on cocaine self-administration. It was shown that daily buprenorphine pretreatment reduced cocaine self-administration by rhesus monkeys to a much greater extent (e.g., 70 to 90 percent below baseline) than food-maintained responding (Mello et al. 1989). In subsequent investigations, tolerance to the effects of buprenorphine on food-reinforced responding was reported to develop following repeated testing with the drug, while cocaine self-administration remained suppressed (Mello et al. 1990, 1992). A more recent study further illustrates the utility of comparing the effects of a putative treatment compound on responding maintained by the drug of interest and food (Katz and Witkin 1992). In that study, doses of the D_1 agonist SKF 38393 had little or no effect on food-maintained responding at doses that resulted in a significant decrease in responding maintained by cocaine.

In addition to using food-maintained responding, some investigators have evaluated the effects of a putative treatment compound on several drugs of abuse. The concurrent maintenance of heroin and cocaine self-administration on alternate days was used to demonstrate the specificity of dopaminergic involvement in the reinforcing effects of cocaine and not heroin (Ettenberg et al. 1982; Pettit et al. 1984). The effects of buprenorphine on responding maintained by different drugs have not been as unequivocal; buprenorphine attenuates cocaine self-administration but also suppresses behavior maintained by other drugs (e.g., phencyclidine, ethanol) and nondrug reinforcers (e.g., saccharin solutions, food) in both rats (Carroll and Lac 1992) and rhesus monkeys trained to smoke cocaine base (Carroll et al. 1992*a*). It has also been reported that buprenorphine does not result in a shift to the right of the dose-effect curve but does result in a downward shift of the curve (Winger et al. 1992). This same downward shift was also observed following the administration of heroin and nalbuphine, two other opioid agonists. Moreover, the dose of buprenorphine required to decrease cocaine self-administration was much greater than doses of the drug required to maintain self-administration or suppress alfentanil self-administration (Winger et al. 1992).

Thus, investigations of the effects of putative treatment compounds on responding maintained by more than one drug provide information on the

specificity of the observed effects. These studies can isolate compounds that may have indirect effects from those that result in a decrease in the reinforcing effects of a drug or drug class.

DEVELOPMENT AND TESTING OF NOVEL TROPANE ANALOGS

Recently, a number of novel cocaine derivatives have been developed and used to define the pharmacophore responsible for the pharmacologic, neurobiologic, and behavioral actions of cocaine (Abraham et al. 1992; Bergman et al. 1989; Boja et al. 1990; Carroll et al. 1992*b*, 1992*c*; Cline et al. 1992; Davies et al. 1993; Kozikowski et al. 1991; Lewin et al. 1992; Madras et al. 1989). An example of the utility of this approach is the development of a series of compounds in which the 3 P-ester linkage of cocaine has been replaced by direct 3ß-aryl derivatives (Clarke et al. 1973). Some of these analogs have a much greater potency than cocaine for binding at the DA transporter (Carroll et al. 19926). Furthermore, the 4-fluorophenyl derivative WIN 35,428, or CFT, (Madras et al. 1989) and the 4-iodophenyl derivative RTI-55 (Boja et al. 1991) are currently used to identify DA transport sites. The synthetic scheme used to develop these compounds, however, is limited because it requires the use of (-)-cocaine as the starting material.

An alternative synthetic strategy using the reaction of vinylcarbenoids with pyrroles (Davies et al. 1991) was used to synthesize novel 2ß-methyl ketone and 2ß-ethyl ketone cocaine analogs (Davies et al. 1993). One of these compounds, 2ß-propanol-3ß-(4-toluyl)-tropane (PTT), has been evaluated for its effects on cocaine self-administration. The compound PTT (30 to 90 µg/inf) substituted for cocaine in single substitution sessions during which the compound was used to replace cocaine (0.33 mg/inf) during a 3- or 6-hour period (Dworkin et al. 1992). In these studies, rats were trained to self-administer cocaine (0.33 mg/kg) under an FR-10 schedule for 3 hours a day. PTT was substituted for cocaine during these sessions.

Figure 3 depicts the effects of substituting different doses of PTT for cocaine during single 3-hour sessions. The data are means and standard errors from five subjects that were exposed to each dose at least twice. These doses of PTT were able to maintain self-administration in this

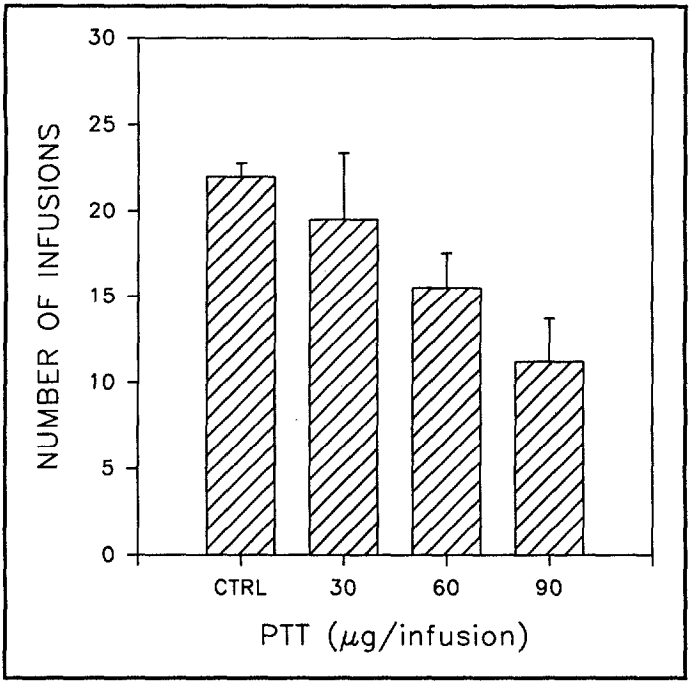

FIGURE 3. *The self-administration of PTT during acute substitutions for cocaine*

acute substitution paradigm. The compound was also able to engender and maintain self-administration in drug-naive subjects (Dworkin et al. 1992).

The temporal pattern of responding maintained by PTT, however, was qualitatively different from the regular intake pattern maintained by cocaine (see figure 4). Responding maintained by PTT consists of periods of low-rate responding at the start of the session, followed by a period of very rapid responding. After several infusions are taken at a very high rate there is a long pause and the pattern is repeated.

The effect of PTT pretreatment on cocaine self-administration was also investigated. Three subjects were trained to self-administer cocaine (0.33 mg/inf) under an FR-10 schedule of drug presentation. Each infusion was followed by a 20-second timeout during which responses were counted but had no programmed consequences. Sessions were

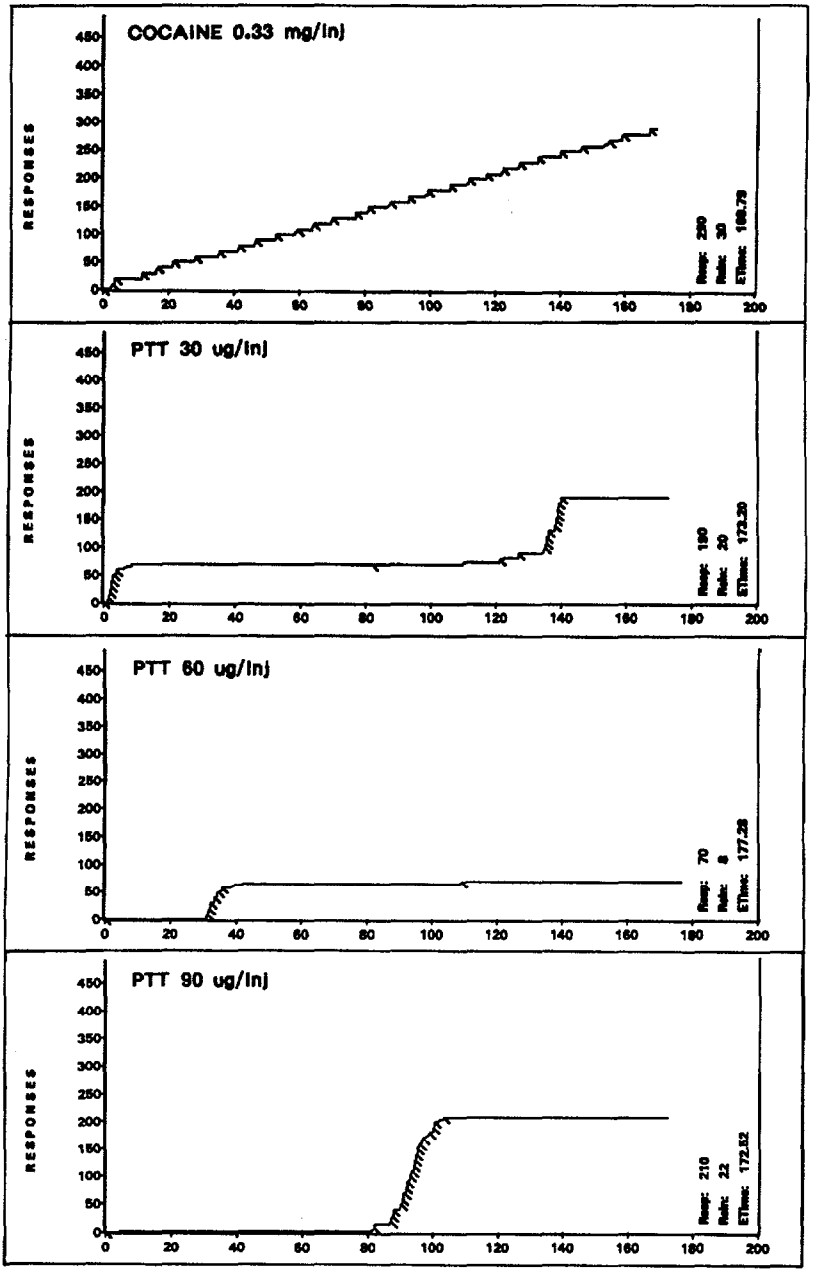

FIGURE 4. *Cumulative records depicting the effects of acute substitutions of PTT doses for the 0.33 mg/infusion dose of cocaine*

3 hours in duration, and occasional double sessions (6 hours) were scheduled. Each session began with a response-independent infusion of cocaine. The effects of PTT (1.0 and 3.0 mg/kg, intraperitoneally [IP]) and cocaine (30.0 mg/kg, IP) were investigated. Presession administration of cocaine and both doses of PTT resulted in a substantial decrease in cocaine self-administration for the first 3 hours following administration (figure 5). The largest effect was observed following the administration of the 3.0 PTT dose. With the exception of this dose, responding returned to baseline during the second 3-hour period.

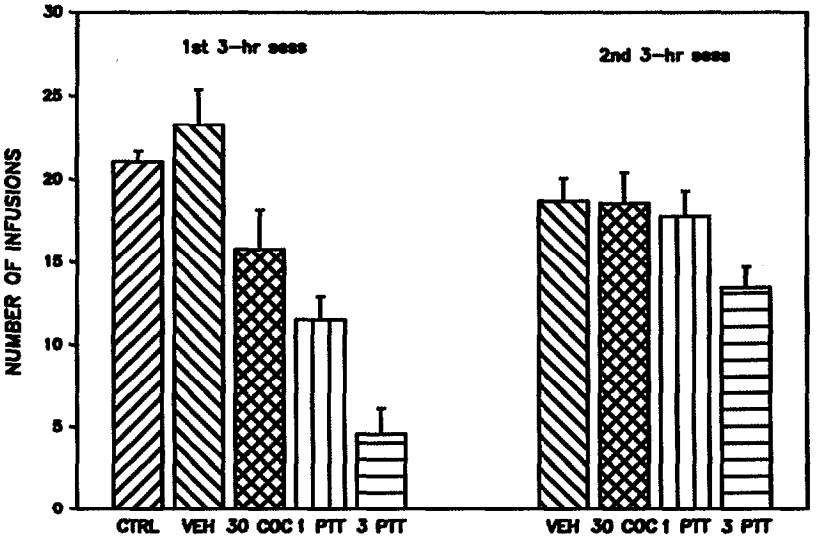

FIGURE 5. *Effects of IP pretreatment with cocaine (30 mg/kg) or PTT (1 mg/kg and 3 mg/kg) on cocaine self-administration*

Representative cumulative records shown in figure 6 depict the effects of the presession administration of cocaine and PTT on cocaine self-administration. The effects of cocaine and PTT pretreatment on responding maintained by food pellet presentation was also evaluated to determine the selectivity of the effects of PTT on cocaine self-administration (figure 7). Six rats were trained on a discrete-trial, FR-10 schedule of food presentation, with a 6-minute intertrial interval (ITI). At the start of the sessions, a light above a response lever was illuminated, and the 10th responses resulted in the delivery of a food pellet. The light was darkened, and a 6-minute ITI was scheduled during which responses

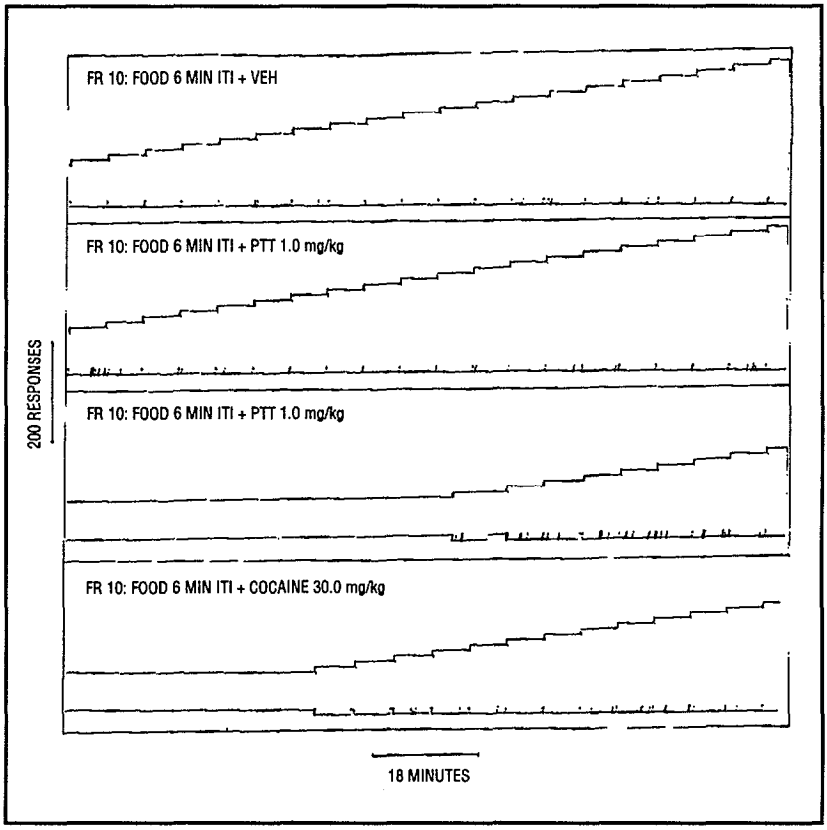

FIGURE 6. *Cumulative records showing the effects of presession administration of PTT on cocaine self-administration*

were counted but had no programmed consequences. The start of the ratio schedule was signaled by illumination of a lever light following the 6-minute ITI. This schedule was used to maintain rates and patterns of food-maintained responding that were similar to those maintained by cocaine self-administration.

Figure 7 depicts the effects of cocaine (30.0 mg/kg, IP) and PTT (1.0 and 3.0 mg/kg, IP) on food-maintained responding. Data are means plus standard deviation (SD). Both cocaine and the larger dose of PTT resulted in a significant decrease in food-maintained responding. Unlike responding maintained by cocaine, the lower dose did not decrease food-maintained responding. Representative cumulative records of responding

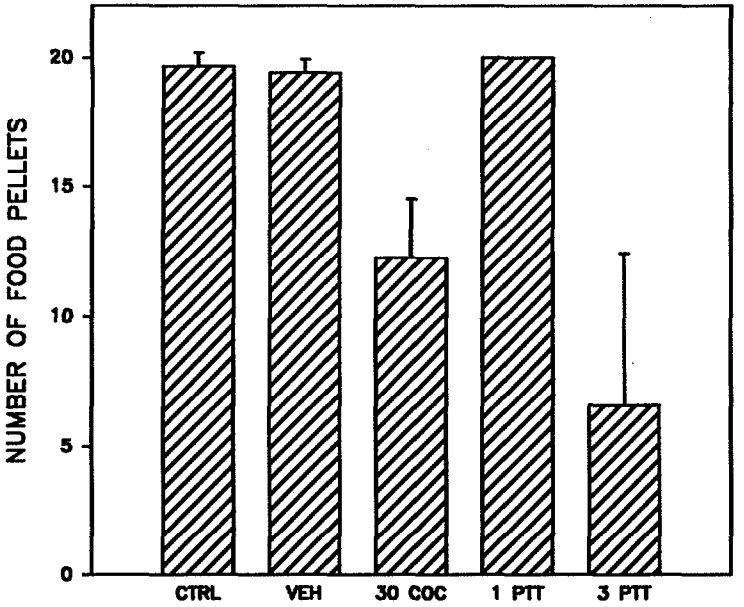

FIGURE 7. *Effects of cocaine and PTT on food-maintained responding*

maintained by this schedule and the effects of cocaine and PTT are displayed in figure 8. The bottom pen was deflected downward during the ITI. Responses during the ITI resulted in momentary upward deflections of the bottom pen. The 3.0 dose of PTT decreased responding maintained by food but increased the number of ITI responses from a mean of 40±17 (SD) to a mean of 407±623.

The results of these studies evaluating the effects of PTT suggest that the compound is reinforcing and can decrease both cocaine self-administration and food-maintained responding. However, decreases in cocaine self-administration occurred at a dose that did not alter food-maintained responding. These results demonstrate the ability to investigate the effects of potential treatment compounds for cocaine abuse.

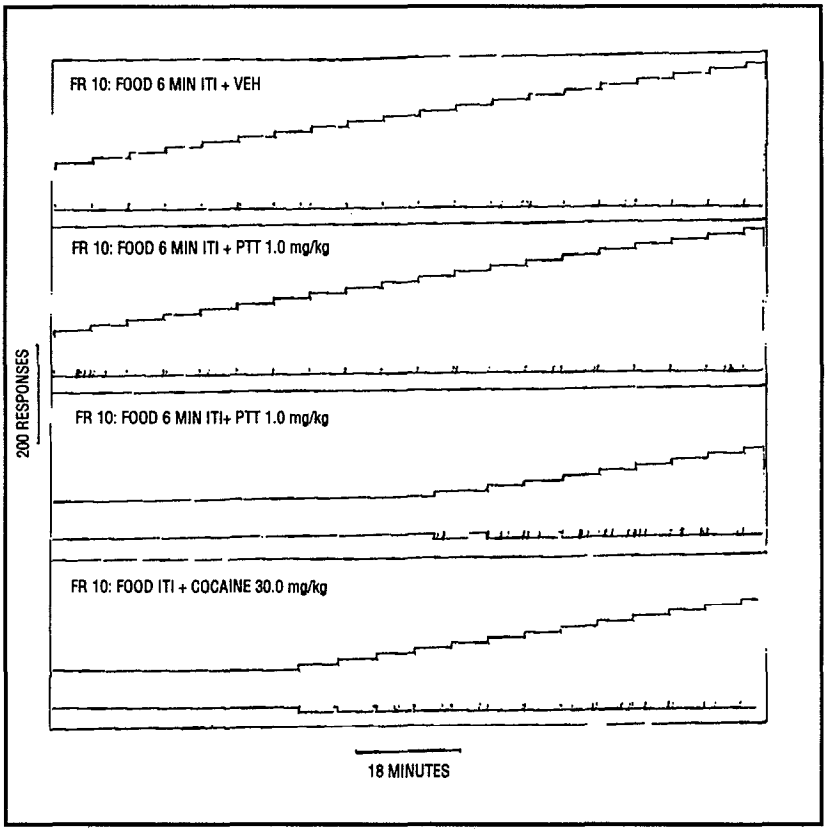

FIGURE 8. *Cumulative records of the effects of PIT on food-maintained responding*

USE OF DELAY OF REINFORCEMENT TO EVALUATE CHANGES IN THE REINFORCING EFFICACY OF A DRUG

A number of variables can influence the effectiveness of a given event as a reinforcer. As suggested earlier, many parallels exist between drugs and other reinforcers (Young and Herling 1986). One variable that has not been studied nearly as extensively with drug reinforcers as with nondrug reinforcers (such as food presentation) is delay of reinforcement. In a typical delay-of-reinforcement procedure, some time elapses between the response that results in reinforcement and the actual delivery of the reinforcer. In general, imposing a delay between responding and reinforcement reduces the effectiveness of an event as a reinforcer, and the reduction in reinforcing effectiveness is a positive function of delay value (Catania and Keller 1981). While this relation appears to hold with

drug reinforcers like cocaine (Stretch et al. 1976), the effects of reinforcement delay on drug-reinforced responding is an underdeveloped research area. The purpose of this line of experiments is twofold: to examine some effects of reinforcement delay on behavior maintained by cocaine delivery, and to provide a possible set of procedures that may help characterize the effects of manipulations designed to reduce the reinforcing effects of abused drugs.

The subjects were six male Fischer F-344 rats implanted with jugular catheters. The rats were studied in standard one- or two-lever operant chambers. Lever pressing was maintained under FR-10 schedules of cocaine injections (0.33 mg in 2.0 mL delivered over 5.6 seconds). Each cocaine injection was accompanied by a tone and was followed by a 20-second timeout.

In three rats (R4, R5, and R6), effects of unsignaled, nonresetting delays were assessed across experimental phases. The delay value for each rat began at 0 seconds (immediate reinforcement) and was increased by 60 seconds until responding was, or nearly was, eliminated. The O-second delay condition was then reinstated. Thus, the schedule of cocaine presentation was a tandem FR-10 FT, with the FT value equal to the programmed delay. Experimental sessions were 4 hours in duration.

For all rats, imposing a delay eventually reduced response rates and the number of injections received during experimental sessions. For rat R4 (figure 9), this decrease did not occur until the programmed delay (FT) value reached 240 seconds; for rats R5 and R6, this decrease occurred at the 60-second delay value. Decreasing the delay value to 0 seconds and reducing the FR value to 1 resulted in a moderate regeneration of responding in rats R4 and R6. Responding by rat R5 did not recover following this manipulation.

Imposing an unsignaled, nonresetting delay (i.e., adding a tandem FT requirement) resulted in a decline and eventual cessation of responding maintained by cocaine injections. These results are similar to those obtained with other reinforcers and thus provide another parallel between nondrug and drug reinforcement processes. In the present study, the effects of this manipulation sometimes persisted long after the delay was removed. This was especially true with rat R5, suggesting the possibility of a permanent change in the reinforcing efficacy of cocaine.

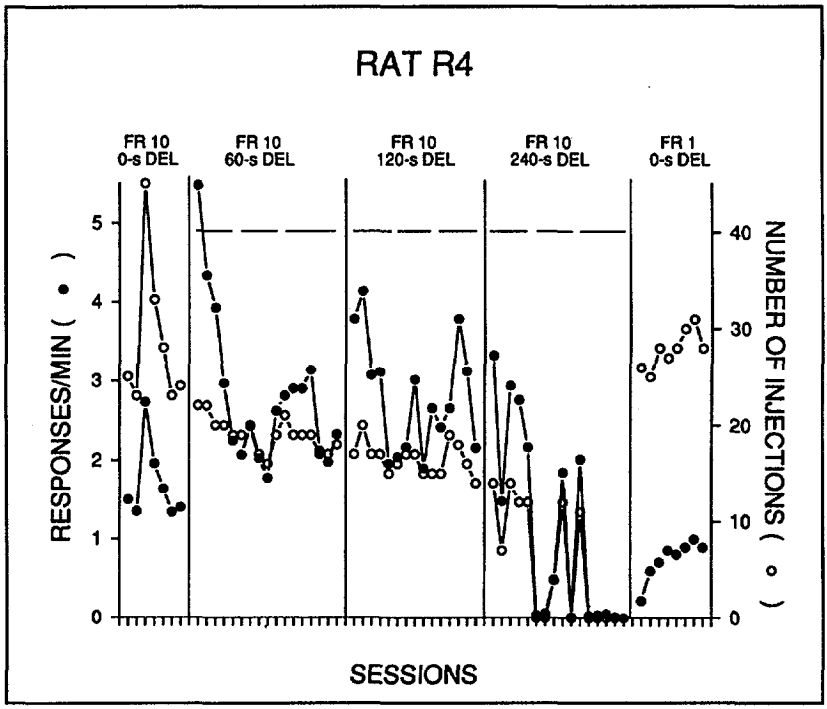

FIGURE 9. *Effects of increasing the scheduled delay of reinforcement on cocaine self-administration*

In a second delay of reinforcement study, three rats (N2, N6, and N10) were exposed to a progressive-delay schedule. Under this arrangement, the first injection occurred with a O-second delay, after which each successive injection was followed by a signaled delay. The duration of the delay began at 30 seconds and doubled with each succeeding injection until 30 minutes passed without a response, or until a 5-hour session time limit was reached. During the delay periods, the experimental chamber was dark, and the response lever was retracted.

This procedure (a chained FR-10 FT schedule with progressively increasing FT values) could be seen as providing a measure of the reinforcing effectiveness of cocaine. After several sessions under this procedure at the training dose (0.33 mg/inj), other doses (.083 mg/inj to 0.83 mg/inj) were occasionally substituted during selected sessions. Each dose tested was substituted at least twice.

For all rats, responding under the progressive delay procedure was well maintained by the training dose (0.33 mg/inj) of cocaine. Breakpoints

ranged between 4,000 and 8,000 seconds. On many occasions the rats would respond throughout the session, terminating the session via the time limit.

Substitution of other cocaine doses resulted in a monotonically increasing dose-effect function for rats N2 and N10 and an inverted U-shaped function for rat N6 (see figure 10). At the higher doses, the sessions for rats N2 and N10 nearly always terminated via the time limit.

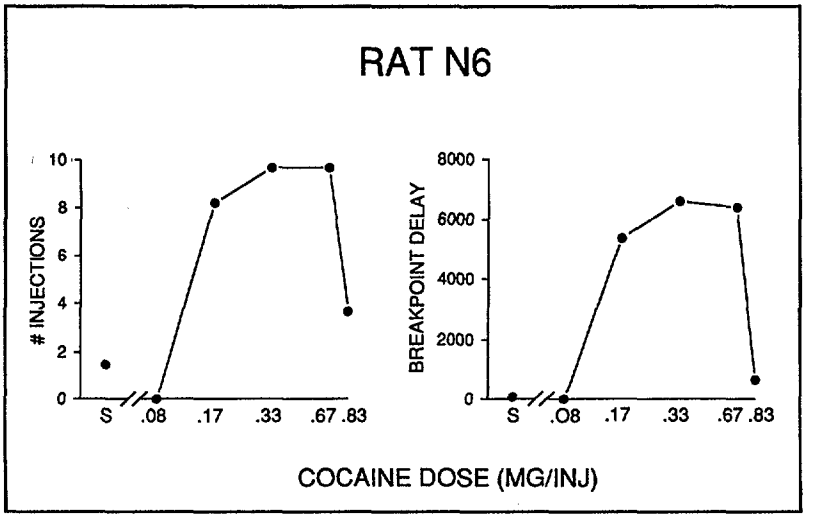

FIGURE 10. *Dose-response curve indicating the effects of the progressive delay schedule on cocaine self-administration*

The results from the progressive-delay schedule show that responding can be maintained when extremely long delays occur between responding and the presentation of cocaine. At the peaks of the dose-effect functions, responding was maintained when delays of over 2 hours occurred. There are a number of possible reasons why responding was maintained at such long delay values. Cocaine is a potent reinforcer, capable of sustaining behavior under extreme circumstances. The delay period was signaled, thus stimuli during the delay period could serve as conditioned reinforcers for responding during the FR-10 schedule component. Also, because relatively short delays always occurred during the early portions of each session, the conditioned reinforcing capacity of the delay-correlated stimuli may have been maximized. Responding could not

occur during the delay (the response lever was retracted). Thus, responding during the long delays could not undergo extinction. The progressive-delay procedure has potential utility as a tool for the assessment of manipulations designed to alter the reinforcing effectiveness of abused drugs.

This procedure may possess advantages over other more commonly used procedures in that breakpoint-like data can be obtained without increasing response requirements. This may be advantageous when assessing the effects of pharmacological agents on self-administered drug with behavioral effects that may themselves depend on response requirement. Increasing dose-effect functions can be obtained over dose ranges that normally produce decreases in most response measures.

CONCLUSION

Studies investigating the reinforcing effects of response-dependent electric shock (Morse and Kelleher 1977) and nicotine administration (Goldberg and Spealman 1983; Spealman 1983; Spealman and Goldberg 1982) demonstrate that almost any environmental stimulus can serve as a reinforcer or punisher under the right environmental conditions. It has been suggested that drugs with the highest abuse potential are those that serve as reinforcers under a wide range of conditions (Johanson and Schuster 1981). A treatment corollary to that assumption would be that an efficacious treatment compound should attenuate self-administration under a wide range of experimental conditions. Since a positive model for the detection of a treatment compound for cocaine abuse has not been found, researchers should continue to pursue a broad behavioral approach toward understanding the important issues.

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Pharmacological and Behavioral Treatment of Cocaine Addiction: Animal Models

Marilyn E. Carroll

Two animal models of drug abuse are reviewed: a rat model in which cocaine is self-administered via indwelling intravenous (IV) catheters, and a primate model in which rhesus monkeys are trained to smoke cocaine base. Two methods have been used to reduce cocaine-reinforced behavior: pharmacological methods or pretreatment with potentially therapeutic drugs, and behavioral methods in which the environment is enriched with alternative nondrug reinforcers. These methods have also been extended to other drugs that are delivered IV in rats or orally in rhesus monkeys, and to behavior maintained by potent nondrug reinforcers.

The results of these animal models have been promising, but they have raised some important methodological issues that have to be considered when designing preclinical treatment studies. First, drug treatment may not selectively alter cocaine-reinforced behavior. It is important to examine the effects of a potential treatment drug on behavior rewarded by food and other nondrug substances. Second, drug and behavioral treatments interact with the behavioral economics of procuring the drug. Their effectiveness depends on how hard the animal works for each milligram (mg) of the drug that is delivered. Thus, it is necessary to test a potential treatment under a range of response requirements. Finally, it is important to evaluate the potential treatment at several phases of the addiction process, such as acquisition, maintenance, withdrawal, and relapse, as treatments may be differentially effective at different stages. Most previous animal work has concentrated on the maintenance phase. There are a few studies that provide animal models of acquisition, withdrawal, and relapse; however, the effects of potential treatment strategies on these behaviors have not yet been determined.

INTRAVENOUS DRUG SELF-ADMINISTRATION IN RATS

Behavioral Treatment

An experiment was conducted to determine whether a nondrug alternative reinforcer, a drinking solution of glucose (3 percent weight by volume [wt/vol]) and saccharin (0.125 percent wt/vol) (G+S), which is a highly preferred substance for rats (Valenstein et al. 1967), would ‘alter the self-administration of IV cocaine. Great difficulty was encountered in training the rats to self-administer G+S and cocaine simultaneously (Carroll et al. 1989). Many of the rats selected one substance and did not self-administer the other, although both were concurrently available. For a subset of the rats, G+S self-administration prevented the acquisition of cocaine self-administration; for another group, cocaine self-administration prevented the acquisition of G+S self-administration (Carroll et al. 1989).

Extensive exposure was necessary to obtain stable baselines for both substances. In the rats that achieved stable behavior, G+S or cocaine access was systematically added or removed to examine the effect on self-administration of the other substance. Figure 1 shows that, in rats that had access to IV cocaine and water to drink (left panels), the addition of G+S for 5 days resulted in a significant decrease in cocaine self-administration. In a group of rats that had access to both cocaine and G+S (center panels), the baseline G+S intake was reduced compared to those without G+S (right panel); when G+S was replaced with water, the cocaine intake more than doubled. When G+S was reinstated, cocaine infusions were again reduced. In a third group that had been self-administering cocaine, when cocaine was temporarily (10 days) replaced by saline, saline infusions were minimal (right panels). They also had access to G+S. When the saline was temporarily (10 days) replaced with cocaine, the number of infusions markedly increased, and G+S intake was reduced by more than half. These findings show that G+S and cocaine compete as reinforcers, and each interferes with maintenance levels of self-administration of the other substance.

A recent attempt was made to more systematically examine this phenomenon using an autoshaping program to objectively and quantitatively measure the rate of acquisition of cocaine self-administration (Carroll and Lac 1993). Under an autoshaping program, a pigeon key is lighted or a rat lever is extended into the chamber (Brown and Jenkins 1968; Messing and Sparber 1983). After a

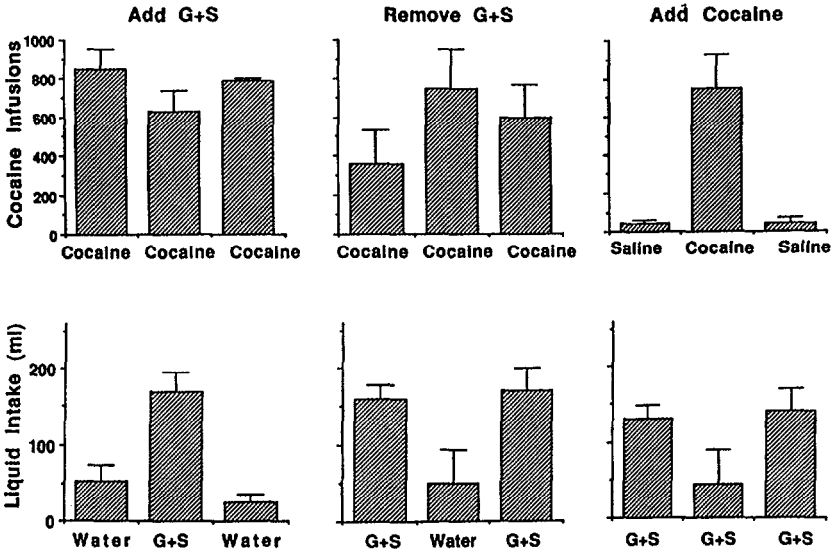

FIGURE 1. *Data are shown for three groups of five rats over successive 5-day blocks. The group on the left initially had access to IV cocaine and water to drink. G+S was substituted for water for 5 days, and then water replaced G+S for 5 days. The group in the center had cocaine and G+S, and then water was substituted for G+S for 5 days, The group on the right was trained to self-administer IV cocaine but was temporarily maintained on saline infusions and G+S was available to drink; then cocaine was substituted for saline for 5 days. Each point represents a mean of 5 rats for 5 days (+ the mean SE across days).*

few seconds, the light is extinguished or the lever is retracted, and a food reinforcer is delivered. In a few sessions animals learn to associate responding on the manipulandum with delivery of the reinforcer. Responses on the response key or lever also result in the light being extinguished or the lever retracting and the reinforcer being delivered immediately.

In the present experiment, rats were autoshaped to press a lever that resulted in a 0.2mg/kg cocaine infusion. There were six autoshaping sessions each day when 60 infusions (10 per hour) were automatically delivered according to a random 90-second schedule. This component was followed by a daily 6-hour self-administration component when the

lever remained extended and every lever press (except those during the infusions) resulted in an infusion. The criterion for acquisition of cocaine-reinforced behavior was arbitrarily defined as 5 consecutive days when the mean number of infusions was 100 or more for the 6-hour self-administration sessions. The experiment was terminated when the acquisition criterion was reached or at 30 days following startup.

Five groups of 12 to 14 rats were compared. The first four groups were factorially arranged according to whether they had G+S and water or only water to drink during autoshaping, and whether they had G+S and water or only water in the home cage for 3 weeks prior to autoshaping in the operant chamber (table 1). These groups all had free access to water in the home cage and operant chamber, and their food intake was limited to 20 g. A fifth group had no G+S, either in the home cage or during autoshaping in the operant chamber, and their food intake was unlimited. This allowed for a comparison of feeding conditions on acquisition of cocaine self-administration.

The results indicated that access to the G+S solution in the operant chamber substantially delayed autoshaping. In group 1 (which had access to G+S in both the home cage and the operant chamber), half of the 12 rats did not acquire cocaine self-administration within 30 days. A history of access to G+S in the home cage but no access in the operant chamber (group 3) did not interfere with acquisition of cocaine self-administration. Figure 2 shows collapsed data for the two groups that had G+S in the operant chamber during autoshaping sessions (N = 24) and for the two groups that had only water during autoshaping (N = 24). The presence of G+S in the operant chamber clearly increased the number of days to acquire cocaine self-administration, and 9 of the 24 rats in this combined group did not acquire cocaine self-administration within 30 days.

Autoshaping in group 5, which had free access to food was highly variable, but a high positive correlation ($t = 7.74$, $df = 12$, $p < 0.01$) was found between the amount of food consumed and the number of days to meet the acquisition criterion. Thus, the acquisition of cocaine-reinforced behavior was reduced or prevented in environments enriched with alternative nondrug substances such as food and a preferred liquid (G+S), compared with an impoverished environment that contained only water and limited access to food (Carroll and Lac 1993). Others have shown that acquisition of cocaine self-administration is enhanced by prior exposure to caffeine (Horger et al. 1991) and naltrexone (Ramsey and

TABLE 1. *Experimental design*

Group no.	Home cage	Operant chamber
Group 1	G+S and water	G+S and water
Group 2	Water only	G+S and water
Group 3	G+S and water	Water only
Group 4	Water only	Water only
Group 5*	Water only	Water only

KEY: * Group 5 had unlimited access to food, while groups 1-4 were limited to 20 g.

Van Ree 1990) and that acquisition of amphetamine self-administration is related to individual differences in locomotor activity (Piazza et al. 1989).

Pharmacological Treatments

Another series of experiments examined pharmacological effects of potential treatment drugs on IV cocaine self-administration in rats. Group designs were used in which separate groups of rats self-administered different doses of cocaine (0.1, 0.2, or 0.4 mg/kg unit doses), Other groups self-administered only G+S. In the first experiment (Carroll et al. 1990*a*), fluoxetine, a serotonin uptake inhibitor, was examined as a potential treatment drug; similar treatments were found effective at reducing amphetamine self-administration in rats (Smith et al. 1986).

Separate groups of rats were injected with three doses of fluoxetine (2.5, 5, or 10 mg/kg) IV twice daily. The rats were allowed to self-administer cocaine during continuous 24-hour sessions, with each infusion contingent upon four responses on the lever (fixed-ratio [FR] 4 [FR-4]). Responding during the 4-second infusion was counted but had no programmed consequences. The groups self-administering G+S responded on a tongue-operated, automatic drinking device that delivered 0.1 mL per tongue-contact response. The basic procedure was to allow all self-administration behavior to stabilize for at least 10 days, and the last 5 days of that period served as the pretreatment baseline. The

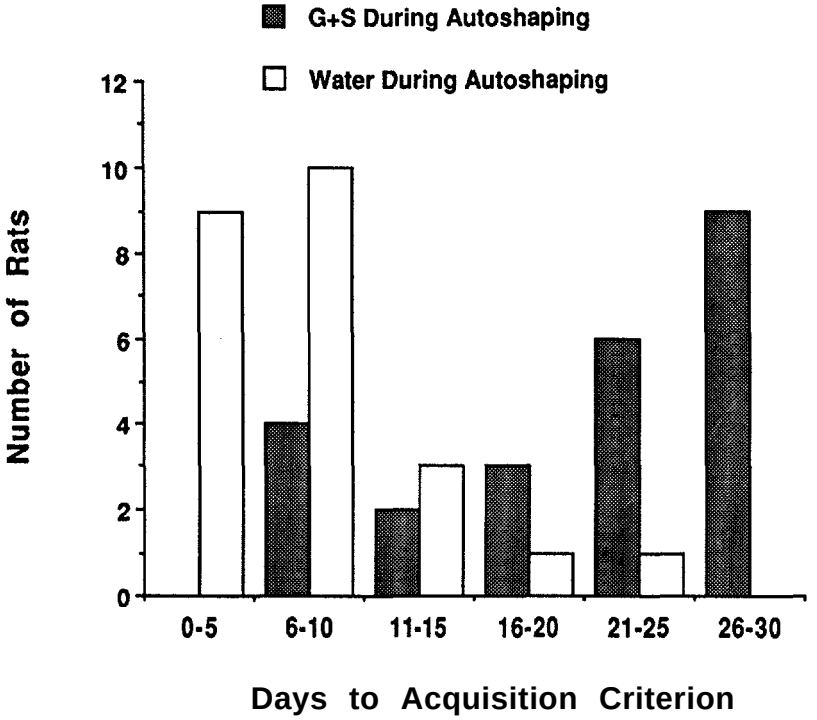

FIGURE 2. *A frequency distribution shows that number of days until the autoshaping criterion was met divided into six 5-day intervals. The number of rats in each group within that interval is represented by the height of each bar. In the bin depicting 26-30 days, all of the rats did not reach the criterion by the 30-day limit.*

treatment drug was then given IV twice daily for 5 days, and behavior was allowed to stabilize for at least 10 days after treatment. Saline control injections were not given to minimize interference with the cannula system; previous research indicated that saline pretreatment had no effect on cocaine self-administration (Carroll et al. 1986).

Fluoxetine produced dose-dependent decreases in cocaine infusions and G+S intake, while food intake in both the cocaine and G+S groups was unaltered by these doses of fluoxetine (Carroll et al. 1990*a*). The cocaine dose-response function was shifted downward and to the left. Fluoxetine had the greatest effect at the lowest cocaine doses and almost no effect at the highest cocaine dose (Carroll et al. 1990*a*). Unit dose and the response requirement under the FR-4 schedule can be combined and

considered as a single variable (Bickel et al. 1990), unit price (responses per mg). In this case, the drug pretreatments were most effective when the unit price of cocaine was high.

To examine the generality of fluoxetine's suppressant effects, the experiment was replicated with groups of rats that self-administered fentanyl, a potent mu receptor agonist (2.5, 5, and 10 µg/kg). Similar results were obtained; fluoxetine produced dose-dependent decreases in fentanyl self-administration at low and moderate fentanyl doses, but it had little effect at the highest fentanyl dose.

Another means of increasing serotonin levels is to increase the amount of L-tryptophan in the diet (Smith et al. 1986). The cocaine self-administration experiment was replicated in other groups of rats that had 2, 4, or 8 percent L-tryptophan added to their standard chow, which already contained 0.29 percent L-tryptophan (Carroll et al. 1990*b*). This dietary manipulation produced concentration-dependent decreases in cocaine and G+S self-administration. The effect of L-tryptophan was greatest at the lowest cocaine dose, and there was almost no effect at the highest dose.

Buprenorphine is a partial mu receptor agonist that has been shown to reduce cocaine craving in methadone patients (Kosten et al. 1989) and to reduce IV cocaine self-administration in rhesus monkeys (Mello et al. 1990). Buprenotphine pretreatment was examined in rats self-administering a range of cocaine doses as well as in groups self-administering G+S (Carroll and Lac 1992). Three buprenorphine doses (0.1, 0.2, and 0.4 mg/kg) were tested in separate groups that self-administered 0.1, 0.2, or 0.4 mg/kg cocaine. Buprenorphine produced dose-dependent decreases in cocaine self-administration at the two lower cocaine doses; however, there was only a minimal effect at the highest cocaine dose. Buprenorphine also produced dose-dependent decreases in G+S self-administration, but there was no effect on food intake in the cocaine groups and only a small decrease in food intake in the G+S groups.

Buprenorphine and fluoxetine were effective at reducing cocaine self-administration in rats, but behavior maintained by the nondrug substance G+S was reduced as well. Food intake was not altered in the present experiment. In the previous study with monkeys, food delivery was contingent on operant responding, and buprenorphine produced a

small but temporary decrease in food-maintained responding (Mello et al. 1990).

Figure 3 summarizes the results of some of the behavioral and pharmacological treatments tested in rats in this laboratory. Cyproheptadine, a serotonin antagonist, did not alter cocaine self-administration; this may have been due to a ceiling effect. Other researchers have found amphetamine self-administration was increased by the serotonin antagonist metergoline (Lyness and Moore 1983). Fentanyl pretreatment increased cocaine self-administration only in a group of rats that had recently acquired cocaine self-administration and had not yet reached the maximum number of cocaine infusions. It had no effect once cocaine infusions stabilized at the maximum level (Carroll et al., unpublished data). Naltrexone increased cocaine self-administration; these results agree with those of other researchers who used similar cocaine and naltrexone doses (Ramsey and Van Ree 1990). Another drug that has been tested in this paradigm is an opioid peptide, dynorphin (1-13), but it had no effect on cocaine self-administration at an IV dose range of 0.12 to 1 mg/kg (Carroll and Lee, unpublished data). The lower frames of figure 3 indicate that free access to food and G+S also reduced cocaine self-administration.

Self-Administration of Smoked Cocaine Base and Orally Delivered Drugs in Rhesus Monkey

Behavioral Treatments. Similar behavioral and pharmacological treatments have been tested in rhesus monkeys. Four monkeys were trained to smoke cocaine base by first training them to self-administer liquids from a lip-operated drinking spout, then replacing the drinking spout with a smoking tube that was similar in appearance to the drinking spout (Carroll et al. 1990*c*). Each smoke delivery was contingent upon completion of a progressive ratio response requirement on a lever. A maximum of eight smoke deliveries (2 mg/kg each) was available, and each smoke delivery was followed by a 15-minute timeout. After behavior stabilized when the monkeys were maintained at 80 percent of their free-feeding body weight, weights were increased or decreased in a nonsystematic manner to examine the effect on cocaine self-administration. Figure 4 shows that cocaine self-administration increased as body weights decreased, and the lowest number of cocaine

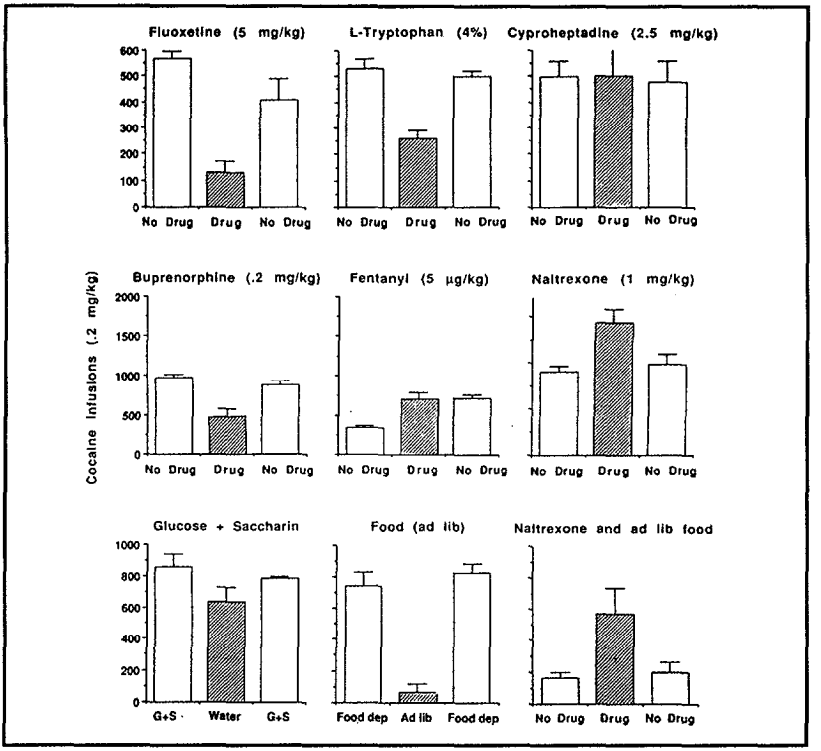

FIGURE 3. *Data are shown for groups of five rats in 5-day blocks. The first bar in each frame represents the no-treatment condition, the second bar is the 5 days of the particular treatment described on the label above the graph, and the third bar is the first 5 days back on the nontreatment condition. Drug treatment doses are indicated in parentheses, and the treatment drugs were administered IV. L-tryptophan was given in ground laboratory chow.*

deliveries was obtained when free access to food was allowed (100 percent of their free-feeding body weight).

Earlier work with orally delivered etonitazene, phencyclidine (PCP), ketamine, amphetamine, and methohexital as self-administered drugs showed similar results due to food deprivation and satiation (Carroll and Meisch 1984; Meisch and Carroll 1987). In addition, when the drug concentration was varied, the suppressant effects of food satiation increased. A similar interaction occurred when PCP self-administration was suppressed by concurrent access to saccharin (0.03 percent wt/vol) or

8 percent ethanol (Carroll et al. 1990*d*). As was the case with the drug pretreatment effects on IV cocaine self-administration in rats, the higher the unit price of the self-administered drug (responses per mg), the greater the suppressant effect of the potential treatment drug or nondrug reinforcer.

In a recent experiment, the unit price concept was studied by varying the FR or price of PCP while keeping the drug concentration constant (Carroll et al. 1991), and the effect of a nondrug alternative reinforcer, saccharin, was examined at a range of PCP prices. As PCP price or FR increased from 4 to 128 responses, the number of deliveries decreased. This function is referred to as a demand curve, and the demand for PCP steadily decreased with increases in price. The price of saccharin deliveries remained fixed at 16, and intake was high and did not change as a function of fluctuations in PCP price. When saccharin instead of water was concurrently available with PCP during the daily 3-hour sessions, the demand curve shifted downward in a parallel manner. However, if the percentage of reduction in PCP deliveries due to concurrent saccharin was considered as a function of the PCP price, concurrent saccharin reduced PCP deliveries by only 20 percent at the lowest PCP price (FR-4), and it reduced PCP deliveries by 90 percent at the highest PCP price (FR-128). This relationship would hold if the data were transformed into unit price, because the dose (mg) per delivery remained constant. Thus, the higher the unit price (responses per mg), the greater the suppressant effect of a concurrent nondrug reinforcer.

Pharmacological Treatments. Drug pretreatment experiments also have been conducted using the monkey models of drug self-administration. Four monkeys that had stable cocaine base-smoking behavior were administered a range (0.01 to 0.8 mg/kg) of buprenorphine doses intramuscularly 30 minutes before their daily smoking sessions for 5 days. Buprenorphine produced dose-dependent decreases in cocaine base smoking. When saline was injected, all monkeys received the maximum allowable (eight) smoke deliveries. Dose-dependent decreases in smoke deliveries resulted when buprenorphine injections were given (Carroll et al. 1992). The same buprenorphine doses were tested in other groups of monkeys self-administering orally delivered PCP, ethanol, and saccharin. Under each of these conditions, buprenorphine produced dose-dependent decreases in self-administration. Thus, buprenorphine's effects were not specific to cocaine-reinforced behavior.

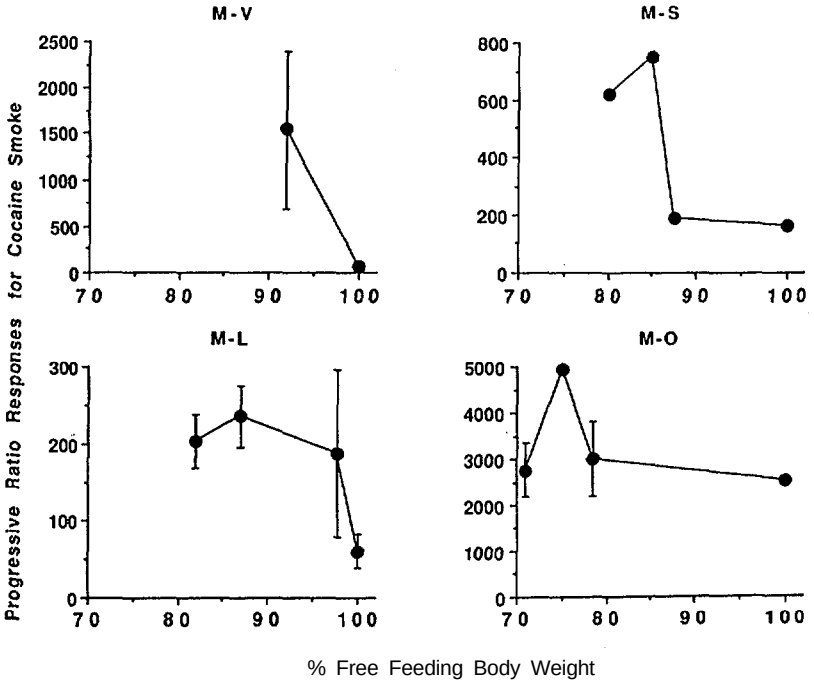

FIGURE 4. *Progressive ratio responses for cocaine smoke are presented as a function of percentage of free-feeding body weight for four monkeys. Each condition was held constant for at least 10 days, and each point represents a mean (±SE) for the last 5 days at that condition.*

Other groups of monkeys were given access to concurrent PCP and saccharin or PCP and ethanol, then treated with buprenorphine to determine whether buprenorphine's suppressant effects would be enhanced under conditions when PCP self-administration was already reduced by a concurrent drug or nondrug reinforcer (Carroll et al. 1992). When PCP and water were concurrently available, the maximum suppression due to buprenorphine was a 65-percent reduction compared to saline pretreatment; however, when saccharin was concurrently available with PCP, buprenorphine reduced PCP self-administration by 90 percent compared to saline pretreatment. These findings indicated that there was an additive effect of behavioral and pharmacological treatments. While concurrent ethanol also suppressed PCP self-administration, buprenorphine did not produce any greater suppressant effect when ethanol was concurrently available than when water was concurrently available (Carroll et al. 1992).

Recent experiments were conducted to determine whether buprenorphine would modify behavioral disruptions due to drug withdrawal. Operant responding for food has served as a sensitive baseline for measuring withdrawal effects when administration or self-administration of many drugs of abuse is terminated. A model of PCP withdrawal was used to examine the effects of buprenorphine (Carroll and Carmona 1991). Food pellets were delivered under an FR-64 schedule, and PCP and water were concurrently available under FR-16 schedules. When behavior had stabilized for at least 10 days, water was substituted for PCP for 8 days. Figure 5 shows that the number of pellet deliveries decreased by almost 90 percent, and there was a slow recovery over the 8-day period. When PCP was reinstated, food deliveries returned to baseline levels. In subsequent replications, either saline or buprenorphine was injected twice daily during the 8-day PCP withdrawal period. Two buprenorphine doses (0.2 and 0.8 mg/kg) were used that had been very effective at reducing cocaine, PCP, ethanol, and saccharin self-administration. Figure 5 shows that the 0.2 mg/kg dose did not alter the course of PCP withdrawal, and the 0.8 mg/kg dose had a similar lack of effect. In earlier work a drug that is similar to PCP, (+) N-allylnormetazocine, eliminated the PCP withdrawal effect on food-maintained behavior when administered under similar conditions (Carroll 1988). In a recent experiment another drug that is similar to PCP, dizocilpine, an N-methyl-D-aspartate (NMDA) antagonist, almost completely reduced the PCP withdrawal effect at doses of 0.05 and 0.1 mg/kg (figure 6) (Carroll et al., in press).

Behavioral disruptions due to drug withdrawal also are affected by behavioral economic conditions and the availability of alternative reinforcers. In a recent study it was reported that the PCP withdrawal effect (disruption in the food baseline) became more severe as the price of food (FR) was increased from 64 to 128 to 258 responses. As the price was increased even further to 5 12 and 1,024, the severity of the disruption did not increase further. At these high response requirements the monkeys were beginning to show weight loss (Carroll and Carmona 1991). Thus, two variables, price of food and body weight, were changing at once.

In a subsequent experiment, the economic conditions were examined further by repeating the withdrawal condition under an open and closed economy (Carroll and Carmona 1991). The monkeys were still allowed to earn food pellets under an FR-1,024 schedule, but under the open

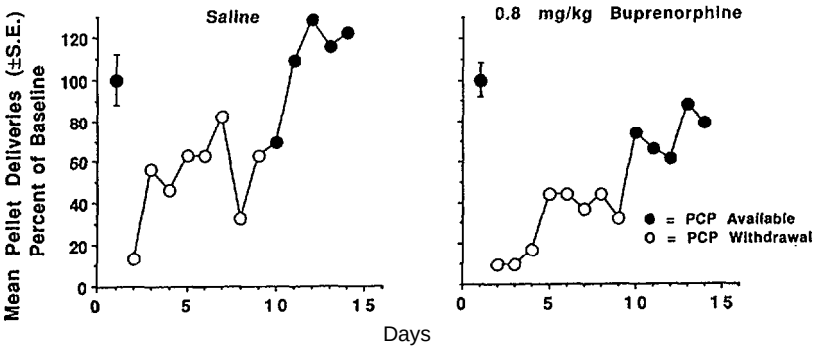

FIGURE 5. *Mean pellet deliveries as a percentage of baseline (unconnected point) are presented as a function of sequential days of PCP withdrawal (8) and reinstatement (5). The frame on the left indicates that the monkey was injected with saline twice daily during the 8 days of PCP withdrawal, and the frame on the right indicates that buprenorphine (0.8 mg/kg) was injected twice daily. Data are presented for one monkey (M-C). Filled circles indicate that PCP was available concurrently with water, and open circles indicate that only water was available.*

economy their earned food was supplemented each day with 100 g of free food delivered by the experimenter. They did not show weight loss under these conditions. Under the closed economy, they earned all of their food under the FR- 1,024 schedule; there was no supplement, and the animals experienced weight loss. Under the open economy condition, which was repeated twice, a typical PCP withdrawal effect was found. Pellet deliveries were decreased by approximately 60 percent; however, no PCP withdrawal effect occurred under the closed economy.

The same amount of food pellets were earned during PCP access and PCP withdrawal, and this was also the same amount that was earned when there was an open economy. Figure 7 is a hypothetical curve summarizing these results. As the price of food was increased, a drug withdrawal effect measured by disruption in food-reinforced responding became more severe. When the price of food became so high that weight loss began to occur, the PCP withdrawal effect decreased as the price of food increased further. A U-shaped function describes the severity of the withdrawal effect as the price of food increased. These results show that

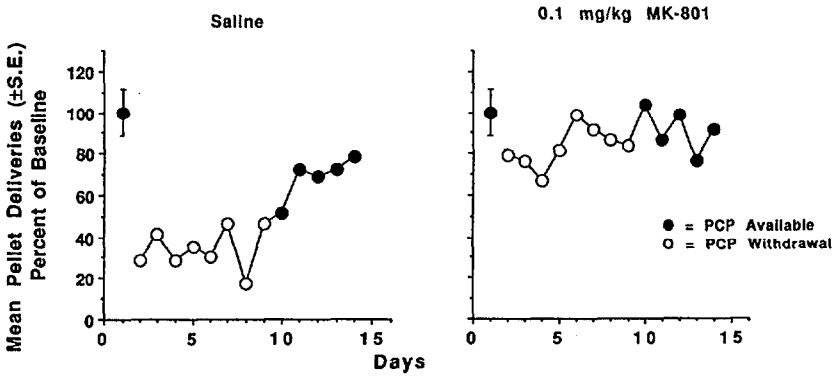

FIGURE 6. *Mean pellet deliveries as a percentage of baseline (unconnected point) are presented as a function sequential days of PCP withdrawal (8) and reinstatement (5). The frame on the left indicates that the monkey was injected with saline twice daily during the 8 days of PCP withdrawal, and the frame on the right indicates that MK-801 (0.1 mg/kg) was injected twice daily. Data are presented for one monkey (M-C).*

a withdrawal effect can range from nonexistent to severe depending upon the price of food and the type of food economy that exists, suggesting that the disruptions in operant behavior during withdrawal are related to motivational deficits rather than physical illness. Thus, it is important to assess withdrawal effects within a range of economic variables.

CONCLUSION

In summary, pharmacological and behavioral treatments were described that reduce self-administration of cocaine and other drugs. The magnitude of effects was similar across several drug classes, different species, and drug and nondrug reinforcers. Factors that influence the effectiveness of these treatments are the phase of the addiction process (acquisition, maintenance, or withdrawal), availability of alternative reinforcers, and the behavioral economics of food or drug reinforcement. Drug and behavioral treatments have greater effects when the unit price (responses per mg) of the drug is high and little or no effect when the unit price is low.

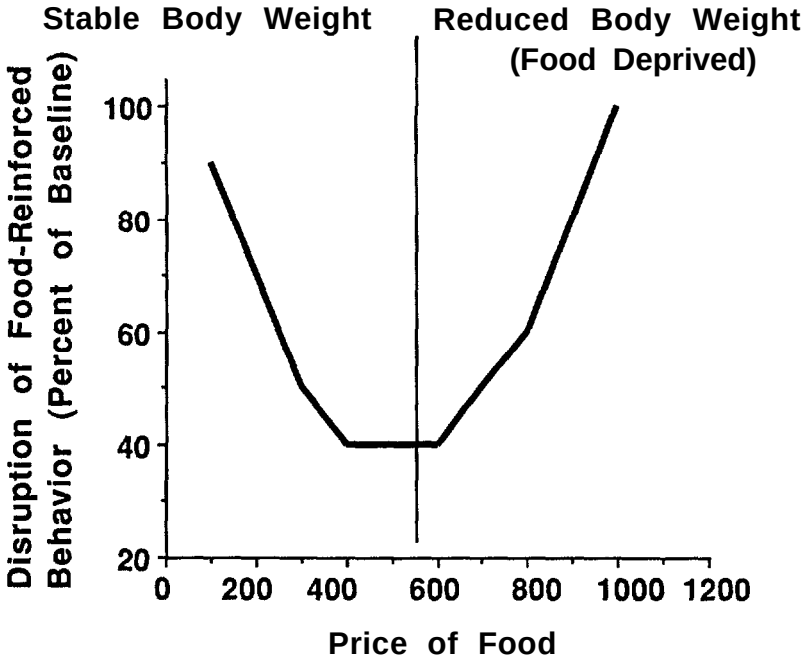

FIGURE 7. *A hypothetical function is presented to describe the relationship between the price of food (FR) and the disruption in food-reinforced behavior due to PCP withdrawal as a percent of baseline when PCP is available. The vertical line and labels at the top indicate that the biphasic function is also due to reduced body weight. To the left of the vertical line the free-feeding body weight is maintained while, to the right of the line, body weight decreases as the price of food increases. This function is based on previous experimental results (Carroll et al. 1991a).*

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Preclinical Assessment of Cocaine' Antagonist Drugs in Squirrel Monkeys

Jack Bergman

Stimulation of dopamine (DA) receptors resulting from the inhibition of monoamine transport appears to play a prominent role in the behavioral effects of cocaine. On this basis, the development of drugs to modify these neurochemical actions of cocaine is a rational approach in developing therapeutics for cocaine abuse and dependence. From a pharmacological perspective, strategies used to develop therapeutics for the treatment of opioid dependence might be applicable in this approach. For example, compounds to serve as replacement therapeutics, much as methadone is used in the treatment of opioid dependence, might be useful pharmacological adjuncts in treatment programs.

The development of drugs to directly block the actions of cocaine represents another strategy that may have clinical utility. This might involve the development of compounds to block the actions of cocaine directly at its presumably presynaptic binding sites or indirectly by blocking the actions of DA at DA receptors. In an analogous manner, opioid receptor antagonists such as naltrexone have been applied in the treatment of problems associated with opioid dependence. More recently, buprenorphine, a partial agonist that produces morphine-like or morphine-antagonist effects under different conditions, is being evaluated as a therapeutic for opioid dependence.

The author and coworkers at the New England Primate Research Center have undertaken systematic studies of compounds that may have some utility as blockers of the effects of cocaine. These experiments were conducted primarily on squirrel monkeys and involved at least two stages of evaluation. In the first stage, subjects responded under fixed-interval (FI) schedules of reinforcement under which cocaine and related compounds have characteristic rate-increasing effects, Drugs also were studied in drug discrimination (DD) experiments in which cocaine and compounds that are either structurally or functionally related to cocaine dose-dependently increase responding on the cocaine-associated lever. In studies involving FI performances or DD procedures, candidate

therapeutics are studied by determining how they might modify the dose-related effects of cocaine. In the second stage of evaluation, compounds that may pharmacologically modify the effects of cocaine on FI performance or in DD experiments are further evaluated for their ability to alter the reinforcing effects of cocaine in drug self-administration studies. In the latter studies, full dose-effect functions for cocaine self-administration are determined in both the absence and the presence of selected doses of the candidate therapeutic. It is important to emphasize that, in each of the procedures, pharmacological antagonism is evaluated on the basis of shifts in the cocaine dose-effect. function.

Using the methods described above, a number of compounds have been evaluated that may regulate dopaminergic activity and thus alter the effects of cocaine. For example, drugs that may bind to the cocaine binding site on the DA transporter have been studied to determine whether those compounds might block or accentuate the effects of cocaine. Opioids and other compounds that may limit or modulate the release of DA from the presynaptic neuron also have been evaluated. However, most of the research has involved ligands for postsynaptic DA receptors and, in particular, DA type 1 (D_1) receptors. In this effort, the research has focused on the effects of D_1 receptor blockade by the D_1 antagonist SCH 39166 and, more recently, by D_1 agonists that have low intrinsic activity and, as partial agonists, may act functionally as antagonists. As shown in the left panels of figure 1, the D_1 antagonist SCH 39166 antagonizes the effects of cocaine on FI responding and in DD experiments. Doses ranging from 0.03 mg/kg to 0.3 mg/kg of the D_1 receptor blocker produce rightward shifts in the dose-effect functions for cocaine in both studies.

The antagonism of cocaine's effect by SCH 39166 appears to be mutual and surmountable; that is, the rate-decreasing effects of the antagonist itself are overcome by cocaine, after which higher doses of cocaine can reproduce the cocaine dose-effect function to the right of its original position. As shown in the bottom right panel of figure 1, the antagonism of cocaine's effects by SCH 39166 also is evident in studies of drug self-administration in squirrel monkeys. In these experiments, squirrel monkeys responded for consequent injections of cocaine under a second-order FI lo-minute schedule of responding during which the completion of each 30-response fixed ratio (FR-30) produced a visual stimulus change. Under this schedule, the first visual stimulus change after the elapse of 10 minutes was accompanied by intravenous (IV) drug injection and followed by a brief timeout period. Daily sessions comprised five or

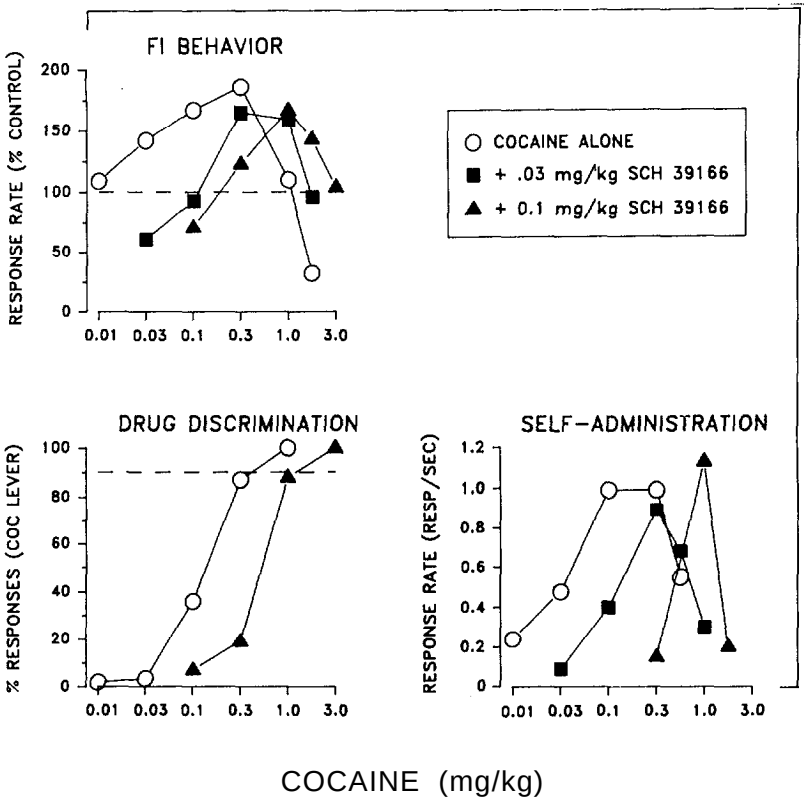

FIGURE 1. *Effects of cocaine in groups of squirrel monkeys (n = 4-6 per group) in experiments involving FI performance under an FI schedule of stimulus-shock termination (top left, cocaine discrimination (bottom left), and IV drug self-administration (bottom right). Abscissae: cumulative dose or, in bottom right, unit dose per injection, log scale; ordinates: rates of responding shown as percentage of control rates (top left) or responses/second (bottom right) and percentage of responses on cocaine-associated lever (bottom left). Open symbols represent the effects of cocaine alone. Filled symbols represent the effects of cocaine redetermined in the presence of the D_1 receptor blocker SCH 39166.*

six presentations of the second-order FI schedule. Pretreatment with SCH 39166 served to antagonize the effects of cocaine and, in most cases, produced a rightward shift in the entire dose-effect function for self-administration, indicative of surmountable antagonism.

The antagonistic effects of SCH 39166 in all the above procedures are of a magnitude comparable to or greater than that observed with DA type 2 (D_2) receptor blockers and suggest that, at the least, D_1 mechanisms play a prominent role in the abuse-related effects of cocaine.

In subsequent experiments, the effects of D_1 agonists that have been shown to have limited efficacy relative to DA were evaluated. Perhaps, as *partial agonists* at the D_1 receptor, these compounds also could attenuate the behavioral effects of an indirect agonist such as cocaine. In ongoing studies, two D_1-selective benzazepines that are thought to act as partial agonists, SKF 75670 and R-SKF 38393, indeed have produced rightward shifts in the dose-related effects of cocaine on schedule-controlled responding, indicative of mutual and surmountable antagonism. For comparison, the effects of SKF 81297, a D_1-selective agonist with actions that can be surmountably antagonized by SKF 75670 or R-SKP 38393, are also being evaluated. As shown in figure 2, SKF 8 1297 appears to have effects in combination with cocaine that differ markedly from those of the D_1 receptor blocker SCH 39166 or, thus far, SKF 75670 or R-SKF 38393. That is, the dose-effect function for cocaine is shifted downward rather than to the right, indicating that the effects of cocaine, although attenuated, are not pharmacologically antagonized by SKF 81297. These data suggest that efficacy may be an important factor in determining how the effects of a D_1 agonist modify those of cocaine. To the extent that limited efficacy D_1 agonists may not have the side effects associated with receptor blockers, they might prove to have therapeutic utility for the management of some aspects of cocaine dependence and are an interesting class of compounds for further study. As discussed above, in addition to the development of candidate therapeutics that act at D_1 receptors, another strategy for developing cocaine antagonists also might involve compounds that modulate DA release into the synapse. For example, attention recently has focused on the involvement of opioid mechanisms in the regulation of DA activity. A growing body of neurochemical evidence indicates that DA release can be modulated in different ways by μ and κ opioids. In this regard, μ opioids may enhance the release of mesolimbic DA, whereas κ opioids may attenuate or diminish its release. Recently, it has been found that the discriminative-Stimulus effects of cocaine in squirrel monkeys may be

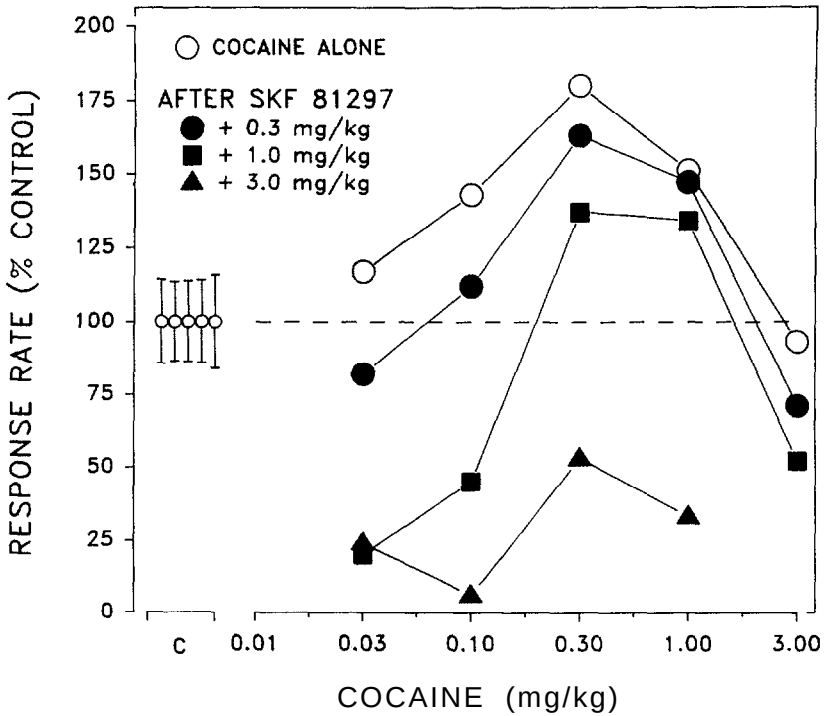

FIGURE 2. *Effects of cocaine in squirrel monkeys (n = 4) under an FI schedule of stimulus-shock termination. Abscissa: cumulative dose, log scale; ordinate: rates of responding as percentage of control rates. Open symbols represent the effects of cumulative doses of i.m. cocaine alone. Filled symbols represent the effects of cocaine redetermined in the presence of the D_1 agonist SKF 81297. Open circles above C represent mean and S.D. of control rates of responding during successive components of the session.*

enhanced by prior administration of μ opioids, and these modulatory effects can be antagonized by the opioid antagonist naltrexone. Consistent with these findings, ongoing experiments suggest that effects of cocaine on schedule-controlled responding and in DD experiments can be reliably modified by prior administration of κ opioids such as U 50,488. As shown in figure 3, doses of U 50,488 that previously have been found to attenuate the effects of cocaine in DD studies also appear to produce a rightward shift in the dose-response function for the effects

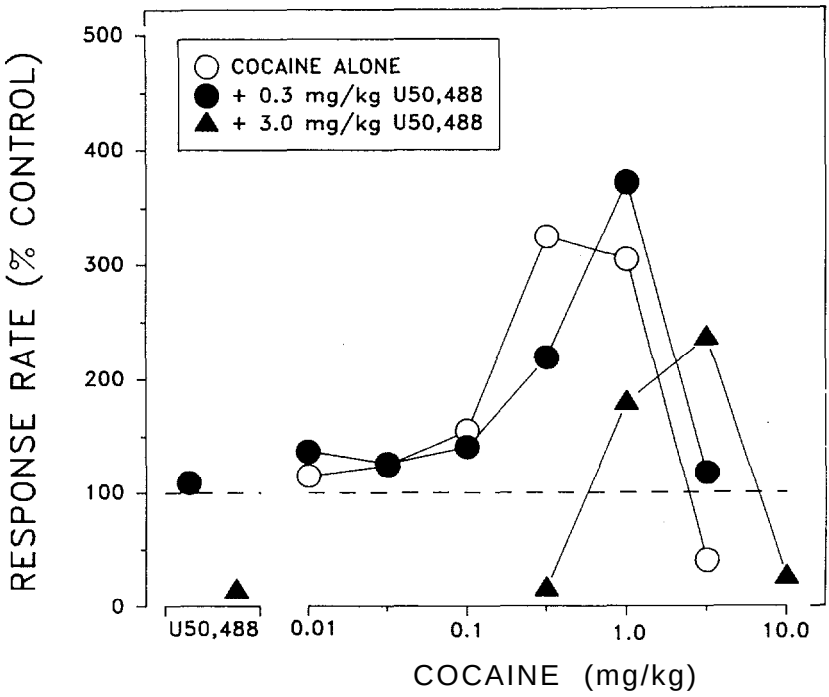

FIGURE 3. *Effects of cocaine in squirrel monkeys (n = 4) under an FI schedule of stimulus-shock termination. Abscissa: cumulative dose, log scale; ordinate: rates of responding as percentage of control rates. Open symbols represent the effects of cumulative doses of intramuscular cocaine alone. Filled symbols represent the effects of cocaine redetermined in the presence of the κ agonist U 50,488. Open circles above C represent mean and S.D. of control rates of responding during successive components of the session.*

of cocaine on FI responding. Although κ opioids have direct behavioral effects that may preclude their development as therapeutics, these data suggest that interfering with the regulation of DA release may be a useful way of modifying the behavioral effects of cocaine.

CONCLUSION

Research results such as these provide further evidence that the behavioral effects of cocaine are prominently mediated by its indirect dopaminergic actions, including increased DA activity at D_1 receptors. Findings that the limited efficacy agonist SKF 75670 can antagonize the

behavioral effects of cocaine have provided an example of the modification of the behavioral effects of an indirect agonist by a postsynaptic receptor ligand with reportedly limited efficacy. Based upon current findings with the use of the partial opioid agonist buprenorphine for the treatment of opioid dependence, it may be that limited agonist efficacy also is a useful feature for cocaine antagonist therapeutics. Additionally, findings with the κ-opioid agonist U 50,488 suggest that another approach to the development of cocaine antagonists might be to dampen the release of DA.

Collectively, these findings indicate that it is feasible to evaluate cocaine antagonists in preclinical studies in monkeys. They illustrate, as well, the importance of full dose-effect determinations for meaningful evaluation of drug interactions. As shown, antagonism by these types of compounds can be characterized as mutual and surmountable, and it is important to keep in mind the limitations of such actions for the treatment of cocaine dependence. First, drugs that antagonize the behavioral effects of cocaine may have effects in their own right that, in turn, may limit their clinical application. Second, the antagonism of cocaine's effects can be overcome by increases in the dose of cocaine, which may further limit the utility of this approach. Nevertheless, antagonists may have a role in the treatment of some cocaine-related problems. For example, antagonists may be useful for the treatment of cocaine overdose and, in some cases, as short-term pharmacological adjuncts for the management of cocaine abuse. However, whether surmountable cocaine antagonists have a role as long-term pharmacological adjuncts in treatment programs is less certain. By analogy, the use of surmountable antagonists in the management of opioid dependence has had only inconsistent success. In this regard, the development of acceptable replacement therapeutics for the management of cocaine dependence at least deserves consideration as an alternative strategy.

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Cocaine Self-Administration Research: Treatment implications

Richard W. Foltin and Marian W. Fischman

Treatment of cocaine abuse over the past decade has increasingly used pharmacological adjuncts to behavioral interventions. Although few double-blind, placebo-controlled research studies have been reported, many case reports and open-label trials have appeared in the clinical literature. A number of different strategies have been used in selecting potential treatment medications, including reduction in cocaine craving, blockade of cocaine-induced euphoria, and other changes in the self-reported effects of cocaine (Kosten 1989). Use of these traditional self-report measures is based on the generally held assumption that the effects of a drug that maintain drug taking are related to drug-induced changes in subjective state, and that what drug users say about the dose of a drug they have just taken can be used to predict the likelihood that the drug will be used excessively and nonmedically (Fischman 1989). As reported elsewhere (Foltin and Fischman 1991*a*), however, the pivotal feature of cocaine abuse is cocaine-taking behavior, and any potentially useful medication must be shown to reduce cocaine-taking behavior within the context of a treatment program.

Clinical research using patient populations is generally not the most efficient design for evaluating potentially useful medications. The level of control required for the collection of data showing both safety and efficacy can best be achieved within a laboratory-based research study. Under controlled laboratory conditions, self-reported effects of cocaine can be measured concurrently with physiological measures and, importantly, this can be carried out within the context of measuring cocaine-taking behavior.

Such a research design is based on laboratory research with nonhumans, where procedures have been developed to evaluate the controlling variables in drug self-administration (Johanson and Fischman 1989). Rhesus monkeys given continuous free access to cocaine readily self-administer it in erratic bursts (or binges), in marked contrast to the stable patterns of drug self-administration seen when the animals are

allowed access to the drug for only a few hours each day. They also fail to eat and, therefore, become severely debilitated (Johanson et al. 1976). Comparable patterns of multiple-dose cycles are seen in cocaine abusers who take the drug repeatedly until their drug supply is exhausted. Since this pattern is the norm for cocaine abuse, it is important that any laboratory procedure attempting to evaluate potential treatments for cocaine abuse incorporate a multiple-dose procedure into the assessment.

This chapter describes the development and utility of a multiple-dose cocaine self-administration procedure in which volunteers were given the opportunity to take repeated doses of cocaine, with doses and patterning approximating those reported in the natural ecology. Of importance is the integration of the more traditional single-dose methodology (Foltin and Fischman 1991*a*), including self-reported and physiological effects, with the most salient feature of cocaine abuse: cocaine self-administration. The relationship between cocaine self-administration and its self-reported effects is complex (Foltin and Fischman 1991*a*), and use of only self-reported effects cannot provide sufficient information to evaluate the potential utility of a new treatment medication.

In all the studies described, normal healthy volunteers with histories of cocaine and other drug use (e.g., heroin, marijuana, alcohol, nicotine cigarettes) participated in daily experimental sessions lasting 2 to 4 hours. Subjects resided in a hospital clinical research unit for the duration of the 2- to 3-week studies and had access to nondrug-related recreational activities. During their daily sessions, subjects were given the opportunity to take multiple doses of cocaine or placebo. Few studies evaluating the self-administration of cocaine by human subjects under controlled conditions have been published (Foltin and Fischman 1991*a*). Two laboratory self-administration procedures have been developed for use with humans. In the first, essentially unlimited access to a single dose is provided, and subjects can determine pattern of intake. The second procedure measures choice between placebo and active drug options, comparing all possible combinations.

In a study on intranasal cocaine self-administration (Foltin et al. 1988), subjects were given access to 96 mg or 4 mg (a placebo dose) of cocaine once every 35 minutes. When 96 mg cocaine was available, the subjects requested the drug as soon as it was available and inhaled approximately five doses. When 4 mg cocaine was available, the subjects requested the drug as soon as it was available and inhaled approximately four doses. The 96-mg dose sessions had to be stopped by the experimenters due to

the subjects' elevated blood presssure, while the 4-mg sessions were not. It is difficult to argue that 96-mg doses maintained more drug-taking behavior than 4-mg doses because medical considerations constrained the free-access design. Thus, with free-access procedures within a single session, it is at times difficult to differentiate placebo from active drug-maintained behavior.

Fischman and Schuster (1982) provided data on the pattern of intravenous (IV) cocaine self-administration in experienced cocaine users. All subjects reliably self-administered cocaine with a 5- to lo-minute inter-injection interval, resulting in about six doses per-hour. A similar pacing of cocaine intake was observed for both 16-mg and 32-mg cocaine doses. Thus, with free-access procedures within a single session, it is at times difficult to differentiate behavior maintained by different doses.

Using free-access procedures, it is often difficult to interpret changes in pattern of intake and amount of intake with respect to drug dose; short sessions and limitations on the number of sessions hinder interpretation of the results. Given these problems, it might be difficult to interpret the effects of a treatment drug on free-access cocaine self-administration by humans.

This chapter describes a series of studies using two dose-choice procedures that circumvent many of the problems described in the preceding paragraphs to analyze variables affecting IV and smoked cocaine self-administration by humans. During each session, subjects were allowed to choose between two unidentified IV injection solutions (saline or different doses of cocaine). They were told that these solutions could be an active or inactive drug. Each subject was told that the right-hand response button and light were associated with a specific drug solution and that the left-hand response button and light were associated with a second drug solution. Subjects were allowed to choose repeatedly between solutions each day in experimental sessions that lasted 2 to 4 hours. In nearly all cases, there was a 14-minute interval between drug choices. This interval roughly corresponds to the interval that subjects report using between IV injections outside the laboratory. Subjects were instructed to sample each of the two available doses during the first two choice trials. During the remaining four to six choices, subjects were instructed to choose the dose of cocaine they preferred.

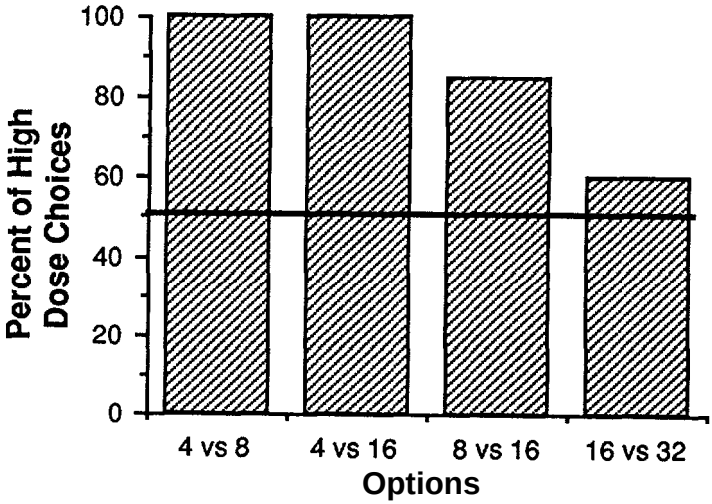

FIGURE 1. *Percent of high cocaine dose choices as a function of the two available doses summarized across a series of studies*

When one option consisted of active cocaine and the other placebo, subjects almost exclusively chose to self-administer the active drug by selecting the active dose in 80 to 100 percent of the trials within a session (Fischman et al. 1990; Foltin and Fischman, unpublished observations). Thus, even in single sessions, robust differences between active drug and placebo were demonstrated in experienced drug users.

The choice of higher cocaine doses over lower doses in 60 to 100 percent of the trials within a session was another robust phenomenon observed in these studies (figure 1) (Fischman et al. 1990; Foltin and Fischman, unpublished observations). Unlike free-access procedures, preferences among available active doses are rapidly demonstrated using choice procedures. Behavior observed under choice procedures provides a rapid assessment of dose preference within a single session and should provide a good behavioral baseline for the assessment of potential cocaine treatment drugs or behavioral interventions.

While the above data indicate the sensitivity of choice procedures to dose, it was also of interest to investigate behavioral factors that might influence cocaine choice. In one study (Foltin and Fischman, unpublished observations), subjects were given a choice between two active doses of cocaine, and the response requirement for the high dose was systematically manipulated. Subjects consistently chose the high

dose of cocaine on four out of four choice opportunities regardless of the response cost associated with that dose. For example, under the fixed ratio 1600 condition, subjects had to respond three times a second for 8 minutes in order to obtain each high dose of IV cocaine. Data from a representative subject are presented in figure 2(a), demonstrating the consistent choice of the high cocaine dose (16 mg) regardless of the response requirement for the high dose. Although all subjects complained bitterly about the "stupid button pressing," they continued to choose the high dose. This relatively simple manipulation of increasing the work necessary to obtain a dose of cocaine was ineffective in altering dose choice. This points to the robust effects of cocaine as a reinforcer and suggests that simply increasing the amount of effort necessary (within limits, of course) to obtain a substantial dose of cocaine is not a useful method for decreasing cocaine intake.

In another study (Foltin and Fischman, unpublished observations), monetary gain was paired with low-dose choices with the prediction that, if paid enough money, subjects would choose low doses paired with money rather than a higher dose that was not associated with money. However, the effects of pairing money with low doses on high-dose choice were minimal. Data from a representative subject are presented in figure 2(b), demonstrating the consistent choice of the high cocaine dose (16 mg) even when choosing the low dose would have resulted in low-dose administration *and* $10. Occasionally, pairing $10 with the low dose did decrease high-dose choice, but these effects were variable. Subjects were asked to indicate how much they would be willing to pay for each of the tested doses. It is interesting to note that there was no relationship between the amount that subjects said they would pay for a high dose of cocaine and the effect of actually paying them on high-dose choice. It might be expected that, if a larger sum of money than the subjects reported the high dose was worth was paired with the lower dose, they would take the lower dose and the money. This was not the case. For example, one subject chose the high dose on three of four opportunities, even when $10 was paired with the low dose. This means that he had the option of receiving the high dose alone, or $10 plus the low dose at each choice. When asked how much he would be willing to pay for the high dose of cocaine, he said that he would not buy such low-quality cocaine.

As with increasing response cost, the relatively simple manipulation of paying subjects to choose the lower dose of cocaine was ineffective in altering dose choice. This suggests that simply increasing the monetary

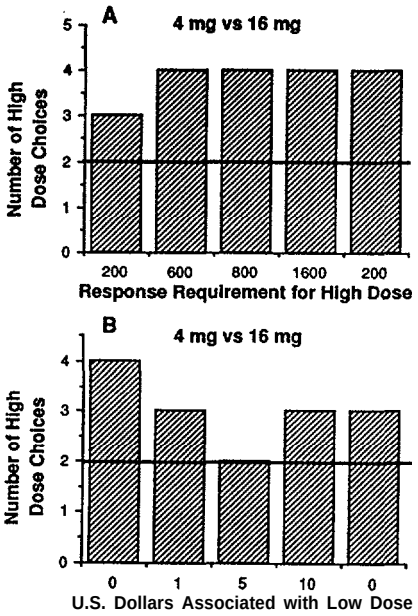

FIGURE 2. *(Panel A): Number of high cocaine dose choices as a function of the response requirement to obtain the high dose. (Panel B:) Number of high cocaine dose choices as a function of the amount of money paired with the low dose.*

cost of the drug (within limits, of course) is minimally useful in decreasing cocaine intake. In combination, these data suggest that cocaine choice is a robust phenomenon that is not particularly sensitive to these two behavioral manipulations.

Recently; the self-administration of cocaine by smoking has risen in prominence and notoriety in the United States and Canada (Cheung et al. 1991; Gawin 1989; Johanson and Fischman 1989; Trebach and Zeese 1990). Cocaine smoking produces rapid rises and peaks in cocaine plasma levels and subjective effects similar to IV administration (Foltin and Fischman 1991*b*; Foltin et al. 1990; Hatsukami et al. 1990; Jeffcoat

et al. 1989; Jones 1990; Paly et al. 1982; Perez-Reyes et al. 1982). Smoked cocaine produces many of the positive effects of IV cocaine (i.e., a rush) without some of the negative aspects: painful self-injection, possible contact with the acquired immunodeficiency syndrome virus, other health risks associated with IV drug use, and the stigma of being an IV drug user. In addition, the widespread availability in some cities of prepared, inexpensive, single-dose units of cocaine base ("crack," "ready rock") has enhanced the probability of cocaine ingestion via smoking.

A previous report (Foltin and Fischman 1991*b*) indicated that the potency of smoked cocaine was about 60 percent of that of IV cocaine; that is, a 50-mg dose of smoked cocaine had effects similar to a 32-mg dose of IV cocaine. Visual analog scale (VAS) ratings of "stimulated," "high," and "liking" were greater at similar plasma levels following smoked cocaine, compared to IV cocaine. Other subjective effects of smoked and IV cocaine were similar.

These differences in ratings of "stimulated," "high," and "liking" scores suggested that smoked cocaine might have a modestly greater abuse potential than IV cocaine. While such differences in subjective effects provide important information about potential differences in abuse liability (de Wit and Griffiths 1991; Preston and Jasinski 1991), studies directly assessing drug self-administration provide a more effective measure of relative abuse liability (Fischman and Foltin 1992). The first purpose of this study was to investigate the relative reinforcing effects of doses of smoked and IV cocaine that produced similar cardiovascular effects. Both a smoked and an IV dose were available during daily self-administration sessions, with subjects choosing which of the doses to self-administer. The second purpose of the study was to compare changes in subjective-effects measures with dose choice to estimate the relationship between cocaine self-administration and the self-reported effects of cocaine.

When given access to placebo IV cocaine and placebo smoked cocaine, subjects chose each option equally often. When given access to placebo IV cocaine and an active dose of smoked cocaine, subjects almost exclusively chose the smoked dose (4.5 times, on average, out of a possible 5 choice trials). Similarly, when given access to placebo smoked cocaine and an active dose of IV cocaine, subjects almost exclusively chose the IV dose. During sessions when subjects were given access to 25 mg of smoked cocaine and an active dose of IV cocaine, subjects chose the low smoked dose on about three choice trials. Finally, when

subjects were given access to 50 mg of smoked cocaine and an active dose of IV cocaine, subjects chose the high smoked dose on about four choice trials. Thus, active doses were exclusively chosen over placebo doses regardless of the route of administration, the low smoked dose was chosen slightly more often than both IV doses, and the high smoked dose was consistently chosen over both IV doses.

In addition to summarizing choice behavior based on the mean number of smoked doses, the data also were summarized on the number of subjects who demonstrated a preference for smoked cocaine, that is, who chose the smoked dose on three or more of the five choice trials. These data (figure 3) show clearly that, when an active dose was paired with a placebo dose, all subjects preferred the active dose. Six subjects preferred the low smoked dose over both IV doses, and at least eight subjects preferred the high smoked dose over both IV doses. Using this criterion, the high smoked cocaine dose was clearly preferred over both IV doses (8 of 10 subjects), while even the low smoked dose was often preferred over the high IV dose (6 of 10 subjects).

It is possible that during sessions in which two active doses were available, choice may have been related more to the first cocaine administration of the day rather than differences between the two doses per se; that is, subjects may have perseverated with the dose that produced the initial change from baseline. Each of the 10 subjects experienced 4 active dose pairs (e.g., 25 mg smoked versus 16 mg IV cocaine), resulting in a total of 40 such sessions. On 22 of these sessions, subjects first chose IV cocaine, and only on 7 of these occasions (32 percent of the time) did subjects choose IV cocaine an additional 3 or more times. In contrast, on 18 of these sessions subjects first chose smoked cocaine, and on 14 of these occasions (78 percent of the time) subjects chose smoked cocaine an additional 3 or more times. This pattern of results supports a preference for smoked cocaine rather than a perseveration of initial dose choice.

These results indicate clearly that the recent increase in cocaine smoking is due, at least in part, to the high abuse liability of smoked cocaine. The robust choice of the high smoked dose over both active IV doses by 80 percent of the subjects in the current study is particularly surprising in that 80 percent of these subjects reported a preference for IV cocaine, not smoked cocaine, during interviews prior to participation.

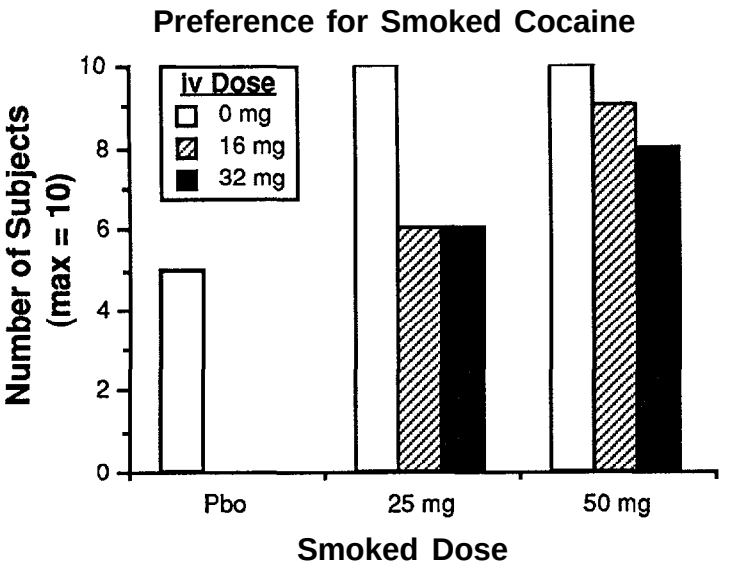

FIGURE 3. *Number of subjects choosing the smoked cocaine dose as a funcion of the dose of smoked and intravenous cocaine available each session*

KEY: Pbo = Placebo

The cardiovascular and subjective effects of cocaine repeatedly were determined during each session in order to examine the possible relationship between these effects and route choice. High cocaine doses, regardless of route of administration, produced the typical spectrum of cocaine effects: increases in systolic and diastolic pressure, heart rate, and rate-pressure product; ratings of "stimulated," "high," and "anxious" for the benzedrine group (BG), morphine-benzedrine group (MBG); and lysergic acid diethylamide (LSD) scores of the Addiction Research Center Inventory (ARCI) (Haertzen 1966); arousal and positive mood scores of the Profile of Mood States (POMS) (McNair et al. 1971); and decreases in pentobarbital-chlorpromazine-alcohol group scores of the ARCI (Fischman et al. 1976, 1983*a*, 19833, 1990; Foltin and Fischman 1991*b*; Foltin et al. 1987, 1990; Kumor et al. 1989; Muntaner et al. 1989; Resnick et al. 1977). With the exception of peak systolic pressure and rate-pressure product following low doses, there were no significant differences between acute doses of smoked and IV cocaine. The absence of significant differences in subjective and cardiovascular effects between routes of administration contrasts with the clear preference for smoked

cocaine. The subjective effects of acute doses of smoked and IV cocaine were not predictive of subsequent route choice.

Analysis of the effects of repeated doses of cocaine across trials within a session indicated that systolic and diastolic pressure, heart rate, rate-pressure product, ratings of "stimulated" and "high," and LSD scores of the ARCI were increased above baseline during the entire session following smoked and IV cocaine administration. As with the acute effects, there were no significant main effects by route of administration.

There were a number of significant interactions between the route of cocaine administration and the cumulative dose that indicate a relationship between the subjective effects of cocaine and route choice. There was a significant positive linear relationship between ratings of "sedated," LSD scores of the ARCI, confusion, elation, positive mood scores of the POMS, and cumulative cocaine dose following smoked cocaine, but *not* following IV cocaine. In addition, the predicted increases in ratings of "high" with cumulative dosing were larger following smoked cocaine than IV cocaine.

Although significant, the predicted increases in effect with increasing smoked cocaine dose were small. With the exception of ratings of "sedated," increases in these measures commonly occur following cocaine administration (Fischman et al. 1976, 1983*a*, 1983*b*, 1990; Foltin and Fischman 1991*b*; Foltin et al. 1987, 1990; Kumor et al. 1989; Muntaner et al. 1989; Resnick et al. 1977). These findings confirm a previous report that indicated the ratings of "stimulated" and "high" were greater at similar plasma levels following two doses of smoked cocaine, as compared with two doses of IV cocaine (Foltin and Fischman 1991*b*). Thus, only with repeated administration did several subjective-effects measures differentiate smoked and IV cocaine and predict route choice.

In addition to using drug self-administration and subjective effects to predict abuse liability, ratings of "quality" and "liking" and estimates of street value also have been used to predict abuse liability of a drug (de Wit and Griffiths 1991; Foltin and Fischman 1991*a*; Preston and Jasinski 1991). Both active doses of cocaine significantly increased ratings of "potency," "quality," "high," "liking," and street value compared to placebo.. The high smoked cocaine dose was associated with significantly greater ratings of "liking" than the high IV cocaine dose. In a previous study comparing the effects of smoked and IV cocaine (Foltin and Fischman 1991*b*), smoked cocaine also was associated with significantly

greater ratings of "liking" than IV cocaine. In combination, these results suggest that subjects' estimates of drug "liking" are predictive of abuse liability.

With the exception of the "liking" rating, there were almost no relationships between after-session ratings of drug effect and route choice. This issue was investigated further by examining ratings on the days that subjects had access to an active dose of smoked cocaine and an active dose of IV cocaine. With one exception, in spite of clear preference for smoked cocaine, there were no significant differences in after-session ratings of the two active cocaine doses. The after-session ratings of "potency," "quality," "high," and "liking," but not street value, were greater for 50 mg smoked cocaine than 16 mg IV cocaine. In addition, no significant correlations between ratings of the smoked dose and the number of smoked-dose choices were observed. It is possible that, while absolute ratings were poor predictors of route choice, the difference between the rating of the smoked dose and the rating of the IV dose may have been predictive of route choice; the greater the difference, the higher the probability of smoked dose choice. However, this was not the case; with one exception, there were no significant correlations between the difference in scores and smoked dose choice.

One purpose of this study was to examine the relationship between the subjective effects of a drug and self-administration of that drug. If smoked cocaine were a new drug, rather than a new route of administration for an old drug, then it would be predicted to have significant abuse liability based on the similarity of the subjective effects to the effects of IV cocaine (de Wit and Griffiths 1991; Foltin and Fischman 1991*a*; Preston and Jasinski 1991). In the present study, despite using doses of smoked and IV cocaine that were matched for initial cardiovascular and subjective effects, smoked cocaine was preferred over IV cocaine, as determined by route choice. Analysis of the effects of repeated cocaine dosing indicated that several subjective effects and ratings of "liking" were predictive of route choice. While these results clearly indicate the necessity of studying drug self-administration in addition to subjective effects, there is a caveat. It is possible that the standardized questionnaires used did not assess the relevant subjective effects that would have predicted route choice. The inclusion of self-report items specifically tailored to assess unique aspects of smoked cocaine may have predicted route choice.

The self-administration model should thus be a useful tool for evaluating the mechanisms of action of pharmacological interventions in the treatment of cocaine abuse via both smoked and IV routes of administration (Foltin and Fischman 1991*b*). Since separate measures can be made of drug taking, cardiovascular effects, and subjective effects, it is theoretically possible to parcel out specific effects of a treatment medication, thereby eventually providing targeted treatment.

The two-dose choice procedure has been used to evaluate the effects of the potential treatment drug desipramine on cocaine-taking behavior (Fischman et al. 1990). Therapy with the tricyclic antidepressant desipramine has been suggested as a pharmacological adjunct for the treatment of cocaine abuse (Extein and Gold 1988; Gawin and Kleber 1984; Giannini and Billet 1987; Giannini et al. 1986). Although not always a sucessful intervention (Amdt et al. 1990), in a double-blind clinical trial (Gawin et al. 1989) about three times as many patients maintained on desipramine as opposed to placebo-remained abstinence for 3 to 4 weeks. Gawin and Kleber (1984) have proposed that repeated cocaine use results in noradrenergic and dopaminergic receptor changes that are similar to those seen in depression. Thus, if the antidepressants are useful, particularly the tricyclic antidepressants, their utility may be as therapeutic adjuncts rather than as pharmacological antagonists of cocaine's effects.

Choices between active doses of IV cocaine and placebo were recorded before and during a period of maintenance on desipramine. Subjects were outpatients during the desipramine maintenance period, reporting to the laboratory daily; blood samples were taken to monitor desipramine blood levels twice each week. Blood levels of desipramine were maintained at approximately 125 ng/mL during the final determination of cocaine dose choice. This protocol allowed evaluation of desipramine's effects on drug taking, dose preference, self-reported drug effects, and cardiovascular effects under conditions in which the drug was taken outside the laboratory (i.e., the opportunity for repeated dosing was available).

As shown in figure 4(a), desipramine had no effect on cocaine-taking behavior: Subjects almost exclusively chose cocaine over placebo both before and during desipramine maintenance. Cocaine could not always be administered because of medical considerations (i.e., diastolic blood pressure above 100 mmHg or heart rate above 131 bpm), which were generally related to the desipramine-induced elevations in baseline

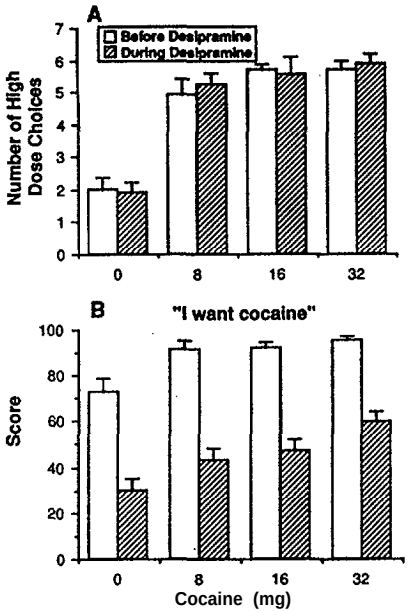

FIGURE 4. *(Panel A): Number of high cocaine dose choices as a function of the available cocaine dose (the alternative was always a placebo injection) before and during desipramine maintenance. (Panel B): "I want cocaine" scores as a function of cocaine dose before and during desipramine maintenance. Error bars represent SEMs.*

cardiovascular measures. The self-administration of cocaine despite potentially detrimental cardiovascular effects is clear evidence for the toxicity of this drug.

Craving is a generally used measure in clinical studies, and decreases in craving for cocaine have been reported for cocaine abusers being treated with desipramine (Gawin and Kleber 1984; Gawin et al. 1'989). A VAS labeled "I want cocaine" was administered as part of the self-report questionnaires answered repeatedly during each session. As shown in figure 5(b), before the period of maintenance on desipramine, subjects' scores on this objective measure of craving were close to the maximum of 100, while scores on this scale were substantially and significantly lower during desipramine maintenance. Despite such shifts in reports of

wanting cocaine, however, the subjects' cocaine-taking behavior remained unchanged. These results are evidence for the importance of multiple measures in assessing the efficacy of potential treatment drugs, and they provide an example of dissociations between changes in subjective-effects measures and drug intake.

Although desipramine maintenance did not appear to affect the self-administration of cocaine, it did modify some of cocaine's self-reported effects. Several patterns of changed effects emerged. The first of these was evident on many of the scales that are sensitive to stimulant drugs, including arousal and positive mood of the POMS and the BG scale of the ARCI (figure 5[a]). Prior to desipramine maintenance, the initial daily dose of cocaine increased these scores in a dose-related fashion. Desipramine maintenance attenuated these dose-related effects of cocaine.

A second pattern of interaction between cocaine and desipramine on other subjective-effects scales was observed. These scales included the POMS confusion and anger scales and the ARCI LSD scale (figure 5[b]), measures of dysphoric drug effects. Desipramine maintenance resulted in lower placebo scores and significantly higher scores in response to cocaine, indicating an enhancement of cocaine's effects on these more negative scales.

Desipramine maintenance did not always change the self-reported effects of cocaine. The effects measured by the series of questions answered at the termination of each choice session (approximately 30 minutes after the last cocaine injection, when blood levels were decreasing) were among the most consistent in this regard. At that time, subjects were instructed to rate the dose over the *entire* session. Regardless of the presence or absence of desipramine, ratings of "high," "liking," "potency," and "How much would you pay?" all showed increases withincreasing doses of cocaine. For example, as shown in figure 5(c), subjects indicated that they would be willing to pay approximately $40 for the 32-mg dose of cocaine. Therefore, there appear to be some effects of cocaine that are dose related and do not change under conditions of desipramine maintenance. This unchanged retrospective rating of cocaine's effects during desipramine maintenance suggests that cocaine abusers maintained on desipramine might continue to take cocaine, at least in the absence of a concomitant behavioral intervention.

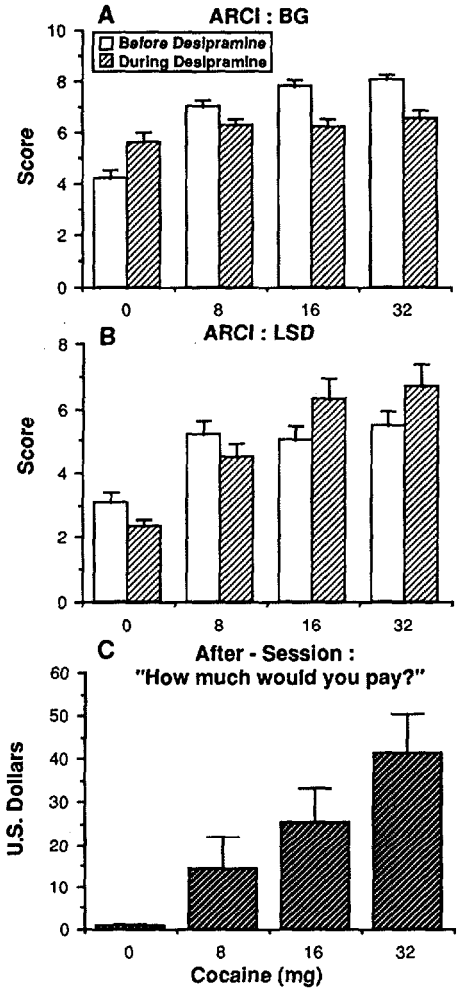

FIGURE 5. *(Panel A): BG scores of the ARCI as a function of the available cocaine dose before and during desipramine maintenance. (Panel B): LSD scores of the ARCI as a function of the available cocaine dose before and during desipramine maintenance. (Panel C): After-session ratings of street value of the cocaine dose received that session as a function of cocaine dose. Error bars represent SEMs.*

The dissociation between the effects of desipramine on cocaine self-administration and the self-reported effects of cocaine clearly suggests that desipramine alone is not an adequate pharmacological intervention for treating cocaine abusers. Under conditions of desipramine maintenance, cocaine remains a potent reinforcer. It is possible, however, that the alteration in cocaine's profile of effects may modify its reinforcing effects so that users participating in a behavioral treatment intervention can learn to use other reinforcers in their environment rather than continuing to take cocaine. The absence of a shift in cocaine choice during desipramine maintenance, paired with the verbal reports of decreased cocaine craving, suggest that subjects would have chosen less cocaine if a nondrug option had been available.

The last study to be described used a procedure involving *three* choices: two different doses of cocaine and a nondrug option. The nondrug option involved tokens exchangeable for reinforcers such as videotaped films, candy bars, and cigarettes. Using tokens as a third nondrug option had modest effects on cocaine choice. When 8 mg and 16 mg of cocaine were available, increasing the number of tokens from one to two had minimal effect on high-dose choice (figure 6). When 16 and 32 mg of cocaine were available, however, increasing the number of tokens from two to four did slightly decrease high-dose choice. Thus, there is some evidence that this nondrug option can compete with cocaine choice.

The three-choice procedure has been used to evaluate the effects of the potential treatment drug fluoxetine on cocaine-taking behavior. Like desipramine, fluoxetine, a selective inhibitor of serotonin uptake (Fuller et al 1991), has been suggested as a pharmacological adjunct in the treatment of cocaine abuse (Pollack and Rosenbaum 1991). As in the previous protocol, choice behavior was recorded before and during a period of maintenance on the treatment drug. During the 3-week maintenance period, subjects reported to the laboratory on weekdays, completed self-report questionnaires, provided a urine sample for determining drug use, and consumed a 20 mg capsule of fluoxetine. Preliminary data obtained with five subjects suggest that fluoxetine maintainence altered choice behavior when subjects had access to low cocaine doses (4 and 8 mg/70 kg) but not when they had access to high cocaine doses (16 and 32 mg/70 kg). When 4 and 8 mg doses of cocaine were available, fluoxetine maintenance affected choice behavior in one subject so that choice shifted to low doses (figure 7). When 8 and 16 mg doses of cocaine were available, there was also a shift to low doses or tokens during fluoxetine maintenance. But when 16 and 32 mg doses

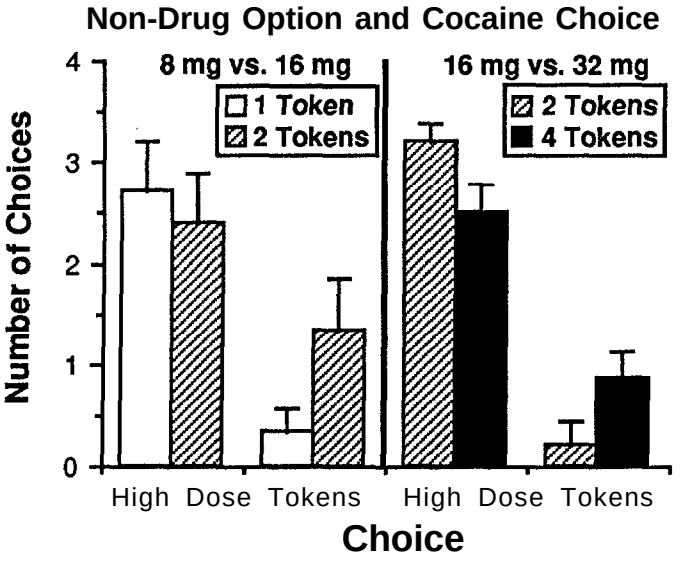

FIGURE 6. *Choice of the high cocaine dose or tokens as a function of the available cocaine doses and the number of tokens delivered following a request for tokens. Error bars represent SEMs.*

were available, fluoxetine maintenance had no effect on choice behavior. While the results have been variable among subjects, choice behavior for all subjects was altered during fluoxetine maintenance on days when 4 and 8 mg doses of cocaine were available.

In contrast to desipramine maintenance, fluoxetine had no effect on subjects' "I want cocaine" scores (figure 8[a]), which averaged between 30 and 50 (out of 100) before and during fluoxetine maintenance. Cocaine administration produced dose-dependent increases in subjects' ratings of "high" after the first dose (figure 8[b]). During fluoxetine maintenance, ratings of "high" were greater after the administration of 4, 16, and 32 mg/70 kg doses of cocaine, suggesting a possible shift to the left of the cocaine dose-response function for some of the behavioral effects of cocaine. This pattern was not evident for other measures of positive changes in mood associated with stimulant use, that is, BG and MBG scores on the ARCI, arousal, and positive mood scores on the POMS. An interesting pattern of changes in after-session ratings of drug effects was evident during fluoxetine maintenance, as compared to before

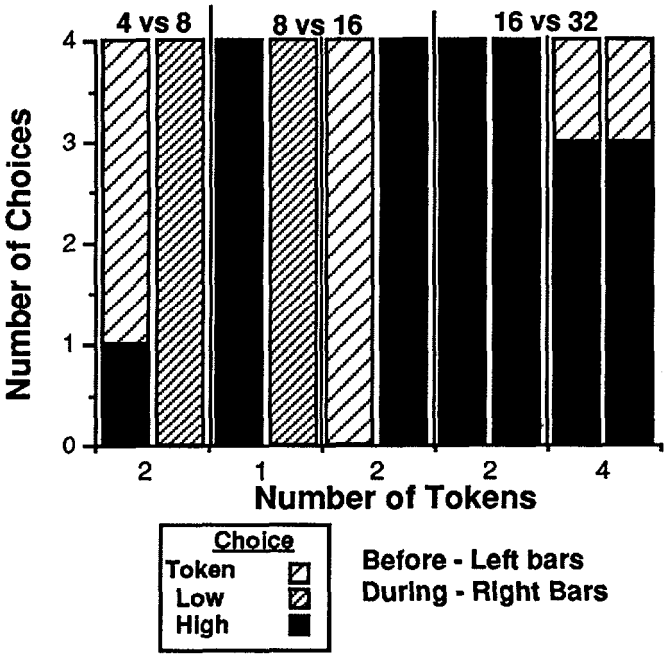

FIGURE 7. *Choice of the high or low cocaine dose or tokens as a function of the available cocaine doses and the number of tokens delivered following a request for tokens before and during fluoxetine maintenance. Error bars represent SEMs.*

fluoxetine maintenance. Fluoxetine maintenance increased subjects' ratings of drug liking for the lowest dose of cocaine (4 mg/70 kg) without affecting ratings of the highest doses (figure 8[c]). A similar pattern was evident for subjects' ratings of drug potency. As described above, increased liking scores would be predictive of greater abuse liability (de Wit and Griffiths 1991; Foltin and Fischman 1991*b*; Preston and Jasinski 1991). When asked to estimate the street value of each dose, subjects' estimated value of the lowest dose was $0 before fluoxetine maintenance, but almost $3 during fluoxetine maintenance (figure 9[d]). In contrast, the estimated values of the two highest doses decreased from $5 and $12 to $3 and $9 during fluoxetine maintenance.

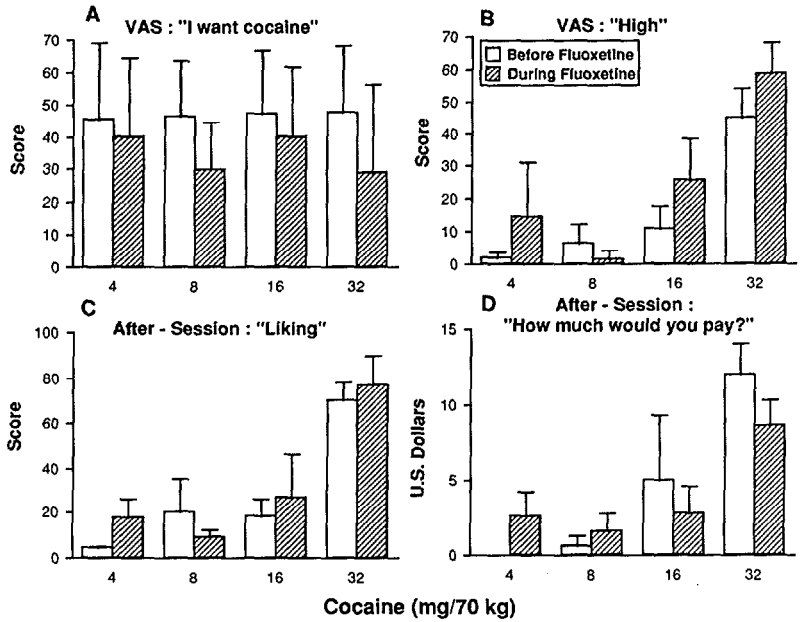

FIGURE 8. *(Panel A): Ratings of "I want cocaine" following the first active dose as a function of cocaine dose before and during fluoxetine maintenance. (Panel B): Ratings of "high" following the first active dose as a function of cocaine dose before and duringfluoxetine maintenance. (Panel C): After-session ratings of "liking" as a function of cocaine dose before and duringfluoxetine maintenance. (Panel D): After-session ratings of street value as a function of cocaine dose before and during fluoxetine maintenance. Error bars represent SEMs.*

These preliminary data on the effects of fluoxetine on cocaine choice and subjective effects indicates that the interaction between fluoxetine and cocaine is complex. As was observed with desipramine, maintenance on an antidepressant had minimal effects on cocaine choice behavior in subjects who were not seeking treatment. Fluoxetine may have altered the discriminability of low doses, accounting for the change in choice behavior at these dose levels. The subjective-effects data suggest that this decrease in discriminability may indicate an enhancement of the effects of the lowest dose of cocaine. Fluoxetine had no effect on cocaine craving, which is in sharp contrast to the effects of desipramine. This absence of an effect on craving suggests that fluoxetine may be less helpful in controlling cocaine use than desipramine. Further data are needed to

interpret the relationship between changes in choice behavior and the subjective effects of cocaine during fluoxetine maintenance. As shown with the choice of smoked cocaine over IV cocaine, it is likely that these relationships are complex.

In summary, this research demonstrates the way in which procedures developed in the laboratory for use with nonhumans can be adapted for use with humans and combined with measures of verbal report. Choice procedures provide a rapid and sensitive measure of drug self-administration. With respect to cocaine, active doses were chosen over placebo, higher doses were chosen over lower doses, high-dose choice was minimally affected by response cost, and pairing money with low doses minimally decreased high-dose choice. The presence of a nondrug option, however, altered cocaine choice at some dose levels.

Combining choice procedures with measures of cardiovascular and subjective effects allows for comparisons across these measures and provides information about factors affecting abuse liability of drugs. For example, smoked cocaine was chosen over IV cocaine even when doses were matched for cardiovascular and subjective effects after an acute administration. However, subtle differences between the effects of cocaine administered by different routes was evident only after repeated dosing. This finding indicates that multiple-dose paradigms should be used to study the effects of cocaine because it is most often taken that way on the street.

It is clear that self-reports do not substitute for measuring actual drug-taking behavior. For example, on the basis of subjects' verbal reports alone, one would predict that desipramine-maintained subjects who showed reduced cocaine craving would not self-administer cocaine. This prediction would have been strengthened by the decreases in the magnitude of verbal reports of stimulant effects and increases in the magnitude of dysphoric drug effects during desipramine maintenance. However, reductions in cocaine self-administration during desipramine maintenance were not observed.

Based on the preliminary data presented here, fluoxetine had minimal effects on cocaine choice and may have enhanced the subjective effects of lower doses. This suggests that fluoxetine, by itself, may have minimal efficacy as a treatment drug for cocaine abuse.

CONCLUSION

In conclusion, it is only by evaluating drug-taking behavior within a behavioral context that one can fully understand and predict the likelihood that a potential treatment drug will be effective in reducing cocaine-taking behavior. In addition, by combining choice procedures with other behavioral measures, including subjective and cardiovascular effects, it is possible to characterize the behavioral mechanism of action of potential treatment drugs for cocaine abuse.

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Neurobiological Mechanisms Underlying the Acquisition and Expression of Incentive Motivation by Cocaine-Associated Stimuli: Relationship to Craving

Agu Pert

INTRODUCTION

The development of pharmacotherapeutics for treatment of cocaine addiction has focused primarily on designing drugs that are effective cocaine antagonists at the dopamine transporter. While this strategy may ultimately yield effective pharmacotherapeutics, greater emphasis should be placed on the development of drugs that prevent or attenuate craving, the process that compels an individual to seek cocaine and is also responsible for recidivism following abstinence. The success of such a program, however, rests on the development of appropriate and simple animal models, as well as on a greater understanding regarding the neurobiological processes involved.

MOTIVATIONAL SUBSTRATES UNDERLYING CRAVING

Craving, unfortunately, is a rather maligned and misunderstood hypothetical construct. Some have, in fact, suggested that craving is not an appropriate construct for scientific inquiry (World Health Organization Committees on Mental Health and on Alcohol 1955). Others have viewed craving as a useful concept and have conceptualized it in a variety of ways. Some, for example, have suggested that craving and other physical symptoms constitute physical dependence (Jellinek 1960), while others have proposed that craving is instead the result of physical symptoms (Eddy 1973; Marlatt 1978). Other, more cognitive models have suggested that craving is a result of cognitive processes modified by both internal and external cues (Ludwig and Stark 1974). More recently, incentive motivational concepts have gained prominence as underlying substrates of craving (Markou et al. 1993; Marlatt 1987; Robinson and

Berridge 1993; Wise 1988). Whatever the underlying neurobiological mechanisms are, it is clear that craving has strong motivational components.

Two motivational processes have been postulated by motivational theorists to energize and direct behavior-drive and incentive motivation (Bindra 1968; Bolles 1967). There are several important distinctions between these two constructs. First, drives are innate or determined through perturbations to innate biological mechanisms, while incentive motivation has to be acquired by learning. Second, drives are thought to be elicited by imbalances in homeostatic mechanisms, while incentive motivation is elicited by environmental or external stimuli. The concept of drive arises from the notion that there exist conditions within an organism that compel it to action. The concept of incentive motivation is derived from the notion that there are objects in the environment to which an organism is attracted. In this sense, drives are thought to "push" behavior while incentives "pull" (Bolles 1967).

Two categories of contemporary neurobiological theories have evolved to account for craving within the constraints of these two motivational constructs. Some have viewed craving to be the direct result of a deficit or aversive state produced by prolonged exposure to drugs of abuse. Koob and Bloom (1988), for example, have proposed that the " . . . 'negative reinforcing' effects (for example, malaise, dysphoria, and anhedonia) are a major etiological and motivational factor in maintaining drug dependence." Others have also viewed the motivational forces underlying cocaine addiction, for example, to be the result of either withdrawal symptomatology (Gawin 1991) or deficit states (e.g., dopamine [DA] depletion) induced by chronic exposure to the drug (Dackis and Gold 1985).

These types of theories assert that drug (e.g., cocaine) use is maintained because the drugs alleviate some type of deficit or aversive state and, for this reason, have been termed "negative-reinforcement theories" (Koob and Bloom 1988; Robinson and Berridge 1993; Wise 1955). The basic motivational process behind these formulations is drive reduction. They have arisen essentially from the study of opiate addiction, where withdrawal symptoms are clearly and readily defined. Whether they have applicability for understanding the addiction to cocaine and other drugs for which withdrawal effects are not very prominent remains to be determined. Robinson and Berridge (1993) have recently provided a concise review of the many problems faced by theories of this nature, the

chief being that they have great difficulty accounting adequately for craving and recidivism following prolonged abstinence.

Other theorists in drug addiction research have emphasized the importance of incentive-motivational mechanisms in the addiction process (Markou et al. 1993; Marlatt 1987; Robinson and Berridge 1993; Stewart et al. 1984; Wise 1988). As noted above, incentive motivation is acquired through learning. Stimuli that are repeatedly associated with a primary reinforcer such as food or drugs are thought to acquire, through classical conditioning, two properties. The first is secondary reinforcement and the second is incentive motivation (Bindra 1968). The secondary reinforcing properties of such stimuli, when they follow a specific behavior, enable them to facilitate and augment performance of the behavior. Secondary reinforcing properties of stimuli associated with drugs of abuse have been demonstrated by several investigators (Davis and Smith 1976; Schuster and Woods 1968). When such stimuli appear prior to a particular behavior, their incentive-motivational properties appear to energize and facilitate initiation of the behavior. Drugs such as cocaine can be thought of as positive incentives similar to food, water, or a sexual partner. Incentive-motivational properties are not established, however, until the pharmacological effect is experienced. Such properties are then conferred to stimuli associated with the drug (white powder, paraphernalia, or environment).

The energizing function of incentive-motivational stimuli has been known for some time. It has been well established, for example, that stimuli repeatedly associated with positive reinforcers such as food can increase general motor activity or energize behavior when presented alone (Bindra and Palfi 1967; Bolles 1963; Sheffield and Campbell 1954). Bindra and Palfi (1967) have suggested that such incentive-motivational activity is characterized by anticipatory excitement often seen during classical appetitive conditioning and appears to be investigatory and goal directed in nature. Bindra (1969) has also proposed that conditioned incentive-motivational stimuli established by pairing with a positive reinforcer such as food acquire similar appetitive properties and come to energize the appetitive-motivational system as a whole and produce a positive incentive-motivational state.

THE ENERGIZING COMPONENT OF INCENTIVE MOTIVATION AS A DETERMINANT OF CRAVING

Figure 1 illustrates findings from a recent study in which the energizing function of stimuli paired with feeding was measured by subsequently assessing their ability to alter locomotor activity. In this study, three groups of rats were employed. The first group was deprived of food for 23 hours and then allowed to consume all of their daily food during 1 hour in a photocell locomotor activity chamber scented with peppermint extract to enhance the saliency of the environmental cues. The second group was deprived of food for 21 hours and then placed in the same locomotor chambers for 1 hour with no food available. These animals were allowed to consume all their daily food in a 60-minute session 1 hour following return to their home cages. The third group had ad lib access to food in their home cages. These animals were also exposed to the locomotor activity chamber for 1 hour.

Training described above was carried out for 3 consecutive days. On day 4, all three groups were returned to the activity chamber for 1 hour. The first two groups were both run under 23-hour deprivation conditions. It was apparent that environmental stimuli paired with feeding enhanced horizontal locomotor activity when they were subsequently presented alone. Such effects were most apparent during the first lo-minute period and then dissipated rapidly thereafter. It is proposed that the increases in motor activity seen in this study reflect the energizing function of incentive motivation.

As noted above, incentive-motivational processes have also been postulated by a number of researchers to underlie and determine craving in drug addicts. Marlatt (1987), for example, has suggested that ". . . craving could be considered to be a conditioned appetitive response much like the conditioned salivary response in anticipation of food observed in Pavlov's dogs. Craving in this sense is viewed as anticipatory in nature, an appetitive motivational state associated with a strong desire for one expected outcome." Several recent reviews of animal studies have also emphasized the importance of incentive motivation as a determinant of drug craving (Markou et al. 1993; Stewart and de Wit 1987; Wise 1988). In addition, Robinson and Berridge (1993) have proposed a rather intriguing model in which incentive-motivational mechanisms are thought to sensitize through neuronal adaptations in response to repetitive drug exposure.

ACTIVITY BY STIMULI ASSOCIATED WITH FEEDING

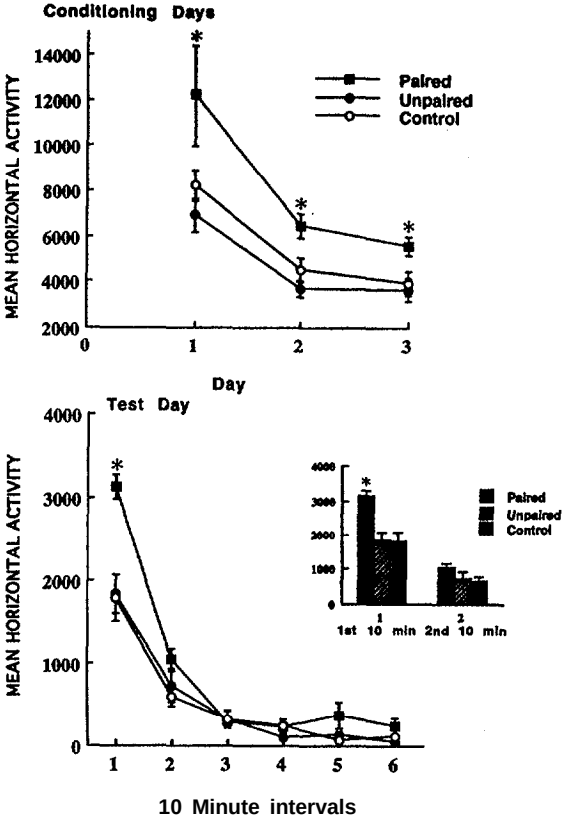

FIGURE 1. *Conditioned locomotor activity by environmental stimuli associated with feeding. (Top): Locomotor activity of the three groups of rats on three training days. (Bottom): Locomotor activity of the three groups over the course of 60 min on day 3. The PAIRED group had activity levels that were significantly higher than the UNPAIRED or CONTROL groups during the first 10-min interval.*

In the context of incentive motivation, it is of interest to note that a number of clinical studies have revealed that cocaine users report craving cocaine in response to presentation of stimuli previously associated with the drug. Such stimuli also precipitate a host of physiological arousal signs, such as reductions in peripheral skin temperature, decreases in skin resistance, and increases in heart rate (Childress et al. 1990; Ehrman et al. 1992).

Approximately six decades ago, Tatum and Seevers (1929) as well as Down and Eddy (1932) reported that dogs develop increased activity, excitement, and eagerness in the presence of situational cues that had been associated with cocaine. Both of these early studies appeared to suggest that stimuli paired with cocaine injections acquire incentive-motivational properties. More contemporary studies with rodents using the place-performance methodology (Hoffman 1989) also have reported the development of such properties by stimuli associated with psychomotor stimulations and other drugs of abuse. Conditioned increases in general locomotor activity (Barr et al. 1983; Bridger et al. 1982; Hinson and Poulos 1981; Pert et al. 1990; Pickens and Crowder 1967; Pickens and Dougherty 1971; Post et al. 1981; Schiff 1982; Stewart and Vezina 1988) and stereotypy (Barr et al. 1983; Schiff 1982) have also been observed following the administration of psychomotor stimulants in the presence of previously neutral stimuli. It is proposed that such increases in motoric output reflect the energizing functions of incentive-motivational processes elicited by stimuli associated previously with the drugs, similar to that seen with other reinforcers, such as food (see above).

NEUROBIOLOGICAL PROCESSES UNDERLYING THE ACQUISITION OF COCAINE-INDUCED CONDITIONED INCREASES IN MOTOR ACTIVITY

Although the behavioral variables regulating the conditioning of drug effects have been extensively studied (Pert et al. 1990), considerably less focus has been directed at the underlying neurobiological processes. Understanding such processes and principles might provide greater insights for designing new pharmacological agents to alleviate craving or for formulating strategies to extinguish it. In work described in this chapter, the author and colleagues at the National Institute of Mental Health utilized a relatively simple and efficient paradigm to study the

processes and neural mechanisms underlying the acquisition, expression, and extinction of cocaine-induced conditioned increase in motor activity. Similar to the food-conditioning study described above, three groups of rats were employed. On day 1, the first group (PAIRED) was injected with a high dose of cocaine HCl (40 mg/kg) intraperitoneally and placed in locomotor activity chambers for 30 minutes. One hour following return to their home cages, these rats were injected with saline. The record group (UNPAIRED) was treated in a similar fashion but received saline prior to placement in the locomotor activity chambers and then cocaine (40 mg/kg) in the home cage. The third group (CONTROL) received saline in both environments. On day 2, all animals were challenged with 10 mg/kg of cocaine immediately prior to placement in the locomotor activity chambers. Figure 2 illustrates the behavioral effects seen on both days. On day 1, the PAIRED group, of course, exhibited a dramatic increase in motor activity in response to 40 mg/kg of cocaine compared to the UNPAIRED and CONTROL groups, which were exposed to the apparatus following saline injections. On day 2, when all groups were reexposed to the activity chambers following injections of 10 mg/kg of cocaine, the PAIRED group exhibited considerably higher activity levels than the other two groups. Since the PAIRED and UNPAIRED groups received the same exposure to cocaine on day 1, the difference in locomotor behavior between them must be related to the context in which the drug was experienced (i.e., conditioning). It has been found that the establishment of such conditioned increase in motor activity depends on associative learning processes (Rothman and Pert, in press) and follows the principles of classical conditioning. For example, the magnitude of the conditioned response appears to be related to the intensity of the unconditioned stimulus (i.e., dose of drug). In addition, the conditioned response decays with time and is subject to extinction, and the conditioned stimulus follows the principle of stimulus generalization (Barr et al. 1983; Hayashi et al. 1980; Hinson and Poulos 1981; A. Pert, unpublished observations; Pickens and Crowder 1967; Tilson and Rech 1973; Weiss et al. 1989).

It should be noted that the conditioning paradigm in these studies was somewhat unconventional in that the unconditioned stimulus was present during the test day, although at a lower intensity (dose). Conditioned increases in locomotor activity in other studies have generally been assessed in the conditioning chamber following injections of saline or the drug vehicle. This may not always be appropriate or adequate to reveal conditioned drug effects in all circumstances, especially when rather

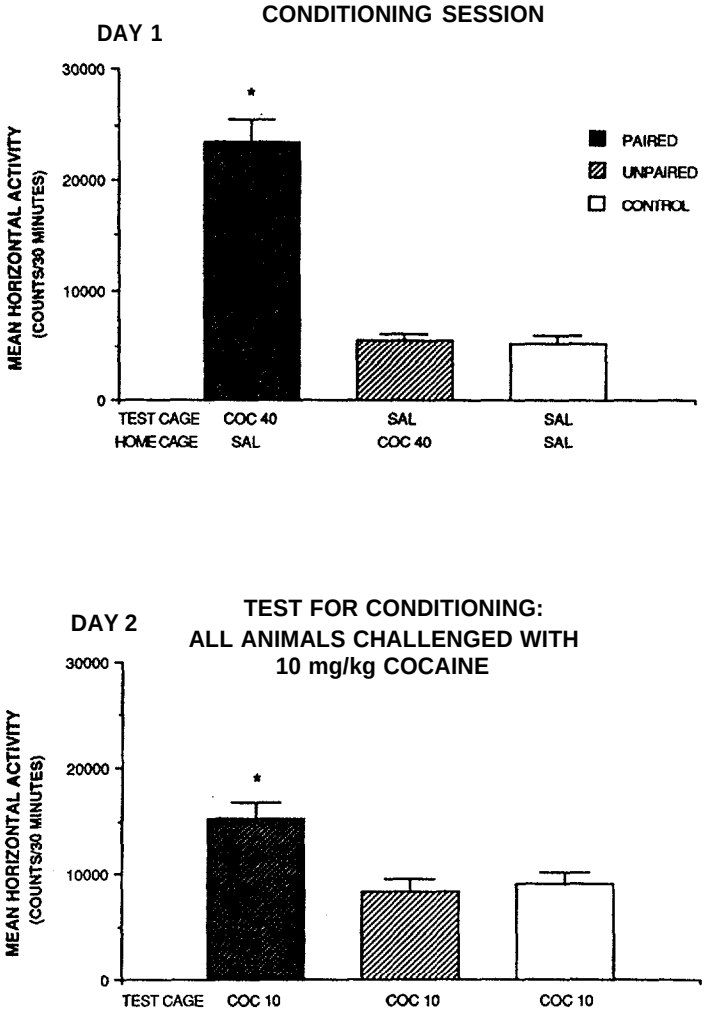

FIGURE 2. *Conditioned increased in locomotor activity following 1 day of training with cocaine. (Top): Horizontal locomotor activity during the training day. The PAIRED rats were injected during the training day. The PAIRED rats were injected with 40 mg/kg of cocaine prior to a 30-min training session. (Bottom): Horizontal locomotor activity during the test day (day 2) when all three groups were tested with 10 mg/kg of cocaine.*

subtle conditioned responses are expected, as in the paradigm discussed above that utilizes a single 30-minute conditioning session. The pharmacological actions of cocaine on the training day produce two critical effects that determine conditioning. First, cocaine has motivationally significant consequences that probably serve as the basis for its ability to act as an unconditioned stimulus (Mackintosh 1974). It has been suggested, in fact, that the locomotor stimulatory effects of drugs like cocaine are related to their appetitive-motivational or rewarding properties (Stewart et al. 1984; Wise and Bozarth 1987). Second, cocaine also produces a variety of interoceptive cues (e.g., alterations in heart rate or blood pressure) through peripheral sympathetic activation, that have the potential of contributing to the total stimulus complex that comes to serve as the conditioned stimulus. It has been shown, for example, that leg flexion reactions in dogs can be conditioned to interoceptive cues produced by peripherally administered epinephrine, norepinephrine, and acetylcholine (Cook et al. 1960). It is likely that the excitatory (appetitive-motivational) effects of cocaine (determined through the central nervous system are conditioned to a stimulus complex consisting of environmental as well as drug-produced interoceptive cues. If this is the case, the most robust conditioned response would be expected to be elicited in the presence of cues that are most similar to those present during the conditioning process (i.e., both interoceptive as well as environmental).

An additional reason to test in the presence of a lower dose of cocaine is to amplify the rather subtle conditioned effects that are likely following a 30-minute conditioning session. There is considerable evidence, for example, to indicate that psychomotor stimulants enhance conditioned responses in other learning paradigms (Robbins 1975, 1978; Robbins and Koob 1978; Robbins et al. 1983, 1989). Using a conditioning paradigm similar to the one described, it was found recently that the rather modest conditioned effects normally seen following a saline challenge on day 2 are accentuated considerably by 10 mg/kg of cocaine (A. Pert, unpublished observations). The strength and persistence of conditioning also appears to depend on the degree of training. The conditioned effects after 1 day of conditioning dissipate rather rapidly and are generally no longer present three days after training. One week of training, on the other hand, produces conditioned effects that are still present up to at least 60 days later. When needed (especially in studies aimed at evaluating mechanisms involved in the expression of cocaine-conditioned behaviors), a more prolonged training regime (3-7 days) has been used.

Since DA is involved in mediating the stimulatory and appetitive properties of psychomotor stimulants, it is not surprising that disruptions in the actions of this brain amine would alter the acquisition of conditioning. For example, neuroleptics, co-administered with either amphetamine (Beninger and Hahn 1983) or cocaine (Beninger and Herz 1986; Weiss et al. 1989) have been found to prevent the development of conditioned locomotor behaviors. More recently, Fontana et al. (19933) found that D_1 or D_2 DA receptor antagonists are equally effective in preventing the formation of cocaine-induced conditioning (figure 3). Likewise, conditioning in the l-day design was found only following administration of a combination of D_1 and D_2 agonists during training and not when either was administered separately (figure 4). This would suggest that concurrent D_1 and D_2 DA receptor occupation is necessary for conditioning to occur.

There are a variety of mechanisms by which DA antagonists could disrupt the acquisition of cocaine-induced conditioning (Fontana et al. 19933). It is most likely, however, that the ability of these drugs to decrease or prevent conditioning to psychomotor stimulants is related to their ability to attenuate the unconditioned effects of the drugs, which are critical in forming the conditioned association. It is proposed that the ability of DA blockers to prevent conditioning is related to their ability to decrease the motivational significance of the unconditioned stimulus (e.g., cocaine). It is well established that the strength of conditioning is directly related to the intensity of the unconditioned stimulus in other conditioning paradigms (Kamin and Brimer 1963; Ost and Lauer 1965; Wagner et al. 1961). Both D_1 and D_2 blockers have been known to be effective in decreasing the reinforcing efficacy of cocaine (Hubner and Moreton 1991), indicating that both receptor subtypes participate in determining the motivational properties of the drug. It is not surprising, therefore, that both D_1 and D_2 DA antagonists are effective in preventing the development of cocaine-induced conditioning.

The critical role of dopamine in the conditioned effects of cocaine is also supported by lesion studies. DA-depleting 6-OHDA lesions of the nucleus accumbens have been found to prevent the conditioned effects of cocaine (Pert et al. 1990) and amphetamine (Gold et al. 1988). Similar lesions to the amygdala also produced modest disruptions to conditioning (Pert et al. 1990) that can be overcome by more extensive training. It is possible that two different components of the conditioning process are mediated through these two structures innervated by the mesolimbic DA system. It is of interest to note that 6-hydroxydopamine (6-OHDA)

DA ANTAGONISTS PREVENT THE ACQUISITION OF COCAINE-INDUCED CONDITIONING

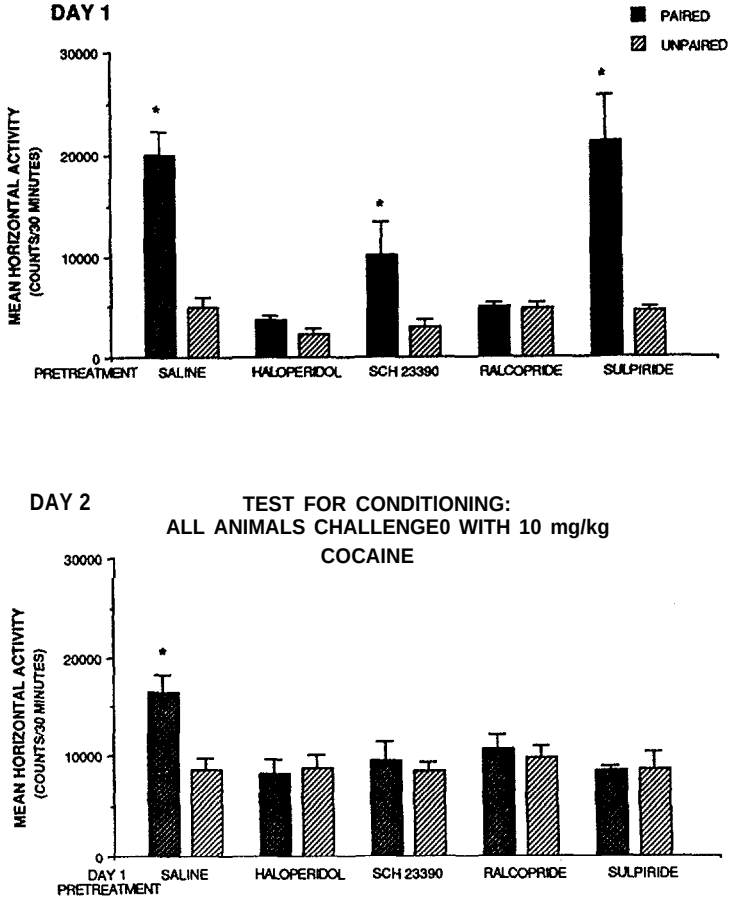

FIGURE 3. *Blockade of cocaine-induced conditioning by D_1 and D_2 antagonist pretreatment. (Top): PAIRED and UNPAIRED rats were pretreated with saline, haloperidol, SCH 23390, raclopride, or sulpiride prior to injections of either 40 mg/kg of cocaine or saline. (Bottom): On day 2, all rats were injected with 10 mg/kg of cocaine prior to a 30-min test session.*

SOURCE: Fontana et al. (19933)

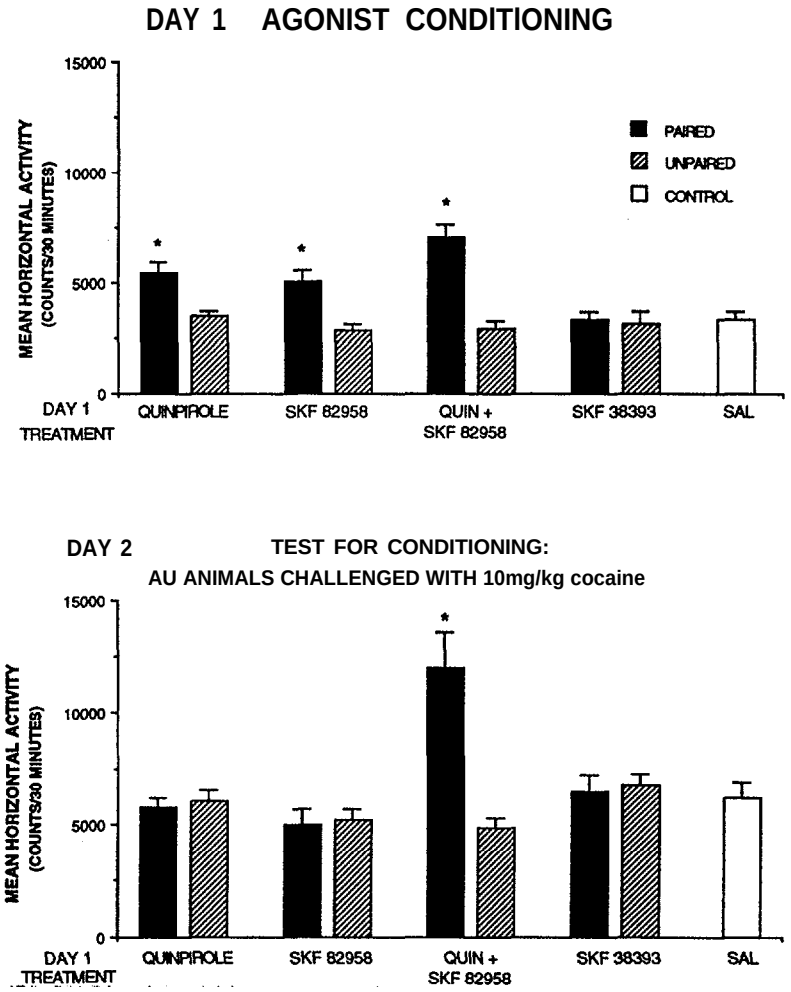

FIGURE 4. *The ability of D_1 and D_2 agonists to induce conditioning. (Top): PAIRED animals were injected with various D_1 agonists prior to placement in locomotor activity chambers on day 1. While the UNPAIRED rats were injected with the respective D_1 or D_2 agonists 1 hour following their return to the home cages, the PAIRED rats received saline. A control group (CONTROL) that received saline in both environments was included for purposes of comparison. (Bottom): Horizontal activity in all groups on day 2 following injections of IO mg/kg of cocaine. * $p < 0.05$ for comparisons of the PAIRED groups with their respective controls. Vertical lines indicate the S.E.M.*

SOURCE: Fontana et al. (19936)

lesions of the striatum or frontal cortex were ineffective as were serotonin-depleting lesions of the dorsal and median raphe nuclei or norepinephrine depleting lesions of the locus coeruleus. The author and colleagues have also failed to disrupt cocaine-induced conditioning with radio-frequency lesions of the ventral and dorsal hippocampus or cerebellum. Such findings, along with the ability of DA antagonists to prevent cocaine conditioning strongly suggest that intact DA function in the nucleus accumbens and, to a lesser degree, in the amygdala is necessary for the formation of incentive-motivational properties by stimuli associated with cocaine.

NEUROBIOLOGICAL PROCESSES INVOLVED IN THE EXPRESSION OF COCAINE-INDUCED CONDITIONED INCREASES IN MOTOR ACTIVITY

While of theoretical interest, understanding the processes involved in the formation of conditioned and incentive-motivational properties of drugs of abuse will probably have little utility for the design of pharmacotherapeutics, unless the mechanisms involved in the acquisition and expression are similar. Relatively little is known regarding the neural processes involved in the expression of cocaine-conditioned increases in motor activity.

Although mixed D_1/D_2 and selective D_1 and D_2 antagonists have been found to prevent the establishment of conditioning to cues associated with cocaine, they have been reported to be relatively ineffective in preventing expression once established. Early studies by Beninger and Hahn (1983) and Beninger and Herz (1986) found that pimozide did not eliminate the differential in behaviors between the conditioned and nonconditioned groups when either amphetamine or cocaine was used as the unconditioned stimulus. Weiss and colleagues (1989) have also found that haloperidol is ineffective in eliminating the behavioral differential between cocaine-conditioned animals and their controls. Fontana and colleagues (19933) have extended these findings by demonstrating that neither D_1 nor D_2 antagonists are effective in altering the differential in performance between the conditioned and unconditioned rats during the test phase (figure 5). Carey (1990) has also found that neither SCH 23390 nor haloperidol is effective in blocking the expression of conditioned rotational behaviors induced by pairing

apomorphine injections with the test environment in rats with unilateral 6-OHDA lesions of the nigrostriatal DA pathways.

On the surface, these findings, together with the ability of DA antagonists to block the acquisition of conditioned behaviors, appear to suggest that, while intact DA function is critical for the development of conditioning to cocaine-associated cues, it is not necessary for the expression of the conditioned response once established. It is possible that nondopaminergic pathways acquire the ability to elicit such conditioned reactions. The second alternative is that DA is involved in the expression of the conditioned behavior and that the differential in activity seen between the conditioned and nonconditioned groups is determined and maintained by increased activity of mesolimbic DA pathways in the former group despite similar partial blockade of DA receptors in all experimental groups. Using a paradigm similar to that described above, a significant elevation has been noticed on day 2 of DA in the nucleus accumbens, measured by in vivo microdialysis (Fontana et al. 1993*a*) in the PAIRED rats, relative to the two control groups (figure 6). Similar increases have not been found in the amygdala or striatum (A. Pert and D. N. Thomas, unpublished observations). Kalivas and Duffy (1990) also have reported increases in mesolimbic DA elicited by stimuli associated with cocaine. Thus, there appears to be a difference in mesoaccumbens DA output between the conditioned and nonconditioned rats during second reexposure to the apparatus.

In order to conclude definitively that DA is not involved critically in the expression of the conditioned response on the basis of the inability of the DA antagonists studies cited above, it must be assumed that the antagonists have achieved total blockade of DA function (an unlikely event considering the doses used). In the presence of partial blockade, the unbound receptors in the conditioned rats are still exposed to higher extracellular levels of DA than those in the control animals, thus providing a neuropharmacological basis for the behavioral differences seen between the groups.

It should also be noted that under some circumstances the conditioned effects of psychomotor stimulants can be antagonized by DA blockers. Drew and Glick (1987) were able to block the expression of amphetamine-conditioned rotational behavior in unlesioned rats with haloperidol, and they concluded that both the unconditioned as well as conditioned effects of amphetamine are mediated by DA. In a

DA ANTAGONISTS DO NOT PREVENT THE EXPRESSION OF COCAINE-INDUCED CONDITIONING

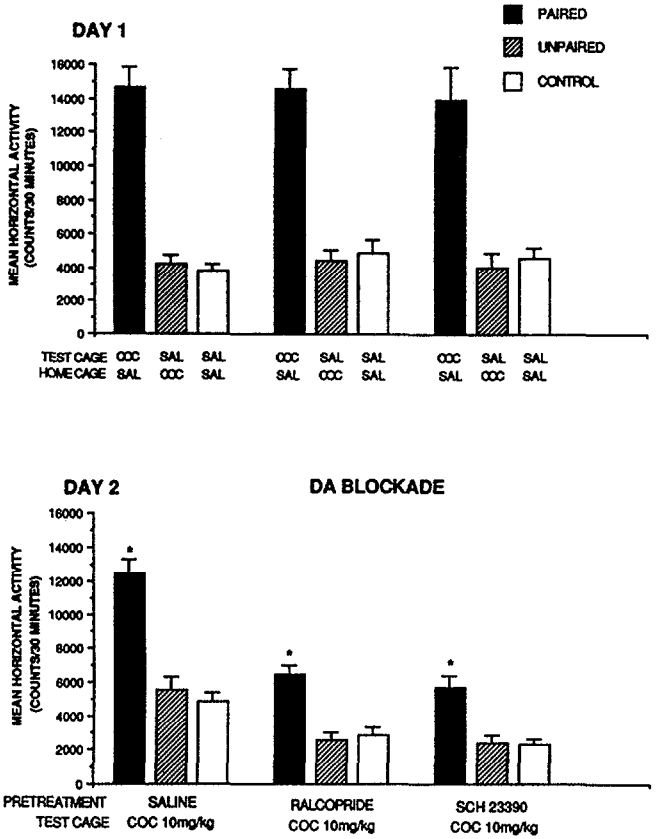

FIGURE 5. *The effects of D_1 and D_2 antagonists on cocaine-conditioned effects when administered prior to the 10 mg/kg cocaine challenge on day 2. (Top): Horizontal activity in PAIRED, UNPAIRED, and CONTROL rats on day I. (Bottom): The effects of raclopride and SCH 23390 on the conditioned effects of cocaine on day 2. * $p < 0.05$ for comparisons of the PAIRED group with its respective UNPAIRED control. Vertical lines indicate the S.E.M.*

SOURCE: Fontana et al. (1993*b*)

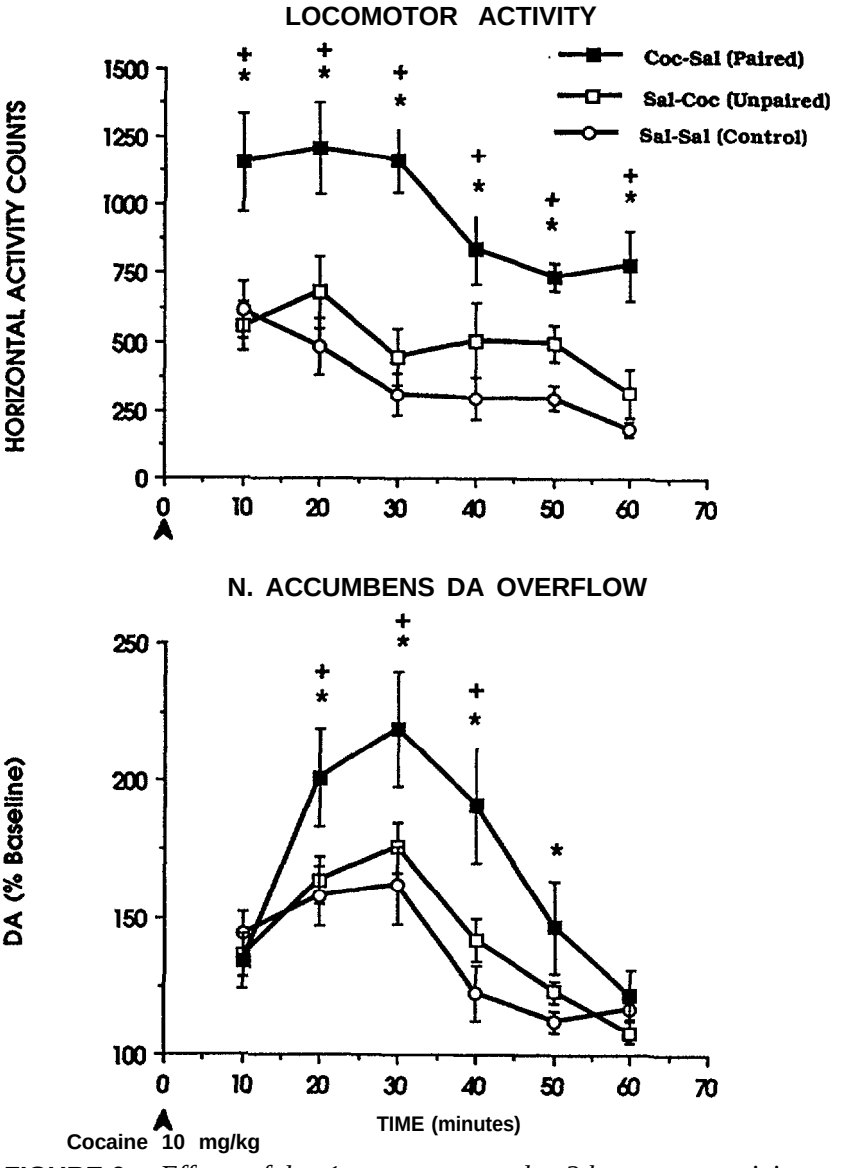

FIGURE 6. *Effects of day 1 treatments on day 2 locomotor activity and nucleus accumbens DA overflow when all groups were challenged with IO mg/kg of cocaine prior to placement in the locomotor chambers. For locomotor activity and DA overflow, * $p < 0.05$ for PAIRED versus UNPAIRED; + $p < 0.05$ for PAIRED versus CONTROL with the Scheffe test.*

SOURCE: Fontana et al. (1993*a*)

subsequent study, the same investigators (Drew and Glick 1990) reported that both the D_1 (SCH 23390) and the D_2 (metaclopramide) antagonists attenuated conditioned rotational behaviors established with amphetamine. Conditioned stereotypy established with apomorphine also has been reported to be antagonized with pimozide (Hiroi and White 1989), although similar behaviors conditioned with amphetamine were only partially blocked by the same antagonist. Poncelet and colleagues (1987) also have reported blockade of amphetamine-conditioned locomotor activity and stereotypy with sulpiride and haloperidol but not pimozide. Further support for a role of mesolimbic DA immediating conditioned behaviors comes from lesion studies. Gold and colleagues (1988) for example, found that DA-depleting 6-OHDA lesions of the nucleus accumbens made following amphetamine-induced conditioning of locomotor behavior were able to block the expression of the conditioned response. A similar ability of 6-OHDA nucleus accumbens lesions to prevent the expression of cocaine-induced conditioned behaviors has recently been found (A. Pert, unpublished observations) (figure 7).

Not all investigators agree, however, that stimuli associated with psychomotor stimulants enhance mesolimbic DA function. Brown and Fibiger (1992), for example, failed to find increases in extracellular DA in the nucleus accumbens following presentation of stimuli previously associated with cocaine, while Brown and colleagues (1992) did not observe increases in c-fos expression in the nucleus accumbens. In the latter study, significant increases in c-fos expression were, however, seen in the cingulate cortex, claustrum, lateral septal nucleus, paraventricular nucleus of the thalamus, lateral habenula, and amygdala, suggesting the participation of these regions (but not the nucleus accumbens) in the expression of cocaine-conditioned behaviors. The reasons for the disparity between the findings of Brown and Fibiger (1992) and those of Fontana et al. (1993*a*) and Kalivas and Duffy (1990) are not readily apparent but may rest with methodological issues (Fontana et al. 1993*a*).

The importance of understanding the precise neural substrates underlying the conditioned effects of cocaine and other drugs of abuse is readily apparent if these conditioned effects indeed reflect craving. The design of pharmacotherapeutics to alleviate craving would depend on which neurochemical system or systems participate in mediating the incentive-motivational properties of drugs of abuse. If mesoaccumbens DA is involved, DA blockers would be expected to aid in attenuating craving.

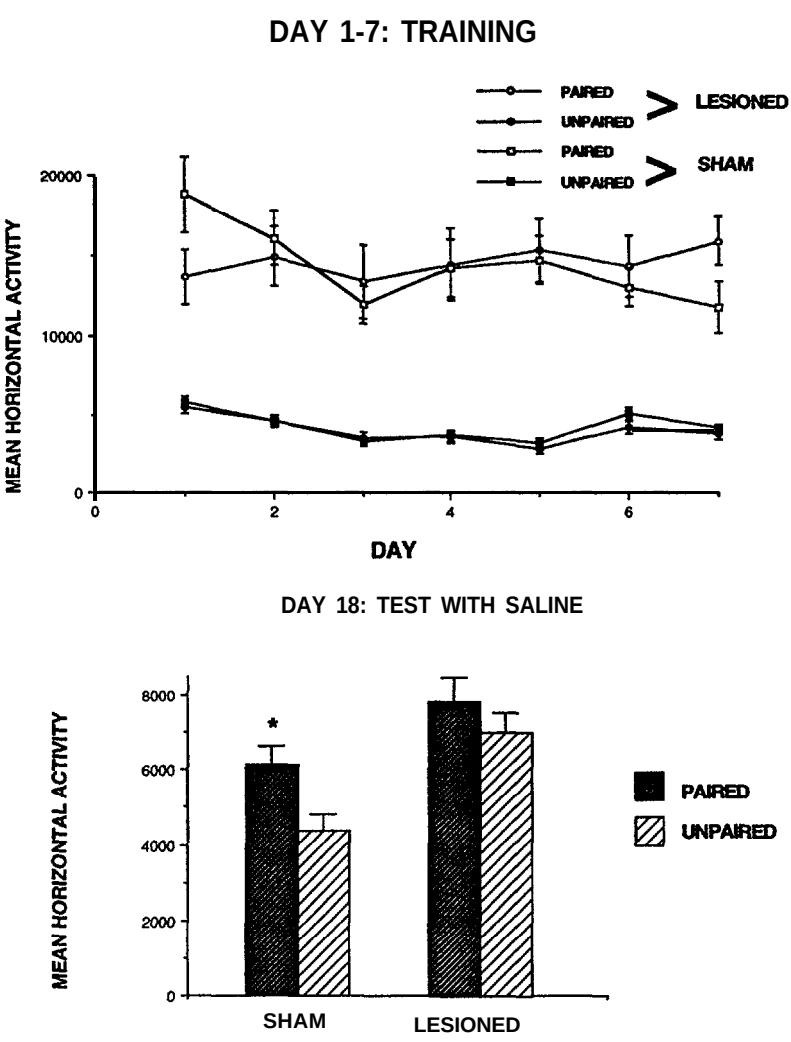

FIGURE 7. *Effects of 6-OHDA lesions of the nucleus accumbens on the expression of cocaine conditioned behaviors. (Top): PAIRED and UNPAIRED rats were trained for 7 days as described in text with 30 mg/kg of cocaine. On day 8, half of the rats in each group were lesioned in the nucleus accumbens with 6-OHDA. On day 15, all rats were tested in the activity chambers following injections of saline. (Bottom): Locomotor activity of all groups on day 15. * $p < 0.05$ for comparisons between PAIRED and UNPAIRED groups.*

If other systems are responsible, it will be necessary to define their coding so that appropriate pharmacotherapeutics can be designed more rationally.

If mesolimbic DA is involved in mediating the expression of cocaine-induced conditioning, it is not working in isolation. Sensory information from conditioned stimuli, for example, needs to gain access to mesoaccumbens DA neurons. Likewise, these neurons need to ultimately activate motor pathways either directly or indirectly. It may be possible to disrupt the expression of cocaine-induced conditioned increases in locomotor behavior by altering the functional activity at any link of this circuit.

As noted, sensory information from conditioned stimuli needs to gain access to mesoaccumbens DA neurons. Although neither the nucleus accumbens (DA terminals) nor the ventral tegmental area (DA perikarya) receive input from primary sensory cortical regions, DA activity in the system could be influenced indirectly through other structures such as the amygdala or frontal cortex. The amygdala, for example, receives polysensory information from cortical sensory association areas and projects in turn to the nucleus accumbens. Since corticofugal neurons are predominately glutamatergic in nature, it should be possible to disrupt both the acquisition and expression of cocaine-conditioned behaviors with excitatory amino acid (EAA) blockers. Figure 8 illustrates findings from a recent study in which pretreatment of rats with various doses of MK-801, a noncompetitive NMDA antagonist, on day 1 prevented the acquisition of cocaine-induced conditioned increases in locomotor activity when tested on day 2. Similar findings have been reported by Kalivas and Alesdatter (1993) using a somewhat analogous design. It would be especially important to determine the role of EAAs in the expression of the conditioned response.

If craving is established predominantly by learning, extinction should be the most effective strategy for attenuating this component of the addictive process. Extinction procedures have been utilized with some degree of success in clinical settings. O'Brien and his colleagues (Childress et al. 1987; O'Brien et al. 1988, 1992) gradually exposed cocaine addicts to drug-associated cues without allowing consumption. Interestingly, craving for cocaine was the most intense as well as the most frequently reported subjective response during the extinction sessions. It was found to decrease gradually in response to drug-related stimuli over the course

EFFECT OF MK-801 ON THE ACQUISITION OF COCAINE INDUCED CONDITIONING

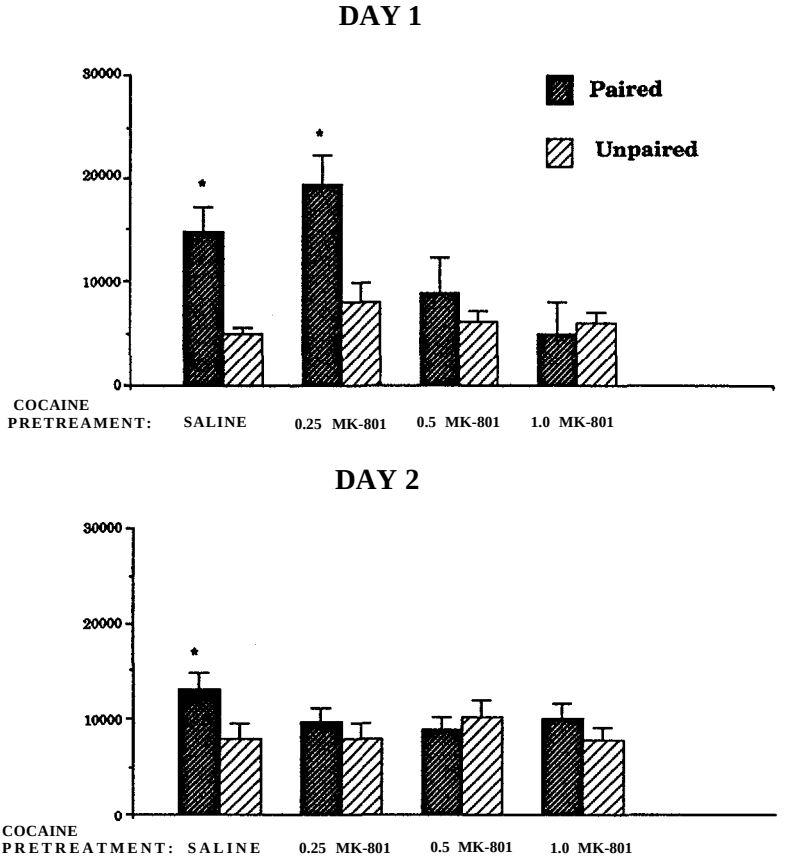

FIGURE 6. *Effects of MK-801 on the acquisition of cocaine-induced conditioning. (Top): PAIRED and UNPAIRED rats pretreated with either saline or various doses (.25, .5, or 1.0 mg/kg i.p.) of MK-801 prior to 40 mg/kg of cocaine. (Bottom): Locomotor activity in all groups after injections of 10 mg/kg of cocaine. MK-801 was not administered on the test day. * $p < 0.05$ for comparisons between PAIRED and UNPAIRED groups.*

of 15 extinction sessions. Alterations in skin temperature and galvanic skin response were also found to decrease over the extinction procedure.

Almost nothing is known regarding the neurobiological mechanisms underlying extinction. Figure 9 illustrates findings from a recent study in which the extinction of cocaine-conditioned increases in locomotor behavior in rats was examined. Three groups of rats (PAIRED, UNPAIRED, and CONTROL), previously described, were trained for 7 days. On days 8-14, animals in all three groups were injected with saline and placed in the locomotor activity chambers for 30 minutes as before. On day 15, all rats were injected with a low dose of cocaine (10 mg/kg) prior to placement in the activity monitors for 30 minutes. Relatively robust conditioning was observed on day 1, as evidenced by enhanced activity in the PAIRED group relative to the UNPAIRED and CONTROL groups. The conditioned response persisted for 4 days. On the seventh session, extinction was apparently complete since there appeared to be no differences in locomotor activity among the three groups. Surprisingly, however, administration of a low dose of cocaine on day 15 reinstated in full the conditioned response in the PAIRED group. These findings suggest that, while apparently extinguished, the incentive-motivational processes elicited by cocaine-associated cues can be fully reinstated with reexposure to the drug. Such reinstatement is very reminiscent of the *priming effect*, which refers to the ability of small priming doses of opiate agonists or cocaine needed to reinstate self-administration behavior in animals extinguished for this behavior (de Wit and Stewart 1981; Stewart and Wise 1992).

One interesting strategy for developing effective pharmacotherapeutics for treating drug addiction might be to screen for compounds that enhance the extinction of conditioned drug effects. At any rate, increasing understanding of the neural mechanisms underlying this process should provide a more rational basis for drug design.

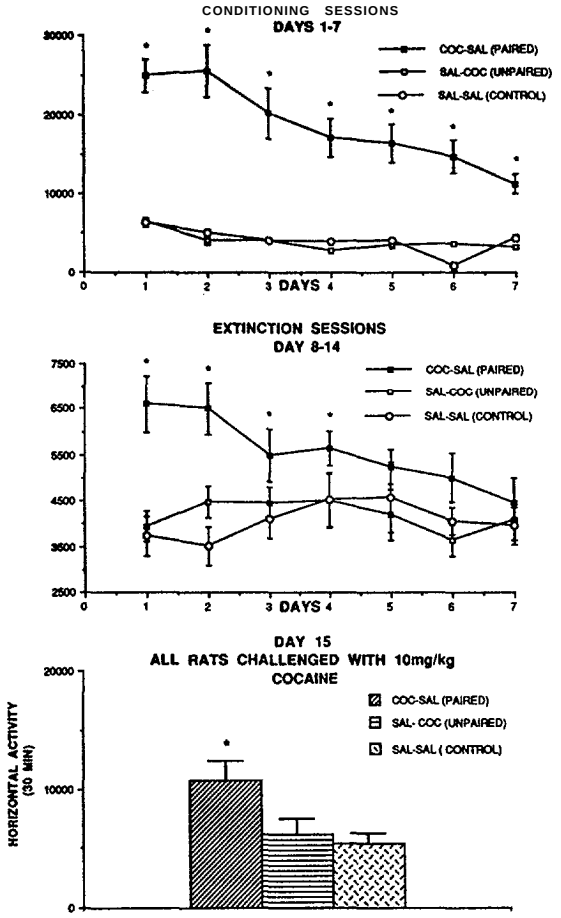

FIGURE 9. *Extinction of cocaine-conditioned behavior. (Top): Locomotor activity of PAIRED, UNPAIRED, and CONTROL groups during 7 consecutive days of training with 30 mg/kg of cocaine or saline. (Top): Performance of all these groups during extinction in which all animals were injected with saline prior to testing. (Middle): Performance of these groups on day 15, when all animals were tested in the activity chambers following injections of 10 mg/kg cocaine. (Bottom):* ***** i.p. < .05 for comparisons between PAIRED and UNPAIRED groups.

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Cocaine Reward and Cocaine Craving: The Role of Dopamine in Perspective

Roy A. Wise

INTRODUCTION

It is now well established that the habit-forming properties of cocaine derive primarily from its ability to block neurotransmitter reuptake-and thus enhance neurotransmitter action-in the mesocorticolimbic dopamine (DA) system (Koob and Bloom 1988; Wise 1978; Wise and Bozarth 1987; Wise and Rompré 1989). Cocaine also blocks noradrenaline and serotonin reuptake, but these actions and cocaine's well-known local anesthetic effects appear to contribute little, if anything, to the rewarding effects of cocaine. Because the nondopaminergic actions of cocaine do not appear to contribute to the drug's habit-forming properties, and because DA is known to play an important role in the rewarding effects of food, water, and direct electrical stimulation of the brain (Wise and Rompré 1989), attempts to find pharmacological treatments for cocaine abuse have focused largely on drug actions that influence dopaminergic function.

There has been particular interest in the potential of DA agonists as aids in the treatment of cocaine craving. The fact should not be overlooked, however, that other transmitter systems play important roles in cocaine reinforcement and may offer useful targets for pharmacological treatment regimens. This chapter offers a brief overview of the evidence implicating DA in the habit-forming effects of cocaine, an assessment of the potential of DA agonists in the treatment of cocaine craving, and a discussion of nondopaminergic circuitry that appears to interact with the mesolimbic DA system and may thus be capable of modulating or contributing to the habit-forming actions of cocaine.

THE ROLE OF DOPAMINE IN THE HABIT-FORMING ACTIONS OF COCAINE

It has long been known that cocaine and amphetamine are indirect monoaminergic agonists. Amphetamine causes impulse-independent (Carboni et al. 1989) release of norepinephrine, DA, and serotonin from brain stem cells that project widely to the diencephalon and telencephalon. Amphetamine also blocks the uptake mechanism that normally clears these transmitters from extracellular spaces (Heikkila et al. 1975). Cocaine does not cause monoamine release; indeed, since it decreases dopaminergic impulse flow (Henry et al. 1989), cocaine is an indirect inhibitor of DA release per se. However, cocaine blocks monoamine uptake mechanisms (Heikkila et al. 1975) and thus, like amphetamine, causes accumulation of monoamines near monoamine-containing nerve terminals (Carboni et al. 1989; Kalivas and Duffy 1990) and dendrites (Kalivas and Duffy 1988).

The first studies that confirmed an essential role for monoamines in the habit-forming actions of cocaine and amphetamine were studies in which the habit-forming actions of these drugs were blocked with monoamine antagonists. Like amphetamine and cocaine themselves, the early antagonists were not selective for specific monoamine receptor types. The first indication that the habit-forming properties of amphetamine and cocaine involved the catecholamines came from the fact that chlorpromazine increased self-administration of amphetamine and cocaine, suggesting a reduction in their rewarding effectiveness (Wilson and Schuster 1972). Since chlorpromazine blocks both noradrenergic and dopaminergic receptors, it was important to challenge amphetamine and cocaine self-administration with more selective antagonists in order to determine which catecholamine was involved.

It soon became clear that it was the dopaminergic, and not the noradrenergic, actions of cocaine and amphetamine that made them habit forming. Selective dopamine blockers, including pimozide (deWit and Wise 1977; Risner and Jones 1976; Yokel and Wise 1975, 1976); haloperidol (Davis and Smith 1975); butaclamol (Yokel and Wise 1976); alpha flupenthixol (Ettenberg et al. 1982); and SCH 23390 (Koob et al. 1987) attenuated the rewarding properties of amphetamine and cocaine (deWit and Wise 1977; Ettenberg et al. 1982; Risner and Jones 1980), while selective noradrenergic blockers like propranolol, phenoxybenzamine, and phentolamine did not (deWit and Wise 1977; Risner and Jones 1976; Yokel and Wise 1975, 1976). Moreover, rats were shown to

readily self-administer the selective DA agonists apomorphine (Baxter et al. 1974, 1976; Davis and Smith 1977; Wise et al. 1976; Woolverton et al. 1984; Yokel and Wise 1978); piribedil (Woolverton et al. 1984; Yokel and Wise 1978); and bromocriptine (Wise et al. 1990; Woolverton et al. 1984), whereas the selective noradrenergic agonists methoxamine (Risner and Jones 1976) and clonidine (Yokel and Wise 1978) were not self-administered, except at a narrow range of doses (Davis and Smith 1977; Woolverton et al. 1982) that were perhaps more relevant to autoreceptor inhibition of noradrenergic systems than to postsynaptic actions on their efferents.

Thus it was well established in the 1970s that one or more of the DA systems was the main substrate of cocaine's abuse liability; the same conclusion would be reached a decade and a half later on the grounds of correlational evidence (Ritz et al. 1987).

While good serotonergic agonists and antagonists had not yet been developed, early studies suggested that lesions and antagonism of the serotonergic projections to the forebrain increased rather than decreased the abuse liability of cocaine and amphetamine (Lyness and Moore 1983; Lyness et al. 1981). More convincing recent studies appear to confirm this initial impression (Loh and Roberts 1990). However, recently developed drugs that act on newly identified subtypes of serotonin receptor may prove to modulate the rewarding effectiveness of cocaine and amphetamine, possibly through serotonin-DA interactions.

The identification of habit-forming actions of cocaine with the mesolimbic and mesocortical subdivisions of the DA system derived from studies involving selective lesions, local injections of antagonists, and studies of direct intracranial drug self-administration. Selective damage to forebrain DA projections reduced or blocked the rewarding properties of cocaine (Roberts and Koob 1982; Roberts et al. 1977, 1980) and amphetamine (Lyness et al. 1979), while damage to noradrenergic systems had no effect (Roberts et al. 1977). These lesions do not discriminate the contributions of nucleus accumbens (NACC) and frontal cortex DA projections, as lesions of the former can damage axons projecting to the latter. However, microinjections of DA antagonists (Phillips et al. 1983) and excitotoxin lesions to the NACC (Zito et al. 1985), each of which spares the mesocortical DA projections, also reduce the rewarding effects of cocaine. These data point clearly to a major role for the NACC in cocaine reinforcement.

In addition, rats have been trained to lever press for injections of amphetamine (Hoebel et al. 1983) and DA (Guerin et al. 1984), but not cocaine (Goeders and Smith 1983), directly into the NACC. Amphetamine injections into the NACC are rewarding, as reflected in the conditioned place preference paradigm (Carr and White 1983, 1986). Thus a role in psychomotor stimulant reinforcement seems clearly established for the NACC.

A role for frontal cortex in the rewarding action of cocaine has also been suggested. Goeders and Smith (1983, 1986) and Goeders and colleagues (1986) were successful in training rats to self-administer cocaine into the frontal cortex but unsuccessful in training them to self-administer cocaine into the NACC. This finding is troublesome because these same researchers have reported that DA itself is rewarding when injected into the NACC (Guerin et al. 1984). It is clear that cocaine binds to DA uptake carriers in the NACC (Boja and Kuhar 1989) and causes elevation of NACC DA (Di Chiara and Imperato 1988); cocaine has such actions even when given by local injection into the NACC proper (Hernandez et al. 1991; Nomikos et al. 1990). Moreover, lesions of frontal cortex do not have a significant influence on intravenous cocaine self-administration (Martin-Iverson et al. 1986). While frontal cortex lesions do seem to alter acquisition of cocaine self-administration habits (Schenk et al. 1991), this may well be explained by effects of frontal cortex DA manipulations on NACC DA turnover (Louilot et al. 1989). Thus, the role of frontal cortex actions in cocaine reward remains unclear on present evidence.

DA AGONISTS IN TREATMENT OF CRAVING

Two pharmacotherapies for opiate addiction have each had some degree of success; they involve the opiate methadone and the noradrenergic agonist clonidine. Each is used in an attempt to reduce drug craving by reducing drug withdrawal symptoms. Methadone maintenance therapy (Dole and Nyswander 1965, 1967) is based on the fact that methadone produces less euphoria than heroin, as well as on the belief that, while it produces physiological dependence in its own right, the cravings associated with methadone withdrawal symptoms are weaker than those associated with heroin. The fact that methadone penetrates the brain more slowly and is more slowly metabolized appears to make methadone a less compulsively self-administered drug than heroin. The fact that it is less compulsively self-administered and the fact that it reduces heroin

craving (essentially by partially satisfying it) makes methadone maintenance among the more successful approaches to the management of heroin addiction.

Clonidine also alleviates opiate withdrawal symptoms (Gold and Kleber 1981; Gold et al. 1978); in addition, it is reported to reduce nicotine and ethanol cravings (Glassman et al. 1984; Walinder et al. 1981). Clonidine is a noradrenergic agonist and is thought to alleviate opiate and other withdrawal symptoms (Gold and Kleber 1981; Gold et al. 1978) by inhibiting the noradrenergic cells of locus coeruleus (Aghajanian 1978)-the primary source of noradrenergic innervation of the forebrain. Opiates also inhibit the cells of the locus coeruleus; opiate withdrawal symptoms include hyperactivity of the locus coeruleus, which is a rebound after effect of chronic inhibition by dependence-producing regimens of opiate administration (Aghajanian 1978).

The possibility that DA agonists might be used to treat cocaine craving (Dackis and Gold 1985*a*, 1985*b*) was suggested on the basis of the evidence that a DA system, rather than a noradrenaline system, plays a role in cocaine self-administration. The first suggestion came from Gold, who had participated (Gold et al. 1978) in the development of clonidine for the treatment of opiate addiction, and the hypothesis seemed to have been based on an attempt to find a clonidine-like drug that would work in the DA system.

Cocaine inhibits the firing of dopaminergic neurons (Henry et al. 1989), though not in quite the same way that morphine inhibits the firing of noradrenergic cells. Moreover, the primary parallel ends there. There is no evidence that hyperactivity of the DA system is a consequence of cocaine withdrawal. Indeed, DA has been suggested to be depleted during cocaine withdrawal and craving (Dackis and Gold 1985*b*), and recent microdialysis studies indicate that hypoactivity of the DA system is a correlate of cocaine withdrawal (Imperato et al. 1992; Parsons et al. 1991; Robertson et al. 1991; Rossetti et al. 1991). Moreover, direct DA agonists are self-administered by laboratory animals (Baxter et al. 1974, 1976; Davis and Smith 1977; Wise et al. 1976, 1990; Woolverton et al. 1984; Yokel and Wise 1978). Clonidine is self-administered only at low doses that appear to be preferential for autoreceptor inhibition of noradrenergic function (Davis and Smith 1977; Risner and Jones 1976; Yokel and Wise 1978). Thus, while DA agonists have been suggested to alleviate cocaine craving, they do so in a way that differs significantly

from the alleviation of heroin craving by the noradrenergic agonist clonidine.

The DA agonists alleviate cocaine craving for a reason more analogous to the reason that heroin craving is alleviated by methadone; these drugs stimulate the same brain mechanism that is stimulated by the abused drug itself. Thus DA agonists like methadone (but unlike clonidine) may have abuse potential of their own. Indeed, bromocriptine, an agonist that has been used in attempts to treat human cocaine users, is not only self-administered by laboratory animals (Wise et al. 1990; Woolverton et al. 1982, 1984); it also precipitates relapse to extinguished habits that were trained under either cocaine or heroin (Wise et al. 1990). This relapse would appear to be due to similarity between the stimulus properties of bromocriptine and cocaine; bromocriptine causes rats to behave as if they have been given a taste of cocaine.

However, while bromocriptine apparently reduces cocaine craving temporarily by satisfying it, and while bromocriptine is self-administered by lower animals, it appears on present evidence to have little abuse liability in humans. The most likely reason is that DA agonists have aversive properties in the brain stem of higher primates. Indeed, apomorphine is used in aversion therapy in humans, despite the fact that it is readily self-administered by rodents. The aversive side effects of bromocriptine and apomorphine appear to keep these drugs from being used compulsively or even recreationally by humans. Nonetheless, recent clinical trials have been disappointing; bromocriptine has not been shown to be effective in permanently eliminating cocaine self-administration habits (Teller and Devenyi 1988).

NONDOPAMINERGIC CONTRIBUTIONS TO REWARD CIRCUITRY

The first indication that the rewarding effects of amphetamine (Davis and Smith 1975; Yokel and Wise 1975) and cocaine (deWit and Wise 1977) depend on a dopaminergic substrate emerged along with evidence that the rewarding effects of hypothalamic brain stimulation also depend on a dopaminergic substrate (Fouriezos and Wise 1976; Fouriezos et al. 1978). The same neuroleptics that block the rewarding effects of amphetamine and cocaine also block the rewarding effects of hypothalamic stimulation (Gallistel and Davis 1983). This finding and the fact that reward sites in the ventral tegmental area (VTA) have the same anatomical dispersion as

the DA cells themselves (Corbett and Wise 1980; Wise 1981) suggests that the first-stage reward neurons of the medial forebrain bundle (MFB) were the DA-containing neurons themselves.

Several findings now rule out the possibility that direct depolarization of dopaminergic fibers by the stimulating current itself plays a major role in the rewarding effects of hypothalamic stimulation-at least when traditional stimulation parameters are used. The dopaminergic fibers are small and unmyelinated, and their thresholds appear to be too high for them to be significantly activated in traditional brain stimulation reward (BSR) experiments. Rather, parametric studies involving paired pulse stimulation implicate fast myelinated fibers (Gallistel et al. 1981; Wise and Rompré 1989) that may, in turn, synapse on the DA cells (Wise 1980) or on their afferents. To date, neither the origin nor the transmitter of the descending reward neurons is known; however, once the descending component of the BSR circuitry is identified, it is likely to offer a nondopaminergic candidate for pharmacological modulation of basal DA activity. Since cocaine is a DA uptake inhibitor, its ability to increase synaptic DA concentrations depends on DA release; thus, drugs that affect dopaminergic impulse flow may well have significant impact on the rewarding effects of cocaine. For this reason, the identification of the descending MFB reward neurons is of potential significance for the development of addiction treatment.

The activity of the dopaminergic cells of the VTA is modulated by a number of neurotransmitters at the level of the cell bodies. Opiate actions in the VTA are strongly habit forming (Bozarth and Wise 1981; Phillips and LePiane 1980; van Ree and de Wied 1980; Welzl et al. 1989). Fibers containing enkephalin and dynorphin each project to this area; indeed, while it is not clear that they are functional, enkephalin-containing axons appear to make direct synaptic contact with dopaminergic dendrites (Sesack and Pickel 1992). Dopaminergic cell bodies do not appear to have opiate receptors (Johnson and North 1992; Lacey et al. 1989), although the possibility should perhaps not be ruled out that such receptors could be localized too distal on the dopaminergic dendrites to respond to iontophoretically administered opiates.

Dopaminergic cells do appear to have gamma aminobutyric acid (GABA) receptors (Lacey et al. 1988), and the firing of dopaminergic cells is inversely related to the firing of local GABAergic neurons. The GABAergic cells have mu opiate receptors, and it appears that the local action of opiates on dopaminergic cell firing involves disinhibition of

dopaminergic cells due to inhibition of GABAergic interneurons (Johnson and North 1992); mu opioids are self-administered into the VTA (Devine and Wise 1990).

Ventral tegmental DA neurons may also receive an excitatory cholinergic input (Lacey et al. 1990) relevant to reward function. Cholinergic blockade eliminates the contribution of the fastest of the MFB reward fibers (Gratton and Wise 1985), and cholinergic antagonists injected directly into the VTA attenuate the rewarding effects of MFB stimulation (Yeomans et al. 1985). In addition, it should be noted that the VTA appears to receive noradrenergic input from the locus coeruleus (Simon et al. 1979) and serotonergic input from the raphe nuclei (Moore et al. 1978; Parent et al. 1981). Since each of these inputs should be influenced by cocaine, each provides a potential modulation of dopaminergic reward signals.

There are several neurotransmitter systems not yet theoretically linked to reward function but nonetheless capable of interacting with the mesolimbic DA system. Cholecystokinin is colocahzed and released by dopaminergic neurons and is known to be capable of modulating dopaminergic function (Phillips et al. 1989). Neurotensin (Kalivas et al. 1983) and substance P (Elliot et al. 1986) are released from nerve terminals in the VTA, and each can modulate DA cell firing.

Finally, drugs could modulate the reward system at some stage efferent to the dopaminergic link in that system. The mesolimbic DA system appears to synapse on GABAergic cells and perhaps cholinergic cells in the NACC, and the GABAergic cells project-through a GABAergic cascade involving synapses in the pallidum, substantia nigra, and superior colliculus-to the pedunculo-pontine nucleus in the mesencephalic locomotor region. This nucleus appears to have reward-relevant functions and may be part of a common final path of reward signals from the forebrain (Bechara and van der Kooy 1992).

CONCLUSION

The afferents to and efferents from the mesolimbic DA system offer multiple targets for pharmacological interventions designed to reduce cocaine reinforcement or craving. Basic studies of the synaptic links in reward circuitry (Phillips 1984; Wise and Bozarth 1984) would appear to

offer the most direct and immediate way to identify additional candidates for pharmacological treatment approaches.

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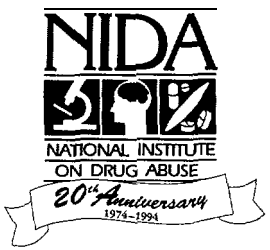

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