The Neurotoxic Effects of Continuous Cocaine and Amphetamine in Habenula: Implications for the Substrates of Psychosis

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INTRODUCTION: THE STIMULANT PSYCHOSES

The experiments described in this chapter have grown out of attempts to develop animal models of psychosis, especially schizophrenia. Because of the difficulties inherent in identifying and quantifying hallucinatory episodes in nonhumans, it is necessary to develop third-order models of psychoses when using animals. Thus, there are endogeneous psychotic states in humans such as occur in schizophrenia and other dementias, there are certain drug-induced states in humans that can be indistinguish-able in many aspects from endogeneous psychoses, and finally there are attempts to replicate similar drug-induced states in animals and thereby clarify the altered neural mechanisms that underlie these abnormal states.

It could be argued that studies attempting to develop heuristic animal models of psychoses by chronically administering those drugs known to induce schizophrenia-like symptoms in humans are inevitably flawed because the symptomatology produced does not mimic schizophrenia in all aspects. But, although these models have limitations, they have proved valuable both in clinical and research settings. Animal models have proved sufficiently reliable that modern psychiatric admission procedures now typically withhold neuroleptic medications for several days in new cases of psychosis to determine whether the psychosis clears rapidly (in which case it was drug-induced) or not (in which case it is treated as an endogenous psychosis). Presently, these drug models in humans are the best available models of schizophrenia, and consequently the derived animal models should be invaluable research tools.

It is generally recognized that there are two principal drug models of psychosis in humans: the stimulant-induced psychoses and

phencyclidine (PCP)-induced psychosis (table 1). The stimulant psychoses are observed following chronic amphetamine or cocaine abuse. The authors have previously reviewed (Ellison and Eison 1983; Ellison 1991) the extensive literature indicating the emergence of a paranoid-like psychosis in chronic amphetamine and cocaine addicts, the chief symptoms of which are motor stereotypies, paranoid delusions, sensory hallucinations (including parasitosis, or the delusion of bugs or snakes on the skin), and a loose-ning of associations. This literature on amphetamine abuse has been reviewed by Connell (1958), Bell (1965), and Ellinwood (1967), and on cocaine abuse by Siegal (1977), Lesko and colleagues (1982), Gawin (1986), and Manschreck and colleagues (1988). A particularly interesting feature of stimulant psychosis is the pronounced parasitosis (Brady et al. 1991; Elpern 1988; Mitchell and Vierkant 1991). The parasitotic groom-ing that develops in animals given stimulants is discussed below.

TABLE 1. Two drug models of psychosis.

Stimulant psychoses
Produced by chronic amphetamine or cocaine abuse
Well documented in addicts who develop speed runs
Chief symptoms are stereotypies, paranoid delusions, parasitosis and other sensory hallucinations, and loosening of associations.
Evidence of persisting alterations in nervous system (Reactivation)
Phencyclidine and ketamine psychosis
Produced by NMDA antagonists (phencyclidine, ketamine)
Bingeing intake pattern develops in addicts
Chief symptoms are flat affect, depersonalization, body image distortion, amnesia, catatonia, and thought disturbances
Evidence of persisting memory deficits

To induce a model of stimulant psychosis in animals it is of paramount importance not only to give the proper drugs but also to do so in the proper drug regimen. The development of speed runs appears to be a key factor for the induction of stimulant psychoses. It

was recognized long ago (Connell 1958) that most amphetamine addicts eventually come to self-administer amphetamine every few hours for up to 5 days and that, towards the end of these binges, they reliably develop paranoid delusions and hallucinations (Kramer et al. 1967). There is a similarly extensive literature from cocaine addict populations of speed runs leading to para-noia. Furthermore, virtually every controlled study eliciting an overt amphetamine psychosis in humans has involved continuous, low-dose administration of the drug every hour for days (Griffith et al. 1972; Angrist et al. 1974); the explanation for the one apparent exception (Bell 1973) is discussed by Ellison (1994). Similarly, Satel and colleagues (1992) found that every one of their subjects who had experienced cocaine-induced paranoia did so while on a binge ranging from 6 hours to5-days in duration.

In an effort to mimic speed runs in animals, the authors developed a slow-release silicone pellet containing amphetamine base (in 300 gram (g) rats this pellet releases 20 milligrams (mg) over a 5-day period). Rats and nonhuman primates implanted with this pellet showed stages of behavioral alterations that were similar in sequence to those reported in the controlled studies in humans, although the precise behaviors elicited were much more complex in the higher organisms. In rats, continuous amphetamine administration initially resulted in a period during which sensitization to amphetamine-elicited motor stereotypies developed (Ellison and Morris 1981), followed by a late stage (3 to 5 days after pellet implantation) when the motor stereotypies decreased and certain distinctive late-stage behaviors emerged (e.g., limb-flicks, wet-dog shakes, spontaneous startle responses, and abnormal social behaviors) (Ellison et al. 1978b). A similar progression, but with even more distinctive and varied late-stage behaviors, occurs in monkeys (Ellison et al. 1981; Ellison and Eison 1983). Many of these behaviors have been called hallucinogen-like because they are normally induced by hallucin-ogens, whereas they are suppressed by acute injections of amphetamine. Another distinctive late-stage behavior is excited parasitotic grooming episodes. In monkeys this is expressed as rapid, slapping hand move-ments directed at the skin surface and moving from limb to limb (Ellison et al. 1981); in rats this is expressed as a change from the normal body washing and grooming behavior to a body-biting sequence similar to that of a dog afflicted with fleas (Nielsen et al. 1980b). There are close similarities between the amphetamine- and cocaine-induced parasitotic effects in humans and those found in animal studies (De Leon et al. 1992).

NEUROTOXIC EFFECTS IN CAUDATE OF CONTINUOUS AMPHETAMINE ADMINISTRATION

Late-stage behaviors induced by continuous amphetamine administration have a number of distinct neurochemical correlates in brain. Amphetamine continuously administered for 5 days induces alterations, including down-regulation of dopamine (DA) type 2 (D2) receptors in striatum (Nielsen et al. 1980a) and a progressive shift of heightened glucose metabolism away from striatal and towards mesolimbic structures (Ellison and Eison 1983). But one of the most striking effects of continuously administered amphet-amine is its well-documented neurotoxic effects on DA terminals in caudate. Studies of catecholamine fluorescence in animals administered continuous amphetamine (Ellison et al. 1978b; Nwanze and Jonsson 1981; Ryan et al. 1990) reveal the appearance of swollen, distinct axons with multiple enlarged varicosities and stump-like endings; similar observations were made using silver stains on degenerating axons (Ryan et al. 1988). These abnormalities did not occur if the same amount of amphetamine was given in daily injections. The unique capability of continuous ampheta-mine administration to induce degeneration of DA terminals in the caudate nucleus has been validated using a variety of techniques. The ampheta-mine can be delivered by slow-release silicone pellets, minipumps, very frequent injections, or by substantial and frequent doses of methampheta-mine, which has a slower rate of clearance and is considerably more potent at releasing DA (Hotchkiss and Gibb 1980; Ricaurte et al. 1980; Steranka and Sanders-Bush 1980). Furthermore, Fuller and Hemrick-Luecke (1980) found that an amphetamine injection administered in combination with drugs that slow its metabolism becomes neurotoxic to caudate DA termi-nals. The amphetamine- or methamphetamine-induced damage to DA endings can be prevented by pretreatment or concurrent administration of drugs such as a tyrosine hydroxylase inhibitor (Wagner et al. 1983), DA uptake inhibitor (Fuller and Hemrick-Leucke 1982; Hanson et al. 1987), and noncompetitive antagonists of N-methyl-D-aspartate (NMDA) (Sonsalla et al. 1989; Fuller et al. 1992). Studies of methamphetamine-induced neurotoxicity (reviewed by Seiden and Ricaurte 1987) typically employ doses that are comparatively higher than those using d-ampheta-mine; these doses also induce damage to serotonin cells, are lethal to some of the animals, and induce widespread neuronal degeneration in a variety of other structures (Ellison and Switzer 1994).

One of the most interesting aspects of this neurotoxic effect is that it is only induced by continuous amphetamine administration. If exactly the same amount of amphetamine (20 mg over 5 days, or about 12-mg/kg/day) is given in daily injections once a day over 5 days, no neurotoxicity is observed. This was initially a rather surprising finding, for the peak brain levels achieved after such large single injections are enormously greater than brain levels found when the drug is administered continuously. However, it now appears that, for a number of pharmacological agents, prolonged plasma levels are more crucial in producing neurotoxicity than higher but more transient plasma levels. Apparently neuronal systems have developed more effective ways to cope with sudden and brief insults than with progressive, more prolonged ones.

NEUROTOXIC EFFECTS IN FASCICULUS RETROFLEXUS OF CONTINUOUS STIMULANT ADMINISTRATION

The authors recently attempted to determine if the findings with amphetamine administration (discussed above) could be generalized to cocaine psychosis. Like amphetamine, cocaine also potentiates DA at the receptor, is a sympathomimetic, and leads to speed runs in chronic addicts who, in some cases, develop a paranoid psychosis similar in many aspects to that induced by amphetamine. The question for the DA model of psychosis that grew out of the amphetamine literature was whether continuous cocaine administration would also have a neurotoxic effect on DA terminals in caudate (i.e., if this was an anatomical correlate of the paranoia). Since continuous cocaine cannot be reliably administered via osmotic minipumps due to local vasoconstrictive and necrosis-inducing properties, an alternative drug delivery system was needed.

Consequently, the authors developed (Lipton et al. 1991) a silicone pellet with a release rate of 103 mg cocaine base over 5 days. Administration induced behavioral stages similar to those caused by continuous amphet-amine (initial hyperactivity, the evolution of stereotypies, a crash stage, and finally late-stage behaviors including limb flicks, wet-dog shakes, and parasitotoic grooming episodes) (Lipton et al. 1991). The authors then looked for persisting alterations in DA receptors produced by continuous cocaine administration as would be expected following DA terminal damage in striatum. No such changes were found at 14 days following continous cocaine administration, although a parallel group that had received continuous amphetamine showed large changes in striatal D1 and D2 receptors (Zeigler et al. 1991). However, the rats that had received

continuous cocaine did show persisting alterations in acetyl-choline (ACh) and gamma-aminobutyric acid (GABA) receptors in caudate, perhaps indicating that continuous cocaine had produced a somewhat different kind of neurotoxicity in caudate and possibly postsynaptic to DA receptors. At this point, the authors began collab-orative studies using silver stain to assess neural degeneration (Switzer 1991; de Olmos et al. 1981). These studies have proved to be very fruitful. By using minimally toxic doses and then searching for selective degeneration in brain, one can search for the weak links in neuronal circuitry induced by continuous stimulant administration. Those path-ways overdriven by incessant drug-induced activity may eventually degenerate, leaving the brain in a persistently altered state.

In the silver-stain studies, rats were given continuous amphetamine, continuous cocaine, or no drugs for 5 days, and then their brains were removed and examined for degeneration at various times following cessation of drug administration. The entire brain from the olfactory nucleus to the mesencephalon was screened. The animals administered continuous amphetamine were found to evidence quite substantial degeneration in caudate, but there was essentially no degeneration observed in caudate in the cocaine-administered animals. However, a very distinctive pattern of extensive degeneration after either continuous amphetamine or cocaine administration was observed in a totally unexpected brain region: the lateral habenula (LHb) and fasciculus retroflexus (FR) (Ellison 1992). Many of these long degenerating axons, when observed several days following pellet removal, showed classical anatomical signs of disintegration (e.g., axons beginning to fragment, the appearance of corkscrew or stump-like endings). These degenerating axons were almost exclusively in the mantle (as opposed to the core) of FR. Figure 1 shows this dramatic degeneration in a saggital section of FR after 5 days of continuous cocaine administration.

These results, coupled with the existing literature, have implications for models of stimulant-produced psychosis and paranoia. It is clear that amphetamine and cocaine are similar in that they are both strong stimulants with potent actions in potentiating DA, and both lead to a pattern of repeated drug intake by addicts over prolonged periods. With both drugs, these runs or binges produce a progressive dysphoria and paranoia followed by a rebound depression upon drug discontinuation. Furthermore, when given continuously to animals, both drugs eventually induce comparable late-stage behaviors. However, these two drugs are markedly different in their persisting effects in caudate. Continuous amphetamine has neurotoxic effects on DA terminals and DA receptors in caudate; continuous cocaine does not. Continuous cocaine produces

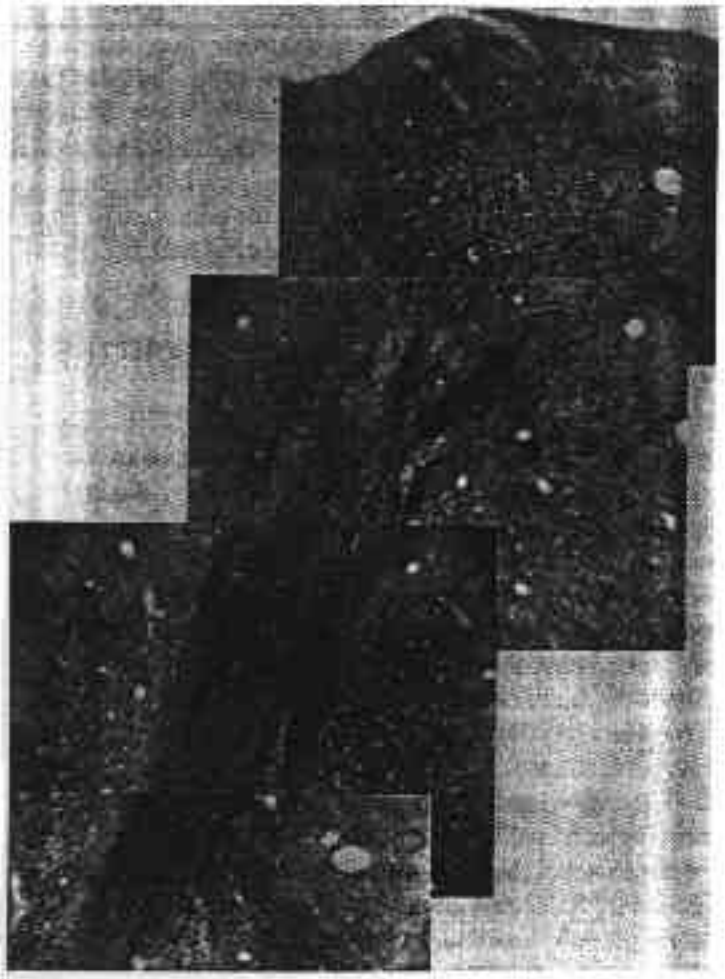

FIGURE 1. *Photomontage showing degeneration in habenula and fasciculus retroflexus following 5 days of continuous cocaine. At the top of the figure is lateral habenula; the more ventral three sections follow fasciculus retroflexus. Because fasciculus retroflexus moves laterally slightly as it projects more ventrally, the bottom two sections are from a section slightly more lateral than the top two. Multiple long darkly stained axons and swollen varicosities can be traced throughout fasciculus retroflexus.*

persisting alterations in GABA and ACh receptors whereas continuous amphetamine does not. However, the two drugs are quite similar in their ability to induce degeneration of axons in LHb extending ventrally into FR. A logical conclusion would be that the neurotoxic alterations in LHb and FR play a critical role in mediating the paranoid psychosis that follows the continuous use of these stimulants and the persistently altered paranoid reactions to the drug that develop in chronic addicts.

THE HABENULA, FASCICULUS RETROFLEXUS, AND THE ANATOMY OF PARANOIA

The recent findings described above suggest a need to reevaluate the role of the LHb and FR in the mediation of DA-related circuitry. Figure 2 illustrates the principal connections of the habenula as described in the classical anatomical studies by Herkenham and Nauta (1977, 1979) and others. The inputs consist predominantly of pathways traveling in stria medullaris terminating in either the medial or lateral habenular nuclei, with two subdivisions: medial septal-limbic and lateral pallidal-limbic. The principal input for medial habenula is cholinergic fibers arising from the septal area (nearly every septal cell projects to the medial habenula), but there are also projections from nucleus accumbens and the diagonal band of Broca. The major input to LHb are GABA fibers from the medial (or internal) globus pallidus (in primates) or its homolog in rat, the entopeduncular nucleus, but there are also inputs from limbic forebrain, including the lateral hypothalamus, diagonal band of Broca, substantia innominata, lateral preoptic area, nucleus accumbens, frontal cortex, and the suprachiasmatic nucleus. Both nuclei also receive less extensive ascending afferents from the central grey and medial raphe, and the LHb receives dopaminergic inputs from the substantia nigra (SN) and ventral tegmental area (VTA).

The principal efferent fibers from the medial habenula, including cholinergic, glutaminergic, and substance P fibers, travel in the core of FR to the interpeduncular nucleus, VTA, raphe nuclei, and SN. The LHb has more varied outputs, with axons travelling principally in the periphery or mantle region of the FR sending projections to several thalamic (mediodorsal and ventromedial) and hypothalamic (lateral, septal, and preoptic) nuclei. But the principal efferents from LHb are to midbrain nuclei such as the dorsal and medial raphe nuclei (constituting one of the major inputs to raphe), to the VTA and SN pars compacta, and also to central grey.

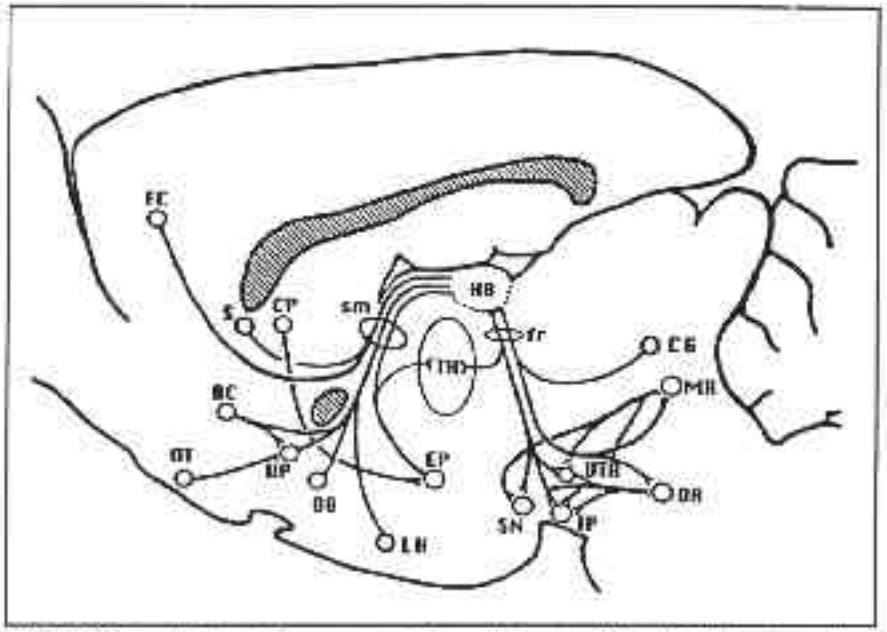

FIGURE 2. *Schematic representation of some of the chief inputs and outputs of the habenular complex. Major descending pathways as shown entering sm, passing through or synapsing in habenula, and descending in fr to a variety of mesencephalic structures. Collaterals from EP and HB to thalamus are also shown.*

KEY: FC = frontal cortex; OT = olfactory tubercle; AC = nucleus accumbens; CP = caudate-putamen; DB = nucleus of the diagonal band; VP = ventral pallidum; sm = stria medullaris thalami; EP = entopeduncular nucleus; fr = fasciculus retroflexus; TH = thalamic nuclei, including dorsalmedial, ventral anterior, and ventral lateral; HB = habenula; SN = substantia nigra; VTA = ventral tegmental area; IP = interpeduncular nucleus; MR = medial raphe nucleus; DR = dorsal raphe nucleus.

Sutherland (1982) described some of the functional roles of what was termed the "dorsal diencephalic conduction system." It has anatomical and functional connections to modulate important functions such as sensory gating through the thalamus, pain gating through the central grey and raphe, and mediation of motor stereotypies and reward mechanisms through the SN and VTA. Lesions of habenula produce a wide variety of behavioral alterations, including alterations in self-stimulation, pain inhibition, avoidance learning, and sexual and maternal behaviors (Ellison 1994).

Studies of glucose utilization have consistently shown the habenula to be highly sensitive to DA agonists and antagonists; in fact, it is the most sensitive region in brain to agonists such as cocaine (London et al. 1986). The dorsal diencephalic system has major and predominantly inhibitory connections onto DA-containing cells. The descending control of mono-amine and other mesencephalic cells carried in FR appears to consist largely of inhibitory influences. Sasaki and colleagues (1990) found that they could markedly attenuate methamphetamine-induced inhibition of SN cells by making lesions of the habenula, of the entopeduncular nucleus, or transections of the stria medullaris. These studies support an important role of the dorsal diencephalic conduction system in inhibiting DA cell bodies and in mediating part of the negative feedback from limbic and striatal DA receptors onto DA cell bodies. These are ideal connections for the media-tion of psychosis on both anatomical and functional grounds. The descen-ding influences from DA-rich and limbic structures are quite unique in brain in that striatal and limbic inputs directly converge. In addition, this circuitry apparently mediates a major part of the descending control over serotonin cells of the raphe complex (in fact, they represent the chief input in all of brain to raphe). An implication of this circuitry is that due to the amphetamine- or cocaine-induced degeneration of the FR fibers, the higher brain areas might no longer be able to regulate dopaminergic and seroto-ninergic cell firing.

DO THE FIBERS IN FR THAT DEGENERATE AFTER COCAINE BINGES CARRY NEGATIVE FEEDBACK FROM DA-RICH-REGIONS ONTO DA CELL BODIES?

There is additional evidence that the LHb and FR mediate part of the negative feedback from DA-rich regions onto DA cell bodies. Lesions of either stria medullaris, LHb, or FR increase DA turnover in prefrontal cortex, nucleus accumbens, and striatum (Lisoprawski et al. 1980; Nishikawa et al. 1986), and electrical stimulation of the habenula inhibits DA-containing cells in SN and VTA (Christoph et al. 1986).

Several recent observations from this laboratory clarify some of the long-lasting effects of continuous cocaine administration and also provide indirect evidence consistent with the hypothesis that the degenerating axons carry part of the DA-mediated negative feedback. The authors have found that there are long-lasting sequelae of 5 days

of continuous treatment with the cocaine pellet which suggest correlates of the neuro-toxicity observed in brain. Cocaine pellet pretreated rats, when tested several weeks following pellet explant, act frightened in open-field tests. At the beginnning of the test they initially "freeze," remaining immobile for prolonged periods (Zeigler et al. 1991), and when tested over pro-longed periods in novel environments they remain hyperactive far longer than the controls (figure3). These observations suggest a lack of habitu-ation to novel sensory stimulation in these animals. It has also been reported that FR lesions in rats lead to decreased spontaneous alternation (Corodimas et al. 1992). The authors have begun to examine if cocaine pellet pretreated rats evidence persisting effects in spontaneous alteration, and figure 4 shows results that suggest long-lasting deficits. All of these observations are highly consistent with increased DA turnover after lesions of LHb.

Using microdialysis techniques, the authors recently attempted to test the hypothesis that the axons which degenerate in FR and LHb following continuous cocaine mediate part of the negative feedback from DA receptors onto DA cell bodies (Keys and Ellison 1994). Rats were pre-treated with either cocaine or control pellets for 5 days, and then 14days later, microdialysis probes were lowered into the caudate nucleus. Baseline DA and GABA levels were not significantly different in the two groups. However, when the animals were perfused locally with the D1 agonist SKF 38393, the controls showed a large decrease in striatal DA overflow and dopaminergic metabolites compared with the cocaine-treated animals (figure 5). Because D1 receptors are largely postsynaptic in caudate, where DA release is governed largely by presynaptic mechanisms, this result suggests a deficiency in the negative feedback pathways extending from caudate onto SN and VTA cell bodies, or locally within striatum. A general conclusion from all of these observations is that animals treated with the cocaine pellet and then given a recovery period show a number of behavioral and biochemical alterations similar to those of animals following lesions of LHb or FR.

REPEATED COCAINE BOUTS: PROGRESSIVE EFFECTS ON BEHAVIOR AND TOXICITY

The authors have also made some very interesting observations on progressive effects of repeated cocaine administration bouts. These arose

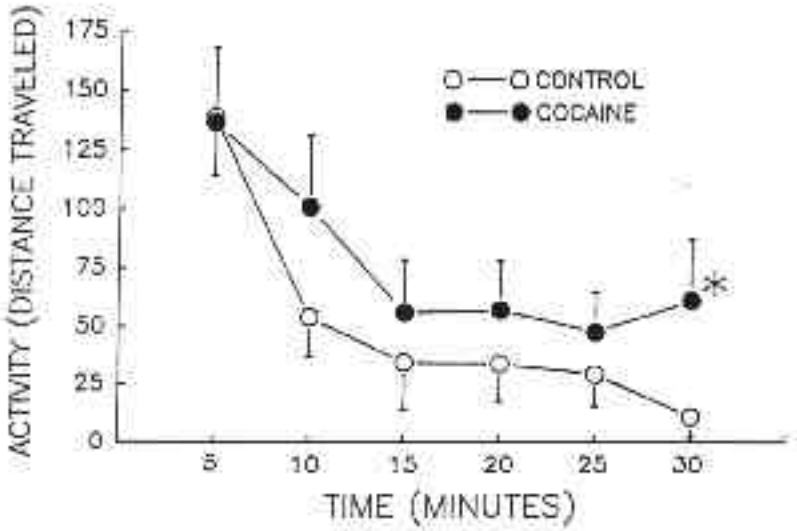

FIGURE 3. *When tested in a novel environment several weeks after pellet removal, cocaine-treated animals remain hyperactive longer than the controls.*

KEY: * = different from controls, $p < 0.05$

from a study that did not work out as had been predicted, but which yielded enormously provocative results. The original experimental design represented an initial attempt to determine if there is any regenera-tion of the degenerating fibers in FR following the cocaine pellet. An experiment was designed to determine if any signs of axonal regeneration could be detected in LHb and FR following the cocaine pellet adminis-tration. Four groups were prepared. A single-pellet exposure group was implanted with cocaine pellets and sacrificed 6 days later, 1 day after pellet removal. The amount of degeneration in LHb and FR in this group was compared with that in a second group of rats implanted with a cocaine pellet for 5days, given a 10-day recovery period, implanted with a second cocaine pellet for 5days, and sacrificed 1 day later. The authors hypothesized that little further degeneration would be observed in this group, since the tracts in these animals had recently degenerated and minimal recovery time had been given. A third group was implanted with a 5-day pellet, given a 3-month drug-free recovery period, implanted with a second 5-day pellet, and sacrificed 1day after the second pellet was removed. It was hypothesized that if any regeneration occurred, this

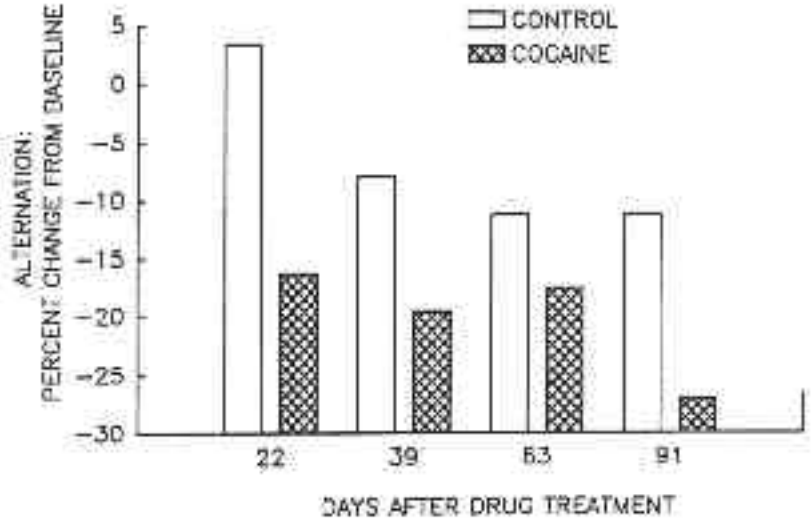

FIGURE 4. *Rats pretreated with the cocaine pellet for 5 days also show extremely persisting deficits in spontaneous alternation in a t-maze. This test is related to immediate memory.*

group would show more degeneration in FR. A fourth group was given 14 daily injections of cocaine, a 10-day drug-free period, implanted with the cocaine pellet for 5 days, and sacrificed 1 day after pellet removal. This type of intermittent drug regimen has quite different effects on behavior than continuous cocaine administration, and so comparisons of degeneration in this group with that in the pellet, 10-day recovery, second pellet group were also of interest.

The actual study results were quite different from those expected. Compared with the single pellet exposure group, there was appreciably more degeneration in the LHb and FR in both of the two-pellet groups. In fact, the degeneration in the 10-day recovery group was slightly greater than in all other groups (figure 6). Thus, rather than providing evidence for any regeneration, this result seems to imply that the single cocaine pellet exposure causes degeneration in only a proportion of the vulnerable fibers since a second pellet administered shortly thereafter (the pellet, 10-day recovery, second pellet group) induces further degeneration. This is an important finding, for it indicates that repeated bouts of cocaine administration in rats spaced 1 or 2 weeks apart appear to be

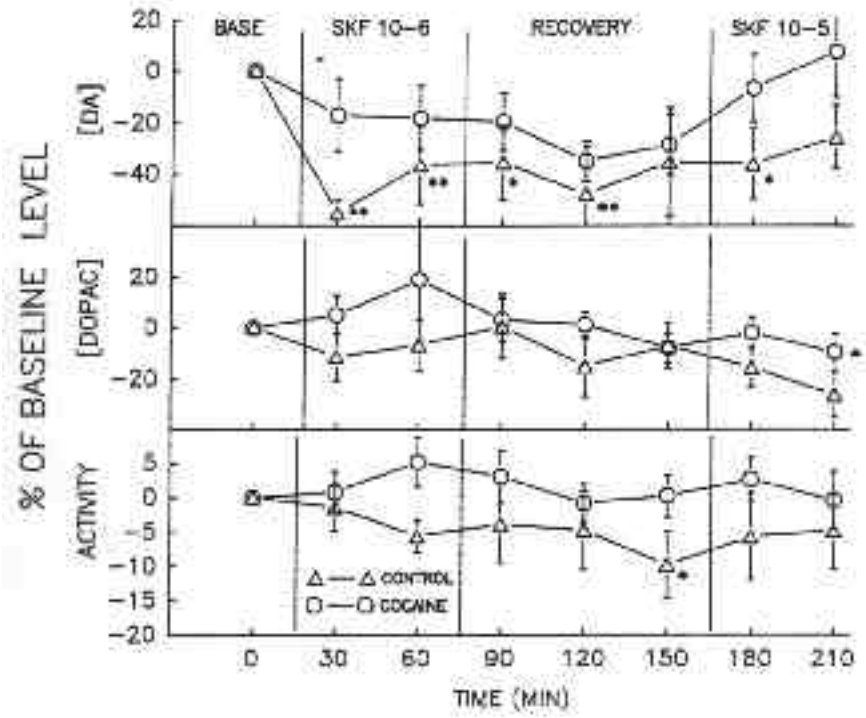

FIGURE 5. *Percent change from baseline levels in striatal DA, DOPAC, GABA, and gross activity during and after local striatal infusion of SKF 38393 10^{-6} followed by a recovery period and then local infusion of SKF 38393 10^{-5}. The cocaine-treated group had been given a 5-day simulated binge several weeks prior to the experiment.*

KEY: * = $p < 0.05$; ** = $p < 0.01$.

extraordinarily neurotoxic. These results imply that a simulated binge induced by a single cocaine pellet clearly does not induce degeneration in all the susceptible fibers, but leaves some of these fibers in a weakened and vulnerable state. It is clear that prior to this study the authors had never really observed animals with the full extent of cocaine-induced degeneration. A second unexpected finding was that pretreatment by spaced daily injections (14 daily injections, each of 10 milligrams per kilogram (mg/kg) cocaine) actually produces an appreciable tolerance to neurotoxic effects induced by the drug given continuously, even though

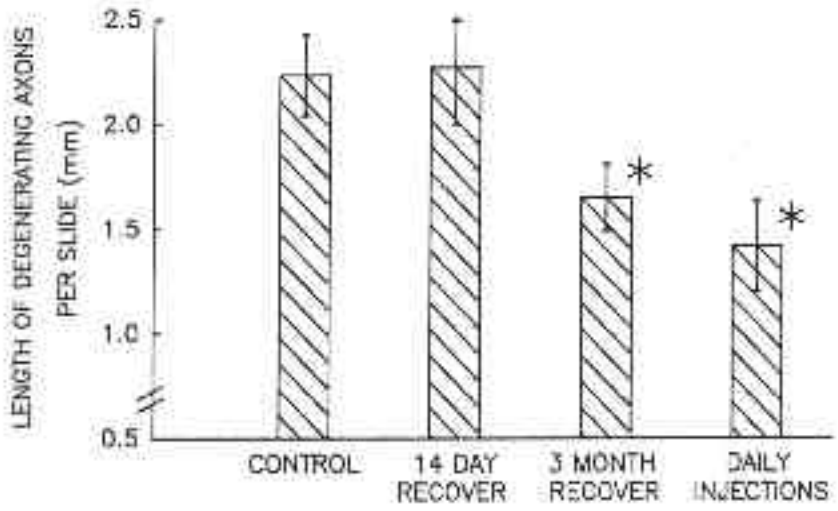

FIGURE 6. *Total amount of unilateral degeneration (sum of all axon lengths) from one slide through LHb and FR. A "blind" observer sketched degenerating fibers using camera lucida, and the resulting ink traces were quantified for total length using imaging software.*

KEY: * = significantly less than control, $p < 0.05$; control = cocaine sham pellet, 14 days recover, cocaine pellet; 14 day = cocaine pellet, 14 days recover, cocaine pellet; 3 month = cocaine pellet, 3 month recover, cocaine pellet; daily inject = 14 inj, 14 days recover, cocaine pellet.

the rats showed a marked potentiation of stereotyped behaviors induced by subsequent pellet administration (see below).

This study also measured behavior during the pellet implant, videotaping the animals automatically every 2 hours throughout the 5 days of the cocaine pellet exposures. Figure 7 shows that, as reported previously, rats implanted with the cocaine pellet go through stages of behavior, from initial exploratory behavior best measured by cage crossings, to motor stereotypies, and finally to late-stage behaviors, including what appears to be parasitotic grooming. The results revealed substantially heightened behavioral alterations in both reimplant groups, both heightened stereotypies and then increased late-stage behaviors. In other words, the behavior was highly

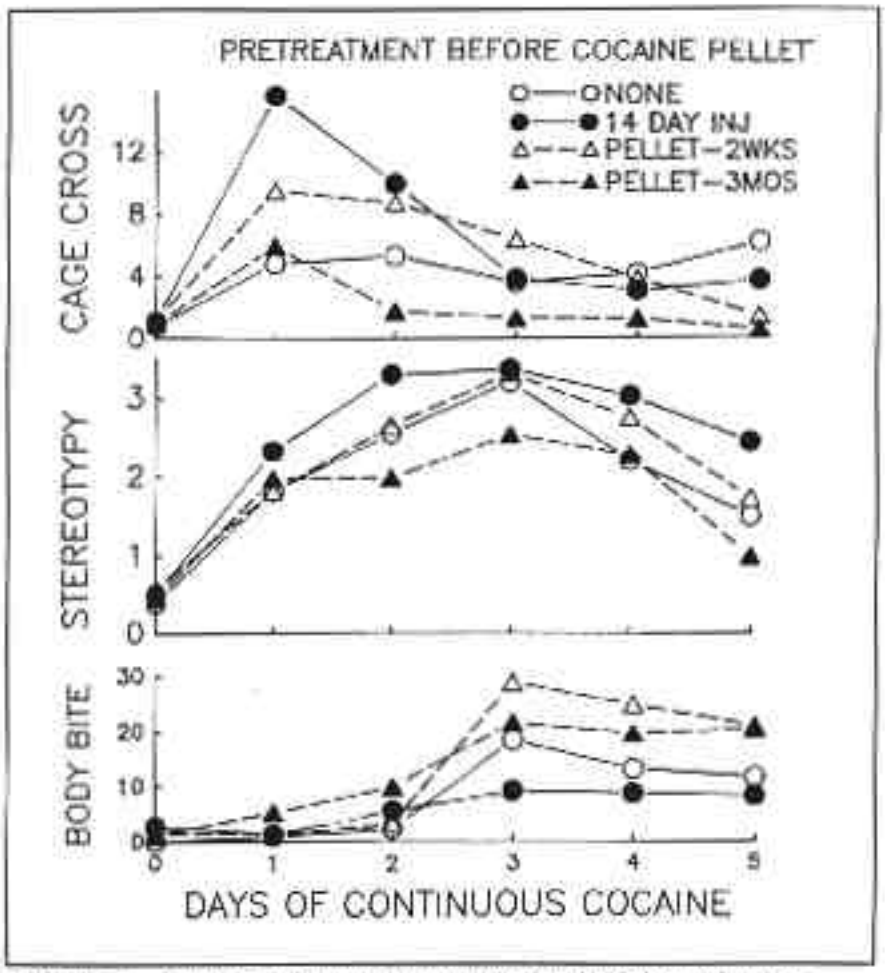

FIGURE 7. *Amount of three behaviors during the 5 days of cocaine pellet action in the four groups. Locomotion was measured as number of cage crossings, motor stereotypy using a conventional rating scale, and duration of body biting quantified as total amount of time computer key depressed.*

correlated with the amount of degeneration observed. Thus, upon implantation with the second pellet, both the 10-day recovery and the 3-month recovery animals showed even more intense stereotypy than the single-pellet treated rats, and then even more late stage behavior upon reimplantation following their first pellet exposure. The 3-month recovery rats showed the greatest degree of parasitotic grooming behavior the authors have ever observed.

Figure 7 shows the total duration of body biting in the four experimental groups during the first or second cocaine pellet exposure (other two groups). This shows the potentiation of the distinctive parasitotic-like behavior, especially in the rats given a 3-month recovery period between implantation of the first and second pellet. While cocaine pretreatments with injections or pellets generally induce tolerance to neurotoxic effects induced by the drug (unless they are too closely spaced), there is a com-plete lack of correlation between various behavioral indices (e.g., motor stereotypies) and neurotoxic effects. In addition to replicating the stages of continuous stimulant exposure (i.e., initial hyperactivity, stereotypy, and late-stage behaviors), these findings add a new twist to the abundant literature on tolerance and sensitization induced by continuous and inter-mittent stimulant exposure. While cocaine pretreatment with intermittent injections led to heightened hyperactivity and motor stereotypies but lessened late-stage behaviors induced by a subsequent pellet implant, the pellet pretreatment led to lessened steroeotypies but heightened parasi-totic grooming. Clearly, the persisting effects of these different drug regimens are much more complex than previously imagined.

It appears that repeated bouts of cocaine exposure in rats may produce progressive alterations in brain and behavior. The authors have never really observed the fully developed late-stage hallucinatory syndrome of behavior, nor have they investigated the full ramifications of how exten-sive the correlated alterations in brain can be. Yet, a recurrent theme in studies of both amphetamine and cocaine addicts (Satel et al. 1992) is how paranoia and parasitosis evolve in the confirmed addict, eventually reaching the point where the initial drug intake can induce them. The cocaine addicts studied by Satel and colleagues (1992) who showed the full syndrome of binge-limited paranoia had been addicts for over 2years and had each consumed an enormous estimated quantity of cocaine (1.34±1.7 kg). The repeated pellet implantation regimen may develop into an extraordinarily interesting paradigm not only for the study of chronic cocaine abuse but also for more general models of sensory hallucinations (such as parasitosis) and of paranoia. These findings may have therapeutic and general scientific implications; the progressive development of parasitosis and paranoia is often cited by addicts as a critical factor in seeking treatment. This repeated binge regimen should prove perfect for the study of metabolic and other regional brain changes correlated with late-stage behaviors.

WHERE ARE THE CELL BODIES THAT GIVE RISE TO FR DEGENERATION?

There are two distinct possibilities for the site of the cell bodies that give rise to the degenerating axons following continuous amphetamine or cocaine administration. They could be located in LHb, projecting ven-trally through FR, but they could also be in midbrain cell groups. The dopaminergic cells of the SN or VTA give rise to ascending DA axons terminating in habenula. The raphe nuclei also project to habenula, as does the central gray.

Three lines of evidence point to the cell bodies in LHb as the source. The first relates to the fact that the degenerating axons are quite highly con-centrated in the mantle of FR. When the anterograde tracer PHAL is injected into LHb (Araki et al. 1988), the pattern of staining observed mirrors almost exactly that seen in the degenerating fibers: a high con-centration of descending fibers in the mantle of FR, with some fibers then entering thalamic nuclei but the majority terminating in regions such as VTA. The ascending fibers such as from SN and VTA projecting to LHb are not so rigidly confined to FR.

A second line of evidence comes from studies in the authors' laboratory. Rats were injected with PHAL in LHb using the Araki and colleagues (1988) protocol, then given 7 days for anterograde transport to occur. The rats were then implanted with either amphetamine or cocaine pellets for 5days. When the animals were sacrificed 2 days after pellet removal, PHAL-stained fibers were observed in FR that had the distinctive characteristics of degenerating fibers (fragmented axons, corkscrew shaped axons, and end stumps). This finding means that at least some of the degenerating axons have cell bodies in LHb.

The third line of evidence comes from the present study of animals that experienced repeated bouts of cocaine administration. When the brains of these animals were stained for degeneration, only a few stained cell bodies were observed (principally in the repeated pellet groups). Most of stained cell bodies were concentrated in the most lateral part of the LHb, with a few in the more medial portion of LHb (figure 8). Furthermore, cell counts of cresyl violet sections from these same animals indicated a decreased number of cells in LHb in the animals repeatedly exposed to cocaine as compared with the controls. When considered altogether, these data support the hypothesis that most, if not all, of the degenerating axons are from cells in LHb.

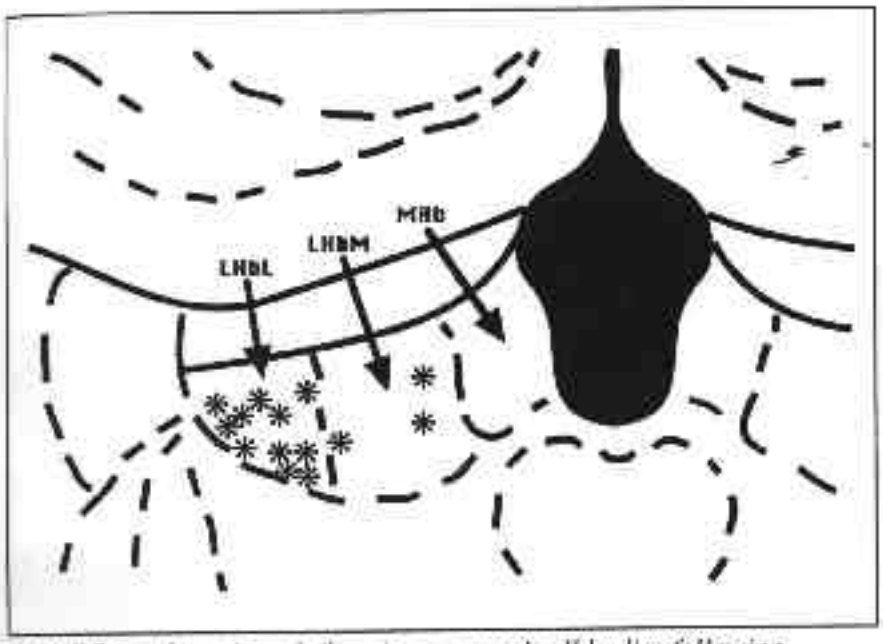

FIGURE 8. *Location of silver-impregnated cell bodies following repeated bouts of cocaine administration. These degenerating cells were palely stained but are concentrated in LHb in the same regions as the c-fos stained cells observed following acute cocaine injections.*

What Are the Mechanisms of this Neurotoxicity?

In LHb and FR, the neurotoxic effects of continuous cocaine and amphetamine administration are unusual in that they are so strongly correlated with a decrease in glucose metabolism in the affected structures. An immense number of studies of glucose utilization have consistently shown that while virtually all DA agonists increase glucose metabolism in DA-rich regions such as caudate nucleus, nucleus accumbens, SN, and VTA, they markedly decrease glucose metabolism in the habenula (reviewed in Ellison 1994). Indeed, some studies reported glucose metabolism in the habenula to be the most sensitive region in all of brain to low doses of DA agonists such as cocaine. Another characteristic of the toxicity in LHb is that the drug administration sufficient to induce this effect must be con-tinuous and extremely prolonged, on the order of many days. This was dramatically validated when it was found that very high doses of metham-phetamine over 8to 10 hours, while producing extraordinary

degeneration in caudate-putamen, are relatively ineffective in producing degeneration in LHb and FR (Ellison and Switzer 1994).

In most other cases of neurotoxicity induced by drugs of abuse, the neuro-toxic effects are observed in brain regions where glucose metabolism is markedly heightened by the drug. Examples are the neurotoxicity pro-duced in caudate by continuous amphetamine administration (Ellison 1994) and the toxicity in several limbic regions produced by NMDA antagonists (Ellison 1995). The possibility that this is an inhibotoxic effect (i.e., that neurons must operate within a normal range, and when they are dramati-cally inhibited for very prolonged periods they begin to show toxic effects) was discussed in Ellison (1994). According to this notion, prolonged inhibition of LHb cells, presumably produced by the powerful GABAergic fibers from entopeduncular nucleus, is responsible for the damage.

More recent data suggest an alternative possibility is more likely to be true. Glucose metabolism, as reflected by 2-deoxyglucose (2DG) uptake, typi-cally reflects the activity in terminals rather than cell bodies (Sharp et al. 1993). Consequently, it is possible that striatal GABAergic efferents to the entopeduncular nucleus are stimulated by the DA agonist administration and, thus, produce a strong inhibition of the entopeduncular efferents to the LHb. The reduced activity in the terminals of these LHb afferents would result in both the reduction of 2DG uptake and the disinhibition of haben-ular cells. This hypothesis (reviewed by Wirtshafter and colleagues (1994)) is supported by the finding that DA agonists induce fos-like immuno-reactivity in cells in the most lateral LHb. In fact, the pattern of induction produced by amphetamine in that study was almost identical to the pattern of cells staining for degeneration (see figure 8).

Wirshafter and colleagues (1994) further found that this fos-like induction could be abolished by 6-hydroxydopamine (6-OHDA) lesions of the nigro-striatal bundle. In collaboration with researchers from the National Insti-tute of Mental Health (NIMH), the authors recently obtained virtually identical findings. Acute injections of cocaine led to an induction of c-fos messenger ribonucleic acid (mRNA) in a large number of cells of the most lateral portions of the LHb. In both of these studies, cells in the more medial aspects of LHb appeared to show c-fos mRNA induction more correlated with general stress, rather than dopaminergic activity. These findings suggest that the neurotoxicity in the LHb and FR induced by continuous

amphetamine or cocaine may be due to the prolonged hyper-activity of the LHb cells produced by the removal of GABAergic inhibitory influences.

DEGENERATION PATTERNS AFTER PSYCHOTOMIMETIC DRUGS OF ABUSE

These findings suggest that the roles of LHb, FR, and the dorsal diencephalic system in general need to be reconsidered in the generation of stimulant-induced and other psychotic states such as schizophrenia. It can be argued that alterations in these pathways are ideal candidates for producing the behaviors that occur during psychosis, and that future considerations of the circuitry underlying psychoses need to include this highly important but relatively neglected system. Because these struc-tures are not large in humans, it is presently very difficult to resolve them in scanning studies. But, the clear prediction is alterations in these struc-tures in cocaine addicts and perhaps in schizophrenics.

It is of considerable interest to determine if similar alterations are present in the second drug model of psychosis, that produced by PCP and the other NMDA antagonists such as ketamine and perhaps dizocilpine. The model psychoses that PCP and ketamine induce mimic a variety of schizo-phrenic symptoms, including flattened affect, a dissociative thought dis-order, depersonalization, and catatonic states. These symptoms can per-sist for prolonged periods, and there is evidence in chronic PCP and ketamine addicts of persisting memory deficits.

PCP, ketamine, and dizocilpine are quite similar in many of their effects, and they all have a neurotoxic effect on neurons in the most posterior cin-gulate cortex (Olney et al. 1989). When the authors administered PCP or dizocilpine to rats in a 5-day binge regimen, there was minimal degener-ation in LHb and FR; however, both of these drugs further induced neur-onal degeneration in a variety other limbic structures. These structures included not only posterior cingulate (retrosplenial) cortex but also rat brain regions related to olfaction such as the olfactory tubercle, anterior olfactory nucleus, and tenia tecta. Additional limbic structures affected were the piriform cortex and the most posterior regions of entorhinal cortex and its projections through the perforant pathway to dentate gyrus and, to a lesser extent, other cells in ventral hippocampus. This finding suggests anatomical substrates for a second drug model of psychosis because most of these same structures are among the

clearest areas where anatomical alterations occur in dementias such as schizophrenia and Alzheimer's disease (Ellison 1995).

THE ANATOMY OF PSYCHOSIS

Although the stimulant and PCP drug models of psychosis have long been recognized as one of the most promising avenues for determining the mechanisms underlying dementias, hallucinogens, and schizophrenia, the insights that have come from these models have been largely pharma-cological rather than neuroanatomical. The study of selective degeneration in brain induced by simulated binges of psychomimetic drugs of abuse lead to some quite unexpected predictions of what parts of brain are the "weak links" in the structures basic to these abnormal states. In the case of the stimulant psychoses, they point toward a pathway almost totally neglected in the "dopamine theory of schizophrenia," while with the NMDA antagonist psychoses, they direct attention toward limbic struc-tures for which the evidence of involvement in schizophrenia is well documented, but which have not been linked with this drug model. Thus, studies of selective degeneration in brain after psychomimetics offer con-siderable promise for the development of new conceptions of the anatomy of psychosis.

CONCLUSION

1. There are alterations in parahippocampus and hippocampus in schizophrenia and Alzheimer's disease. Disordered cell arrangements, decreased cell number, and decreased total area in hippocampus and entorhinal cortex are found in schizophrenia (Kovelman and Scheibel 1984; Bogerts 1993; Jeste and Lohr 1989). Roberts (1991) concluded that probably all schizophrenics have abnormalities in medial temporal lobe structures centering about entorhinal cortex. Positron emission tomography (PET) studies (Liddle et al. 1992) of brain blood flow found that the left parahippocampal region, which includes the ento-rhinal cortex, correlated highest with total schizophrenic symptoma-tology; the authors conclude that alterations in this area are central in schizophrenia.

Entorhinal cortex shows the earliest evidence of neurofibrillary tangles, and remains the most severely affected brain region in Alzheimer's disease throughout the progression of the disease (Braak and Braak 1991). Extent of degeneration in hippocampus and

entorhinal cortex of Alzheimer's patients correlates highly with performance on the Mini-Mental State Examination (Kesslak et al. 1991).

2. There is evidence for anatomical and functional alterations in olfactory regions in schizophrenia and Alzheimer's disease. Olfactory dysfunc-tion is well documented in schizophrenia (Kopala et al. 1993). This is not due to chronic antipsychotic medications (Wu et al. 1993). Schiz-ophrenic patients have decreased glucose metabolism in most brain regions, but it is greatest in patients with olfactory agnosia (Clark et al. 1991).

There is a substantial loss of olfactory functions present in Alzheimer's disease (Feldman et al. 1991; Serby et al. 1991), and this is among the first signs of Alzheimer's (Doty 1991). This is reflected as decreased metabolic rates in medial-temporal cortex, especially during olfactory memory tasks (Buchsbaum et al. 1991). In Alzheimer's disease, a sizable increase has been reported in neurofibrillary tangles and neuritic plaques in olfactory cortex compared to many other brain regions (Reyes et al. 1993); the olfactory bulb also shows substantial pathology (Struble and Clark 1992).

3. There is also evidence for alterations in posterior cingulate cortex in schizophrenia and Alzheimer's disease. Across a variety of brain regions in schizophrenics, the largest alterations in serotonin receptor number are in posterior cingulate, hippocampus, and temporal cortex (increases in both 5-HT1A and 5-HT2 receptors) (Joyce et al. 1993).

The highest concentration of neuritic plaques and neurofibrillary tangles in retrosplenial cortex of Alzheimer's disease patients are in lamina III and V (Chun et al. 1994), corresponding well with the location of the degenerating pyramidal cells following NMDA antagonists. Substantial alterations occur in receptor binding in posterior cingulate cortex in Alzheimer's patients (Vogt et al. 1990), as well as dramatically decreased glucose metabolism in posterior cingulate in Alzheimer's (Minoshima et al. 1994).

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