Stimulant Preexposure Sensitizes Rats and Humans to the Rewarding Effects of Cocaine

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A great deal of research has focused on initiation into drug use and factors that increase the risk of initiation or protect against it. Initiation into the use of some drugs (such as alcohol) is extremely common, whereas initiation into use of other drugs (such as cocaine) is less frequent (Kandel 1975). Regardless of initiation rate, most individuals who try a particular drug do not continue into a pattern of abuse, although different substances appear to differ in their abuse potential. For example, many adults in the United States can be considered "social" drinkers, but a much smaller percentage are considered "problem" drinkers. The abuse potential of cocaine is considered to be much higher among those individuals who continue to use on a regular basis. Newcomb (1992) found that about 15 percent of young adult alcohol users had developed a pattern of dependency, whereas about one-third of those who had used cocaine within the previous 6 months showed a pattern of dependency. Thus, different substances appear to differ in abuse potential, but, in addition, different individuals also vary in their vulnerability to abuse. A wide variety of psychological and social factors contribute to this variability; the purpose of this chapter is to present a series of animal studies, and more limited human data, which suggest one biological model that may explain differing responses to cocaine. Different individuals, as a result of previous exposure to other stimulants, may initially experience cocaine as more (or less) positive; these different responses will influence the likelihood of continuing to take cocaine and the timecourse for the development of a pattern of abuse.

Propensity to self-administer stimulants in animals can be experimentally altered via a number of environmental and pharmacological conditions. For example, rats that were reared in socially isolated conditions developed cocaine self-administration in adulthood with shorter latencies than rats that were reared in groups (Bozarth et al. 1989; Schenk et al. 1987). Repeated application of four 1-minute daily exposures to tailpinch also facilitated the development of amphetamine self-administration by rats (Piazza et al. 1990). Exposure to the self-administered drug can also increase the responsiveness of rats and monkeys to the subsequent effects of

the drug (Downs and Eddy 1932; Horger et al. 1990; Lett 1989; Piazza et al. 1989; Woolverton et al. 1984). Therefore, following exposure to these environmental or pharmacological variables, subjects appear sensitized to subsequent drug exposures. During the past two decades, models have been developed to investigate the conditions under which behavioral sensitization occurs and to try to understand the neurochemical basis for this phenomenon.

BEHAVIORAL SENSITIZATION: A MODEL FOR THE DEVELOPMENT OF COCAINE ABUSE

The earliest reports of sensitization with repeated stimulant exposure (Downs and Eddy 1932) observed that chronic treatment with cocaine resulted in a progressive increase in motor activity with repeated lower dose exposures. More recent experiments (Post and Rose 1976; Robinson and Becker 1986) have attempted to quantify sensitization to cocaine's motor-activating effects more elaborately. The results have indicated that behavioral sensitization primarily functions to increase the maximum behavioral output. In other words, the motor-activating effects of a given stimulant dose appear to increase. The dose-response curves for this behavioral effect may not be shifted to the left but, rather, may be shifted up vertically for effective doses of the drug. In addition, the effects of intermittent exposure also appear to be enduring, lasting for several months following the treatment (Robinson and Becker 1986; Robinson et al. 1988; Zahniser and Peris 1992). Finally, both a context-dependent and a context-independent form of sensitization appear to be operating. These two forms may be separable and may be dependent on long-term changes in different neuronal substrates. The context-independent form of sensitization has been hypothesized to be due to interactions between dopamine (DA) and other neuronal systems in the somatodendritic regions of the ventral tegmental area (Kalivas and Stewart 1991).

The use of motor activity as a behavioral assay has many advantages. For example, it is a relatively simple assay requiring no sophisticated surgical procedures. Also, drug-induced motor activation is easily quantified. Portions of the circuitry for drug-induced motor activation have been well delineated, at least for psychomotor stimulant-induced hyperactivity, and they are known to be dependent on mesocorticolimbic DA systems. The overlap of these systems with those underlying the reinforcing effects of these drugs led to the formulation of a psychomotor stimulant theory of addiction (Wise and Bozarth 1987). If correct, then a study of the factors that

contribute to the development of sensitization to the motor-activating properties of psychomotor stimulants may relate to the development of drug abuse. However, there are numerous reports in the literature of manipulations that differentially affected motor activity and self-administration, with a report from the laboratory of the senior author of the theory (R.A. Wise) discussing these differences with a specific focus on sensitization (Wise and Munn 1993). The possibility is raised at the end of that paper that "some modification of the various psychomotor stimulant theories of reward will be necessary" (page 199). Thus, effects of manipulations on motor activity may not always reflect manipulations in reward-related behavior. As a result, self-administration models have been used to address directly the basis for a predisposition to drug abuse.

The development of cocaine self-administration in laboratory animals is highly variable (Deneau et al. 1969), and the retrospective reports of reactions of humans to their initial cocaine exposure range from highly positive to negative (Davidson et al. 1993). In the authors' laboratory, a great deal of variability in the latency to acquire cocaine self-administration by rats is routinely observed suggesting that the variability is due to differences in the sensitivity of rats to cocaine's reinforcing properties. That is, some rats may become more quickly sensitized to cocaine's reinforcing properties than others.

Using alternate paradigms, a small number of investigations have attempted to demonstrate sensitization to the reinforcing effects of drugs with repeated exposures. For example, Lett (1989) demonstrated an increase in the conditioned place preference produced by repeated cocaine or morphine exposure and Shippenberg and Heidbreder (1995) have shown a shift to the left in the dose-response curve for cocaine-induced conditioned place preference following two exposures to cocaine. Kokkinidis and colleagues (Kokkinidis and Zacharko 1980; Predy and Kokkinidis 1984) have shown sensitization in the ability of repeated injections of amphetamine to potentiate the reinforcing effects of brain stimulation, although it has been suggested that these sensitizing effects on brain reward mechanisms may be site specific (Wise and Munn 1993).

Studies using the self-administration paradigm have consistently demonstrated sensitization to the reinforcing effects of drugs following preexposure. For example, Woolverton and colleagues (1984) found that the reinforcing effects of methamphetamine were enhanced following preexposure. Doses that were initially

subthreshold for self-administration became capable of maintaining responding in two out of three monkeys following a period of intermittent methamphetamine administration. Therefore, the dose-response curve for self-administration shifted to the left following the stimulant exposure. Piazza and colleagues (1989, 1990) have similarly shown that preexposure to four noncontingent administrations of 1.5 mg/kg amphetamine was sufficient to turn rats that had initially failed to self-administer amphetamine into reliable self-administrators. This more direct examination of the development of drug reinforcement involving an examination of the development of intravenous (IV) self-administration provides support for the notion that responsiveness to the reinforcing effects of drugs of abuse can be increased by preexposure. The investigation of factors that contribute to the development of the proposed sensitization will ultimately lead to an understanding of why some subjects appear susceptible to drug abuse whereas others appear to be relatively resistant.

This has been the objective of the research in the authors' laboratory during the past several years. The working hypothesis has been that the magnitude of the initial reinforcing effects of cocaine (latency to acquisition of a response that produces IV infusions) is determined, in part, by the pharmacologic history of the animal. In this chapter, data from both rats and humans are presented that support this hypothesis.

ANIMAL STUDIES

The study of sensitization to cocaine's reinforcing effects has been influenced greatly by learning theorists of the 1950s. The basic principle that the strength of a reinforcer and the latency to acquisition of a response that produces it are inversely related was clearly demonstrated in these earlier studies. When either food or sucrose served as the reinforcer for lever pressing or T-maze running, rats receiving higher concentrations of sucrose (Guttman 1953) or larger quantities of food (Reynolds 1950) acquired the task with shorter latencies. In studying the acquisition of cocaine self-administration, this basic principle has been applied to assess the effects of pharmacological treatments on the reinforcing efficacy of cocaine.

Since studies examining the response to the initial reinforcing effects of cocaine in the self-administration paradigm were sparse,

establishment of criteria to be used to determine the latency to acquisition of cocaine self-administration was the authors' first concern. Subsequently, the authors examined the relationship between the latency to acquisition of cocaine self-administration and the dose of cocaine that served as the reinforcer. Finally, the authors assessed the effects of preexposure to a variety of stimulants on this dependent measure.

Determination of Latency to Acquisition of Cocaine Self-Administration

The authors' self-administration laboratory contained 16 operant chambers, each containing two levers. Depression of one results in the delivery of a cocaine infusion whereas depression of the other has no effect. The experimental protocol involved a single experimenter-delivered "priming" infusion of cocaine at the start of each daily session. Thereafter, the infusions were delivered on a fixed ratio (FR) 1 schedule of reinforcement by depression of the active lever. Therefore, there was no training of lever pressing. Rather, the latency to spontaneous acquisition of the operant task was examined.

To achieve this latency measure, the authors developed a set of criteria for acquisition of self-administration that would determine the day on which a rat develops a preference for the active lever. First, the number of reinforced responses for an individual rat must exceed the criterion set by the number of inactive lever responses of the group. Second, individual active lever responses must exceed individual inactive lever responses.

A criterion number of active lever responses was determined for each rat based on the average number of inactive lever responses for the group, as illustrated in figure 1. The average number of active and inactive lever responses for a representative group of rats given daily 2-hour sessions of access to cocaine (0.25 mg/kg/infusion) is shown. On the first day of testing, responding on both levers is high; with repeated days of testing, responding on both levers is initially reduced, and then active lever responding increases steadily until day 9 of testing.

The shaded region of this panel represents the upper limit of a 99 percent confidence interval placed about the mean number of inactive lever responses. This upper limit was chosen as a cutoff to establish the day on which each rat has acquired self-administration (Horger et al. 1991, 1992).

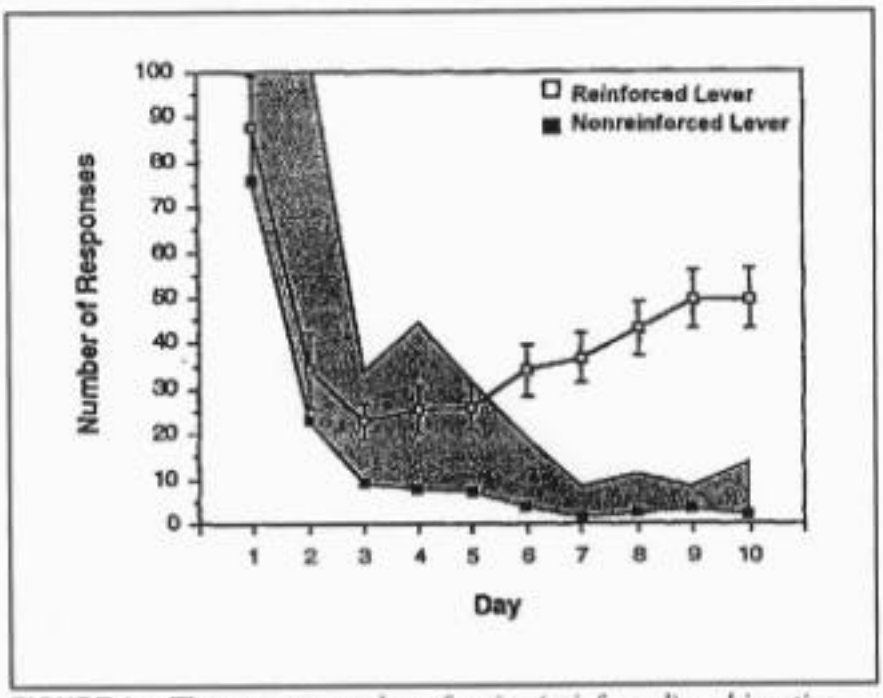

FIGURE 1. *The average number of active (reinforced) and inactive (nonreinforced) lever responses for a representative group of rats (N = 10) self-administering 0.25 mg/kg/infusion cocaine over 10 days. The shaded region shows the upper limit of a 99% confidence interval placed about the mean number of inactive lever responses. This upper limit is a cutoff that establishes one criterion for the number of active lever responses that are required on each day of testing in order for self-administration to be considered reliable.*

This method of data reduction provides a means of comparing acquisition of self-administration that is not based on absolute rates of responding but, rather, is based on the *relative* rates of cocaine taking. This becomes particularly important when acquisition of self-administration of different doses of cocaine is compared (where ultimately rates are dramatically different) or when comparing the effects of manipulations that may alter absolute intake without necessarily altering latency to acquisition. As shown below, this also standardizes the data to answer the question of whether a manipulation affected the acquisition of cocaine self-administration.

Although the method of data reduction reported here is one that has been published by the authors' laboratory (Horger et al. 1992), it is noteworthy that

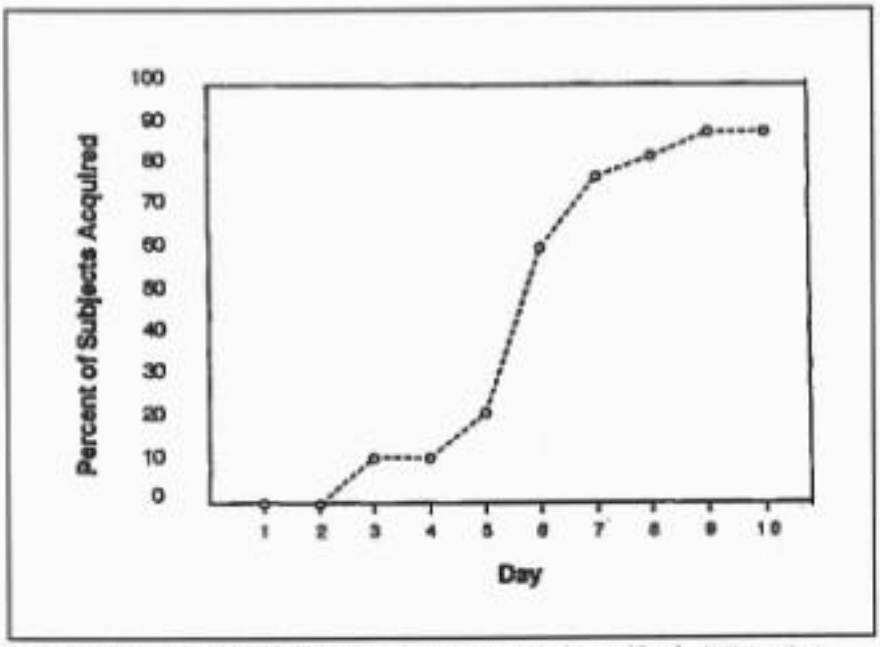

FIGURE 2. *Application of the three criteria for self-administration allows one to reduce the raw data to a curve relating percentage of subjects that had acquired cocaine self-administration to each day of testing. In this group of rats (raw data are presented in figure 1), the percentage of rats that acquire cocaine self-administration (exceeding the inactive lever response criterion (figure 1) and have a greater number of active than inactive lever responses) increases between days 3 and 9 of testing. Some rats appear more sensitive to cocaine's reinforcing properties since they acquire self-administration with fewer days' exposure.*

application of a number of other "reasonable" criteria provide exactly the same curves. For example, if the criteria of 30 active lever responses and a ratio of active:inactive responses of 3:1 are used to determine the day on which each rat acquired cocaine self-administration, the acquisition data (percentage of rats that meet the criteria on each day of testing) are as shown in figure 2.

Dose Dependency of the Latency to Acquisition of Cocaine Self-Administration

If this measure of the acquisition of cocaine self-administration is a measure of sensitivity to cocaine's reinforcing properties (i.e., those rats that are more sensitive will meet the criteria with shorter latencies), then latency to meet the criteria should be inversely

related to reinforcement magnitude (i.e., dose of cocaine). In a study designed to assess this assumption, acquisition of cocaine self-administration was determined for three cocaine doses (0.125, 0.25, and 0.5 mg/kg/infusion). When the criteria for self-administration are applied to these data, the dose dependency is clearly and statistically demonstrated (see figure 3, adapted from Schenk et al. 1993). When higher doses of cocaine serve as the reinforcer, the acquisition curve is shifted to the left with more animals acquiring the operant with a shorter latency than when lower doses serve as the reinforcer. These data lend support to the hypothesis that larger doses of cocaine are more efficacious than smaller doses.

Effects of Pretreatment With Psychostimulants

The authors' initial studies determined equipotent doses of psycho-stimulant drugs to be used in the pretreatment phase of the subsequent self-administration experiments. First, dose-response curves for the motor-activating effects of various stimulants were determined. Horizontal activity was measured in open field boxes (38.1 (38.1 (38.1 cm) with grid floors. For caffeine, methylphenidate, cocaine, and amphetamine, there was an initial increase in activity with increasing doses. As the dose was further increased, horizontal activity decreased slightly. Peak drug effects were found for 20.0 mg/kg caffeine, 20.0 mg/kg methyl-phenidate, 10.0 to 20.0 mg/kg cocaine, and 1.0 mg/kg amphetamine.

The effects of nicotine were also examined. The profile of the acute motor-activating effects of this drug was different than for the other stimulants in that the initial exposure produced motor depression. With repeated exposures, however, tolerance developed to the depressant effects and an excitatory effect was observed (Horger et al. 1992). A dose of 0.6 mg/kg (base weight) was used since repeated exposure produced increases in motor activity that were comparable to the acute effects of the other stimulants. Doses of the other stimulants that produced peak increases in motor activity were used in subsequent self-administration experiments.

In an initial study (Horger et al. 1990) both the motor-activating effects of cocaine (10.0 mg/kg, intraperitoneally (IP)) and the acquisition of IV cocaine self-administration (0.225 or 0.45 mg/kg/infusion) were determined for rats having received 12 daily exposures to cocaine (10.0 mg/kg, IP) or the saline vehicle. Exposure to cocaine under these conditions led to a sensitized response to a challenge injection when the behavioral output of interest was

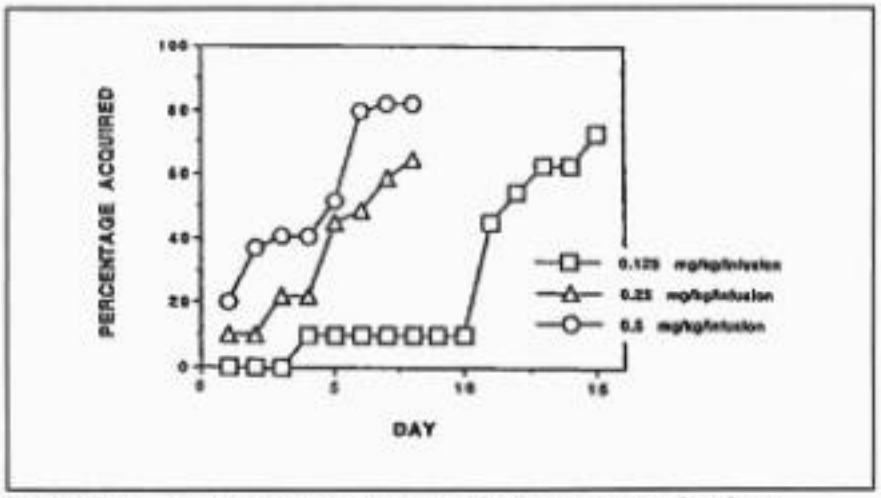

FIGURE 3. *Acquisition of cocaine self-administration for three separate groups of rats that acquired self-administration of three different doses of cocaine (N = 14-22). There is a shift to the left on the curve relating the percentage of subjects that had acquired cocaine self-administration on each day of testing with increasing doses of cocaine. Chi-square analyses confirmed that the differences between the curves for adjacent doses were significant. Thus, the latency to acquisition of cocaine self-administration is inversely related to dose.*

horizontal motor activity. Exposure to cocaine reduced the latency for acquisition of self-administration of both cocaine doses and increased the percentage of rats that reliably self-administered the drug within the 9-day test period.

Followup studies examined the effects of preexposure to nicotine and amphetamine on these same measures. Animals were pretreated with nine daily exposures to either amphetamine (1.0 mg/kg, IP) or nicotine (0.6 mg/kg base weight, subcutaneously (SC)). Repeated exposure to amphetamine resulted in progressive increases in motor activity and cross-sensitization to cocaine-induced motor activation (Schenk et al. 1991*b*). Initial exposure to nicotine produced primarily motor suppression. However, with repeated exposure, an excitatory effect of nicotine emerged. When the effects of cocaine on motor activity were subsequently assessed, the nicotine-exposed animals were tolerant and failed to show an excitatory response to any dose of cocaine tested (2.5 to 20.0 mg/kg, IP). When the acquisition of cocaine self-administration (0.25 mg/kg/infusion) was measured in rats exposed to either nicotine or amphetamine under

identical preexposure parameters, latency to acquisition of self-administration was reduced by exposure to both drugs. Thus, cross-sensitization to the reinforcing effects but not to the motor-activating effects was apparent. Further, the magnitude of the shift to the left in the acquisition curve for self-administration was comparable for both nicotine- and amphetamine-exposed rats.

The effects of repeated caffeine administration on motor activity were also measured. The effects of this drug were fairly consistent with repeated exposures (Schenk et al. 1989); neither sensitization nor tolerance was observed. However, when cocaine was administered following preexposure to caffeine, the motor-activating effects were enhanced when compared to vehicle-exposed animals. Thus, although repeated caffeine failed to modify the effects of an acute caffeine injection, it effectively sensitized rats to the motor-activating effects of cocaine. When caffeine (20.0 mg/kg, IP) was administered once daily for 9 days the latency to acquisition of cocaine self-administration (0.25 mg/kg/infusion) was also significantly reduced (Horger et al. 1991). Therefore, caffeine preexposure also sensitized rats to the reinforcing effects of cocaine.

In all of these initial studies, the preexposure treatments were administered in the test cage. Although there was no indication in the activity tests that there were conditioned effects associated with the exposure regimen, it was entirely possible that context-dependent sensitization contributed to the effects observed in the self-administration paradigm. In order to minimize the contribution of these potential conditioning factors, the pretreatments were subsequently administered in the homecage. Under these conditions, the effects of nine daily amphetamine exposures (2.0 mg/kg, IP) on acquisition of self-administration of a number of cocaine doses were tested (0.125 to 0.5 mg/kg/infusion, Schenk et al. 1993).

Application of the criteria revealed the dose dependency of these data (figure 4). As the dose of cocaine was increased, the latency to acquisition of cocaine self-administration was reduced. Most importantly, the curves for each dose of cocaine, when compared to the same data from control rats that were preexposed with saline, are shifted to the left. That is, during the early days of testing more of the amphetamine-exposed rats acquire self-administration of each dose of cocaine. Thus, amphetamine exposure increased the initial reinforcing effects of cocaine in a manner comparable to increasing the dose of the drug. These data also suggest a context-independent form of sensitization.

Persistence of the Sensitization Effects

All the data shown earlier were derived when self-administration testing began 1 day following the last of the pretreatments. Thus the data represent the immediate sensitizing effects of stimulant exposure. To investigate the persistence of these sensitizing effects, acquisition of cocaine self-administration was assessed 45 days following the last amphetamine pretreatment (2.0 mg/kg once daily for 9 days). A single dose (0.25 mg/kg/infusion) of cocaine for self-administration was tested. Amphetamine-preexposed rats still demonstrated a reduced latency to acquisition of cocaine self-administration, suggesting that sensitization to cocaine's reinforcing effects is enduring (Valadez and Schenk 1994).

As a preliminary test of whether preexposure to other stimulants produces similar enduring sensitization to cocaine's reinforcing effects, the effects of caffeine and amphetamine exposure on acquisition of cocaine self-administration (0.125 mg/kg/infusion) were compared when testing began 3 weeks following the last of the pretreatment injections. As in the earlier studies, caffeine (20.0 mg/kg, IP) or amphetamine (1.0 mg/kg, IP) were administered in single daily injections for 9 days. The effects of preexposure with caffeine were persistent; effects were apparent 3 weeks following the last of nine daily injections and were

comparable in magnitude to the effects of preexposure with nine daily injections of 1.0 mg/kg amphetamine (figure 5). Therefore, these effects are enduring.

Sensitization: A Kindling Phenomenon?

Since behavioral sensitization is enduring, the underlying mechanisms are likely to involve long-term changes in brain structure and function. Studies of electrical kindling of the brain, a widely accepted model of neural plasticity, have implicated the glutamate system and in particular enhanced sensitivity of the N-methyl-D-aspartate (NMDA) receptor (McNamara et al. 1988).

Data also suggest that the NMDA receptor may be critically involved in the development of behavioral sensitization produced by repeated exposure to dopaminergic agonists (Trujillo and Akil 1995). Sensitization to the motor-activating effect of cocaine was blocked by coadministration of the non-competitive NMDA receptor antagonist

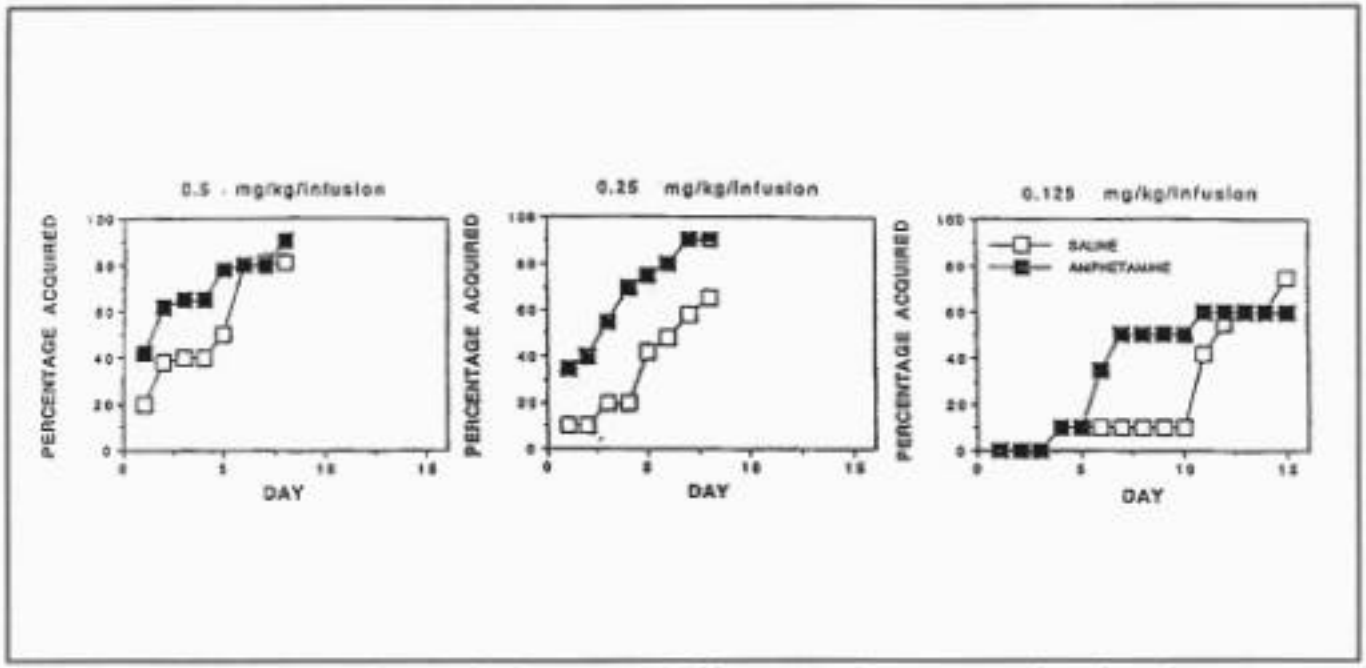

FIGURE 4. *The percentage of control subjects (N = 14-22; nonstimulant preexposed) and amphetamine-exposed subjects (N = 10-25) that acquire cocaine self-administration on each day of testing is inversely related to dose of cocaine. Further analyses indicated that differences in latency as a function of amphetamine exposure were apparent for each dose of cocaine tested.*

SOURCE: Adapted from Schenk et al. (1993).

MK-801 (dizocilpine) (Karler and Calder 1992; Karler et al. 1989). Coadministration of MK-801 also blocked the ability of amphetamine to sensitize rats to the behavioral effects of subsequent injections (Wolf and Khansa 1991). This effect appears to be manifested in the ventral tegmental area (VTA) or amygdala since local injections of MK-801 into these sites (but not into the nucleus accumbens) blocked the ability for a single injection of high-dose cocaine (30 mg/kg) to sensitize rats to the effects of a second lower dose (15 mg/kg) injection (Kalivas and Alesdatter 1993). Since a critical role for glutamatergic NMDA receptors in neuronal plasticity has been demonstrated, blockade of the NMDA receptor should block the development of sensitization as it does the development of electrical kindling if sensitization produced by pre-exposure to stimulants represents a form of pharmacological kindling (McNamara et al. 1988; Morimoto et al. 1991).

In a preliminary test of this possibility, rats were pretreated with nine daily injections of either amphetamine (2.0 mg/kg, IP) or saline (Schenk et al. 1993). Half of each group were also given an injection of either MK-801 (0.25 mg/kg) or the water vehicle. Thus, this was a 2 (2 design to assess the effects of NMDA receptor blockade on the development of sensitization produced by amphetamine preexposure. One day following the last of the pretreatments, acquisition of cocaine self-administration (0.25 mg/kg/infusion) began. Amphetamine-pretreated rats had reduced latencies for the acquisition of cocaine self-administration. When the amphetamine-pretreated rats were also administered MK-801 (0.25 mg/kg, 30 minutes before each amphetamine injection), acquisition of self- administration proceeded as for saline-pretreated rats. That is, MK-801 had blocked the development of sensitization to cocaine's rewarding properties produced by exposure to amphetamine. The 9-day preexposure regimen whereby rats received MK-801 by itself did not alter the latency to acquire cocaine self-administration. Because of the role of glutamate and NMDA receptors in the development of electrical kindling, electrical kindling may be a means of sensitizing the mesolimbic inputs to the nucleus accumbens and VTA. Using multiple stimulation sites, it may be possible to establish which of these glutamatergic projections are involved in the plasticity that is observed with sensitization to cocaine's effects.

There are data implicating the medial prefrontal cortical reward substrate in the phenomenon of sensitization. First, the acquisition of medial prefrontal cortical self-stimulation is a protracted process (Corbett et al. 1982), suggesting that repeated stimulation of this site

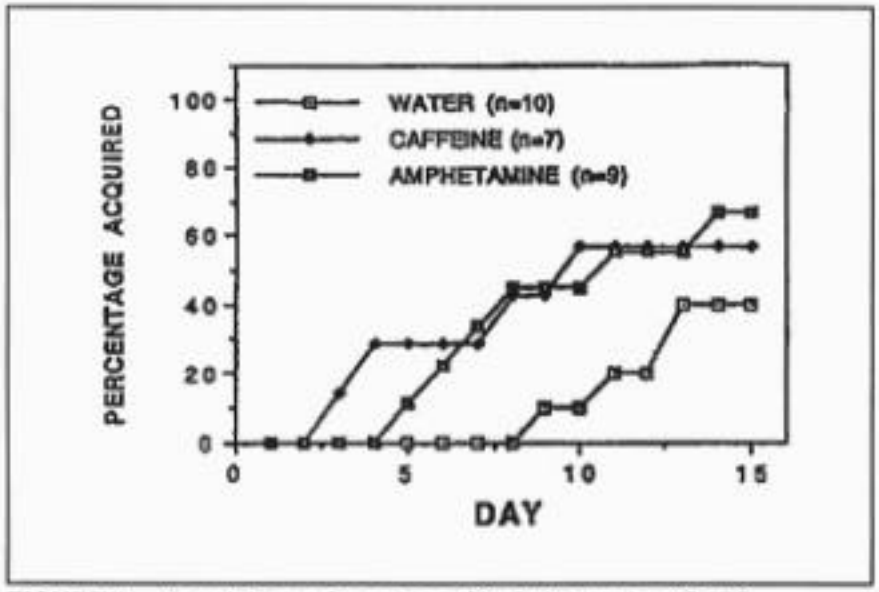

FIGURE 5. *Acquisition of cocaine self-administration (0.125 mg/kg/infusion) for rats that had received nine daily injections of amphetamine, caffeine, or the water vehicle. Self-administration testing began 3 weeks following the last of the injections. When the acquisition criteria are applied to these data, both caffeine and amphetamine shifted the curve to the left. Thus, the effects of preexposure on acquisition of cocaine self-administration are enduring and persist for at least 3 weeks.*

produces sensitization to the reinforcing effects of the stimulation. The latency for this process, however, can be significantly reduced by prior noncontingent delivery of electrical stimulation to the site (Corbett et al. 1982) as well as by prior exposure to amphetamine (West and Michael 1986). Based on this interaction between rewarding stimulation of the medial prefrontal cortex and amphetamine, the authors hypothesized that sensitization may be due to facilitated transmission in a medial prefrontal cortical substrate with repeated activation.

In a study designed to investigate this possibility (Schenk and Snow 1994), single trains of electrical stimulation were delivered either to the medial prefrontal cortex or to the hippocampus. Sham animals were implanted and handled daily but received no electrical stimulation. Daily stimulation sessions continued until stage 5 seizures developed, about 30 to 35 days (Racine 1972). After a 14-day period to allow the immediate effects of the stimulation to

subside, the ability of cocaine (0.0, 5.0, or 10.0 mg/kg) to increase horizontal motor activity was determined. Sham-operated and electrically kindled animals demonstrated a dose-dependent increase in motor activity following cocaine administration. The dose of 5.0 mg/kg was subthreshold, and a significant elevation in motor activity was found following administration of 10.0 mg/kg cocaine. Electrical kindling of the medial prefrontal cortex sensitized rats to the motor-activating effects of cocaine (Schenk and Snow 1994). These rats were more responsive to the 10.0 mg/kg dose of cocaine than either the sham-operated or hippocampal-kindled rats. These effects were not due to a generalized and diffuse activation of the brain since hippocampal kindling did not produce comparable effects. The hippocampal-kindled rats were not different from sham-operated rats in terms of their response to cocaine. Rather, the data suggest that specific activation of prefrontal cortical efferents interacted with cocaine-sensitive sites to enhance the subsequent behavioral response to cocaine. It will be critical to determine whether these effects are also observed when the reinforcing effects of cocaine are measured in the self-administration paradigm. Also of interest will be to examine the effects of kindling of other brain sites, including the amygdala, on the development of behavioral sensitization.

The ability of electrical kindling of the medial prefrontal cortex to enhance cocaine's behavioral effect suggests that repeated activation of prefrontal cortical output cells via their participation in the convulsive activity of the kindled seizures may have sensitized central cocaine-sensitive systems and, as a result, sensitized rats to the behavioral effects of cocaine. Neuro-chemical correlates of the sensitization phenomenon have been obtained in an attempt to address this possibility with a specific outlook to evaluating the role of mesolimbic and mesocortical DA systems.

Neurochemical Correlates of Sensitization to Cocaine's Reinforcing Effects

Given the large database implicating DA in the rewarding properties of cocaine (Roberts and Koob 1982; Roberts et al. 1977, 1980; Robledo et al. 1992; Schenk et al. 1991*a*), it is possible that drug preexposure and kindling of the medial prefrontal cortex facilitated the behavioral response to cocaine by increasing the dopaminergic response to cocaine in these central systems. This hypothesis has been examined using in vivo microdialysis (Horger et al. 1991, 1994). In control rats, cocaine (15.0 mg/kg, IP) caused DA overflow in the ventral striatum (nucleus accumbens) to increase to 200 to 300

percent of baseline. When rats were pretreated with caffeine (Horger et al. 1991) or amphetamine (Horger et al. 1994) under conditions that led to behavioral sensitization, the ability of cocaine to increase DA overflow in the nucleus accumbens was enhanced as compared to saline-pretreated rats. Similar effects of amphetamine pretreatment were found when DA was measured in the medial prefrontal cortex (Horger et al. 1994).

The effect of amphetamine preexposure on the response to cocaine in the prefrontal cortex was different from the response in the ventral striatum. First, the magnitude of the sensitized neurochemical response to cocaine was smaller in the prefrontal cortex. Second, the timecourse of the response to cocaine was different; the response of the cortical substrate was delayed in the amphetamine-preexposed rats relative to both the response in saline-treated controls and to the response of the ventral striatal substrate of amphetamine-treated rats. These differences may be related to differences in autoregulation between these two systems. Another possibility is that the prefrontal cortical system is more responsive to stress than is the ventral striatal system (Sorg and Kalivas 1993). Therefore, the injection regimen itself may produce a larger effect on DA overflow in these amphetamine-pretreated rats due to cross-sensitization. As a result, the effect of amphetamine over and above the effect of stress may be blunted. Unfortunately, this possibility was not addressed in the microdialysis work since, at the time, the interaction between stress and stimulants in producing sensitization to subsequent stimulant administration or stress-induced behaviors was not as well demonstrated. This possibility should be pursued in additional studies.

Another interesting aspect of these neurochemical data is the finding that nicotine exposure failed to increase the response of the mesolimbic or mesocortical DA system to cocaine. This finding is consistent with some of the behavioral data indicating that nicotine exposure failed to sensitize rats to the motor-activating properties of cocaine, but is inconsistent with the self-administration data that indicated sensitization following nicotine preexposure (Horger et al. 1992). Since nicotine preexposure failed to increase the response of either of these systems to cocaine, a different mechanism must account for the behavioral sensitization observed following pretreatment. Thus, although the amphetamine data are consistent with the hypothesis that sensitization in one or both of these DA systems may be a sufficient condition for sensitization to cocaine's reinforcing properties, another system must be responsible for the

enhanced behavioral response to cocaine following preexposure to nicotine.

HUMAN STUDIES

Efforts to evaluate the sensitization hypothesis in humans have taken two forms: The first involves an attempt to document variability of initial response to cocaine, and the second involves evaluating cocaine use and abuse in a group of subjects who had received exposure to a different stimulant.

Initial Response to Cocaine

There is a relative paucity of studies that document variability in response to cocaine's initial effects in humans. Thus, the first step in validating the animal model required determining whether the response to cocaine exhibited variability among a sample of relatively inexperienced users and whether frequency of cocaine use and pattern of use were related to self-reported magnitude of the positive response to cocaine. It was hypothesized (Davidson et al. 1993) that the subjects who responded in a positive way to cocaine would be more likely to use cocaine again and to use it a second time with a shorter latency than subjects who did not experience as positive an initial effect of the drug. To measure the initial response to cocaine, the authors adapted the expectancy questionnaire developed by Schafer and Brown (1991).

Items from scales that had the highest alpha levels, indicating high internal consistency, were used. The questions related to global positive effects of cocaine were of particular interest since these were most likely to be related to abuse potential of the drug. Eight of the questions probed positive aspects of the cocaine experience and seven probed negative aspects.

The data from this sample of college students indicated that there was substantial variability in the magnitude of the initial positive response to cocaine. The mean Global Positive response measured as an average of the individual positive responses was 2.41 (Å standard deviation of 0.722). The relationship between Positive and Negative reaction was not significant ($r(80) = 0.11$), suggesting that the variability was not determined primarily by variability in the dosage of cocaine that had been used. If this were the case, these measures would have been highly correlated.

Two indices of cocaine use were chosen. One was latency to second use since an individual who was at high risk for subsequent abuse might be expected to have a shorter latency between first and second use. The other measure was frequency of cocaine use. It is logical that the greater the abuse potential, the greater the frequency of use of a compound.

It was expected that the initial response would be a good predictor of subsequent use. That is, those with the highest Global Positive responses would be most likely to have shorter latencies to second use and higher frequencies of cocaine use. Support for this hypothesis was obtained. The subjects who had the highest Global Positive scores reported the shortest latency to second cocaine use ($r = -0.43$, $p < 0.001$) and the highest frequency of cocaine use ($r = 0.44$, $p < 0.001$). The Global Negative Effect was not a good predictor of either of these measures of subsequent abuse. However, one Negative Effect question concerning "craving for cocaine" turned out to be the sole predictor of both measures of cocaine use. The correlations between this question ("I was never satisfied when I was on cocaine ... I always wanted more"), and the latency to second cocaine use ($r = -0.32$) or frequency of cocaine use ($r = 0.43$) were higher than for almost all correlations for individual Positive Effects items.

These preliminary data established that the magnitude of the initial positive response to cocaine predicted subsequent frequency of use of cocaine and pattern of use: Higher positive responses on first exposure to cocaine predicted higher lifetime frequencies of use and shorter latencies between first and second cocaine use. A critical question is whether the variability in response to cocaine in humans could be predicted on the basis of pharmacologic history.

History of Stimulant Preexposure

If the animal sensitization model is correct, then a form of sensitization may occur in humans who are exposed to stimulants, and it may engender these individuals predisposed to cocaine's reinforcing properties. This is a difficult hypothesis to evaluate in humans because they may not be very accurate in reporting levels of exposure. Therefore, documented histories of stimulant exposure are preferable. One such group of humans with a medically documented history of stimulant exposure is children who are diagnosed with Attention Deficit Hyperactivity Disorder (ADHD). Based on the animal model of cross-stimulant sensitization, one would predict that

methylphenidate exposure may be a risk factor for subsequent use of cocaine in adolescence or adulthood.

There are some retrospective human data to support this hypothesis. A high percentage of treatment-seeking cocaine abusers have been reported to have prior ADHD diagnosis (Cocores et al. 1987; Rounsaville et al. 1991). Similarly, elevated drug use in adults with prior ADHD diagnosis has been reported (Weiss et al. 1979, 1985; Gittleman et al. 1985), although these differences have been mainly attributed to elevated use of alcohol and marijuana.

The interaction among methylphenidate exposure, ADHD, and cocaine use was recently examined by Dr. Nadine Lambert at the University of California, Berkeley (Davidson et al., in preparation) in a sample of individuals in their mid to late 20s who had used cocaine on at least one occasion. These subjects are a subset of a cohort that participated in a study of treatment of ADHD 15 to 20 years ago. At intake, these subjects were classified as either situationally hyperactive (rated by teachers or parents) or pervasively hyperactive (rated by both teachers and parents) as defined on the school and home forms of the Children's Attention and Adjustment Scale.

In this recent followup, three subgroups of these subjects were tested. One was comprised of situationally or pervasively ADHD subjects who also had a medical diagnosis of hyperactivity and had received treatment with methylphenidate for periods ranging from 1 to 10 years. A second group of subjects were ADHD behavior controls who also were situationally or pervasively ADHD, but had not received treatment with methylphenidate or other central nervous system (CNS) stimulants. Severity of symptoms was roughly equivalent for the two groups of ADHD subjects as indicated by equal proportions of situational and pervasive classification of the subjects. The major difference in the two groups was the presence or absence of stimulant medication. A third group was comprised of age-mate controls. These subjects were originally selected from classrooms in which the hyperactive subjects were enrolled and were matched by birth date. ADHD subjects who received stimulant medication provide a unique test because their exposure history does not require retrospective self-reports but rather is determined from medical histories and is therefore a more reliable index of level of exposure.

Frequency of lifetime cocaine use was established on a rating scale of 1 (once or twice), 2 (3 to 9 times), 3 (10 to 19 times), 4 (20 to 39

times), and 5 (more than 40 times). Subjects were administered a computerized version of the DSM-III-R to further assess the presence of cocaine abuse. Generally, this category included frequency of use as well as legal and social problems associated with cocaine use. Questions concerning nicotine, amphetamine, marijuana, and hard liquor use were also included in the followup.

The medicated ADHD subjects showed the highest percentage of cocaine abuse, as indicated by DSM-III-R diagnosis, double that of either the nonmedicated subjects or the age-mate controls. This was not simply a function of greater exposure to the drug since equal percentages of subjects from all groups had tried cocaine at least once.

A hierarchical regression analysis was performed to determine the contribution of various factors to the frequency rating of lifetime cocaine use for the subjects who had used cocaine. The variables (1) gender, (2) presence or absence of ADHD symptoms, (3) presence or absence of conduct problems, (4) presence or absence of stimulant medication, and (5) tobacco exposure (whether or not 100 cigarettes had been smoked lifetime) were entered. As a comparison, the contribution of these variables to marijuana and hard liquor use was also determined.
Eleven percent of the variance in cocaine use, 18 percent of the variance in marijuana use, and 8 percent of the variance in alcohol use was attributed to these variables. Presence of ADHD symptoms or conduct disorder in childhood did not contribute significantly to any drug use. Exposure to stimulant medication contributed significantly to the explained variance in cocaine use ($r^2(145) = 0.034$, $p = < 0.027$), whereas significant amounts of variance in marijuana use ($r^2(195) = 0.001$, NS) or alcohol use ($r^2(224) = 0.0005$, NS) were not explained by early medication history. Tobacco use contributed to the explained variance for use of all these drugs (cocaine: $r^2(145) = 0.07$, $p = < 0.002$; marijuana: $r^2(195) = 0.085$, $p < 0.001$; alcohol: $r^2(224) = 0.055$, $p < 0.001$). Gender, while contributing significantly to variance in the use of marijuana ($r^2(195) = 0.021$, $p < 0.001$) and alcohol ($r^2(224) = 0.065$, $p = < 0.029$) use, did not significantly contribute to the variance in cocaine use ($r^2(145) = 0.003$, NS).

The use of a community-based sample is particularly important because, in this sample, ADHD status and medication status are not confounded as they are in most clinic-based samples. The availability of a behavior-matched nonmedicated group allowed the evaluation of ADHD and medication as separate contributors to the frequency of cocaine use and abuse. That methylphenidate was still capable of

explaining a small but significant proportion of the variance in cocaine use even after approximately 15 years is of great importance. Although this too was predicted by the animal model, which has shown that behavioral and neurochemical sensitization is enduring (Valadez and Schenk 1994), the number of variables that could interact with the medication effect in humans is relatively high. That the effect was still significant attests to the potency of methylphenidate as a sensitizing agent.

Another particularly interesting aspect of the human data was the finding that smoking also explained a significant amount of the variance in the use of cocaine and other drugs. Since nicotine exposure was sufficient for inducing sensitization to cocaine's reinforcing effects in rats, these findings in humans may be another reflection of the sensitization process. It will be important, of course, to determine whether the initiation of nicotine use preceded the use of cocaine.

FUTURE DIRECTIONS

The data presented here represent preliminary studies of the effects of manipulations on the initial reinforcing effects of cocaine. The objective of this research has been to provide animal models that would allow identification of factors that may predispose subjects to cocaine abuse. The results of these studies have been encouraging, particularly when coupled with the results of the human study. Essentially, stimulant preexposure appears to sensitize rats to the initial reinforcing properties of cocaine, and possibly other stimulants, and can explain a significant amount of the variance in cocaine use in humans.

A number of interesting questions have arisen from the results of the studies presented here that warrant further investigation. For example, pretreatment with *stimulants* has consistently been shown to reduce the latency for acquisition of self-administration. A question of great interest is whether these effects are restricted to stimulants or represent a more general phenomenon of drug exposure. An answer to this question will require parametric studies aimed at comparing the effects of a number of doses of a number of pretreatment drugs (both stimulants and nonstimulants) on the acquisition of cocaine self-administration.

Another question of interest is whether the positive sensitizing agents (stimulants and whatever other drugs prove to provide similar effects on latency to acquisition of self-administration) produce effects that are specific to cocaine reinforcement or also generalize to nondrug reinforcers. The answer to this question will require parallel investigations into the effects of preexposure on self-administration of alternate reinforcers.

These preliminary data pave the road for additional parametric work to "nail down" the phenomenon. For example, experiments that examine the effects of combinations of doses of effective drugs will determine whether a common neurochemical mechanism underlies sensitization produced by drug preexposure. Additional experiments will be required in order to establish what that mechanism is. This may be particularly telling in light of the differences in the ability of amphetamine and nicotine preexposure to alter the response of central dopaminergic systems to cocaine.

Finally, examination of longitudinal databases, such as the one at Dr. Lambert's laboratory at the University of California, Berkeley, may allow for further validation of the animal models and may allow additional variance in cocaine use to be explained by other variables.

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