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Sensitization and Tolerance in Psychostimulant Self-Administration

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SCHENK, S. AND B. PARTRIDGE. *Sensitization and tolerance in psychostimulant self-administration.* PHARMACOL BIOCHEM BEHAV **57**(3) 543–550, 1997.—Under some conditions, stimulant preexposure sensitizes rats to the reinforcing effects of cocaine and other stimulants, whereas under other conditions exposure decreases the reinforcing efficacy of cocaine. This paper reviews the literature on the effects of stimulant preexposure on self-administration, focusing on methodological and interpretative issues. It is concluded that both sensitization and tolerance occur following stimulant preexposure but that these two effects can be dissociated temporally, with sensitization occurring during the development of drug self-administration and tolerance occurring in response to high doses of stimulants administered to experienced self-administering rats. The relative contribution of both of these effects to compulsive drug-taking is discussed, with emphasis on the development of cocaine as a reinforcer, maintenance of self-administration, and relapse to drug-taking. © 1997 Elsevier Science Inc.

Sensitization Tolerance Psychostimulants Self-administration

IT is well documented that drugs of abuse function as positive reinforcers, and it has been hypothesized that these reinforcing properties are critical for the development and maintenance of compulsive drug-taking. The magnitude of the response to the positively reinforcing properties of psychostimulants can be influenced by the pharmacological history of the animal. Repeated exposure to these drugs can modify both the latency to acquisition of self-administration and the self-administration pattern exhibited by experienced rats. Some laboratories have suggested that repeated exposure to stimulants sensitizes subjects to the positive-reinforcing properties of subsequent exposures, whereas others have suggested that repeated exposures render subjects tolerant to the positive effects of subsequent exposures. Although these interpretations appear to be inconsistent, they are derived from results of studies on different phases of self-administration. Data consistent with the sensitization interpretation have been derived from studies that have examined the acquisition of drug-taking, whereas data consistent with the tolerance interpretation have been derived from studies conducted in experienced self-administering animals. In addition, the dosing regimens that are required to produce sensitization or tolerance are different, as are the duration following treatment that each effect purportedly persists.

Recently, questions concerning the interpretation of sensitization to the reinforcing effects of drugs following preexposure have been raised (11). Specifically, Di Chiara [(10), p. 117], while acknowledging the data suggesting sensitization, has questioned "the extent this effect can be regarded as an index of behavioral sensitization. In fact, the observation of a faster rate of acquisition is not equivalent to evidence of an increased reinforcing property of the drug." However, the generation of dose–effect curves for acquisition of self-administration demonstrated that latency to acquisition of cocaine self-administration (measured as the average number of days for a group to meet a criterion for self-administration) is inversely related to the dose of cocaine that serves as the reinforcer (31–33; see below). Thus, a decrease in the latency to acquisition of cocaine self-administration is a reflection of a leftward shift in the dose–effect curve for acquisition of cocaine self-administration. Di Chiara [(10), p. 117] has also questioned how sensitization can occur when "moreover repeated exposure actually results in tolerance." As will be discussed below, both of these phenomena appear to occur, albeit under different conditions of preexposure and testing.

This paper will review the data that propose sensitization or tolerance to cocaine's reinforcing properties and will compare the conditions under which each occurs. It will be suggested that both of these effects of stimulant exposure occur. The contribution of each to acquisition of self-administration, maintenance of self-administration, and relapse to drug-taking will be discussed.

ACQUISITION OF COCAINE SELF-ADMINISTRATION

When animals are given limited access to psychostimulant self-administration (2–3 h daily), there is large across-subject

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variability in the latency to acquisition of an operant for this behavior. Deneau, Yanagita, and Seevers (7) originally described some monkeys as "resistant" and others as "susceptible" based on their propensity to acquire self-administration. In our laboratory, we routinely observe that some rats acquire self-administration within just a few days of testing (susceptible), whereas for others, acquisition is protracted, requiring several test sessions to achieve criterion responding (resistant).

Figure 1 shows responses on an active (cocaine) and inactive lever during daily 2-h self-administration sessions (0.25 mg/kg/infusion) for four rats. Three of the rats (panels A, B, and C) showed a pattern of responding that was fairly characteristic. During the early days of testing, the number of responses on the two levers was comparable. There was an abrupt increase in responding on the active lever (sometimes with a concomitant decrease in responding on the inactive lever) that reached asymptote within 1 day. Data from a fourth rat (panel D) are shown as a pattern that is also occasionally seen. For this rat, the increase in responding on the active lever occurred more gradually, and asymptotic responding was achieved following several additional days of testing.

The day on which cocaine self-administration was acquired is unambiguous for rats whose data are depicted in panels A (day 5), B (day 9), and C (day 10). The data in panel D are more difficult to interpret because of the gradual increase in active lever responding between days 4 and 7.

MAINTENANCE OF SELF-ADMINISTRATION

Once acquisition occurs, the minimum dose that will maintain self-administration remains fairly stable over long periods of daily testing. This stability is depicted in Fig. 2. These data were derived using a within-session dose–effect curve determination procedure modeled after Winger et al. (38). For these tests, self-administration of each dose of cocaine was obtained during 30-min bins with cocaine being delivered on an FR 5 schedule of reinforcement. After each 30-min bin, there was a 10-min timeout before the next dose was avail-

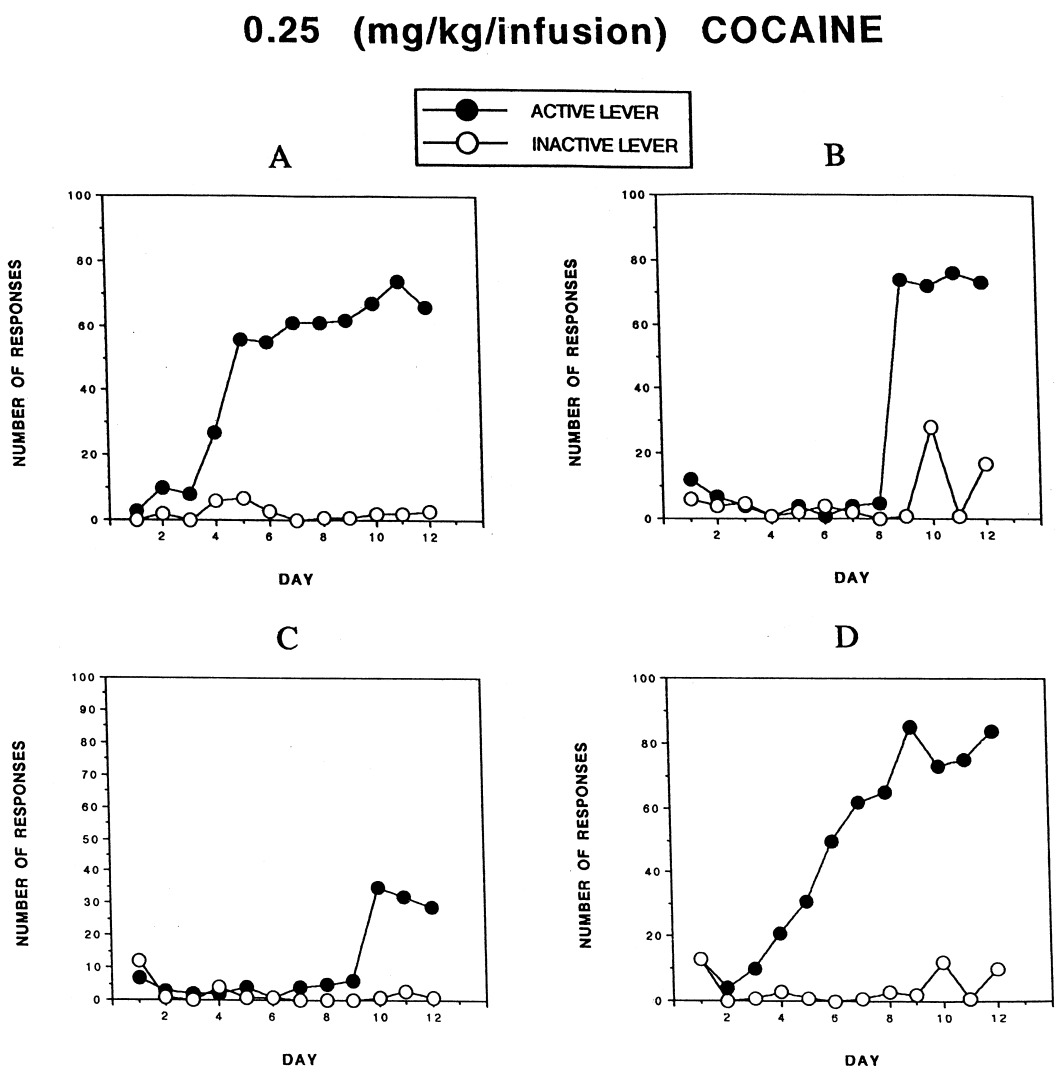

FIG. 1. Number of responses on an active and an inactive lever during daily 2-h self-administration sessions. Data are presented for four individual subjects during acquisition of self-administration of cocaine. Depressions of the active lever were reinforced according to an FR 1 schedule of reinforcement.

able. Doses were run in descending order. At the start of each 30-min session, an infusion of the available cocaine dose was experimenter-delivered. Thereafter, infusions were delivered according to an FR 5 schedule of reinforcement. A sufficient number of cocaine doses was run to obtain both the rising and falling portion of the dose–effect curve.

Data shown are from experienced rats that had been tested daily over a period of more than 30 days once criteria for stability in threshold were obtained. Generally, these rats had received at least 15 previous daily test sessions during acquisition of self-administration (FR 1 schedule) and within-session dose–effect training. Thus, these data represent responding during a minimum of 45 days following the first cocaine exposures.

For three of these rats (numbers 109, 110, and 203), the minimum dose that maintained reliable responding was consistent across trials (0.03 mg/kg/infusion for rat 203 and 0.06 mg/kg/infusion for rats 109 and 110). For the other rat (number 102) there was a small shift to the left in the minimum dose that would maintain reliable self-administration. Noteworthy is that all rats demonstrated an increase in the number of responses emitted for the cocaine doses that were on the falling portion of the dose–effect curve with extended testing. That is, although the minimum dose for self-administration remained fairly stable or decreased slightly across days, doses above threshold were generally taken more rapidly with repeated testing.

Increases in drug-taking for high doses of cocaine are characteristic of antagonism of the drug's reinforcing effects. Indeed, a number of laboratories have shown increases in responding following administration of dopaminergic antagonists (5,21). These findings are generally interpreted as indicating partial blockade of a system that is relevant for the drug's rein-

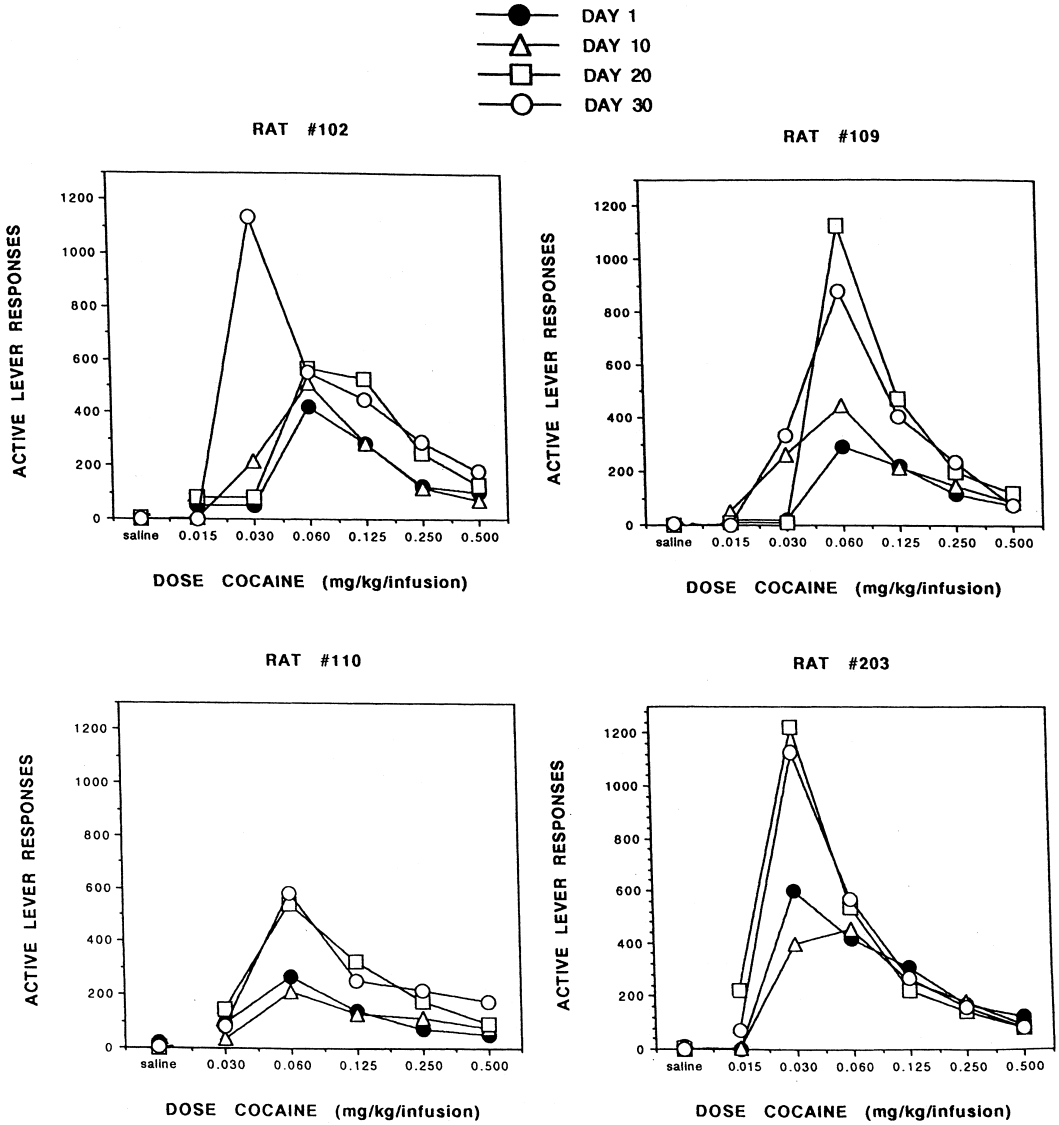

FIG. 2. Cocaine self-administration as a function of cocaine dose and day of testing for four individual rats. Data were derived using a multidose within-session procedure. Responses were reinforced according to an FR 5 schedule of reinforcement.

forcing effect, with the increased responding compensating for the block. A small number of rodent studies and a larger number of primate studies have indicated that these same manipulations shift the dose–effect curve for cocaine self-administration to the right (1,25,36,41). These data have been widely used in support of the dopamine theory of reinforcement, which posits that these systems mediate the reinforcing effects of cocaine.

The increases in responding that we observed are not easily interpreted within this framework because the increase was not accompanied by a shift to the right in the dose–effect curve. Instead, an increase in responding for some doses was found. These findings may indicate that with repeated testing and daily exposure to high levels of cocaine (20–25 mg/kg IV) through self-administration, tolerance develops to some of the rate-limiting effects of cocaine (20). Thus, effective doses may be self-administered more rapidly not because of a change in the subjective or reinforcing effect of the drug, but because the rat is capable of responding more rapidly. This interpretation of the data accounts for the failure to observe a horizontal shift in the dose–effect curve because it proposes that the reinforcing effect has not changed as a result of repeated exposure to the drug.

Further examination of Fig. 2 reveals that the minimum dose for cocaine self-administration (0.03 or 0.06 mg/kg/infusion) was much lower than the dose that was capable of producing self-administration during acquisition studies. For example, following 15 days of acquisition testing (2-h daily sessions, FR 1 schedule of reinforcement), approximately 40% of the rats failed to achieve criterion responding when the available dose of cocaine was 0.125 mg/kg/infusion (31). Acquisition of self-administration of lower doses of cocaine was not achieved by any rats within a 20-day period of daily 2-h tests (unpublished observations). However, when higher doses of cocaine served as the reinforcer, virtually all rats acquired self-administration within 8–10 days [control groups from (6–18,31,33)]. That lower doses were reliably self-administered by all rats once self-administration had been acquired suggests that experience with cocaine in a self-administration context sensitized rats to the reinforcing properties of the drug. The stability of threshold doses once acquisition had occurred suggests that the development of sensitization may be a process that is restricted to the acquisition phase of cocaine self-administration.

SENSITIZATION TO THE REINFORCING EFFECTS OF STIMULANTS

A small number of investigators have noted that after experience with cocaine or other stimulants, lower doses than would initially maintain self-administration become effective reinforcers. For example, Woolverton et al. (40) 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 et al. (26,27) 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, again suggesting a shift to the left in the dose–effect curve.

Goeders (personal communication, April 1996) has also found that once cocaine self-administration is acquired, lower doses become capable of maintaining self-administration. This was followed up systematically by conducting repeated dose–effect determinations. Data from his laboratory (unpublished; reported here with permission) are presented in Fig. 3. Male Wistar rats were tested for cocaine self-administration during daily 1-h tests. The rats were pretrained to press a lever located on the opposite wall of the chamber for food. They were then given weekly tests (Monday through Friday) for cocaine self-administration. Each Monday, lever pressing was established using the food reinforcer. On the remaining days, responding for cocaine was measured. During the first week, responding for saline was measured and in subsequent weeks the different cocaine doses were tested in ascending order. Once the first dose–response determination was completed, a second determination was run following the same procedure as for the first. As is evident, doses that were unable to maintain responding during the first dose–response determination became effective reinforcers during the second dose–response determination, once self-administration of higher doses had been acquired (Fig. 3). These data support those of Woolverton et al. (40) and support the conclusion that following exposure to cocaine during the first dose–response determination, the rats had become sensitized to cocaine's reinforcing properties, as indicated by a leftward shift in the dose–effect function.

Recently, we have tried to determine the parameters of cocaine administration that will produce a sensitized response to the reinforcing properties of cocaine. Rats were treated for 5 days with either a single daily injection of cocaine (10.0 or 20.0 mg/kg) or two daily injections separated by 1 h. The pretreatments were administered in the animal colony, and the rats were returned to their cages immediately after each injection. This procedure was followed so as to minimize the contribution of conditioning to any subsequent effects of cocaine. Three days following the last of the pretreatments, the acquisition of cocaine self-administration (0.25 mg/kg/infusion) was

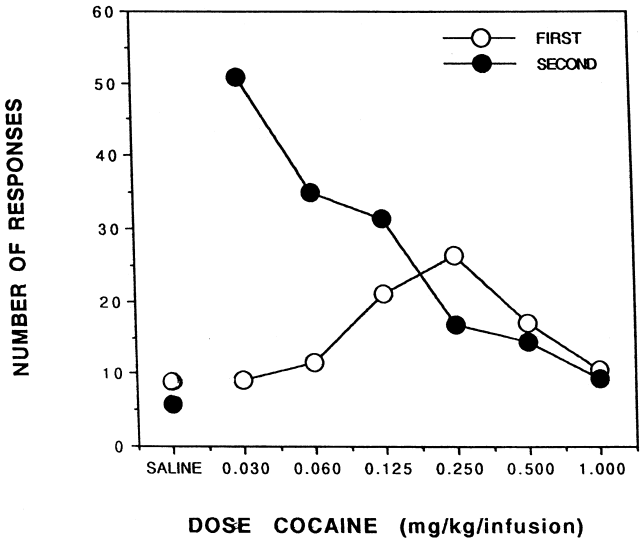

FIG. 3. Cocaine self-administration data (from Goeders, unpubl.) during a first and second dose–effect determination (see text for details). During the first determination, obtained during acquisition of self-administration, the threshold for self-administration is high. With experience with cocaine, lower doses became effective reinforcers, as indicated by the data obtained during the second dose–effect determination.

determined for the various groups and compared with data from rats that received injections of the saline vehicle.

During acquisition testing, the rats were given access to cocaine during 2-h daily self-administration tests. The first infusion of each daily test was experimenter-delivered, and subsequent infusions were delivered according to an FR 1 schedule of reinforcement. Three criteria were used to determine the number of days to needed acquire cocaine self-administration. First, the number of reinforced responses had to exceed 30 during the 2-h session. Second, the ratio of responses on the lever that was positively linked to a cocaine infusion (active lever) and a "dummy," inactive lever, had to be greater than 3:1. Finally, these two criteria had to be met for 3 consecutive days.

As we have previously reported, control rats required an average of 7.1 days to acquire self-administration of this dose of cocaine. Similar data were obtained from rats pretreated with the single daily exposure to cocaine (10.0 or 20.0 mg/kg) or with two daily injections of 10.0 mg/kg cocaine. However, acquisition of cocaine self-administration occurred with a significantly ($p < 0.05$) shorter latency (average of 4.1 days) for the rats that received two daily injections of 20.0 mg/kg cocaine on each of the 5 days that comprised the pretreatment phase.

There may be a trade-off between the number of pretreatments and the dose of cocaine required to produce the sensitized response such that the lower doses may become effective with an increased number of exposures. Indeed, we have previously demonstrated sensitization in this acquisition procedure when rats received 12 daily exposures to a single injection of 10.0 mg/kg cocaine (17). This sensitized effect is produced by exposure to a number of other noncocaine stimulants (16,18,33) as well as by a variety of environmental manipulations (2,15).

RELEVANCE OF SENSITIZATION TO COCAINE SELF-ADMINISTRATION

Predisposition to Cocaine Abuse

In a study on humans by Davidson et al. (6), many of the participants reported that the first several exposures to cocaine were not positive, and these same individuals reported lower cocaine use than subjects who reported that the initial cocaine experiences were very positive. Thus, individuals who experienced cocaine as more positive on initial use tended to use the drug a second time more quickly and to use it more frequently than subjects who did not experience these positive effects of cocaine. These findings suggest that for some individuals cocaine is a strong positive reinforcer, whereas for others the drug is not and that the magnitude of the initial response is a good predictor of subsequent risk for abuse.

The animal data are consistent with this finding; the magnitude of the initial reinforcing effect of cocaine, as indicated by latency to acquisition of an operant to obtain cocaine infusions, exhibits a large amount of across-subject variability. An important question that emerges concerns why some individuals appear more susceptible to the positive reinforcing effects of cocaine.

We have hypothesized that sensitization may be a process that contributes to the development of cocaine as a reinforcer in some subjects. As a result of genetic or environmental predispositions, some subjects may become more easily sensitized to cocaine and may therefore be predisposed to cocaine abuse. To assess this possibility, our laboratory has tried to characterize sensitization to the reinforcing effects of cocaine.

As noted above, across-subject variability in cocaine self-administration is most pronounced during acquisition of self-administration; for some subjects the latency to acquisition is short, whereas others require extended test sessions. We have suggested that latency to acquisition is an index of sensitivity to cocaine's initial reinforcing effects, and we have supported that hypothesis by demonstrating that the number of test days required to acquire cocaine self-administration is inversely related to the dose of cocaine that serves as the reinforcer (31–33). Thus, increasing the magnitude of the reinforcer by increasing the dose of cocaine reduced the latency to acquisition of cocaine self-administration. Although virtually all subjects will eventually self-administer cocaine, some appear more sensitive to cocaine's initial reinforcing properties and acquire self-administration with short latencies (as though the dose of cocaine is higher), whereas others appear relatively insensitive to cocaine's initial reinforcing properties and acquire the operant with longer latencies (as though the dose of cocaine is lower). Thus, sensitization is viewed as a process that increases the vulnerability to cocaine's positively reinforcing properties.

However, it is also important to note that, given a sufficient number of exposures to cocaine, all rats will eventually acquire self-administration. This highlights the ultimate risk of continued exposure. We have also hypothesized that, at this time, once acquisition has occurred, the subjects have all become sensitized through exposures to cocaine. This explains why there is so little across-subject variability in the threshold for cocaine self-administration. Most of the variability apparent on initial exposure has been overcome as a result of subsequent exposures. We further hypothesize that the sensitization procedure is all or none. The data in Fig. 2 support this hypothesis, in that thresholds for cocaine self-administration remain consistent over days.

Relapse

In addition to the development of reliable self-administration, sensitization has also been proposed to play a role in drug-seeking (relapse). With repeated presentations, cocaine may become capable of eliciting "cocaine-induced craving" (19), which may lead to the compulsive drug-taking characteristic of the binge in abusers. Thus, once self-administration is acquired and relevant circuits become fully sensitized, the drug itself may serve to trigger drug-seeking, which leads to continued drug-taking. In addition, associative processes likely also become sensitized so that drug-related cues become capable of eliciting drug-seeking, thereby leading to continued drug-taking.

This has been elegantly demonstrated by Shippenberg and colleagues (34,35). They have shown that repeated exposure to cocaine shifts the dose–effect curve for the development of a cocaine-induced conditioned place preference to the left. Thus, cocaine exposure increases the ability of environmental cues to acquire conditioned reinforcing properties. This loop of drug and environment serving to maintain drug-taking during a binge may be the sensitized "drug wanting" referred to by Robinson and Berridge (29).

There are data from humans and animals that support this notion. For example, abusers (those who are fully sensitized to cocaine) report strong craving in response to either cocaine itself or to cues that have been associated with cocaine (3). Administration of noncocaine stimulants (like caffeine) can also elicit craving for cocaine in abusers (30), possibly by providing relevant interoceptive cues. In animal models, extinguished cocaine self-administration can be reinstated by the noncontingent administration of cocaine (4,9,37,42) and by the presentation of cues that had been associated with cocaine self-administration (9).

TOLERANCE TO THE REINFORCING EFFECTS OF STIMULANTS

In a series of papers, Emmett-Oglesby and his group (12,13) have studied the effect of more stringent preexposure regimens on the subsequent self-administration of cocaine. In these studies, experienced cocaine self-administering rats were administered cocaine (20.0 mg/kg IV every 8 h for 7 days), *d*-amphetamine, or methamphetamine (0.32, 1.0, or 3.2 mg/kg every 12 h for 7 days). Both prior to and following the chronic dosing, a multidosing and progressive ratio method were used to determine the magnitude of the reinforcing effects of cocaine.

After the chronic cocaine dosing regimen, high doses of cocaine (approximately 0.5, 1.0, and 2.0 mg/kg/infusion) were subsequently self-administered more rapidly (12,13). There was a parallel shift downward in the curve that relates interreinforcement time to dose of self-administered cocaine. Similar results were obtained when rats were pretreated with the highest dose of either amphetamine or methamphetamine (24). The higher rates of intake produced by cocaine preexposure were transient, and interreinforcement times for the three cocaine doses returned to pretreatment values by 3 days following the chronic dosing.

These data have been interpreted as indicating tolerance to the reinforcing effects of cocaine, because lower doses of cocaine are self-administered more rapidly than higher doses. Unfortunately, full dose–effect curves were not run, and so these data must be interpreted cautiously, particularly in light of the data presented in Fig. 2. However, the progressive ratio procedure was also used to assess changes in cocaine's reinforcing effects following the chronic treatments. In this procedure, the number of responses that must be emitted for each successive infusion of cocaine increases logarithmically within a session. It has been shown that as the dose of cocaine is increased, the number of responses that an animal will emit for a single infusion also increases (28). The last ratio completed for any dose of cocaine is termed the break point. When the progressive ratio paradigm was used to assess the effectiveness of cocaine as a reinforcer following chronic dosing, break points were reduced, suggesting that the motivation to self-administer cocaine had decreased. These data also suggest that the decreased interreinforcement intervals observed when a fixed ratio schedule was used do not simply reflect an increase in the ability of rats to respond due to tolerance to the disruptive effects of the drug. If this were the case, one would have expected the break points to increase in a like manner. Because the break points decreased, the most parsimonious interpretation of the increase in responding is that under some chronic dosing regimens, tolerance to the reinforcing effects of cocaine can be demonstrated.

ROLE OF TOLERANCE IN DRUG SELF-ADMINISTRATION

It is hard to imagine how tolerance to the reinforcing effects of cocaine might play a role in the acquisition of cocaine self-administration. It is also difficult to incorporate tolerance to the reinforcing effects of drugs into a model where this phenomenon maintains drug-taking. Thus, although tolerance to cocaine's reinforcing effects appears to occur following exposure, it does not seem that this phenomenon plays a role in drug self-administration. Rather, tolerance to cocaine's reinforcing effects may be a component of the syndrome that comprises cocaine withdrawal.

Following a binge of cocaine self-administration (12–48 h), the sensitivity of endogenous reinforcement pathways is decreased, as measured by increased thresholds for intracranial self-stimulation (22,39). The self-stimulation thresholds remained elevated for as long as 24–48 h. At this time, animals are resistant to self-administration, as indicated by the decreased break points for cocaine self-administration (24). Thus, tolerance may be a reflection of the generalized decreased sensitivity of endogenous reinforcement systems produced by high-level cocaine exposure.

SUMMARY

Sensitization and tolerance are both produced following preexposure. We have demonstrated sensitization to the positively reinforcing properties of cocaine by showing a reduced

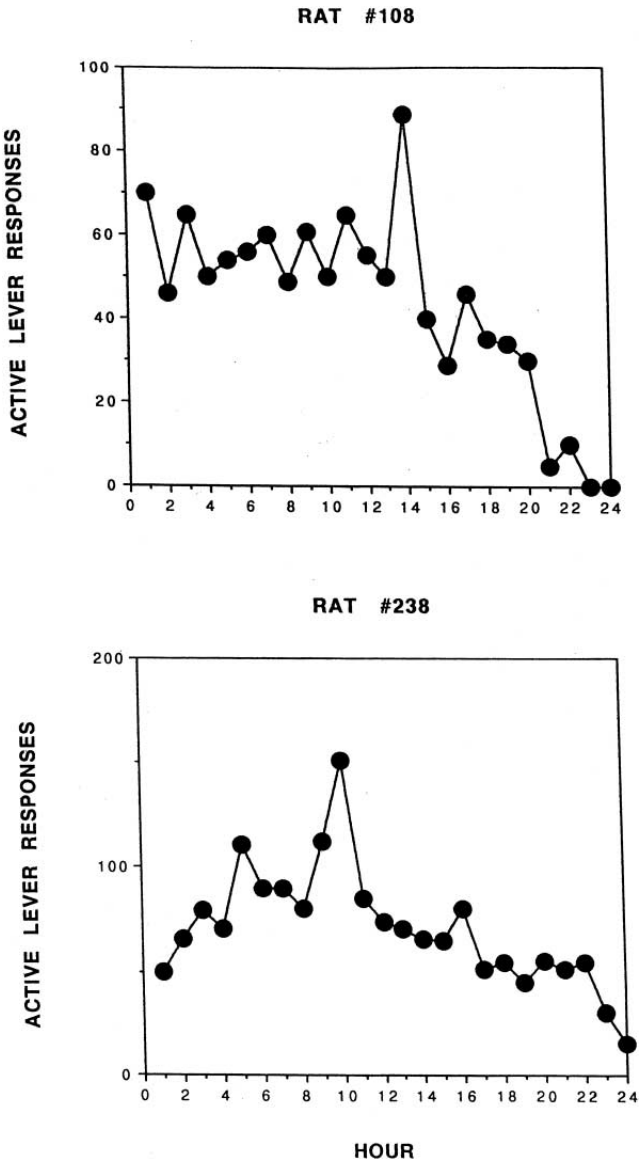

FIG. 4. Number of responses per hour for two rats that had unlimited cocaine available for a 24-h session. Lever depressions were reinforced according to an FR 5 schedule of reinforcement. Note that responding is maintained at a steady rate for at least 16 h. Thereafter, responding progressively decreases for the remainder of the session.

latency to acquisition of self-administration following intermittent exposures to low doses of cocaine. Tolerance to the positively reinforcing properties of cocaine is produced by higher dose preexposures to experienced rats. Thus, sensitization and tolerance are behavioral effects of repeated psychostimulant administration that can be dissociated temporally as well as according to the magnitude and chronicity of the dosing regimen. Further, tolerance is transient, lasting only a few days, whereas sensitization appears to be enduring.

Both of these effects of repeated psychostimulant administration may define different phases of cocaine use. Sensitization in reinforcement systems is proposed to occur during the development of cocaine as a positive reinforcer, a prerequisite to compulsive drug-taking. Thereafter, sensitized systems may play a role in maintenance of drug-taking during a binge, when they are activated by cocaine itself (cocaine-induced craving), or in relapse to cocaine use triggered by cocaine-associated cues. Tolerance, on the other hand is a consequence of large-dose cocaine administrations and may be a reflection of decreased sensitivity of reinforcement systems that characterize cocaine withdrawal.

These notions are consistent with some aspects of the incentive–sensitization theory proposed by Robinson and Berridge (29). The theory proposes that tolerance to the "liking" of cocaine occurs during a self-administration "binge" and that drug-taking then comes under the control of a sensitized "wanting" system. Indeed, humans report within-session tolerance to the subjective effects of cocaine (14), and drug-taking persists in spite of the development of tolerance. If tolerance develops to cocaine's reinforcing effects during a binge, rates of responding for cocaine would be expected to increase to compensate for the decreased effectiveness of the drug. However, during a 24-h binge, no consistent increases in responding for cocaine were observed (see Fig. 4).

The failure to observe tolerance during the binge may not be inconsistent with the incentive–sensitization theory (29), because it proposes that there is a shift in the process that is controlling self-administration during a binge. If the incentive properties of the drug itself dominate drug-taking (due to a sensitized "wanting" system) as the animals become tolerant to the reinforcing effects of the drug, increases in responding may not be expected. This is because the reinforcing effects of the drug (which have now decreased due to tolerance) are no longer controlling behavior.

Tolerance may only be apparent when measured following the binge, during short-duration self-administration tests during which responding may be controlled primarily by the magnitude of the reinforcing effects of cocaine [Emmett-Oglesby and coworkers (8,12,13) restricted the number of cocaine infusions in their tests to 15]. There are a number of models that purport to measure drug-seeking ("craving") (23). If "wanting" is indeed sensitized during the period when "liking" is tolerant, it is expected that the ability of cocaine to induce drug-seeking would be increased at a time when the reinforcing effects of cocaine are decreased.

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