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BRIEF COMMUNICATION

Persistence of the Ability of Amphetamine Preexposure to Facilitate Acquisition of Cocaine Self-Administration

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VALADEZ, A. AND S. SCHENK. *Persistence of the ability of amphetamine preexposure to facilitate acquisition of cocaine self-administration.* PHARMACOL BIOCHEM BEHAV **47**(1) 203–205, 1994.—This study assessed the enduring effects of amphetamine preexposure on the subsequent reinforcing effects of cocaine. Rats received nine daily injections of either *d*-amphetamine SO_4 (2.0 mg/kg, IP) or vehicle 45 days prior to testing of the acquisition of cocaine (0.25 mg/kg/infusion) self-administration. The latency to acquire reliable cocaine self-administration was shorter (day 3) in the amphetamine-preexposed rats than in the vehicle-preexposed rats (day 6). These data are comparable to those observed when testing was carried out 1 day following the treatment. In previous studies, shorter latencies to acquisition also occurred when the training dose of cocaine was increased, suggesting that the treatment had sensitized rats to cocaine's reinforcing properties. These effects of amphetamine exposure persist for 45 days following treatment, which suggest a long-lasting phenomenon.

Cocaine Amphetamine Self-administration Sensitization

WHEN low doses of stimulants are administered on an intermittent, repeated schedule, the locomotor activating effects are progressively augmented (10,19). These increased responses to stimulants persist for extended periods of time (10), suggesting that long-term changes in the response of central systems to stimulants underlie sensitization. The sensitized behavioral response is accompanied by an increased response of the mesolimbic dopamine (DA) system following a challenge injection of the drug (10,19). This system is generally believed to mediate the motor activating effects of dopaminergic agonists (17). Thus, behavioral sensitization is accompanied by neurochemical sensitization in relevant central systems.

Although not as thoroughly examined, sensitization to the reinforcing properties of stimulants following preexposure has also been demonstrated. For example, amphetamine exposure results in shorter latencies to the subsequent acquisition of intravenous amphetamine self-administration (8). Woolverton et al. (18) demonstrated that repeated administration of methamphetamine enhanced subsequent self-administration in rhesus monkeys.

We have demonstrated cross-sensitization between various stimulants and cocaine when intravenous self-administration was assessed. When low doses of cocaine were used as the reinforcer, preexposure to cocaine (2), amphetamine (1), nicotine (1), and caffeine (3) reduced the latency to subsequent acquisition of intravenous cocaine self-administration. These studies assessed the reinforcing properties of cocaine 1 day following the last day of a 9-day pretreatment schedule. The present study focuses on the enduring properties of this stimulant-induced sensitization to cocaine's reinforcing properties by examining latency to acquire self-administration 45 days following the preexposure regimen.

METHOD

Subjects

Thirty-six male, Sprague-Dawley rats (Harlan, TX), weighing between 350 and 400 g, were used. They were housed individually in standard plastic cages in a temperature (20°C)-controlled room. The colony was maintained on a 12 L : 12 D cycle, with lights on at 0800 h. Standard rat chow and water was available ad lib. The rats were acclimated to laboratory conditions for 1 week prior to any manipulations.

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Procedure

Between 1000 and 1200 h, rats received a daily injection of either *d*-amphetamine SO_4 (2.0 mg/kg, IP) or an equal volume of the saline vehicle (1.0 ml/kg). This dose of amphetamine and the injection regimen was chosen because we have previously shown a decreased latency to acquire cocaine self-administration when rats were tested 1 day following the last injection (1,13). Following the final injection, a 40-day waiting period ensued. During this time, normal cleaning of cages and replenishment of food and water proceeded. Aside from this, the rats were left untouched.

Surgery

On the 41st day following the last amphetamine injection, the rats were implanted with chronic intrajugular cannulae. Deep anesthesia was produced by separate injections of sodium pentobarbital (20 mg/kg, IP) and ketamine (60 mg/kg, IP). Silastic cannulae were implanted into the external jugular vein according to a modification of Weeks (16). A 22-gauge stainless steel tube was attached to the distal end of the cannula and was passed subcutaneously to an exposed area of the skull. The steel tube was then secured to the skull with dental acrylic mounted with four screws in the skull. To prevent clotting and infection, each cannula was flushed daily with a 0.1 ml saline (0.9%) solution containing heparin (1.25 units/ml), penicillin G sodium (250,00 units/ml), and streptokinase (1900 units/ml). Four days following surgery, self-administration testing began.

Apparatus

Sixteen operant boxes (Med Associates, ENV-001), equipped with two levers were used. Depression of one (the active lever) resulted in a 12-s intravenous delivery of 0.10 ml of cocaine HCl dissolved in sterile saline. Coincident with drug delivery was the illumination of a house light located above the lever. Depression of the other lever (the inactive lever) had no consequence. Drug was delivered by motorized pumps (Razel, A with 1 rpm motors) controlled by two IBM computers that were interfaced with the chambers through the OPN software package (15).

Testing

All testing was carried out during the light portion of the cycle. At the start of each daily 2-h session, an initial priming infusion of cocaine (0.25 mg/kg/infusion) was delivered by the experimenter. Subsequent infusions of cocaine (0.25 mg/kg/infusion) were delivered on an FR1 schedule. Testing continued for 10 days. At the end of the tenth day, the cannulae were infused with sodium pentobarbital (20 mg/kg, IV). An immediate loss of the righting reflex confirmed the patency. Five rats from the amphetamine treatment group and four rats from the saline treatment group failed this barbiturate test and, thus, were not included in any analyses. Data from the remaining 27 rats (amphetamine = 13, saline = 14) are presented.

Data Analysis

The number of active and inactive lever responses was recorded during each of the 10 daily 2-h self-administration sessions. These data were analyzed using individual repeated measures ANOVAs (lever × days). The day on which the number of active lever and inactive lever responses were significantly different was determined by Tukey post hoc tests.

Drugs

Cocaine HCl was supplied by the NIDA (Research Triangle Park, NC); *d*-amphetamine SO_4 was obtained from Sigma Chemicals Co. (St. Louis, MO). All drug weights are based on the salt.

RESULTS

Figure 1 shows the number of active and inactive lever responses per session across 10 days of testing. The data from

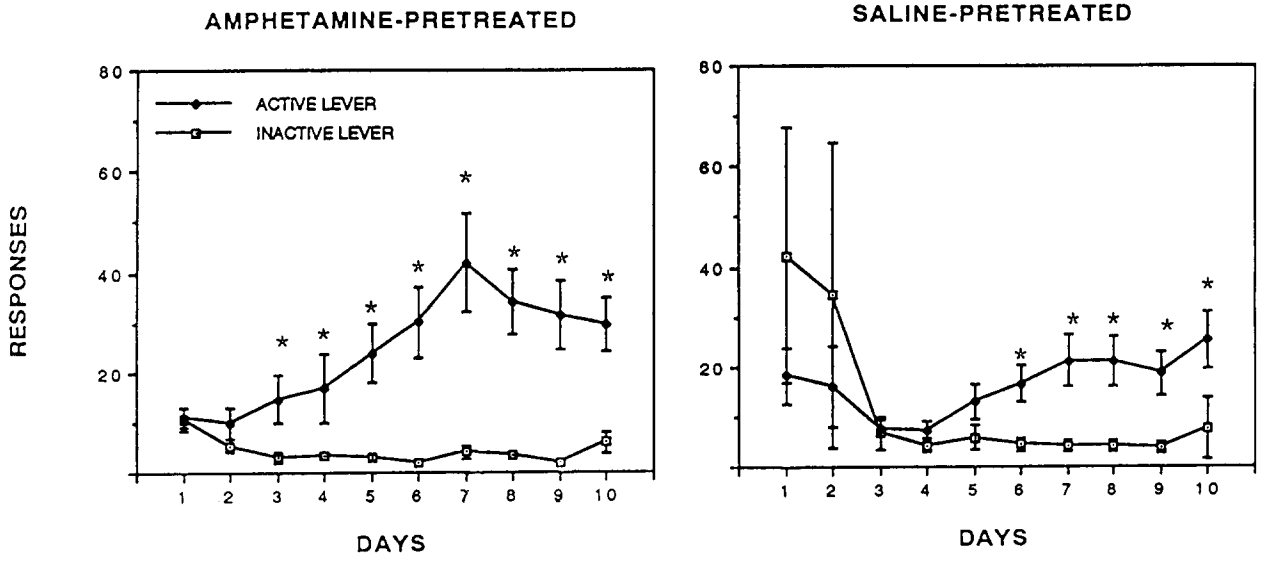

FIG. 1. Mean number (±SEM) of active and inactive lever responses per each daily 2-h cocaine self-administration (0.25 mg/kg/infusion) test for rats that were pretreated for 9 days with amphetamine (left panel) or saline (right panel).

the amphetamine- and saline-preexposed rats are presented in the left and right panels, respectively.

For the saline-preexposed group, a repeated measures ANOVA (lever × days) on the number of responses for each 2-h session indicated a significant interaction between levers and days, $F(9, 117) = 2.689$, $p = 0.0071$. Tukey post hoc tests revealed that a preference for the active lever developed on day 6.

For the amphetamine-pretreated rats, a repeated measures ANOVA (lever × days) also revealed a significant interaction effect, $F(9, 108) = 9.992$, $p = 0.0001$. Tukey post hoc test revealed that a preference for the active lever developed by day 3 of testing.

DISCUSSION

In previous studies, when testing was carried out 1 day following preexposure, amphetamine-treated rats developed a significant preference for the active lever by day 3 of testing. Saline-preexposed rats developed a preference for the active lever by day 6 of testing (14). Thus, the effects of preexposure to amphetamine were the same when tests were carried out 1 day or 45 days following exposure. Furthermore, rates of responding on the active lever were similar to that of the groups in the present study.

A decreased latency to develop a preference for the active lever was also observed when the dose of cocaine that served as the reinforcer was increased (1,14). Thus, amphetamine exposure produces effects that are comparable to when the dose of cocaine is increased. One possibility for reduced latency is that amphetamine-preexposed animals may exhibit heightened activity in response to cocaine (12) and, therefore, come into more frequent contact with the active lever. However, if this were the case, one would expect the amphetamine-exposed rats to also exhibit higher rates of inactive lever responses. This was not observed. A more likely explanation is that amphetamine treatment had sensitized rats to cocaine's reinforcing effects.

The reinforcing effects of cocaine are generally accepted as being a result of the drug's effects on central dopaminergic systems (4,5,7,14,17,19). Alterations in the response of the mesolimbic dopamine system to cocaine following treatment regimens that result in behavioral sensitization have been demonstrated. For example, following exposure to cocaine, amphetamine, and caffeine, the response of the mesolimbic dopamine system to stimulant challenges is enhanced under conditions that lead to behavioral sensitization (3,6,7,9,11). The present data provide an additional criterion of persistence of the effect that should be met if a neurochemical correlate of behavioral sensitization to cocaine's reinforcing effects is to be considered a viable candidate.

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