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RAPID COMMUNICATION

Cocaine and Amphetamine Facilitate Retention of Jump-Up Responding in Rats

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JANAK, P. H. AND J. L. MARTINEZ, JR. *Cocaine and amphetamine facilitate retention of jump-up responding in rats.* PHARMACOL BIOCHEM BEHAV **41**(4) 837–840, 1992.—The effects of cocaine and *d*-amphetamine administration on the acquisition of an automated jump-up active avoidance task were examined in two separate experiments. On days 1 and 2, male Sprague-Dawley rats received one escape-only training trial, followed immediately by the intraperitoneal injection of cocaine, amphetamine, or saline. On day 3, subjects received eight escape/avoidance trials. The posttraining administration of cocaine (2.75 and 5.55 mg/kg) and amphetamine (0.3 and 1.0 mg/kg) on days 1 and 2 facilitated jump-up avoidance performance on day 3. Importantly, both cocaine and amphetamine enhanced learning and memory under experimental conditions that allowed for drug-free training and testing.

Cocaine Amphetamine Active avoidance Memory modulation Posttraining Rats

POSTTRAINING amphetamine facilitates the later performance of rats or mice at test in a number of conditioning situations, including: passive (13,23,25), one-way (22), and two-way (6,10) active avoidance responding; conditioned suppression of drinking (3,39); Y-maze (4,5,19) and radial maze (31,35) performance; and lever-press response acquisition (30).

The effects of cocaine on learning and memory are less well characterized. The majority of research thus far examined the conditioning effects of cocaine administered either before training (4) or before testing (2,7,15,20,21,36,38). Since cocaine produces a variety of behavioral effects including changes in locomotion (8), attention (11), and schedule-determined responding rates (40), the effects of cocaine on performance measured while a subject is under the influence of the drug is difficult to ascribe to an effect of cocaine on learning and memory.

An early study (4) found that the posttraining administration of cocaine to mice trained in a Y-maze discrimination procedure did not affect retention performance; however, only a single 10-mg/kg dose of cocaine was examined. Recent research indicates that posttraining cocaine administration facilitates acquisition of a one-way trough active avoidance task in rats (17) and mice (37), and facilitates retention of a passive avoidance task in mice (16). The present study compares the memory-enhancing effects of posttraining cocaine and amphetamine administration on acquisition of a jump-up active avoidance response in rats.

METHOD

Subjects

Male Sprague-Dawley rats (270–320 g), obtained from Simonsen (Gilroy, CA), were housed individually under standard laboratory conditions. Subjects were maintained on a 12 L:12 D cycle (lights on at 7 a.m.) and allowed continuous access to food and water. Rats were allowed 6 days to acclimate to housing conditions before experimentation began. All subjects were weighed 24 h prior to experimentation. Housing conditions and experimental protocols were approved by the Animal Care and Use Committee, University of California, Berkeley, and are in accordance with National Institutes of Health guidelines.

Apparatus

The conditioning chamber (Automated Shelf-Jump, Lafayette Instruments) was a 9 × 8 in. rectangle with two opposing lucite walls and third metal wall (all 8 in. tall). The fourth wall contained a rectangular metal compartment, which (when open) was recessed 5 in. from the chamber proper, was 8 in. in length, and was elevated 3.5 in. from the floor of the chamber. When the shelf was in the closed posi-

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tion, the back wall of the platform was brought flush with the two side lucite walls, appearing then as a continuous metal wall. The floor of the chamber consisted of a steel-rod grid floor, through which a constant current foot-shock was delivered. A houselight was mounted 6 in. from the floor on the metal wall opposite the shelf. A pressure-sensitive switch under the platform registered jump-up responses. All equipment was controlled by an Apple IIe computer interfaced with solid-state control equipment (Lafayette Instruments).

Active Avoidance Conditioning

Conditioning consisted of three consecutive daily sessions. Subjects were brought into the testing room at 9 a.m. on day 1; training began 3 h later. On day 1, each rat was placed on the floor of the chamber, with the shelf in the closed position. Ten s after the initiation of the trial, three events occurred simultaneously: 1) the back wall of the platform withdrew, exposing the platform; 2) the conditioned stimulus (houselight) came on; and 3) a foot-shock of 310 μA was delivered to the floor of the chamber. The foot-shock and houselight remained on for 30 s or until the subject escaped by jumping up onto the exposed platform. Each subject was then removed from the apparatus, injected with drug or vehicle, and replaced into the home cage. Procedures on day 2 were exactly the same as on day 1. On day 3, each rat received seven conditioning trials identical to those on days 1 and 2 except the platform was exposed and the houselight came on 10 s prior to foot-shock onset; therefore, the subject could avoid foot-shock by jumping onto the exposed platform prior to shock initiation. Following a 30-s intertrial interval, the back wall of the platform moved forward, gently depositing the rat on the steel-rod platform and initiating the start of the next trial. Subjects that did not learn the escape response on days 1 or 2 were excluded from the study (10%). During all sessions, a Tensor lamp provided dim lighting and a fan provided masking noise.

Drugs

Cocaine hydrochloride and *d*-amphetamine sulfate, both obtained from Sigma (St. Louis, MO), were dissolved in physiological saline and administered to rats intraperitoneally in a volume of 1 ml/kg. Cocaine doses administered were 2.75 and 5.55 mg/kg and amphetamine doses administered were 0.3 and 1.0 mg/kg. All drugs were blind coded so the experimenter was unaware of which treatment a subject received until the conclusion of the experiment.

Data Analysis

Jump-up avoidance responses were analyzed using a two-way analysis of variance (ANOVA), within-subjects design, with treatment as the between-subjects' variable and performance on each trial as the within-subjects' variable (18).

RESULTS

The first study examined the effects of posttraining cocaine treatment on jump-up avoidance response acquisition. When analyzed in a two-way repeated measures (trial × treatment) ANOVA, there was not a significant overall main effect of posttraining cocaine treatment, $F(2,36) = 1.52$, $p = 0.23$; there was a significant effect of trial, $F(6,216) = 30.86$, $p < 0.0001$. The overall trial × treatment interaction was significant, $F(12,216) = 1.98$, $p < 0.03$. This significant interaction is not due to a simple drug effect of either cocaine-treated group compared to saline-treated subjects as neither dose produced a significant effect of drug treatment across all seven trials [2.75 mg/kg; $F(1,36) = 2.28$, $p = 0.13$; 5.55 mg/kg: $F(1,36) = 2.28$, $p = 0.14$]. However, treatment with both doses of cocaine produced significant trial × treatment interactions when compared to saline-treated subjects [2.75 mg/kg: $F(6,126) = 2.4$, $p < 0.03$; 5.55 mg/kg: $F(6,216) = 2.5$, $p < 0.03$]. Further analysis indicated that the trial × treatment interactions are accounted for by a significant effect of cocaine treatment on Trials 3-7, both for 2.75 mg/kg cocaine, $F(1,36) = 4.79$, $p < 0.04$, and for 5.55 mg/kg cocaine, $F(1,36) = 4.13$, $p < 0.05$. Thus, as can be seen in Fig. 1, animals receiving 2.75 and 5.55 mg/kg cocaine following training displayed steeper acquisition functions on day 3 than saline-treated control subjects, indicating that more of these subjects avoided foot-shock during Trials 3-7; in fact, all cocaine-treated (2.75 and 5.55 mg/kg) subjects avoided foot-shock on Trial 7. The interaction arises from the fact that the saline-treated rats showed better performance than cocaine-treated rats for Trials 1 and 2. This analysis is confirmed by comparing the shape of the learning curves produced in this study by conducting an analysis of linear trend interaction. This analysis showed that animals receiving either dose of cocaine following training displayed a significantly steeper acquisition function on day 3 than saline-treated control subjects [2.75 mg/kg: $F(1,36) = 9.6$, $p < 0.005$; 5.55 mg/kg: $F(1,36) = 8.47$, $p < 0.007$].

The second study examined the effects of posttraining amphetamine treatment on acquisition of the jump-up avoidance response. The analysis of the results obtained for amphetamine-treated subjects revealed a significant overall effect of amphetamine treatment, $F(2,34) = 4.19$, $p < 0.03$, and a significant overall effect of trial, $F(6,204) = 23.28$, $p < 0.0001$. The main effect of amphetamine treatment is accounted for by a significant effect of both doses of amphetamine on subjects' jump-up avoidance performance on day 3: [0.3 mg/kg: $F(1,34) = 6.17$, $p < 0.02$; 1.0 mg/kg: $F(1,34) = 6.48$, $p < 0.02$]. In contrast to the results observed in cocaine-treated subjects, there was no significant trial × treatment interaction or linear trend interaction for either dose of

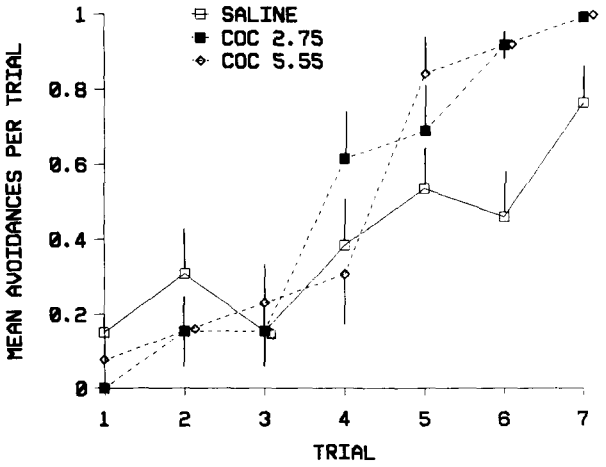

FIG. 1. Effect of IP cocaine (2.75, 5.55 mg/kg) administration following training on days 1 and 2 on later jump-up avoidance performance on day 3. Cocaine-treated subjects performed better than saline-treated control subjects for Trials 3-7 ($p < 0.05$). $n = 13$ for each group.

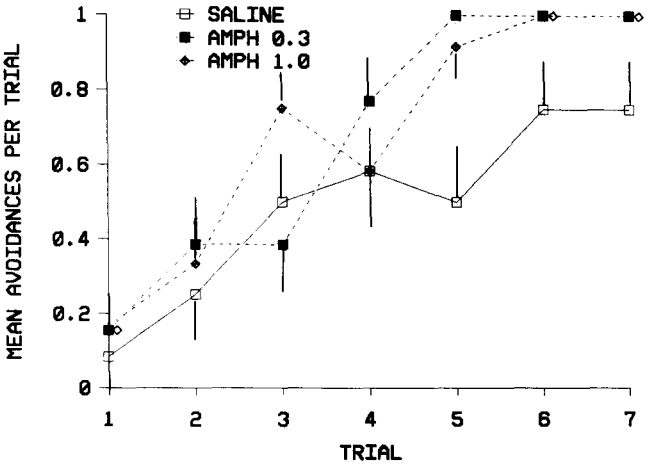

FIG. 2. Effect of IP amphetamine (0.3, 1.0 mg/kg) administration following training on days 1 and 2 on later jump-up avoidance performance on day 3. Amphetamine-treated subjects (0.3 and 1.0 mg/kg) performed better than saline-treated control subjects for most of the seven trials ($p < 0.04$). Group n's are as follows: amphetamine 0.3 mg/kg, $n = 13$, 1.0 mg/kg, $n = 12$; saline, $n = 12$.

amphetamine. Thus, amphetamine-treated animals performed better than saline-treated rats across the seven test trials. All amphetamine-treated (0.3 and 1.0 mg/kg) subjects avoided foot-shock on Trials 6 and 7. These acquisition functions are depicted in Fig. 2.

DISCUSSION

The present studies demonstrate for the first time that the posttraining administration of either cocaine or amphetamine enhances later performance of a jump-up active avoidance task in rats. These results extend our previous findings that both cocaine (17,37) and amphetamine (22) enhance active avoidance conditioning in a one-way trough apparatus, and are in agreement with previous reports of memory enhancement produced by the posttraining administration of cocaine in other aversive tasks (16) and amphetamine in other aversive (4,6,10,23,25,39) and appetitive (5,19,30,31,35) tasks.

Importantly, because the drug treatments were given immediately following escape response training, animals were trained in a drug-free state. Therefore, the stimulant drugs did not influence locomotor, attentional, or motivational processes during training (26). Posttraining drug treatments are believed to interact with the processes that underlie the consolidation of the preceding training experience (24,26). Thus, we suggest that cocaine and amphetamine injected after training (days 1 and 2) interacted with the neural processes that subserve consolidation of the training situation such that stimulant-treated subjects displayed superior retention of the jump-up response at test, which was expressed as an increased mean number of avoidance responses on day 3. It is likely that cocaine or amphetamine injected posttraining was completely metabolized by the time testing began as the plasma half-life of cocaine following a 20-mg/kg subcutaneous injection of cocaine to rats is 1 h (27), while in the dog the plasma half-life of an intraperitoneal injection of 10 mg/kg amphetamine is 7 h (1). Therefore, the stimulants could not have had a proactive effect on avoidance performance on day 3.

The finding that both cocaine and amphetamine enhanced learning and memory in the studies reported here is not surprising since the two stimulant drugs share similar pharmacological profiles. Both drugs increase synaptic concentrations of dopamine, norepinephrine, and serotonin (1,14,33,34), although cocaine does so primarily by inhibiting neurotransmitter reuptake (12,28,34) while amphetamine primarily promotes neurotransmitter release (9,32,33). Thus, cocaine-produced increases in striatal dopamine levels are tetrodotoxin dependent (dependent upon action potential released dopamine), while amphetamine-produced increases in striatal dopamine are tetrodotoxin independent (independent of neuronal firing) (29). Cocaine and amphetamine also produce similar effects on behaviors such as locomotor activity, operant responding, and eating (8).

The results reported here also demonstrate interesting differences between the two psychostimulants. The enhancing effects of amphetamine on avoidance performance were statistically more robust than the effects of cocaine on avoidance responding. At test, amphetamine-treated rats reached perfect performance by Trial 6, while cocaine-treated rats reached perfect performance by Trial 7 (saline-treated rats did not reach perfect performance in either experiment). Perhaps these differences are accounted for by pharmacokinetics; as mentioned above, cocaine is a shorter-acting compound relative to amphetamine. Since posttraining drug treatments are hypothesized to interact with the consolidation of recent experiences (24,26), the length of time the drug is available to influence the laying down of fresh experiences may be a critical variable in its efficacy for altering memory formation.

Few other studies have compared directly the effects of posttraining cocaine and amphetamine on learning and memory. One study reported that the daily posttraining administration of amphetamine to mice for 3 days enhanced performance in a water Y-maze discrimination task on the fourth day while cocaine did not (4). However, the generality of these results must be questioned because only a single dose of cocaine was examined.

In conclusion, the present report represents the first demonstration of memory enhancement by cocaine and amphetamine in the jump-up avoidance task under conditions that allow both training and testing to be carried out in drug-free subjects. This facilitation of learned behavior is likely a reflection of an effect of the stimulants on memory itself rather than an effect on some other performance variable.

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