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# Amphetamine Affects the Extinction of Self-Stimulation Differently in Prefrontal Cortex and Posterior Hypothalamus of Rats

CHARLES H. K. WEST AND RICHARD P. MICHAEL

*Department of Psychiatry, Emory University School of Medicine*
*Georgia Mental Health Institute, 1256 Briarcliff Road, N.E., Atlanta, GA 30306*

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WEST, C. H. K. AND R. P. MICHAEL. *Amphetamine affects the extinction of self-stimulation differently in prefrontal cortex and posterior hypothalamus of rats.* PHARMACOL BIOCHEM BEHAV **36**(3) 479–484, 1990.—The effects of amphetamine on the extinction of intracranial self-stimulation (ICSS) and on postextinction ICSS performance were examined in rats implanted with electrodes either in medial prefrontal cortex (mPFC) or in the posterior hypothalamus-ventral tegmental area (PH-VTA). Lever-pressing for ICSS was allowed to stabilize in daily 15-minute sessions before each animal was exposed to 5 minutes of extinction (responding without reward). Animals were administered either 0.25 mg/kg *d*-amphetamine or saline before baseline, extinction and postextinction sessions. After amphetamine treatment, the number of lever presses during extinction was higher in mPFC animals and lower in PH-VTA animals compared with saline-treated controls. Rates did not change immediately after extinction but, one day later, rates had increased in all saline-treated animals (both PH-VTA and mPFC animals) and had decreased in all amphetamine-treated animals. These findings demonstrated that the effects of amphetamine on the extinction of ICSS were different in cortical and hypothalamic sites, possibly because of regional differences in stimulus-evoked reinforcement and inhibitory processes.

Extinction Intracranial self-stimulation Amphetamine Medial prefrontal cortex Posterior hypothalamus Rats

INTRACRANIAL self-stimulation (ICSS) behavior maintained by sites in medial prefrontal cortex (mPFC) has several characteristics which differ from that maintained by sites along the trajectory of the medial forebrain bundle in the hypothalamus. These differences include the effects of drugs, food deprivation and changes in stimulus current intensity (2, 9, 10, 16), and there are also differences in the pattern of increase in brain metabolism, in the rate of acquisition of the ICSS task and in the neural substrate activated (12, 17, 18, 23).

We have previously demonstrated that administration of amphetamine before each training session facilitated the acquisition of a lever-pressing task for ICSS in mPFC but not in the posterior hypothalamus-ventral tegmental area (PH-VTA) (21,22). One possible explanation for this difference is that amphetamine differentially affected the learning processes associated with ICSS acquisition in these two sites. When the reinforcing stimuli were withheld from previously trained animals, extinction of ICSS behavior occurred and extinction, like acquisition, may proceed differently at different brain sites (5, 13, 20). The first aim of the present study was to investigate the effect of amphetamine on the extinction of ICSS in animals implanted in PH-VTA or mPFC in order to evaluate differences in this form of learning at these sites. The second aim was to examine the effect of a brief period of extinction, with or without amphetamine treatment, on subsequent ICSS performance in both PH-VTA and mPFC.

## METHOD

### *Animals and Surgery*

Fifty adult male Sprague-Dawley rats weighing 310–475 g at the time of surgery were used. They were bred in our laboratory from stock purchased from Charles River Laboratories (Wilmington, MA). Animals were housed 3–4 per cage in a colony room lighted between 7:00 a.m. and 7:00 p.m. with free access to fresh food and water. For the implantation of electrodes, rats were anesthetized with sodium pentobarbital (50 mg/kg IP) and given atropine sulfate (0.25 mg SC) to minimize any respiratory discomfort. When full surgical anesthesia was attained, animals were positioned in a stereotaxic device, and the skull was exposed and

[1]Requests for reprints should be addressed to Charles H. K. West, Ph.D., Georgia Mental Health Institute, Room 504-N, 1256 Briarcliff Rd., N.E., Atlanta, GA 30306.

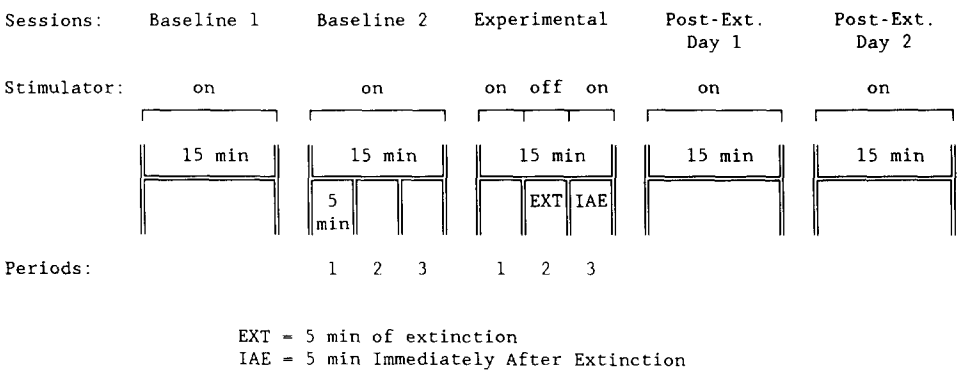


FIG. 1. Illustrates the testing sequence of the five test sessions given each animal. Each session was 15 minutes, and the Baseline 2 and Experimental sessions were divided into three periods of 5 minutes each. Every lever press by the animals was reinforced except during Period 2 of the Experimental session when the stimulators were turned off.

opened. After the dura was cut, a 125 μm diameter bipolar platinum electrode (Plastic Products Co., Roanoke, VA) was lowered into position. With the incisor bar 5.0 mm above the interaural line, the coordinates for posterior hypothalamus-ventral tegmental area were: AP 3.0, Lat. 1.0, Vert. −2.0 and for medial prefrontal cortex were: AP 10.5, Lat. 0.7, Vert. −2.7 in this case from the dural surface (15). The electrode was anchored securely to the skull by 6 stainless steel screws and cranioplastic cement. Animals were administered 100,000 U of benzathine penicillin G and procaine penicillin G IM postoperatively together with 1 mg/kg flunixin meglumine (Banamine®, Schering, Kenilworth, NJ) to prevent postoperative discomfort.

*Apparatus*

The self-stimulation operant chamber had inside dimensions of $31 \times 30 \times 29$ cm high and was housed inside a sound-attenuating cabinet. When placed in the chamber, animals were free to move and receive brain stimulation while connected to the stimulus source by way of a commutator and a spring-shielded wire. Depressing a $5 \times 1.3$ cm lever (Gerbrands, Arlington, MA) on one wall 10 cm above the grid floor activated a stimulator. Stimuli were generated by two model S44 stimulators (Grass Instrument Co., Quincy, MA) each connected to a stimulus isolator and a constant current unit. A modified biphasic output was produced by triggering one stimulator, set for a positive pulse train, and then the other stimulator, set for a negative pulse train, on alternating lever presses. For all animals, the reinforcing stimulus was a 200 msec train of square-wave pulses at 100 Hz with a pulse duration of 0.2 msec. Throughout training and testing, the stimulus intensity was 200 μA for the PH-VTA animals and 400 μA for the mPFC animals. These current parameters were based on previous experience with acquisition testing and current threshold estimates of animals implanted in these regions. It was critical to the experimental design that every lever press be reinforced prior to extinction. Earlier work with ICSS in mPFC and PH-VTA (21,22) has shown that it is very difficult to equalize lever-pressing rates for the two sites without reducing PH-VTA stimulus intensities to the point at which responding becomes sporadic and irregular and premature extinction occurs. Therefore, no attempt was made to equalize lever-pressing rates for the two ICSS sites by changing stimulus intensities or schedules of reinforcement.

*Procedure*

After a two week postsurgical recovery period, daily 15-minute sessions of ICSS training and testing were conducted 5 days per week between 1:00 p.m. and 4:00 p.m. Animals were allowed to acquire the lever-pressing task for ICSS on their own, with little or no shaping by the experimenter. Animals were run for 20 sessions before testing was started, and their performance of the ICSS task had completely stabilized during this time. Testing consisted of the five test sessions for each animal as illustrated in Fig. 1.

During Baseline 1, all animals received subcutaneous injections of saline 15 minutes before testing. Baseline 2 and Experimental sessions (also of 15 minutes each) were divided into three periods of five minutes. Comparisons of data from the Experimental sessions were made with those from the corresponding periods of the Baseline 2 sessions. Data from postextinction day 1 and day 2 sessions (15 minutes) were compared with data from the Baseline 2 session (15 minutes).

Prior to the Experimental session, it was critical that every lever press was reinforced to avoid the premature occurrence of extinction. Because of either failure to reach a stable level of ICSS or the premature exposure to extinction (stimulator failure), 3 of the 24 PH-VTA rats and 4 of the 26 mPFC rats could not be studied further. During Period 1 of the Experimental session, each lever press was reinforced as usual, but during Period 2, the stimulators were turned off and behavior during extinction was observed. This was the only period during which lever-pressing was not reinforced. The stimulators were again turned on during Period 3 of the Experimental session to obtain ICSS data for the 5-minute period immediately after the extinction experience (IAE). The animals were not given any external signal to indicate whether the stimulators were on or off.

*Drugs*

The four treatment groups were as follows: Group A consisted of 11 of the 21 PH-VTA animals and received saline injections (1 ml/kg SC) 15 minutes before the start of each of the five test sessions. Group B consisted of the remaining 10 PH-VTA animals and received saline injections 15 minutes before Baseline 1 session and *d*-amphetamine injections (0.25 mg/kg SC) 15 minutes before Baseline 2, Experimental, Postextinction day 1 and Postextinction day 2 test sessions. Group C consisted of 11 of the 22 mPFC animals and received saline treatment similar to that for Group A. Group D consisted of the remaining 11 mPFC animals and received drug treatment (saline, amphetamine) similar to that for Group B. *d*-Amphetamine sulfate (Sigma Chemical Co., St. Louis, MO) was dissolved in 0.9% saline with concentration calculated as free base.

TABLE 1

EFFECTS OF AMPHETAMINE ON SELF-STIMULATION IN PH-VTA AND mPFC

| | | Baseline 1 | | Baseline 2 | |
|---|---|---|---|---|---|
| Group | N | Treatment | Number of Lever Presses | Treatment | Number of Lever Presses |
| | | | PH-VTA | | |
| A | 11 | Saline | 1704 ± 172 | Saline | 1766 ± 198 |
| B | 10 | Saline | 1645 ± 190 | Amphetamine | 1875 ± 243* |
| | | | mPFC | | |
| C | 11 | Saline | 350 ± 36 | Saline | 344 ± 28 |
| D | 11 | Saline | 325 ± 27 | Amphetamine | 379 ± 21* |

Values given are mean ± SEM number of lever presses per 15 minutes. Baseline 2 is one day, and Baseline 1 is two days, before extinction. All animals were given saline before Baseline 1 and either saline or 0.25 mg/kg *d*-amphetamine before Baseline 2. Significant differences (repeated measures design, analysis of variance) between Baseline 1 (saline) and Baseline 2 (amphetamine) rates for Groups B and D are indicated by *$p<0.01$. N = number of animals.

*Data Analysis and Histology*

All data were expressed as the mean ± SEM number of lever presses per 15-minute session or per 5-minute period of a session. The significance of differences between mean lever-pressing rates 1) by the four groups of animals to evaluate the effects of amphetamine, 2) during extinction (without reinforcement) for the four groups, and 3) during baseline and postextinction sessions, were determined by analyses of variance (SPSS/PC+, SPSS Inc., Chicago, IL). Lever-pressing rates by Groups B and D during Baseline 1 (saline treatment) and Baseline 2 (amphetamine treatment) were compared using repeated measures. Baseline 2 and postextinction means were further evaluated by Scheffé's test. To facilitate comparisons, postextinction scores were expressed as percentages of Baseline 2 scores because of large interanimal differences in the preextinction rates of ICSS. The relation between Baseline 2 and Extinction scores was evaluated by Pearson's product-moment correlation (SPSS/PC+).

After completing the experiment, the animals were given a large overdose of sodium pentobarbital and perfused with 10% formalin via the heart. Frozen sections of the fixed brain tissue were cut at 50 μm and stained with cresyl violet. The locations of the electrode tips were verified by viewing the stained sections under a microprojector. All experimental procedures were in accordance with Institutional regulations and with the *NIH Guide for the Care and Use of Laboratory Animals* (NIH publication No. 85-23, revised 1985).

## RESULTS

*Rates of ICSS*

Lever-pressing rates were higher in PH-VTA than in mPFC. For Baseline 1 when animals in all four groups received saline injections only, mean (± SEM) numbers of lever presses per 15 minutes were 1676 ± 125 (n = 21) for PH-VTA and 338 ± 22 (n = 22) for mPFC. The effects of amphetamine on lever-pressing rates were examined in two ways (Table 1). When the Baseline 2 means for Groups A and C were compared with those for Groups B and D, respectively, there were no significant differences because of the large interanimal variation. However, when repeated measures in the same animals were used to compare ICSS rates from Baseline 1 with those from Baseline 2 for Groups B and D, a significant rate-increasing effect of amphetamine was observed: Group B, $F(1,9) = 14.30$, $p<0.01$, and Group D, $F(1,10) = 13.74$, $p<0.01$.

*Extinction Effects*

Analysis of variance of lever-pressing rates during extinction for all four groups showed a highly significant two-way interaction between drug treatment and brain site, $F(1,39) = 52.39$, $p<0.001$ (Fig. 2). For PH-VTA animals, the mean number of nonreinforced lever presses during the 5-minute extinction period was significantly lower for Group B (amphetamine) than for Group A (saline), $F(1,19) = 20.70$, $p<0.001$. For the mPFC animals, the mean number of nonreinforced lever presses was significantly higher for Group D (amphetamine) than for Group C (saline), $F(1,20) = 36.86$, $p<0.001$ (Fig. 2). There were no significant differences between Period 1 of Baseline 2 sessions and Period 1 of Experimental sessions in all four groups of animals (Table 2). To examine the relation between rates of lever-pressing both with reinforcement (Baseline 2 sessions, Period 2) and without reinforcement (Experimental sessions, Period 2), correlation coefficients were determined for all animals and for animals grouped according to drug, brain site and the interaction between the two. Correlation coefficients were significant (two-tailed) for all animals (Groups A, B, C and D), $r = .432$; $p<0.01$, and for all saline-treated animals (Groups A and C), $r = .677$; $p<0.001$, but there were no other significant correlations.

*Postextinction Effects*

The rate of ICSS during the 5 minutes immediately after extinction (IAE) (Experimental Period 3) was not significantly different from the corresponding Baseline 2 (Period 3) for any of the four groups. For PH-VTA animals, the means for Baseline 2 vs. IAE were 607 ± 76 and 634 ± 77, respectively, for Group A (n = 11) and were 665 ± 85 and 572 ± 104 for Group B (n = 10). For mPFC animals, the means for Baseline 2 vs. IAE were 126 ± 11 and 133 ± 9, respectively, for Group C (n = 11) and were 160 ± 14 and 141 ± 9 for Group D (n = 11). Although there was no change in rates immediately after extinction, one day later, rates were different from those of the preextinction Baseline 2 (set at 100%) (Table 3). There was an increase in rate in both of the saline-treated groups (A and C), and this was confirmed by analysis of variance both for PH-VTA, $F(2,20) = 7.21$, $p<0.01$, and for mPFC, $F(2,20) = 21.17$, $p<0.001$. In contrast, there was a decrease in rate in both of the amphetamine-treated groups (B and D), and this was confirmed by analysis of variance for PH-VTA, $F(2,18) = 4.65$, $p<0.05$, and for mPFC, $F(2,20) = 9.91$, $p<0.005$. Two days after extinction, the rates for each group no longer differed significantly from baseline (Table 3).

*Histological Findings*

The locations of the electrode tips are shown in Fig. 3, and, within a given site, there was no association between their locations and either Baseline rates of ICSS or extinction scores. There was no evidence of current-induced tissue damage around any of the electrode tips.

## DISCUSSION

The principal finding of this study was that a dose of 0.25 mg/kg amphetamine had diametrically opposite effects on the extinction of lever-pressing for ICSS in cortical and hypothalamic

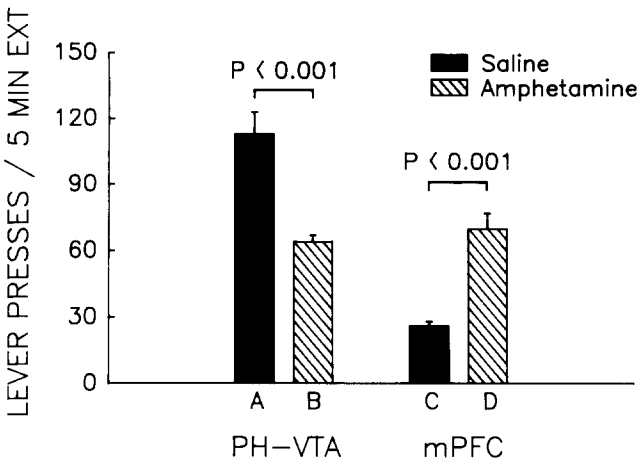


FIG. 2. The effects of 0.25 mg/kg *d*-amphetamine on the mean (±SEM) number of nonreinforced lever presses during 5 minutes of extinction of responding for ICSS in posterior hypothalamus-ventral tegmental area (PH-VTA) or medial prefrontal cortex (mPFC) of the rat. Significance of differences between saline and amphetamine scores (analysis of variance) are indicated above bars. For Groups A, C and D, n = 11; and for Group B, n = 10.

sites. Lever-pressing during extinction was significantly increased by amphetamine in mPFC animals but was significantly decreased by amphetamine in PH-VTA animals (Table 2, Fig. 2). This was consistent with some earlier results showing that the acquisition of lever-pressing behavior for ICSS in mPFC sites differed from that in hypothalamic sites. Acquisition of ICSS in mPFC was facilitated by amphetamine (21); in contrast, treatment with 0.25 mg/kg *d*-amphetamine, the same dose used in the present study, did not enhance the acquisition of ICSS in PH-VTA (22). Although certain procedural details were different in these acquisition studies, the notion that learning processes associated with extinction might also differ in these sites was supported by the present results. For both acquisition and extinction, amphetamine produced different effects on essentially the same task in the two brain regions. It is possible that amphetamine changed the reinforcement value or the ability to respond for reinforcement differently in cortical and hypothalamic sites. For example, it has been proposed that for ICSS in mPFC the limit in the speed of acquisition is due to a behavioral inhibition produced by electrical stimulation of that brain region (19). An amphetamine-induced reduction of such inhibition could allow more efficient acquisition of the ICSS task and also facilitate behavioral responses shortly after cessation of mPFC stimulation during extinction. In this regard, lesions in prefrontal cortex increased responding during extinction of a classically conditioned response, perhaps due to the loss of normal inhibitory control (6). Alternatively, it is possible that enhancement of dopamine transmission by amphetamine increased the reinforcement value of ICSS in mPFC (8), which would facilitate acquisition and increase resistance to extinction.

Unlike stimulation in prefrontal cortex, stimulation in hypothalamic ICSS sites produces arousal and behavioral activation rather than inhibition, and rats acquire ICSS in PH-VTA more rapidly than in cortex (22). Therefore, in PH-VTA, amphetamine may be less able to facilitate the already rapid acquisition of ICSS and to arouse animals further during extinction. This would be in agreement with the findings of previous investigators using appetitive tasks: Cole (3,4) found that amphetamine (0.5–2.0 mg/kg) depressed responding on a food reward schedule that intermixed 5-minute periods of continuous reinforcement and extinction, and Belleville (1) showed that amphetamine decreased responding during extinction in rats trained on a variable interval schedule for food reward. However, in a study similar to the present one using ICSS in the posterior hypothalamus, Olds (14) showed that 2.0 mg/kg amphetamine markedly increased responding during extinc-

TABLE 2

EFFECTS OF AMPHETAMINE ON EXTINCTION SCORES OF PH-VTA AND mPFC ANIMALS

| | | Baseline 2 | | Experimental | |
|---|---|---|---|---|---|
| Group | N | Period | Number of Lever Presses | Period | Number of Lever Presses |
| | | | PH-VTA | | |
| A | 11 | 1 (Reinforced) | 569 ± 53 | 1 (Reinforced) | 597 ± 68 |
| B | 10 | 1 (Reinforced) | 592 ± 89 | 1 (Reinforced) | 608 ± 84 |
| A | 11 | 2 (Reinforced) | 589 ± 71 | 2 (Nonreinforced) | 113 ± 10 |
| B | 10 | 2 (Reinforced) | 619 ± 74 | 2 (Nonreinforced) | 64 ± 3* |
| | | | mPFC | | |
| C | 11 | 1 (Reinforced) | 104 ± 11 | 1 (Reinforced) | 104 ± 12 |
| D | 11 | 1 (Reinforced) | 104 ± 9 | 1 (Reinforced) | 115 ± 9 |
| C | 11 | 2 (Reinforced) | 114 ± 9 | 2 (Nonreinforced) | 26 ± 2 |
| D | 11 | 2 (Reinforced) | 125 ± 8 | 2 (Nonreinforced) | 70 ± 7* |

Values given are mean ± SEM number of lever presses per 5 minutes with and without reinforcement (extinction). Animals were given saline (Groups A and C) or 0.25 mg/kg *d*-amphetamine (Groups B and D). There were no significant differences between treatments during Baseline 2. Amphetamine significantly decreased rates in PH-VTA and significantly increased them in mPFC (*$p<0.001$ in each case by analysis of variance). N = number of animals.

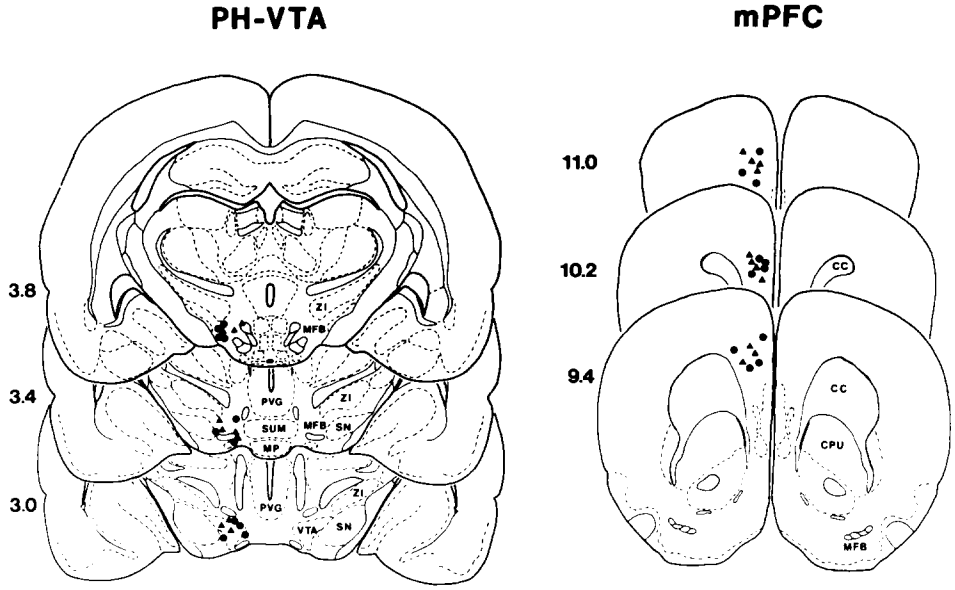


FIG. 3. Locations of electrode tips shown on coronal sections of the rat brain [from atlas of Pellegrino *et al.* (15)] through posterior hypothalamus-ventral tegmental area (PH-VTA) and medial prefrontal cortex (mPFC). Saline animals shown by filled circles; amphetamine animals shown by filled triangles. Numbers beside sections give planes anterior to interaural zero. Abbreviations: CC, corpus callosum; CPU, nucleus caudate-putamen; MFB, medial forebrain bundle; MP, posterior mamillary nucleus; PC, cerebral peduncle; PVG, periventricular gray substance; SN, substantia nigra; SUM, supramamillary nucleus; VTA, ventral tegmental area; ZI, zona incerta.

tion. In contrast to the very abrupt decrease in responding during extinction in our saline-treated animals, the amphetamine-treated animals of Olds continued to respond at high rates throughout the entire 60-minute extinction period. This difference might be explained by a study of Evenden and Robbins (7) on the effects of amphetamine (0.2–3.2 mg/kg) on response switching and perseveration in various test settings. They found that both response switching and perseveration were increased by amphetamine, even when this did not increase the probability of reinforcement.

TABLE 3

POSTEXTINCTION EFFECTS ON RATE OF SELF-STIMULATION IN PH-VTA AND mPFC

| | | Postextinction Day 1 | | Postextinction Day 2 | |
|---|---|---|---|---|---|
| Group | N | Treatment | Rate of ICSS % of Baseline 2 | Treatment | Rate of ICSS % of Baseline 2 |
| | | | PH-VTA | | |
| A | 11 | Saline | 110 ± 3%* | Saline | 105 ± 4% |
| B | 10 | Amphetamine | 94 ± 2%† | Amphetamine | 99 ± 1% |
| | | | mPFC | | |
| C | 11 | Saline | 113 ± 3%‡ | Saline | 99 ± 2% |
| D | 11 | Amphetamine | 92 ± 3%* | Amphetamine | 105 ± 3% |

Values are expressed as mean ± SEM percentages of Baseline 2 rates. Animals were given either saline (Groups A and C) or 0.25 mg/kg *d*-amphetamine (Groups B and D). Significant differences from Baseline 2 rates are given by *$p<0.05$, †$p<0.01$, ‡$p<0.001$ (analysis of variance, Scheffé's test). N = number of animals.

Perseveration, however, generally occurred at higher doses than those that increased switching. In the present study, the dose of 0.25 mg/kg amphetamine may have increased switching by PH-VTA rats so that they changed readily from lever pressing to other behaviors during extinction while the dose of 2.0 mg/kg amphetamine used by Olds may have primarily increased perseveration.

The experimental design used here was intended to simplify the comparison of data from two sites with widely different basal response rates. Equalization of response rates by altering stimulus intensities or schedules of reinforcement was not attempted because we were concerned to avoid non- or weakly reinforced lever presses prior to extinction. The response-rate factor was therefore a confounding variable. All animals were given minimal shaping during acquisition and showed vigorous, stable ICSS behavior for at least 7 sessions prior to the extinction tests. In PH-VTA animals, amphetamine decreased lever-pressing during extinction, whereas it tended to increase the rate of ICSS. Therefore, it is unlikely that the correlation between Baseline 2 rates and those during extinction could account for the completely opposite effects of amphetamine on behavior elicited from the two sites. This correlation was perhaps due to the generally higher number of extinction presses by PH-VTA animals than by mPFC animals because when each ICSS site was considered individually, the correlation was not significant for either PH-VTA animals ($r = .126$) or mPFC animals ($r = .239$).

Both saline groups showed an increase in rate one day postextinction, whereas amphetamine produced opposite effects in PH-VTA and mPFC animals. Reduced amounts of ICSS on the day of extinction (10 vs. 15 minutes) were unlikely to have caused the effect one day postextinction because ICSS rates were not changed immediately after extinction. It is possible that the rate increase in the saline groups was due to a stress-like effect of extinction (11) occurring independently of site. Since it is known

that amphetamine can produce stress-like effects of its own, it is not possible to tell if the different effects in saline- and amphetamine-treated animals were caused by the presence of amphetamine during extinction, during postextinction tests or during both.

ACKNOWLEDGEMENT

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## REFERENCES

1. Belleville, R. E. Control of behavior by drug-produced internal stimuli. Psychopharmacologia 5:95–105; 1964.
2. Carey, R. J.; Goodall, E.; Lorens, S. A. Differential effects of amphetamine and food deprivation on self-stimulation of the lateral hypothalamus and medial frontal cortex. J. Comp. Physiol. Psychol. 88:224–230; 1975.
3. Cole, S. O. The depression of operant behavior and retarding action on discrimination learning by amphetamine. Psychon. Sci. 10:19–20; 1968.
4. Cole, S. O. The relationship of amphetamine-induced anorexia and freezing under a multiple CRF-EXT operant schedule. J. Gen. Psychol. 83:163–168; 1970.
5. Deutsch, J. A.; Howarth, C. I. Evocation by fear of a habit learned for electrical stimulation of the brain. Science 136:1057–1058; 1962.
6. Eichenbaum, H.; Potter, H.; Papsdorf, J.; Butter, C. M. Effects of frontal cortex lesion on differentiation and extinction of the classically conditioned nictitating membrane response in rabbits. J. Comp. Physiol. Psychol. 86:179–186; 1974.
7. Evenden, J. L.; Robbins, T. W. Increased response switching, perseveration and perseverative switching following *d*-amphetamine in the rat. Psychopharmacology (Berlin) 80:67–73; 1983.
8. Ferrer, J. M. R.; Sanguinetti, A. M.; Vives, F.; Mora, F. Effects of agonists and antagonists of D1 and D2 dopamine receptors on self-stimulation of the medial prefrontal cortex in the rat. Pharmacol. Biochem. Behav. 19:211–217; 1983.
9. Goodall, E. B.; Carey, R. J. Effects of *d*- versus *l*-amphetamine, food deprivation, and current intensity on self-stimulation of the lateral hypothalamus, substantia nigra, and medial frontal cortex of the rat. J. Comp. Physiol. Psychol. 89:1029–1045; 1975.
10. Lorens, S. Comparison of the effects of morphine on hypothalamic and medial frontal cortex self-stimulation in the rat. Psychopharmacology (Berlin) 48:217–224; 1976.
11. Mason, S. T. The neurochemistry and pharmacology of extinction behavior. Neurosci. Biobehav. Rev. 7:325–347; 1983.
12. Nassif, S.; Cardo, B.; Libersat, F.; Velley, L. Comparison of deficits in electrical self-stimulation after ibotenic acid lesion of the lateral hypothalamus and the medial prefrontal cortex. Brain Res. 332: 247–257; 1985.
13. Olds, J.; Milner, P. Positive reinforcement produced by electrical stimulation of septal area and of other regions of rat brain. J. Comp. Physiol. Psychol. 47:419–427; 1954.
14. Olds, M. E. Comparative effects of amphetamine, scopolamine, chlordiazepoxide and diphenylhydantoin on operant and extinction behavior with brain stimulation and food reward. Neuropharmacology 9:519–532; 1970.
15. Pellegrino, L. J.; Pellegrino, A. S.; Cushman, A. J. A stereotaxic atlas of the rat brain, 2nd ed. New York: Plenum Press; 1979.
16. Robertson, A.; Laferriere, A.; Franklin, K. B. J. Amphetamine and increases in current intensity modulate reward in the hypothalamus and substantia nigra but not in the prefrontal cortex. Physiol. Behav. 26:809–813; 1981.
17. Robertson, A.; Laferriere, A.; Milner, P. M. Development of brain stimulation reward in the medial prefrontal cortex: Facilitation by prior electrical stimulation of the sulcal prefrontal cortex. Physiol. Behav. 28:869–872; 1982.
18. Schenk, S.; Shizgal, P. The substrates for lateral hypothalamic and medial pre-frontal cortex self-stimulation have different refractory periods and show poor spatial summation. Physiol. Behav. 28: 133–138; 1982.
19. Spence, S. J.; Silverman, J. A.; Corbett, D. Cortical and ventral tegmental systems exert opposing influences on self-stimulation from the prefrontal cortex. Behav. Brain Res. 17:117–124; 1985.
20. Thompson, R. K. R.; Webster, D. M. Delayed extinction and drive level effects: Septal self-stimulation compared with natural reward. Physiol. Behav. 12:907–912; 1974.
21. West, C. H. K.; Michael, R. P. Acquisition of intracranial self-stimulation in medial prefrontal cortex of rats facilitated by amphetamine. Pharmacol. Biochem. Behav. 24:1617–1622; 1986.
22. West, C. H. K.; Michael, R. P. Handling facilitates the acquisition of lever-pressing for brain self-stimulation in the posterior hypothalamus of rats. Physiol. Behav. 39:77–81; 1987.
23. Yadin, E.; Guarini, V.; Gallistel, C. R. Unilaterally activated systems in rats self-stimulating at sites in the medial forebrain bundle, medial prefrontal cortex, or locus coeruleus. Brain Res. 266:39–50; 1983.