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Effects of Catecholamine Manipulations on Three Different Self-Stimulation Behaviors[1]

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WHITE, N., Z. BROWN AND M. YACHNIN. *Effects of catecholamine manipulations on three different self-stimulation behaviors. PHARMAC. BIOCHEM. BEHAV.* 9(5) 603–608, 1978.—Rats with self-stimulation electrodes in the medial part of lateral hypothalamus (LH) or in the lateral part of LH were trained to bar press, to run in a continuous, square-shaped runway, and to move their tails from side to side while otherwise restrained, all using LH stimulation on an FI 2 sec schedule as the reinforcement. At low doses of pimozide (a dopaminergic blocker) or of FLA-57 (a dopamine beta-hydroxylase inhibitor) different effects on rates of responding were observed on each of the three tasks at the two electrode placements, indicating that the rate reductions were not the results of specific performance effects of the drugs. The patterns of rate changes suggested that the effects of LH stimulation on behavior in the runway were primarily, but not exclusively mediated by a dopaminergic system; that the effects of LH stimulation on tail movement were primarily, but not exclusively mediated by a noradrenergic system; and that the effect of LH stimulation on bar pressing was mediated by both, or either of these substrates. These results suggest that the reinforcement of behavior by LH stimulation is flexibly mediated by at least two different neural systems.

Self-stimulation Catecholamines Noradrenergic Dopamine Response mechanisms Reinforcement

RATES of bar pressing for electrical self-stimulation of the brain are affected by systematically or intraventricularly administered drugs which alter noradrenaline (NA) function [8, 20, 25, 26], or dopamine (DA) function [5, 10, 16, 31]. However, rather severe alterations in catecholamine function have been required to produce these effects on bar pressing and this, as well as other evidence, has led some investigators to suggest that such drugs do not really affect the reinforcing properties of brain stimulation, but that they act directly to inhibit motor performance or operant responding [9, 21, 22]. For this reason, the value of self-stimulation data in explaining the effects of these systemically administered drugs on the catecholamine substrate has remained equivocal.

One variable that has not been considered in these studies is the nature of the behavior that the animals are required to perform to obtain brain stimulation. A number of studies show that this can be an important factor in determining the precise nature of the neural substrate that mediates the effects of brain stimulation on behavior [13, 19, 27, 34, 35, 36]. Because of these data we decided to reexamine the effect of two systemically administered drugs which alter catecholamine function—pimozide, a blocker of DA neurotransmission [1]) and FLA-57, a dopamine beta-hydroxylase inhibitor [11]—on three different self-stimulation behaviors. The three behaviors studied were those for which evidence suggesting that different neural substrates may mediate their reinforcement by lateral hypothalamic (LH) stimulation is already available [27, 35, 36].

METHOD

Animals

Ten male, hooded rats (250–300 g) underwent standard stereotaxic surgery under 50 mg/Kg sodium pentobarbital anesthesia to implant a single monopolar electrode. In 5 rats the electrode was aimed at the dorsolateral quadrant of LH (deGroot [7] coordinates: AP, 4.2; L, 1.8; V, –2.0); in the remaining 5 rats the electrode was aimed at the ventromedial quadrant of LH (AP, 4.2; L, 1.2; V, –2.2). One week after surgery each rat met a self-stimulation criterion in the bar pressing apparatus such that a rate of at least 25 responses per minute was attained at a stimulation current level equal to approximately 75% of the current required to produce the rat's maximum response rate. These current levels were used in all subsequent training and testing.

Apparatus

The electrodes were made of single lengths of 0.2 mm diameter stainless steel wire insulated with Formvar except for the cross sectional area of the tip. The electrode as-

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semblies were fastened to the rats' skulls with 4 stainless steel screws which served as the indifferent electrode. Electrical stimulation of the brain was delivered in 0.5 sec trains of sine wave current at 60 Hz in each of the 3 self-stimulation apparatuses.

The bar press (BP) apparatus was a wooden box with a Plexiglas front (20×20×40 cm). The box was fitted with a bar (5×7.5 cm) in the middle of one side wall, 3.0 cm from the floor. The runway (RY) was 11.5 cm wide, 64.0 cm deep, and was built in the shape of a square, 60 cm on the outside. A photocell beam crossed each corner of the runway, 3 cm from the floor. Interruption of a beam was the required response; consecutive responses required the interruption of different beams. The tail movement (TM) apparatus [35] was a restraining cage fitted with 2 microswitches at one end so that the tail of a rat restrained in the cage lay between levers that activated the switches. Tail movements greater than 11 mm to either side were the required responses.

Procedure

The initial bar press session on continuous reinforcement for each rat was kept as short as possible (less than 15 min). In the same session all rats were immediately shifted to an FI 2 sec schedule of reinforcement, and this schedule was used throughout all subsequent training and testing on all tasks. Each rat was trained in each of the 3 apparatuses for 20 min on each of 4 days on the FI 2 sec reinforcement schedule. The stimulation current levels used were those determined in the initial session, and the order in which each task was presented to each rat was varied randomly.

Three days after the last training session testing with pimozide (Janssen Pharmaceuticals) began. There were a total of 4 pimozide tests at 48 hr intervals. Each test consisted of an intraperitonneal injection followed, 4.5–5.5 hr later, by 15 min of testing on each of the 3 tasks. The rats were switched between tasks with a minimum of delay. The order in which the rats were tested, the order in which each rat was tested on each task, and the day on which each rat was injected with each dose of pimozide were all determined by different sequences of random numbers. The doses of pimozide used were 0.0, 0.1, 0.2, 0.4 mg/Kg. The 0.0 dose was 0.5 ml of the tartaric acid vehicle (pH=3.0) used to dissolve the pimozide.

Four days after the last pimozide test all rats were "retrained" by performing for 20 min on each of the three tasks in a no-drug condition. Forty-eight hr later testing with FLA-57 (Astra Pharmaceuticals) began. There were 3 FLA-57 tests separated by 48 hr. The procedure for these tests was identical to that described for pimozide. The doses of FLA-57 used were 0, 15, 30 mg/Kg. The 0 dose was 0.5 ml of the sodium hydroxide and acetic acid vehicle (pH=8.0–8.2) used to dissolve the FLA-57.

In each drug condition each rat was tested on each task for 15 min. The first 5 min of each 15 min test was designated as a "warm up" period: during this time, the various factors determining the rats' performance rates on each task (contrast effects, electrode polarization, etc.) were allowed to equilibrate. The rates for this period were analyzed on a minute-by-minute basis. The final 10 were taken as representative of the final rate produced by the experimental conditions. These rates were taken simply as the total number of responses made in 10 min.

Several weeks after the last test day 9 of the rats used in the experiments were injected with 30 mg/Kg FLA-57. Three rats that were housed with the experimental animals but underwent no surgical or other experimental procedures were injected with the sodium hydroxide-acetic acid vehicle. Five hours later the rats were killed and their brains were quickly removed. The brain of each experimental rat was cut in half longitudinally. The half without the electrode track was immediately frozen and subsequently assayed for concentrations of NA and DA using fluorometric procedures [3,23]. The half with the electrode track was fixed in Formalin for two weeks and then frozen, sliced at 30 μ, mounted, and stained with thionin to permit verification of the electrode placements. The whole brains of the 3 unoperated control rats were assayed.

RESULTS

The results of examining the histological material are shown in Fig. 1. The medial placements lie along the border of the fornix and mamillothalamic tract. The lateral placements center around the ventromedial tip of the cerebral peduncle. The median stimulation current for the rats in the medial group was 157 μA (range=60–200 μA) and for the rats in the lateral group the median was 100 μA (range of 4 rats=90–120 μA, one rat=310 μA). The results of the brain assays following injections of FLA-57 are shown in Table 1. The concentration of NA was reduced to about 50% of normal levels; the concentration of DA was unaffected.

The minute-by-minute analysis of the first 5 min of each test period showed that the changes in rate were very small and inconsistent. In virtually every case, the rate of responding observed during the first minute was within 5 responses per minute of the rate during the fifth minute, and these changes did not occur in any consistent direction. These initial rates were equally close to the average rates for the final 10 min of the test period. It is possible, however, that some consistent changes in initial response rates would have been detected if 15 or 30 sec intervals and continuous reinforcement (as were used in 10) had been used.

For the final 10 min of responding in each 15 min session the number of responses made were summed to give the raw scores for the data analysis. Each rat's score on each task in the vehicle condition (0 dose) for each drug was taken as a baseline score. To permit comparisons among the different placement groups, drug conditions, and behaviors, each animal's scores on each task in each drug condition were expressed as percentages its own baseline score.

The baseline scores are summarized in Table 2. An analysis of variance was computed on these scores using electrode placement, drug group and behavior as the three factors. The main effect for electrode placement was the only significant F value in the analysis, $F(1,8)=10.03$, $p<0.05$. It is apparent from Table 2 that the rats with medial placements performed at lower rates than the rats with lateral placements. The maximum number of reinforcements (trains of stimulation) available during the 10 min periods was 300 on the FI 2 sec reinforcement schedule so the interstimulation intervals were reasonably well equalized for the rats in the lateral group. At 200 responses in 10 min (the lowest mean rate in Table 2) the rats obtained a reinforcement every 3 sec on the average, instead of every 2 sec as permitted by the FI 2 sec schedule. Therefore, the interstimulation intervals varied between these two values in the medial group.

The main results of the experiment is summarized in Fig. 2. At low doses, pimozide caused preferential decreases

TABLE 1

RESULTS OF ASSAY OF BRAINS OF RATS INJECTED WITH FLA-57

	N	Mean NA Concentration ng/g ± SEM	% Control	Mean DA Concentration ng/g ± SEM	% Control
Experimental Rats	9	195.7 ± 31.3	48.8	626.6 ± 31.5	94.4
Control Rats	3	400.9 ± 21.3		663.5 ± 52.5	

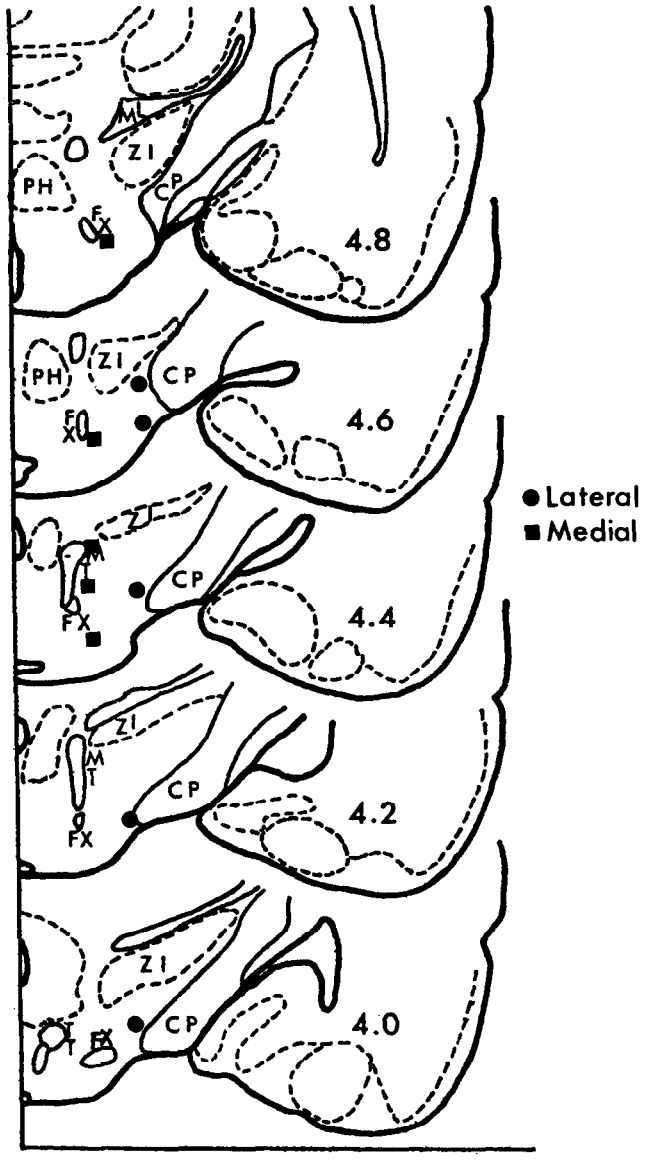

FIG. 1. Locations of the electrode tips for the rats in the medial and lateral LH groups. Abbreviations: CP, cerebral peduncle; FX, fornix; ML, medial lemniscus; MT, mammillothalamic tract; PH, posterior hypothalamus; ZI, zona incerta.

TABLE 2

MEAN NUMBER OF RESPONSES (±SEM) IN 10 MIN IN BASELINE (VEHICLE) TEST SESSIONS

Group	Vehicle	Bar Press	Tail Movement	Runway
Lateral	Pimozide	438 ± 32	369 ± 25	398 ± 70
	FLA-57	351 ± 43	276 ± 74	411 ± 93
Medial	Pimozide	256 ± 33	214 ± 26	203 ± 14
	FLA-57	276 ± 40	208 ± 41	212 ± 43

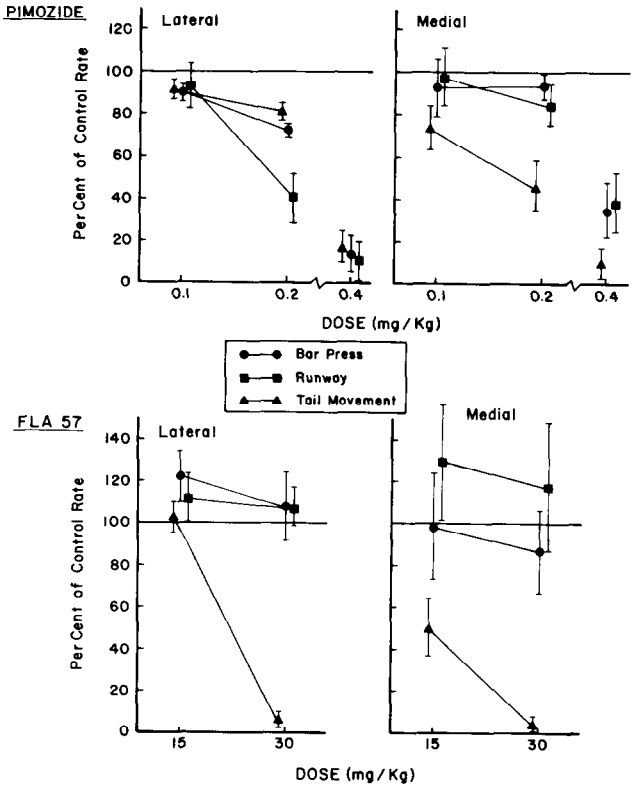

FIG. 2. Effects of pimozide and FLA-57 on rates of responding on three different self-stimulation behaviors at two electrode placements in lateral hypothalamus. The control data (see Table 2) on which these percentages are based were obtained during sessions when the rats were injected with the appropriate vehicle for each drug. Variability indicators are standard errors.

in rates of responding on RY in the lateral group and on TM in the medial group. At a higher dose (0.4 mg/Kg) pimozide virtually stopped responding on all tasks in both groups. At this dose there were no significant differences (t-tests) between the rates on any behaviors, either within or between groups.

For the data at 0.1 and 0.2 mg/Kg pimozide an analysis of variance was computed using the two drug doses, the two electrode placements and the three behaviors as the main factors. There was a significant three-way interaction among these factors, $F(2,16)=4.72$, $p<0.05$; a significant electrode placement by behavior interaction, $F(2,16)=5.33$, $p<0.05$; and a significant main effect of dose, $F(1,8)=21.55$, $p<0.01$. Newman-Keuls comparisons were used to compare the effects of pimozide on the three behaviors at the 0.2 mg/Kg dose. In the lateral group the mean RY score was lower than the mean BP score ($p<0.01$) and lower than the mean TM score ($p<0.01$). In the medial group the mean TM score was lower than the mean BP score ($p<0.01$) and lower than the mean RY score ($p<0.01$). The behaviors that were affected by pimozide at 0.2 mg/Kg were compared across the two placement groups. The RY score for the lateral group was lower than the RY score for the medial group ($p<0.01$); the TM score for the medial group was lower than the TM score for the lateral group ($p<0.05$).

FLA-57 preferentially decreased responding on TM in both electrode placement groups, and showed some tendency to increase rates on the other behaviors, especially on RY in the medial group. An analysis of variance identical to that computed for the pimozide data showed a significant three-way interaction, $F(2,16)=4.50$, $p<0.05$; a significant interaction between behavior and dose, $F(2,16)=23.17$, $p<0.01$; and significant main effects of task, $F(2,16)=19.95$, $p<0.01$ and dose, $F(1,8)=23.59$, $p<0.01$. Newman-Keuls comparisons for the lateral group at 30 mg/Kg showed that the mean score for TM was lower than the mean scores for both BP ($p<0.01$) and RY ($p<0.01$). In the medial group the mean score for TM was lower than the mean score for BP at 15 mg/Kg ($p<0.01$) and at 30 mg/Kg ($p<0.01$); the mean score for TM was also lower than the mean score for RY at both doses (15: $p<0.01$; 30: $p<0.01$). At 15 mg/Kg the mean score for TM was lower in the medial group than in the lateral group ($p<0.01$). In the medial group RY was significantly higher than BP at both 15 mg/Kg ($p<0.05$) and at 30 mg/Kg ($p<0.05$).

DISCUSSION

Partial depletion of NA or partial blocking of DA neurotransmission each produced a different pattern of changes in the rates of responding associated with reinforcing LH stimulation, when these reinforcing effects were assessed with several different behaviors. Moreover, the specific rate changes observed interacted with electrode placement. As there is no reason to expect the position of an electrode in a rat's brain to influence the systemic action of either of the two drugs used in the study, this latter finding makes it highly unlikely that the effects observed at the lower doses of pimozide or of FLA-57 were simple actions of the drugs on performance. For example, at 15 mg/Kg FLA-57 the rate of responding on TM was normal in the rats with lateral electrodes, but significantly reduced in the rats with medial electrodes. The hypothesis that the lowered rate in the medial group was due to an effect of FLA-57 on the ability of rats to move their tails does not explain the normal rate of the lateral group under the same drug treatment. The same argument applies to the decreased rates on RY in the lateral group and on TM in the medial group associated with the low doses of pimozide, as well as to the effect of FLA-57 on RY in the medial group.

At the higher doses of both drugs (0.4 mg/Kg) pimozide and 30 mg/Kg FLA-57) however, the present data offer no grounds for rejecting the hypotheses that pimozide affected the ability of rats to perform a variety of operant responses, or that FLA-57 produced a form of motor disability that is somehow specific to tail movements. In the following discussion, only the effects of 0.1 and 0.2 mg/Kg of pimozide and of 15 mg/Kg of FLA-57 are considered. If the rate reductions produced by these doses were not due to general performance effects of the drugs, the reductions must have been the results of an action of the drugs on the neural substrates mediating the effect of brain stimulation on the behaviors tested. Moreover, to the extent that the doses of the two drugs used act on specific substrates, the patterns of rate reductions permit a differentiation between the effects of the stimulating electrodes on noradrenaline and dopamine containing neurons.

At the lateral stimulation sites the only effect on brain stimulation reinforcement at the low doses of either drug was produced by pimozide. This drug selectively reduced the rate of performance on the RY task, suggesting that the reinforcement of this task depended upon a normally functioning DA substrate, and that reinforcement of the other tasks was less dependent upon normal DA neurotransmission.

At the medial stimulation sites, pimozide did not affect the rate of responding on RY, suggesting that, at this site, some non-DA substrate was involved in mediating the effects of the stimulation on this behavior. The possibility that this non-DA substrate may include NA-containing neurons is suggested by the selective increase in the rates of responding on RY produced by FLA-57. Koob *et al.* [15] and Will *et al.* [32] have also reported increased rates of reinforced operant responding at times of lower than normal NA levels. The significance of this phenomenon for an understanding of the role of NA in mediating reinforcement remains to be determined.

At the medial stimulation sites reinforcement of the TM task was sensitive to low doses of both pimozide and FLA-57, neither of which affected the performance of this response at the lateral sites. One possible explanation for the fact that DA blocking affected the rates of TM responding at the medial, but not at the lateral sites is based on the location of the stimulating electrodes with respect to the DA-containing neurons which course through the dorsolateral part of LH [14, 17, 18, 30]. The lateral stimulation sites were centered in the area of these axons and would have produced a high level of activation in them. The partial DA block produced by the low dose of pimozide would have reduced the amount of DA neurotransmission resulting from this activation, but the results show that the degree of reduction was not sufficient to cause a reduction in the rate of TM responding. In the medial group there was some distance between the stimulation sites and the main concentration of DA-containing axons, so they would have produced considerably less activation. Consequently, the addition of pimozide would have resulted in a much lower level of DA neurotransmission; a level sufficiently low to reduce the reinforcement of the TM response. The normal functioning of the DA substrate is clearly less critical for the reinforcement of TM than it is for the reinforcement of RY. For TM,

heavy dependence on a non-DA substrate at the lateral sites is suggested by the lack of effect of pimozide. The effect of FLA-57 on this response at the medial sites suggests that this substrate may include NA.

The TM behavior requires proximal, tactual guidance to control a simple, arbitrary muscle movement. The RY behavior requires visual guidance in response to distal stimuli to control whole-body orientation and movement. These are examples of two different types of behaviors rats can learn to perform. It was previously suggested [36] that the reinforcement of each of them may be primarily associated with the activation of an independent neural substrate mediating the effect of brain stimulation reinforcement on behavior. The data of the present study suggest that the mediation of the reinforcement of behaviors requiring the integration of visual detection of distal stimuli, and whole body orientation and movement is heavily dependent upon a DA substrate at lateral sites, and that at medial sites an NA substrate becomes involved in a way that is not presently understood. The reinforcement of behaviors requiring proximal, tactual control of simple muscle movements (or combinations of simple movements) appears to depend upon a minimal level of DA neurotransmission, and to be heavily dependent upon NA, although the degree of this dependence was also related to the stimulation site.

The BP behavior contains elements of both of the types of behavior already discussed [36]. To perform this behavior rats locate the bar visually, orient to it and approach it repeatedly. If they are already in position, they can perform simple, tactually guided muscle movements to obtain the stimulation. Because of the dual nature of this behavior the two neural systems mediating the effects of LH stimulation may be equally functional when the rat is in the BP situation. This hypothesis is consistent with the data of the present experiment showing that neither NA depletion nor DA blocking alone affects response rates on BP, even though roughly similar levels of debilitation of *both* the NA and DA systems do reduce BP rates [2, 28, 29]. Only very severe depletions of a single catecholamine system can affect the reinforcement of BP [5, 8, 12, 25, 26]. On the basis of independent evidence, Crow [6] has also suggested that the brain stimulation reinforcement of BP can be mediated by NA-containing or by DA-containing neurons.

In several previous studies conventional lesion techniques [27,35] and electrophysiological analysis [36] were used to study the mediation of LH brain stimulation reinforcement of the three behaviors used in the present study. With the addition of the present results there are now data using three different types of brain manipulations which point to the hypotheses that at least two different neural systems mediate the effects of reinforcing brain stimulation in LH, and that these systems function differentially and flexibly to mediate the reinforcement of different behaviors a rat can learn to perform.

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