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Free-Operant and Auto-Titration Brain Self-Stimulation Procedures in the Rat: A Comparison of Drug Effects

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SCHAEFER, G. J. AND S. G. HOLTZMAN. *Free-operant and auto-titration brain self-stimulation procedures in the rat: A comparison of drug effects*. PHARMAC. BIOCHEM. BEHAV. **10**(1) 127–135, 1979.—Rats were implanted with bipolar stimulating electrodes aimed at the medial forebrain bundle of the lateral hypothalamus, and trained to press a lever in one of two different procedures in order to receive electrical stimulation through the electrodes. In a free-operant procedure, each response produced a 200 msec train of electric pulses at a suprathreshold current, the intensity of which remained constant throughout the session. In an auto-titration procedure, each response produced an electrical stimulus which was initially set at a suprathreshold intensity. Every 15th response reduced the stimulation current by 3 μA. The animal could reset the current to its initial intensity at any time by pressing a second lever in the test chamber. The average current at which the animal pressed the reset lever was defined as the reinforcement threshold. Dose-response functions were determined for *d*- and *l*-amphetamine, alpha-methyltyrosine, and haloperidol. The reinforcement threshold was decreased by both *d*- and *l*-amphetamine, increased by haloperidol, and not changed by alpha-methyltyrosine. These effects on reinforcement threshold were not consistently related to the drug-induced changes in response rate in either procedure. The auto-titration procedure may be useful for distinguishing between drugs which cause nonspecific changes in the rate of ongoing behavior and those which specifically modify the reinforcement efficacy of brain stimulation.

Free-operant brain stimulation Auto-titration brain stimulation Amphetamine Alpha-methyltyrosine Haloperidol Brain catecholamines Reinforcement threshold

SINCE the initial observation [14] that rats would perform a learned response to electrically stimulate a discrete area of their brain, response rate has been the most widely used quantitative measure of reinforcement strength. However, as previously noted [24], response rate may provide misleading information about the relative reinforcement value of brain self-stimulation, particularly after experimental manipulations such as drug administration. In order to quantify changes in reinforcement strength which do not rely on response rate alone, various procedures designed to measure the threshold current or minimum stimulus intensity for supporting self-stimulation have been developed. In these procedures rats have been trained to alternate between two levers placed adjacent to each other in an operant chamber [20, 21, 22], to shuttle back and forth in a two compartment chamber [25], to respond concurrently on a continuous reinforcement and fixed-ratio schedule for brain stimulation [5,11], or to respond in a discrete trial procedure using brain stimulation as a discriminative stimulus [7,13].

In all the procedures used to measure the reinforcement threshold, the subject must emit a detectable, easily quantifiable response indicating that the threshold has been reached. In one such procedure [22], the reinforcement threshold was determined by the point at which the animal reset the current to a suprathreshold value. Although the reinforcement threshold may not represent the lowest current intensity which will support self-stimulation, the intensity at which the animal resets the current has been found to be reliable and sensitive to changes in either direction by the administration of drugs [20]. The experiments presented in this report were conducted in order to systematically evaluate the effects of drugs on a modification of the earlier auto-titration technique [22], and to directly compare the auto-titration and free-operant self-stimulation paradigms under controlled conditions in the same laboratory. The drugs used to compare the two procedures have previously been demonstrated to interact with the catecholaminergic system and to predictably modify responding for brain stimulation (e.g., [10]). The results of the study suggest that our modified auto-titration procedure will be useful for assessing the effects of drugs on the reinforcement efficacy of electrical brain stimulation.

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METHOD

Animals

The animals used in these experiments were male CFE rats (Carworth, Division of Charles River Breeding Laboratories, Wilmington, Mass.). Eight rats were used in the auto-titration experiments and five were used in the free-operant experiments. Four of the five animals used in the free-operant experiments had been used in a previous brain self-stimulation study [19]. The rats weighed 310–390 g at the time that electrodes were implanted. An additional 58 rats, which did not receive electrodes, were used for the determination of brain catecholamine levels. Between experimental sessions the rats were housed two per cage in a large colony room where they had free access to food and water. The colony room was artificially illuminated between 06:00 and 18:00 hr.

Apparatus

The auto-titration experiments were conducted in a dimly-illuminated rat chamber (Model 1110-L, Grason-Stadler Co., Bolton, MA) which was housed within a ventilated enclosure that was light-proof and sound-attenuating. On one wall of the chamber a conventional rat lever (Model G6312, Ralph Gerbrands Co., Arlington, MA) was positioned 10 cm above the grid floor. An omnidirectional lever (Model ODL-023, BRS/LVE, Beltsville, MD) was suspended from the ceiling near the opposite wall of the chamber. A plastic extension was mounted on the end of the omnidirectional lever such that the bottom of the lever was 7 cm above the grid floor. The chamber was provided with a constant level of white noise in order to mask extraneous sounds from the laboratory. An identical test chamber without an omnidirectional lever was used for the brain stimulation experiments with free-operant responding.

Electrical pulses for the titration experiments were produced by a model S 9 square wave stimulator (Grass Instruments, Quincy, MA) and were passed through a titration device before being transmitted to the animal. The titration device was a 22-contact rotary stepping switch which was programmed to move one step after every fifteenth lever press for brain stimulation. The starting current produced by the titrator could be set at any value from 0 to 210 μA. Each step reduced the current by 3 μA; if step 22 was reached, the animal continued to receive the current associated with that step until the reset manipulandum was pressed. A Zener diode maintained a constant current at each step. When the omnidirectional lever was pressed, the stepper was reset to the first step and the starting current was again available. The electrical stimulus was a 200 msec train of 100 unidirectional pulses per second with a pulse direction of 2 msec. The electrical stimuli were delivered to the animal through two channels of a four-channel mercury slip-ring assembly that was mounted on the top of the test chamber. The four-pronged connector of the slip-ring assembly extended into the test chamber and could be connected to a length of spring-shielded standard hearing aid cord (Plastic Products Co., Roanoke, VA) which, in turn, was plugged into the electrode on the head of the animal. Throughout the experimental sessions the electrical stimuli were displayed on a type 502 dual-beam oscilloscope (Tektronix, Inc., Beaverton, OR) which permitted the investigator to determine whether or not the titrator was functioning properly and the correct stimulus current was being delivered. For the free-operant experiments the pulses were also produced by a model S 9 square wave stimulator and were then passed through a model CCU 1 constant current unit (Grass Instruments).

Schedule contingencies for both the auto-titration and free-operant experiments were controlled by conventional automatic relay programming equipment. Data were recorded on electromagnetic counters and cumulative response recorders.

Surgery and Histology

Rats were anesthetized by the administration of sodium pentobarbital (55 mg/kg, IP) and atropine sulfate (2.5 mg/kg), and were then positioned in a stereotaxic instrument. After drilling a hole in the exposed skull, a bipolar platinum electrode (tip diameter=0.25 mm, Plastic Products Co.) was placed in the lateral hypothalamus at coordinates AP 5.2, L 1.7, H −2.2 [15]. Jewelers screws were fastened to the rat's skull forming a perimeter around the electrode. Dental cement was then applied to the jewelers screws and electrode forming a pedestal which firmly anchored the electrode in place. Following surgery, the animals were given an IM injection of 100,000 units of benzathine penicillin G as prophylaxis against infection.

At the end of the experiment, the animals were overdosed with sodium pentobarbital and perfused intracardially with 10% Formalin. Fifty μ sections were cut and every fourth section was stained with cresyl violet. Electrode placements were determined by microscopic examination of the histological material. One animal died after a test session in which it had received 10 mg/kg of *l*-amphetamine and its brain was not saved for histological examination.

Procedure

Beginning one or two weeks after surgery, rats used in the auto-titration procedure were placed in the test chamber and trained to press the conventional response lever in order to receive brain stimulation on a continuous reinforcement schedule. When the rate of responding became stable from session to session (e.g., 2000–4000 responses per hour), training on the titration schedule began. As in the preliminary training phase, brain stimulation reinforcement with a suprathreshold stimulus was available on a continuous reinforcement schedule. However, every fifteenth lever press decreased the current by 3 μA. When the current was reduced to a nonreinforcing level, the animals were trained by successive approximations to turn around and press the omnidirectional lever suspended from the ceiling near the back panel of the chamber in order to reset the current to the starting level. In addition, pressing the omnidirectional lever resulted in the blinking of the house light in the test chamber and a brief presentation of a tone from a Sonalert® speaker. However, a response on the omnidirectional lever did not produce brain stimulation. The animals were trained in the titration procedure until the individual auto-titration thresholds had clearly stabilized.

The procedure for pharmacological testing was as follows. The animals were tested six days per week. In each session the animals were given an initial 10 min warmup period. During the warmup phase, brain stimulation was available on a continuous reinforcement schedule. The current intensity remained constant during the warmup period and was the same intensity as the starting level during the

titration phase. This was done to ensure that the animals were all responding at a high, stable rate at the beginning of the titration session. Immediately at the end of the warmup period the animals were injected with either saline (Monday, Tuesday, Thursday and Friday) or a test drug (Wednesday and Saturday); doses in each drug series were administered in a random sequence. The animals were injected in the operant chamber with the commutator lead attached and remained in the chamber between the warmup period and the titration period with the house light turned off, except for the 4 hr pretreatment with alpha-methyltyrosine during which they were returned to their home cage. After the pretreatment time had elapsed, the animals were tested in the titration procedure for 30 min as described above.

An additional group of animals was trained in the free-operant procedure. When response rates stabilized between 2000–4000 responses per hour, the animals were tested in a schedule similar to the group in the auto-titration experiments except that the sessions were conducted four days a week rather than six. Each session began with a 10 min warmup period. At the end of the warmup period, the animals were injected with either saline (Monday and Thursday) or a test drug (Tuesday and Friday); doses in each drug series were administered in a random sequence. Following the injection, the animals remained in the test chamber until the pretreatment time had elapsed, except for the 4 hr pretreatment with alpha-methyltyrosine.

In order to determine the effects of alpha-methyltyrosine on brain catecholamine levels, additional groups of animals were administered saline, 10, 30, 56 or 100 mg/kg of alpha-methyltyrosine 1 or 4 hr prior to being sacrificed. The animals were sacrificed by decapitation at the appropriate times and whole-brain levels of norepinephrine and dopamine were determined fluorometrically [1].

Data Analysis

The following data were collected during each auto-titration session: total number of responses during the session, the current intensity at which the animal pressed the reset lever for each titration series, and total number of titration series during the session. The average current intensity at which the animal reset the current to its starting value was defined as the reinforcement threshold. The mean reinforcement threshold value after each dose of drug was compared with the threshold value after saline. Response rates during drug tests are presented as a percentage of the response rate of saline control sessions in order to facilitate comparisons between the auto-titration and the free-operant procedures.

In order to analyze the data, the saline values of each animal were averaged for each drug series. Analyses of variance according to a randomized block design [12] were performed on the response rate, reset current intensity, and the number of resets during the auto-titration session. F-ratios were further evaluated with Dunnett's test [12] to compare differences between reinforcement threshold values, response rates, and number of resets after saline and after graded doses of drug. Response rate data from the free-operant procedure were treated identically to the response rate data obtained in the auto-titration procedure. Analysis of variance [12] was also used to evaluate changes in brain catecholamine levels.

Drugs

The drugs were *d*- and *l*-amphetamine sulfate (a gift from Smith Kline and French Laboratories, Philadelphia, PA), haloperidol (generously provided by McNeil Laboratories, Inc., Fort Washington, PA), and *dl*-alpha-methyl-paratyrosine methyl ester hydrochloride (Sigma Chemical Co., St. Louis, MO). The *d*- and *l*-amphetamine and alpha-methyltyrosine were dissolved in 0.9% saline. Haloperidol was dissolved in a solution of 8.5% lactic acid and 1 N sodium hydroxide mixed in a ratio of 3 to 2. Alpha-methyltyrosine was administered IP; all other injections were SC. The injection volume was 1.0 ml per kg of body weight and all drug doses are expressed in terms of the free base. The following pretreatment intervals were used in both the auto-titration and the free-operant procedures: 15 min for *d*- and *l*-amphetamine, 30 min for haloperidol, 1 or 4 hr for alpha-methyltyrosine.

RESULTS

Stable performances of the rats in the auto-titration procedure were obtained at starting current intensities ranging from 108 to 176 μA. In order to determine whether the animals were merely resetting the current to its starting value after a constant number of presses on the conventional lever, or were actually responding on the basis of changes in current intensity, the effects of increasing and decreasing the starting current were ascertained. Three animals were each tested twice by reducing their starting current by 12 to 36 μA from that used during the drug testing experiments. Under these conditions the animals titrated their reinforcement threshold to 103 ± 9.2% (mean ± SEM) of the threshold current determined during saline sessions. Similarly, four animals were each tested twice by increasing their starting current by 18 to 36 μA from that used during the drug testing experiments. The mean (± SEM) threshold value under these conditions was 107 ± 3.5% of the threshold current determined during saline sessions. These data indicate that the animals were responding to changes in current intensity and were not simply emitting a fixed number of responses on the reinforcement lever before pressing the manipulandum to reset the current.

Amphetamine

Figure 1A shows that both *d*-, $F(4,15)=26.4$, $p<0.01$, and *l*-amphetamine, $F(4,15)=8.6$, $p<0.01$, significantly reduced the threshold for brain self-stimulation in a dose-dependent manner. The *d*-isomer was almost 10 times more potent than the *l*-isomer in this regard. A decrease in response rate also occurred after high doses of both *d*- and *l*-amphetamine (Fig. 1B), although the analysis of variance indicated that only the dose-response curve for the *l*-isomer was significant, $F(4,15)=13.4$, $p<0.01$. In addition, a significant decrease in the number of resets occurred after high doses of both *d*-, $F(4,15)=18.6$, $p<0.01$, and *l*-amphetamine, $F(4,16)=13.1$, $p<0.01$ (Table 1). Representative cumulative response records illustrating the effects of *d*-amphetamine on the pattern of responding of one rat in the auto-titration procedure are presented in Fig. 2.

In the free-operant brain self-stimulation experiments, both amphetamine isomers produced biphasic effects on response rates (Fig. 1C). Increases in response rate at lower doses were followed by decreases in response rate at higher

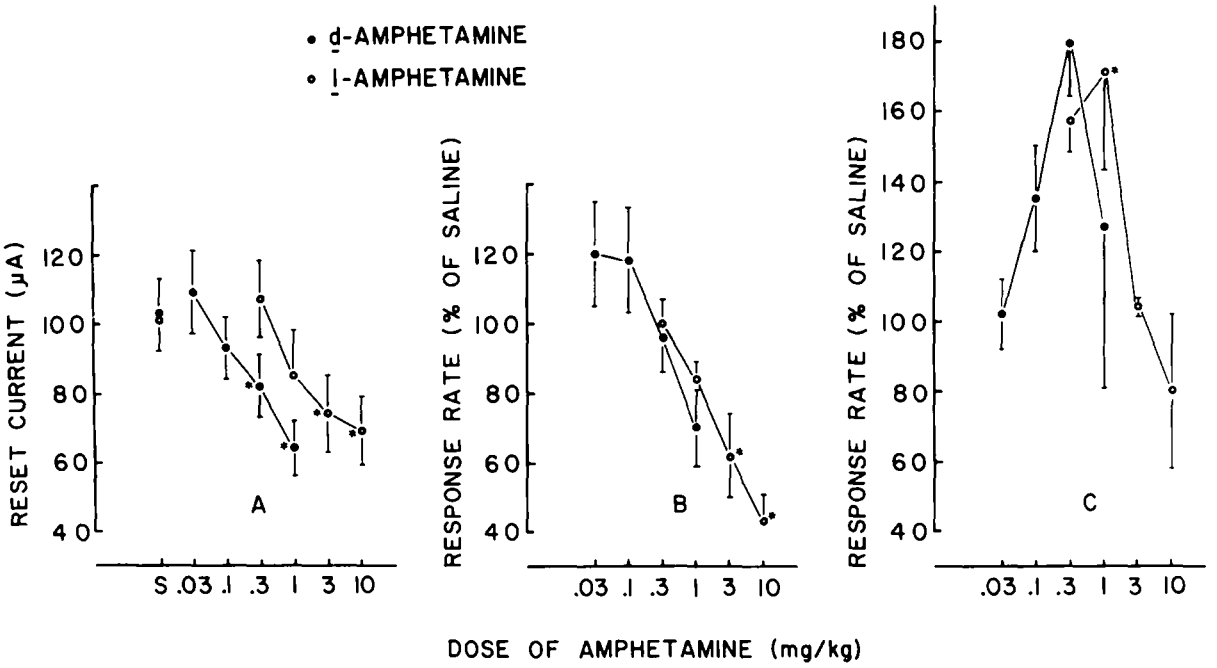

FIG. 1. Effects of *d*- and *l*-amphetamine on reset current and response rate in the auto-titration procedure (A and B), and on response rate in the free-operant procedure (C). The effects of saline on reset current are indicated by the points at S. Each point represents the mean of one observation in each of 5 rats in A and B, except for the 0.03 mg/kg dose of *d*-amphetamine and the 0.3 mg/kg dose of *l*-amphetamine where 4 rats were used. Each point in C represents the mean of one observation in each of 4 rats. The vertical lines represent ± 1 SEM. For greater clarity, the SEM is shown on only one side of a point in some instances. The mean control response rates ± SEM in the atuo-titration experiments were 1837 ± 279 and 2180 ± 190 responses per 30-min session for *d*- and *l*-amphetamine, respectively. The mean control response rates in the free-operant experiments were 1166 ± 88 and 1451 ± 201 responses per 30-min session for *d*- and *l*-amphetamine, respectively. *Significantly different from saline, $p<0.05$.

TABLE 1
RESETS/SESSION

Drug	Dose (mg/kg)				
	Saline	0.03	0.10	0.30	1.0
d-Amphetamine	18*	15	16	9†	2†
	Saline	0.30	1.0	3.0	10
l-Amphetamine	22	15	12†	5†	2†
	Saline	10	30	56	100
Alpha-methyl-tyrosine	21	21	23	9	11
	Saline	0.017	0.023	0.03	0.056
Haloperidol	20	19	2†	4†	1†

*Each value is a mean based upon observations in 4–5 rats.
†Significantly different from saline ($p<0.05$).

doses. However, the analysis of variance revealed significant differences only for *l*-amphetamine, $F(3,12)=5.8$, $p<0.01$.

Alpha-methyltyrosine

Alpha-methyltyrosine administered intraperitoneally 4 hr prior to the start of the titration session had no significant effect on the brain self-stimulation threshold (Fig. 3A). However, a significant dose-related decrease, $F(3,12)=5.5$, $p<0.01$, in response rate occurred during the titration procedure (Fig. 3B). The reduction in response rate was also accompanied by a decrease, $F(3,12)=3.4$, $p<0.05$, in the number of resets to approximately 50% of saline values (Table 1).

In order to determine the time course and degree of behavioral effects produced by alpha-methyltyrosine, dose-response curves were determined in the free operant procedure using both a 1- and 4-hr pretreatment time. Both time- and dose-dependent decreases in response rate were observed, as shown in Fig. 3C. The analysis of variance was significant for both the 1-, $F(4,16)=3.9$, $p<0.01$, and 4-hr, $F(4,16)=8.1$, $p<0.01$, pretreatment time.

In order to determine the effect of alpha-methyltyrosine on brain catecholamine content, rats were administered the drug and sacrificed one or four hours later. Alpha-methyltyrosine (10–100 mg/kg) produced dose- and time-dependent decreases in whole-brain levels of both norepinephrine and dopamine. The largest decrease in catecholamine levels occurred 4 hr after the 100 mg/kg dose: norepinephrine content was reduced to 50 ± 0.7% (mean ± SEM) of the saline control value (0.361 ± 0.012 μg/g of tissue); dopamine content was reduced to 39 ± 2.6% of the saline control value (0.757 ± 0.045 μg/g of tissue).

The analyses of variance performed on each of the four dose-response curves were significant: norepinephrine, 1 hr, $F(4,16)=10.3$, $p<0.01$, and 4 hr, $F(4,16)=111.5$, $p<0.01$,

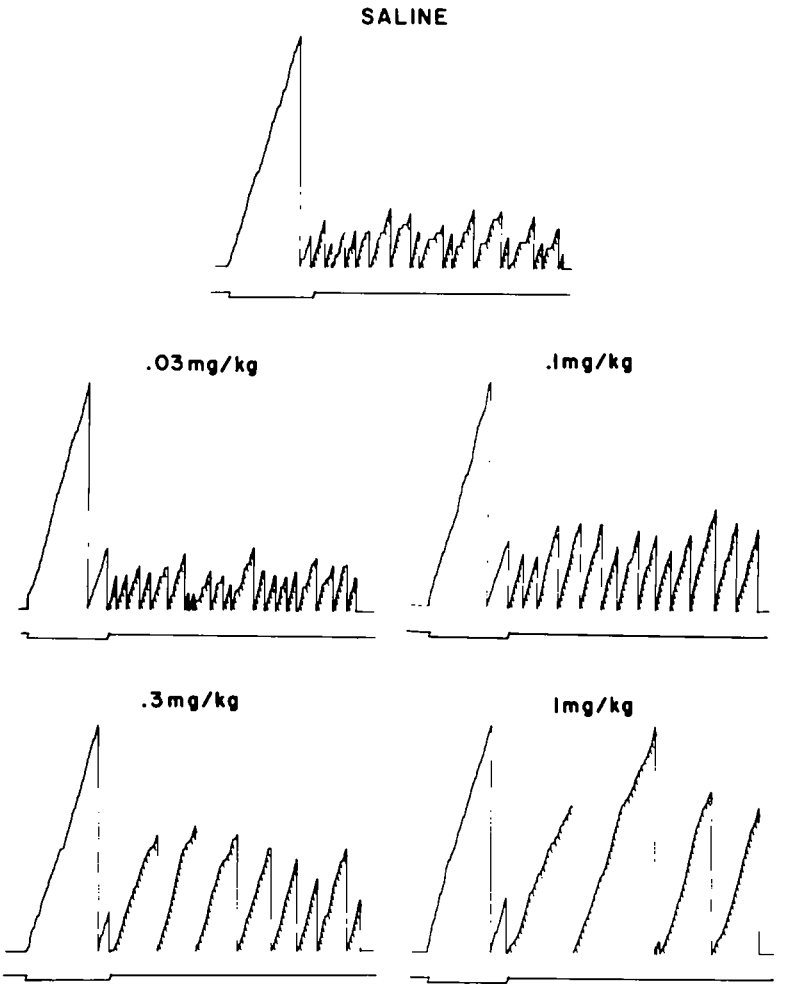

FIG. 2. Cumulative response records of one rat (R147) illustrating the effects of *d*-amphetamine on the pattern of responding in the auto-titration procedure. The records represent the initial 10 min warmup period, during which the event pen is offset downward, followed by the 30 min test session (see Method). The upper record is of a representative control session in which saline was administered. The remaining records show the dose-dependent effects of 0.03, 0.1, 0.3 and 1.0 mg/kg of *d*-amphetamine. Downward deflections of the response pen indicate a 3 μA drop in the stimulation current. The response pen reset automatically either after a total of 550 responses had been emitted or the omnidirectional lever was pressed to reset the stimulation current to its initial intensity.

dopamine, 1 hr, $F(4,16)=23.3$, $p<0.01$, and 4 hr, $F(4,16)=79.9$, $p<0.01$.

Haloperidol

With a 30 min pretreatment time, haloperidol produced a significant, $F(2,7)=5.0$, $p<0.01$, increase in the threshold current for brain stimulation (Fig. 4A). However, along with the increase in threshold, a marked decrease, $F(2,7)=14.4$, $p<0.01$, in response rate also occurred (Fig. 4B). Additionally, a significant, $F(2,7)=6.7$, $p<0.01$, decrease in the number of resets was recorded (Table 1). When a group of animals was administered haloperidol in the free-operant experiment, a significant, $F(4,16)=26.7$, $p<0.01$, decrease in response rate also occurred (Fig. 4C). The curves for the effects of haloperidol on response rate were exceptionally steep. In the titration procedure, 0.017 mg/kg did not alter the response rate, while doses of 0.023 mg/kg or greater reduced response rates to at least 20% of saline levels. In addition, the number of resets was dramatically lowered after doses of 0.023 mg/kg and greater. A similarly steep dose-dependent decrease in response rate was observed in the free-operant procedure.

Histology

Figure 5 shows the approximate site of the electrode tips for seven of the animals used in the titration experiments and four of the animals used in the free-operant experiments. For both groups of animals the electrode tip terminated in or near

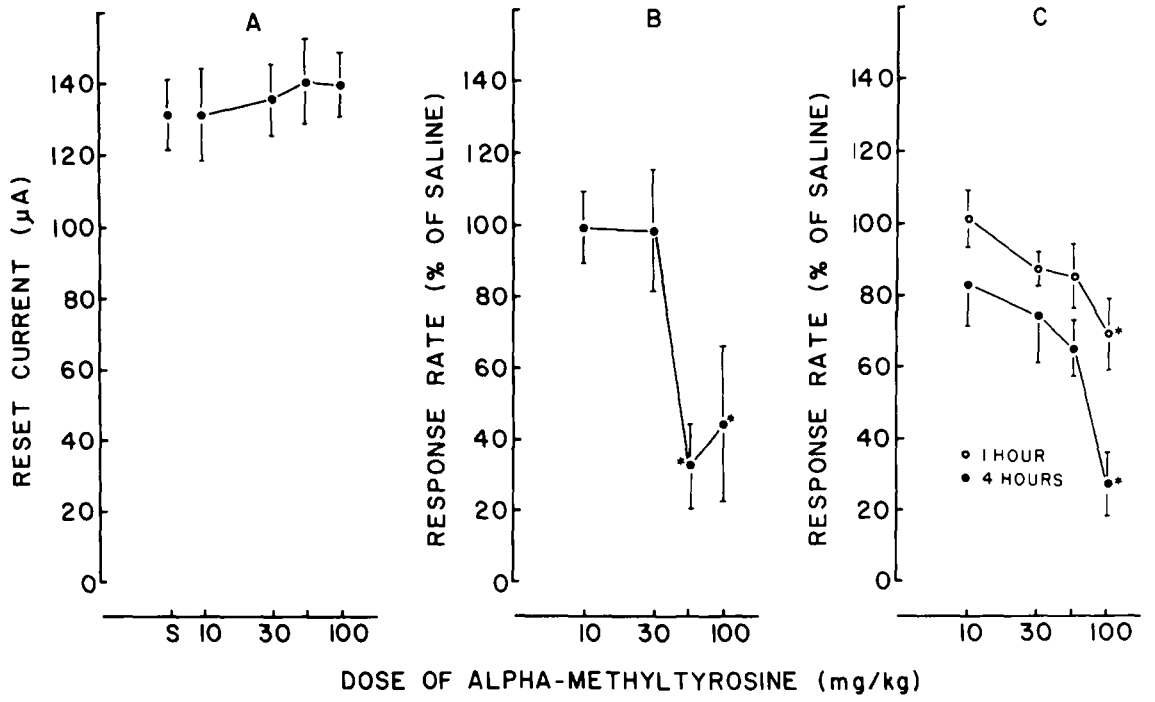

FIG. 3. Effects of alpha-methyltyrosine on reset current and response rate in the auto-titration procedure (A and B), and on response rate in the free-operant procedure (C). The effect of saline on reset current is indicated by the point at S. Each point represents the mean of one observation in each of 4 rats in A and B, and of 5 rats in C. The vertical lines represent ± SEM. For greater clarity, the SEM is shown on only one side of a point in some instances. The mean control response rate ± SEM was 2424 ± 700 responses per 30 min session in the auto-titration experiment and 1828 ± 263 responses per 30 min session in the free-operant procedure. *Significantly different from saline, $p<0.05$.

the lateral hypothalamic portion of the medial forebrain bundle.

DISCUSSION

The present series of experiments reconfirms previous findings that rats can learn a chain of responses in order to self-select their threshold for positively reinforcing brain self-stimulation. Furthermore, the animals appear to select the threshold on the basis of stimulus intensity, rather than on the basis of the number of presses emitted since the last resetting of the current as evidenced by the fact that the rats titrate themselves to the same threshold current even when the starting current is increased or decreased from baseline values. In addition, our studies demonstrate that the measurement of several response variables allows the investigator to discriminate between the nonspecific behavioral arousal or disruptive effects of a drug and its possible effect on the central reinforcement system.

The reinforcement threshold is sensitive to modification in either direction by drugs. The value of this variable was increased by haloperidol and decreased by both *d*- and *l*-amphetamine. The *d*-isomer of amphetamine was nearly 10 times more potent than the *l*-isomer in this respect. In related threshold procedures, *d*-amphetamine [5] as well as both *d*- and *l*-amphetamine [20] have also been demonstrated to lower the threshold current. Together, these data suggest that amphetamine increases the rewarding aspect of brain self-stimulation.

The dose-response curves for the response rate data differ for the auto-titration and free-operant procedures. In the auto-titration procedure, a slight increase in rate of responding occurred with the two lower doses of *d*-amphetamine, followed by a decrease with the highest dose. Only a dose-dependent decrease in response rate occurred with *l*-amphetamine. In the free-operant procedure, a dose-related increase in response rate up to a dose of 0.3 mg/kg of *d*-amphetamine was followed by a return to baseline with the highest dose. An increase in response rate with the two lower doses of *l*-amphetamine was followed by a decrease at the highest dose. These differences in drug effects may be a consequence of the different schedule contingencies in the two procedures, or may be a function of the different baseline rates of responding: the auto-titration procedure engendered response rates that were about 50% higher than those occurring in the free-operant procedure (see Fig. 1 legend). In addition, the animals used in the free-operant procedure had also been used in a previous brain self-stimulation study [19]. However, with both procedures, the differences between the *d*- and *l*-isomers were not as great as previously reported [4, 9, 17]. On the other hand, there is a considerable variability among subjects in relative sensitivity to the effects of the *d*- and *l* isomers of amphetamine on rates of responding for brain stimulation [9,23]. Within the hypothalamus, the further lateral the electrode placement, the smaller is the difference between the potency of the *d* and *l* isomers, and, in some placements, a reversal of potencies occurs [23].

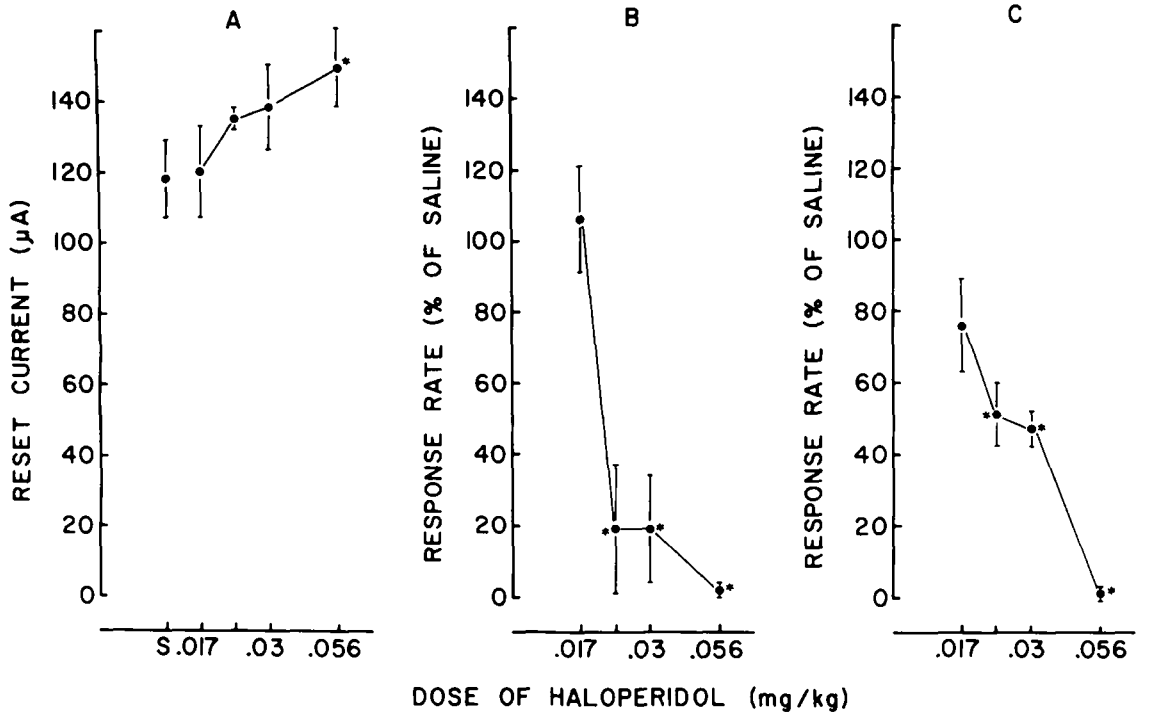

FIG. 4. The effects of haloperidol on reset current and response rate in the auto-titration procedure (A and B) and on response rate in the free-operant procedure (C). The effect of saline on reset current is indicated by the point at S. Each point represents the mean of one observation in each of 3 rats in A and B, except for the 0.056 mg/kg dose where 2 rats were used. In C each point represents the mean of one observation in each of 5 rats. The vertical lines represent ± SEM. The mean control response rate ± SEM was 2546 ± 242 responses per 30 min session in the auto-titration experiment, and 1828 ± 278 responses per 30 min session in the free-operant procedure. *Significantly different from saline, $p<0.05$.

The differential effects of alpha-methyltyrosine on the brain self-stimulation reinforcement threshold and performance were equivocal. We did not find a significant increase in threshold as would have been predicted by a prior study [3]. We did, however, note a significant, dose-dependent reduction in response rate in the titration procedure. Similarly, a time- and dose-dependent decrease in response rate occurred in the free-operant procedure, consistent with previous reports [3,18]. In an earlier report [3], the effects of alpha-methyltyrosine were compared between a free-operant procedure and a threshold measure [25] in which the animals were required to cross back and forth in a shuttle-box in order to obtain the brain stimulation reinforcement. Unlike the present study, the previous report [3] found that the decrease in response rate in the free-operant procedure was paralleled by a significant increase in the reinforcement threshold.

A recent report [6] may bear upon the problems of interpreting the alpha-methyltyrosine data. Rats were implanted with electrodes in the lateral hypothalamus and running speed was subsequently measured in an alley runway for brain self-stimulation. Whereas alpha-methyltyrosine reduced running speed in all animals (a performance factor), the reward value of the stimulus, as measured by the sharp rise in a function relating running speed to the number of pulses received, was reduced in some animals but not in others. Furthermore, animals in which the reward value was reduced by alpha-methyltyrosine could not be separated on the basis of electrode placement from animals in which the reward value was not altered. Similarly, in our titration experiments, all four animals that received alpha-methyltyrosine had reduced rates of responding while only two out of the four animals showed increases in the reward threshold. Electrode placement did not appear to be the determining factor in our study either. Therefore, it is difficult to make a general statement about alpha-methyltyrosine's effects on the rewarding aspect of brain self-stimulation. This is all the more perplexing in view of the reliable dose- and time-dependent reductions in brain catecholamine levels that occur with alpha-methyltyrosine administration.

Haloperidol produced a dose-dependent increase in the reinforcement threshold. However, this was accompanied by a marked reduction in both the response rate and the number of reset responses on the omnidirectional lever. In the free-operant procedure a similar dose-dependent reduction in response rate occurred. Previous investigators [2, 8, 16, 26] have also reported a steep dose-dependent reduction in response rate after haloperidol and have proposed that haloperidol's primary effect is to impair the performance of operant behavior rather than to modify the threshold for reinforcement. Further, the marked reduction in the number of responses on the reset lever which occurred after haloperidol's administration, and which also occurred with the other drugs tested in these experiments, raises the issue of the degree of confidence which is justified when only a few responses on the reset lever occur. It is likely that at least some of our data, especially those obtained with haloperidol, reflect a nonspecific performance deficit. On the

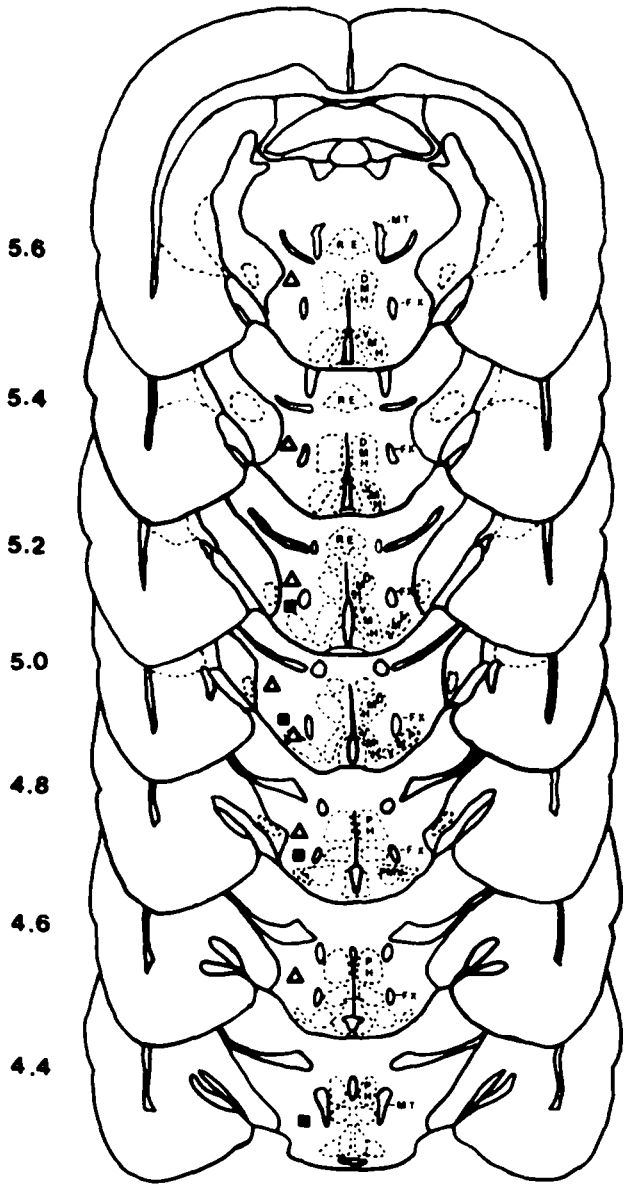

FIG. 5. Reconstruction of the locations of the electrode placements, adapted from [15]. Open triangles indicate electrode placements for animals used in the auto-titration experiments; closed squares indicate electrode placements for animals used in the free-operant experiments. Numbers to the left of the sections indicate the anterior posterior location of the section relative to vertical zero plane (0.0–vertical zero plane). Abbreviations: RE–nucleus reuniens thalami; DMH–dorsomedial nucleus of hypothalamus; MT–mamillothalamic tract; VMH–ventromedial nucleus of hypothalamus; FX–fornix; PMV–ventral premamillary nucleus; PH–posterior nucleus of hypothalamus.

other hand, doses of neuroleptics which reduce responding for brain self-stimulation, cause an increase in responding in other operant conditioning paradigms, such as drug self-administration, suggesting that neuroleptics may reduce self-stimulation responding by specifically attenuating the reward value of the stimulation [27]. Furthermore, while *d*- and *l*-amphetamine and haloperidol all decreased the rate of responding in the auto-titration experiments, the amphetamine isomers and haloperidol had opposite effects on the reinforcement threshold. Thus, despite its generally disruptive effects on ongoing behavior, it is still possible that haloperidol does, indeed, specifically reduce the rewarding

value of brain self-stimulation. The additional information afforded by the auto-titration technique should provide a broader basis for discriminating between those drugs which produce nonspecific behavioral disruption and those which specifically alter the brain's "reward system."

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