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Effects of Amphetamine and Nomifensine on Intracranial Self-Stimulation Discrimination Behavior in Rats

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SCHAEFER, G. J. AND R. P. MICHAEL. *Effects of amphetamine and nomifensine on intracranial self-stimulation discrimination behavior in rats.* PHARMACOL BIOCHEM BEHAV **41**(2) 391-397, 1992. — Rats implanted with electrodes in the medial forebrain bundle-lateral hypothalamus were trained in a discrete trial procedure to make a differential response (right or left lever press) in the presence or absence of brain stimulation [intracranial self-stimulation (ICSS)]. When animals reached a high level of accuracy (95% correct) in the discrimination task, testing was begun. In the first experiment, we compared the effects of saline and 0.3 mg/kg *d*-amphetamine when the intertrial interval (ITI) was 1, 5, 10, and 15 s. In the second experiment, animals were tested either with saline, 0.3 mg/kg *d*-amphetamine, or 1, 3, or 10 mg/kg nomifensine and the ITI was held constant at 5 s. Increasing the ITI from 1-15 s did not produce a drug-induced change in the discriminative stimulus properties of ICSS, although it did produce changes in total numbers of lever presses and numbers of intertrial lever presses. In the second experiment, neither *d*-amphetamine nor nomifensine altered the discriminative stimulus properties of ICSS, but a dose-response increase occurred in the time to complete the test session and in total number of lever presses and in presses on the initiating lever. Under conditions known to increase extracellular dopamine (DA) levels in brain, both amphetamine and nomifensine produced large increases in locomotor activity, but neither drug produced changes in the detection threshold for ICSS. Results indicated that the internal cues produced by ICSS are different from those produced by these psychomotor stimulant drugs.

d-Amphetamine Nomifensine Brain self-stimulation Discriminative stimulus properties
Detection threshold Locomotor activity

INTRACRANIAL self-stimulation (ICSS) supports various forms of operant behavior. Rats can be trained to press a lever on continuous or intermittent schedules of reinforcement for ICSS and will learn to press more than one lever for ICSS reward (22). It is assumed that in these more complex procedures ICSS serves as a conditioned stimulus with discriminative properties, and there is evidence that ICSS may serve as a discriminative stimulus in its own right (1,10). Many drugs also have discriminative stimulus properties and psychomotor stimulants, such as amphetamine, are particularly effective in this regard (9,15). Amphetamine also has marked effects on ICSS behavior: It increases the rate of responding and lowers the reinforcement threshold (24).

An issue of some interest is whether amphetamine and other psychomotor stimulants alter the detection threshold for ICSS as well as the reinforcement threshold. In a previous study using a drug discrimination paradigm, amphetamine did not alter the detection threshold for ICSS when electrodes were implanted in the medial forebrain bundle-lateral hypothalamus (MFB-LH) (25). These results were consistent with some other data on amphetamine (8) and with data on cocaine also (3,14), but were not consistent with the amphetamine results of Druhan et al. (11). In the latter, it was found that amphetamine altered the detection threshold only when the discriminative stimulus was presented for a longer time period.

Because of these different findings, we reexamined conditions that might alter the detection threshold for ICSS in the discrimination procedure. To do so, we studied the effects of amphetamine while systematically changing: 1) the parameters of the intertrial interval (ITI) and 2) the frequency of the stimulating current. We also 3) compared the effects of amphetamine with those of another psychomotor stimulant, nomifensine. Both amphetamine and nomifensine increase extracellular dopamine (DA) concentrations in brain areas such as the striatum and nucleus accumbens (2,7), although by dif-

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ferent mechanisms (18); these areas appear to be critical in ICSS-motivated behavior (32). In drug discrimination studies, the discriminative stimulus properties of nomifensine can substitute for those of amphetamine (28), and both amphetamine and nomifensine are self-administered by animals (6,30). If over the dose range and time frame of the changes in DA concentrations produced by amphetamine and nomifensine there were no significant changes in the detection threshold for ICSS, it would suggest that the internal cues produced by these drugs and by ICSS are not directly similar to each other. To help interpret results, several performance factors were measured during the detection threshold procedure and changes in locomotor activity were assessed in an independent group of animals.

METHOD

Subjects

Subjects were 18 male Sprague-Dawley-derived rats born from stock purchased from Charles River (Wilmington, MA). Animals (n = 8) used in the brain self-stimulation experiments weighed 365–545 g at the time of electrode implantation (60–105 days old), and those used in the locomotor activity study (n = 10) weighed 505–695 g at the beginning of activity testing (100 days old). Animals were maintained in group cages (three to four per cage) with fresh food and water, and were housed in a colony room on a 12L:12D cycle with lights on at 7:00 a.m. All housing, surgical, and experimental procedures were conducted according to the institutional regulations and the NIH Guide for the Care and Use of Laboratory Animals (NIH publication No. 85-23, revised 1985).

Apparatus

The test chamber has been described previously (25). On one wall, there were two conventional levers 11 cm apart separated by a Plexiglas partition. These levers were called the "choice levers." On the opposite wall, an omnidirectional lever called the "initiating lever" was suspended from the ceiling. The present experiments were programmed and data collected by an IBM XT computer using commercially available interface equipment (Models PIO12 and ERB-24, MetraByte, Taunton, MA), and the programming was done in-house. Two different outputs were produced by the biphasic, constant-current stimulator. Pressing a choice lever produced a 1000-ms train of pulses with a pulse duration of 0.5 ms with no delay between the positive and negative pulse. The frequency was either 60 or 100 Hz depending upon the experiment. The stimulus produced by the initiating lever was identical to that produced by the choice lever except that its intensity was always a proportion (0–100%) of that produced by the choice lever. The stimulus intensity was determined by the computer on a semirandom schedule for each trial.

An OmniTech Digiscan RXY activity monitor (Columbus, OH) interfaced with a Behavioral Control Unit (23) was used to measure locomotor activity. The device measured horizontal activity by counting the total number of interruptions of infrared beams. In addition, the Behavioral Control Unit measured the speed at which beam interruptions occurred and the amount of time the animals spent at rest.

Surgery and Histology

Rats were injected IP with 50 mg/kg sodium pentobarbital to produce surgical anesthesia and were also given SC 0.25 mg atropine sulfate to reduce any respiratory distress. Following positioning in a stereotaxic instrument, a small burr hole was drilled in the exposed skull and the dura was incised. A bipolar platinum electrode (tip diameter = 0.125 mm, Plastic Products, Roanoke, VA) was lowered into the brain aimed at the MFB-LH using coordinates AP 5.2, L 1.7, H −2.2(21). Four or five stainless steel screws were fixed to the skull prior to positioning the electrode, and the screws and electrode base were covered with cranioplastic cement to form a rigid, permanent anchor for the electrode. Animals were then given 100,000 U benzathine penicillin G and procaine penicillin G IM, together with 1 mg/kg flunixin meglumine (Banamine, Schering, Kenilworth, NJ) to prevent any postoperative discomfort. When ICSS testing was completed, animals were killed with a large overdose of sodium pentobarbital and perfused via the heart with 10% formalin. The tissue was fixed, and frozen sections were cut at 50 μm. Alternate sections were stained with cresyl violet and Weil's stain and viewed under a microprojector to locate the site of the electrode tips.

Procedure

Discrimination training. Rats were trained in a discrete trial procedure to make a differential response (right or left lever press) in the presence or absence of brain stimulation. For each trial, the animal was required to respond first on the initiating lever and then on one of the two choice levers for ICSS. The first response on the initiating lever produced a 1-s tone from the Sonalert speaker. When stimulation occurred during the auditory signal, the animal was required to press the right-side choice lever to obtain further ICSS. The right-side lever was, therefore, designated the ICSS choice lever. The first response on the ICSS choice lever also terminated the trial. During training sessions, stimulus parameters of the initiating lever and the ICSS-choice lever were identical. If the animal pressed the left-side choice lever, the trial was terminated without further stimulation. When ICSS did not accompany the auditory signal with the first press of the initiating lever, the animal was required to press the left-side choice lever to obtain stimulation. The left-side lever was, therefore, designated the No-ICSS choice lever. The first response on the No-ICSS choice lever terminated the trial. Pressing the right-side lever in this condition terminated the trial without stimulation. Therefore, reinforcement was available on one of two choice levers in each trial. For half the animals, the position of the ICSS and No-ICSS choice lever was reversed. The beginning of a trial was signalled by illuminating the house light and the lights above the choice levers. A trial was terminated only by the completion of the two-response chain or the end of a session. To vary the time frame, the intertrial interval (ITI) was changed from 1–15 s depending upon the experiment, and during this time the test chamber was dark. Animals were trained until they reached 95% accuracy (95 out of 100 trials) on 4 consecutive days. In these experiments, the eight animals learned to discriminate between zero current and 100–160 μA (median = 150 μA).

Discrimination testing. Testing with vehicle and with drugs each took place twice a week (Monday and Thursday = vehicle; Tuesday and Friday = drug). Test sessions differed in two respects from training sessions. First, both choice levers produced ICSS; this prevented an animal from determining which lever was "correct" for a given test (29). Second, the initiating lever produced a stimulus that ranged from 0–100% of the training current in 12 steps. An average of 10 trials occurred at each of the 12 stimulus currents and these 10

trials were randomly interspersed during the 120-trial session. Several additional measures of performance were obtained in the detection threshold experiment. These measures were: 1) total time to complete the test session, 2) total number of lever presses on all three levers, 3) number of intertrial presses on the initiating lever, 4) number of intertrial presses on the ICSS choice lever, and 5) number of intertrial presses on the No-ICSS lever.

Locomotor activity. Animals were first habituated to the apparatus for 20 min. After this habituation phase, animals were administered either saline vehicle or drug, immediately returned to the apparatus, and activity was measured for the next 60 min. Each animal was tested once per week for a single 1-h session (after the 20-min habituation phase).

Drugs

Drugs were *d*-amphetamine sulfate (Sigma Chemical, St. Louis, MO) and nomifensine maleate (a gift from Hoechst-Roussel Pharmaceuticals, Somerville, NJ). Both drugs were dissolved in 0.9% saline and were expressed in terms of the free base, and were administered 15 min before the beginning of the ICSS experiment. However, *d*-amphetamine was administered SC in a dose of 0.3 mg/kg and a volume of 1 ml/kg, while nomifensine was administered IP in doses of either 1.0, 3.0, or 10 mg/kg and in a volume of 10 ml/kg. In the locomotor activity study, animals were injected immediately after the 20-min warm-up phase and activity monitoring began as soon as animals were injected and placed back into the test chamber.

Data Analysis

Data for detection threshold testing consisted of the number of trials completed on the ICSS choice lever at each stimulus current. To evaluate these data, the number of trials completed on the ICSS choice lever at each current step was computed for saline and for each dose of drug. A log-probit transformation was performed on these data and the resulting regression lines were evaluated for parallelism, stimulus intensity that produced 50% responding on the ICSS choice lever (ED_{50}), and relative potency. This was achieved by the method of Litchfield and Wilcoxon (17), using the computerized version of Tallarida and Murray (31). The Litchfield-Wilcoxon procedure can be used when the dependent variable is an either-or response (left or right lever press) that increases or decreases as a function of systematic changes in the independent variable (stimulus current). This method determines whether or not two parallel regression lines differ from each other, indicating that the administration of a drug or drug combination has a significant effect on the animal's choice behavior, or whether the drug manipulation has disrupted performance in some manner, producing nonparallel regression lines. This procedure has been used to evaluate individual differences in ICSS detection thresholds (25), as well as the discriminative stimulus properties of amphetamine compounds (5,28). Changes in relative potency were interpreted as changes in the detection threshold for ICSS reinforcement. Analyses of variance (ANOVA's) were performed on the five performance measures, and the significance of differences was further evaluated with Dunnett's test.

Locomotor activity data were collected every 20 min during the 1-h test session. Values for each parameter were averaged across animals and results with drug administration were compared with values when vehicle was administered. Animals served as their own controls. Data were analyzed using ANOVA followed by Dunnett's test.

RESULTS

Effects of Changing the ITI

In the first series of experiments in which animals were tested with vehicle or 0.3 mg/kg *d*-amphetamine while the ITI was increased in steps from 1-15 s, stimulation frequency remained constant at 100 Hz. Figure 1 shows the detection thresholds produced by saline and amphetamine at each of the four ITI's. Regardless of the ITI employed, amphetamine administration did not alter the detection threshold, although an ITI of 10 s appeared to disrupt performance to some extent because the regression lines deviated from parallelism. It can be seen that 0.3 mg/kg amphetamine affected operant performance at ITI's of 1, 5, and 10 s but not at 15 s (Table 1). The time to complete the test session was reduced, and the total numbers of lever presses and the numbers of ITI presses on the initiating lever were increased. Thus, while amphetamine induced changes in performance at some ITI's, there was no indication that the detection threshold was lowered in any way.

Effects of Amphetamine and Nomifensine

In this series of experiments, animals were tested with vehicle, 0.3 mg/kg *d*-amphetamine, and graded doses of nomifen-

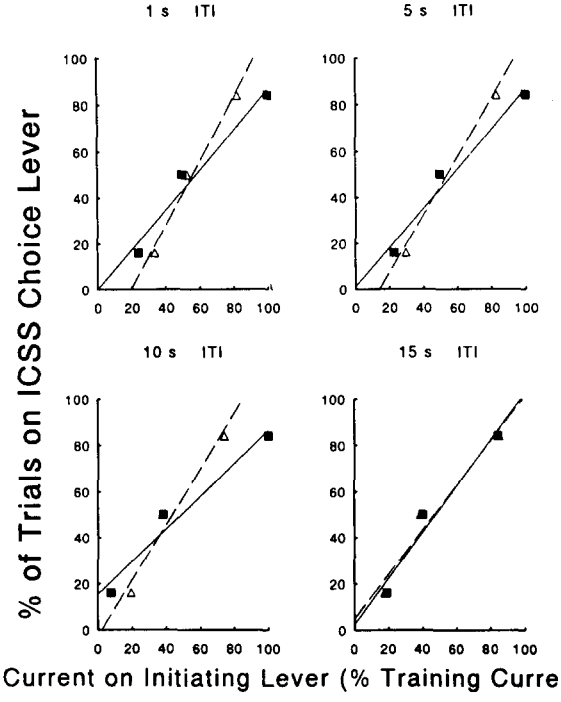

FIG. 1. Effects of saline (■) and 0.3 mg/kg *d*-amphetamine (△) on the percentage of trials completed on the choice lever appropriate for brain stimulation when the ITI was increased from 1-15 s. The abscissa indicates the current produced by the initiating lever, which has been converted to a percentage of the maximum (100-160 μA) used during training sessions. $N = 8$ rats. Regression lines were produced by the Litchfield-Wilcoxon (14) analysis and give the ED_{50} value along with the 95% confidence limits (16 and 84% values).

TABLE 1

EFFECTS OF SALINE AND 0.3 mg/kg *d*-AMPHETAMINE ON OPERANT PERFORMANCE WHEN THE ITI WAS CHANGED FROM 1-15 s

Parameter	1-s ITI		5-s ITI		10-s ITI		15-s ITI	
	Sal	Amp	Sal	Amp	Sal	Amp	Sal	Amp
Time to complete session (±SEM)	1267 ± 123	1156 ± 113*	2004 ± 126	1868 ± 38	3221 ± 78	3085 ± 57*	4422 ± 114	4456 ± 158
Total lever presses (±SEM) during session	876 ± 50	801 ± 42*	1275 ± 96	1518 ± 125*	1894 ± 152	2074 ± 161	1953 ± 163	2190 ± 182
Intertrial lever presses (±SEM) on initiating lever	22 ± 9	16 ± 8	448 ± 62	673 ± 79*	1104 ± 128	1253 ± 133	1172 ± 144	1381 ± 158
Intertrial lever presses (±SEM) on ICSS choice lever	55 ± 18	44 ± 17	51 ± 20	70 ± 23*	60 ± 27	70 ± 30	64 ± 30	62 ± 26
Intertrial lever presses (±SEM) on No-ICSS choice lever	68 ± 20	66 ± 20	49 ± 17	76 ± 26*	53 ± 14	61 ± 23	52 ± 13	61 ± 14

Each value is the mean of the data from one session with eight rats.
*Significantly different from corresponding saline value, $p < 0.05$-0.01.

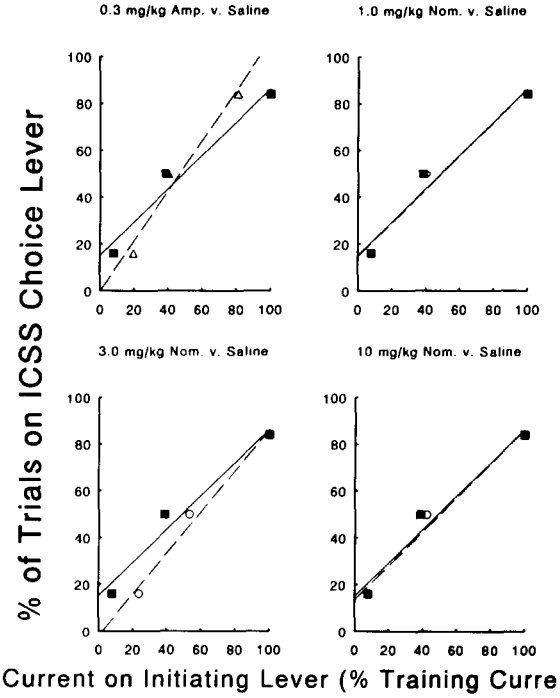

FIG. 2. Effects of saline (■), 0.3 mg/kg *d*-amphetamine (△), and increasing doses of nomifensine (1.0, 3.0, and 10 mg/kg) (○) on the percentage of trials completed on the choice lever appropriate for brain stimulation. The ITI was kept constant at 5 s. The abscissa indicates the current produced by the initiating lever, which has been converted to a percentage of the maximum used during training sessions. $N = 8$ rats. Regression lines were produced by the Litchfield-Wilcoxon (14) analysis and give the ED_{50} value along with the 95% confidence limits (16 and 84% values).

sine (1.0, 3.0, or 10 mg/kg). The ITI was kept at 5 s and stimulation frequency was 60 Hz. The effects on detection thresholds are shown in Fig. 2. No dose of either drug significantly altered the detection threshold. After 3.0 mg/kg nomifensine, there was a small shift to the right, suggesting an increase in threshold, but the effect was not significant. These drugs, however, produced interesting changes in performance. Following 0.3 mg/kg amphetamine, there was a decrease in the total time to complete the test session (Fig. 3), but with increasing doses of nomifensine there was a progressive increase in this parameter, $F(4,28) = 14.2$, $p < 0.001$. Nomifensine significantly increased the total number of lever presses (Table 2), $F(4,28) = 9.8$, $p < 0.001$, as well as the number of intertrial presses on the initiating lever (Fig. 3), $F(4,28) = 9.1$, $p < 0.001$. However, neither drug significantly altered the number of intertrial presses on either the ICSS choice lever or the No-ICSS choice lever (Table 2).

Effects on Locomotor Activity

Figure 4 shows the effects of saline, 0.3 mg/kg *d*-amphetamine, and graded doses of nomifensine on locomotor activity from 20-60 min after drug or vehicle administration; this approximates the time animals were in the operant chamber. Amphetamine and the two higher doses of nomifensine significantly increased locomotor activity in the Digiscan, $F(4,36) = 15.9$, $p < 0.001$. With the highest dose of nomifensine (10 mg/kg), there was a seven-fold increase in activity above saline values.

Histology

There was a lateral distribution of the electrode tips from the fornix to the internal capsule and a vertical distribution from the zona incerta to the premamillary nucleus of the hypothalamus. No consistent relationship was observed between the detection threshold for each animal and the site of the electrode tip.

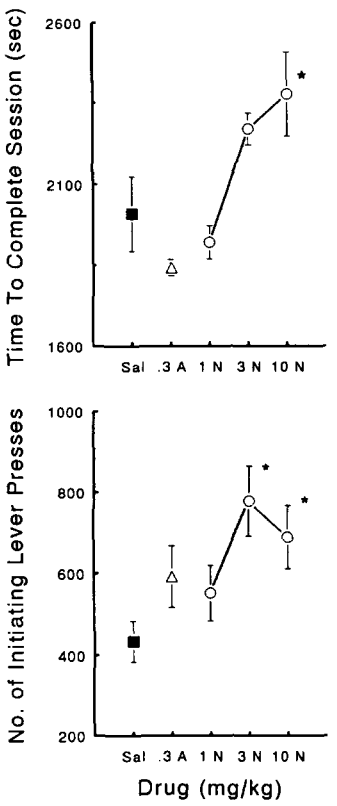

FIG. 3. Effects of saline (■), 0.3 mg/kg *d*-amphetamine (△), and increasing doses of nomifensine (○) on (top) total time (s) to complete the session and (bottom) total number of intertrial presses on the initiating lever. The ITI was 5 s in this experiment. It can be seen that while *d*-amphetamine decreased the time relative to saline, nomifensine produced a graded increase. $N = 8$ rats. * Significantly different from saline, $p < 0.05$–0.01.

DISCUSSION

These studies demonstrated that manipulations that are thought to increase DA availability did not alter detection thresholds for ICSS. Clear and consistent changes occurred in the performance of operant behavior, but discriminative stimulus properties were not changed. Thus, choice behavior in an ICSS task is not critically dependent upon the brain levels of DA.

There is much evidence that amphetamine affects ICSS, and nomifensine has been shown to act similarly. Low to moderate doses of amphetamine increased responding for ICSS on continuous as well as intermittent schedules of ICSS reward, and amphetamine lowered the reinforcement threshold for ICSS in various paradigms (16). Amphetamine will also facilitate the acquisition of brain self-stimulation with electrodes in the MFB-LH (27), and nomifensine has been shown to increase the rate of responding for ICSS over the dose range of 2.5–10 mg/kg (12). In addition, pretreatment with 1.0 mg/kg nomifensine increased the release of DA in the nucleus accumbens of rats lever pressing for MFB-LH ICSS(20). We recently compared amphetamine (0.1–1.0 mg/kg) with nomifensine (1.0–10 mg/kg) in a reinforcement threshold procedure and found that both drugs produced a graded decrease in threshold (26).

Neither changing the electrical parameters nor changing the ITI altered detection thresholds. In these experiments, we used a relatively long train duration (1 s) and relatively long pulses (0.5 ms). Coupled with a short ITI of 1 s, this would be expected to produce sustained brain stimulation and our parameters appeared to be within the range of those producing increased DA levels in brain (19). Under these conditions, there was no change in detection thresholds, and no change occurred when the ITI was increased to 15 s. In a previous report (25), we used a 500-ms train of pulses with a pulse duration of 1.0 ms at 100 Hz. There was no change in the detection threshold over an amphetamine dose range of 0.03–1.0 mg/kg. The effects of 0.3 mg/kg amphetamine on operant performance were very similar to those found in the present study using a 5-s ITI. These and our prior results can be contrasted with those reporting that amphetamine decreased ICSS detection thresholds (11). A number of procedural dif-

TABLE 2

EFFECTS OF SALINE, 0.3 mg/kg *d*-AMPHETAMINE, AND INCREASING DOSES OF NOMIFENSINE ON OPERANT PERFORMANCE DURING THE DISCRIMINATION PROCEDURE

Parameter	Saline	*d*-Amphetamine 0.3 mg/kg	Nomifensine (mg/kg) 1.0	3.0	10
Total lever presses (±SEM) during session	1191 ± 100	1392 ± 126	1351 ± 117	1678 ± 143*	1764 ± 123*
Intertrial lever presses (±SEM) on ICSS choice lever	55 ± 25	61 ± 32	56 ± 18	34 ± 10	84 ± 28
Intertrial lever presses (±SEM) on No-ICSS choice lever	52 ± 16	64 ± 21	53 ± 18	60 ± 18	65 ± 19

Each value is the mean of the data from one session with eight rats.
*Significantly different from saline value, $p < 0.05$–0.01.

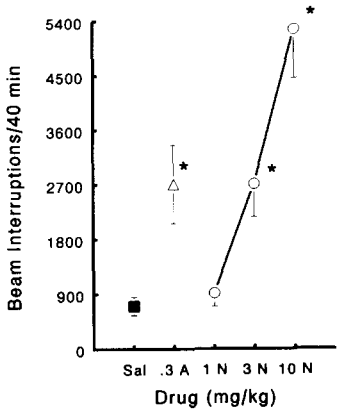

FIG. 4. Effects of saline (■), 0.3 mg/kg *d*-amphetamine (△), and increasing doses of nomifensine (○) on locomotor activity (beam interruptions) during the period of 20–60 min after drug/saline administration. This corresponds to the time when animals were tested in the ICSS discrimination procedure. $N = 10$ rats. *Significantly different from saline, $p < 0.05$–0.01.

ferences might account for these differences. The Druhan study used rats implanted with electrodes in the VTA, while in this study rats were implanted in the MFB-LH. In the Druhan study, rats learned to discriminate between high- and low-stimulus currents (10 vs. 22 μA), while in our study animals learned to discriminate between zero and suprathreshold current. In the Druhan study, animals were given 24 presentations of 200-ms trains of 60-Hz sine wave stimulations delivered 200 ms apart. In the present study, animals received a single 1-s train of 0.5-ms biphasic square wave pulses on triggering the initiating lever. Some combination of these different parameters may well account for the different results. A crucial question, of course, is whether or not dopamine may underlie the differences in threshold determinations. To resolve this issue, it would be necessary to demonstrate that, under the experimental conditions of the Druhan study, DA concentrations in brain were altered, while under our experimental conditions they were not.

These data, however, reemphasize two fundamental issues regarding brain stimulation. The first is that mechanisms that underlie the rewarding properties of ICSS may differ from those mediating its discriminative effects (14). The second issue concerns the long-running debate on the neurotransmitter systems involved in ICSS. While the preponderance of evidence suggests that DA is critical (32), there may also be considerable involvement of cholinergic neurons in the rewarding and, perhaps, discriminative effects of MFB-LH ICSS (13). Therefore, a more prudent course would be to thoroughly examine those mechanisms that mediate the conditioned or discriminative stimulus effects of ICSS (4).

Drugs were clearly effective in the present study; both, for example, increased total numbers of lever presses and numbers of intertrial presses on the initiating lever. Of interest was the finding that while amphetamine decreased the time to complete the session, nomifensine produced an increase in this measure. Also of interest was the finding that neither drug altered the number of intertrial presses on either the ICSS choice lever or the No-ICSS choice lever. This indicated that the drugs did not nonselectively bias responding on either choice lever. That the doses generally caused psychomotor stimulation was clear from the locomotor activity results; amphetamine produced a three-fold increase in activity, as did 3.0 mg/kg nomifensine, while the highest dose of nomifensine increased activity by seven-fold.

Both amphetamine and nomifensine by themselves have been shown to increase extracellular DA using a microdialysis technique (2,7). Further, there is good evidence that DA is involved in the discriminative stimulus properties of amphetamine (28) and this is presumably so for nomifensine as well (33). Although DA concentrations were not measured in these studies, the electrical parameters employed, as well as the drugs administered, should have combined to flood with DA the sites critical for ICSS. In spite of these favorable conditions for increased DA release, the animal's choice behavior for ICSS reward was not changed. Whatever mechanisms underlie the discriminative stimulus properties of ICSS and of psychomotor stimulants, they are clearly not the same.

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