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The Effects of Long-Term Administration of Antidepressant Drugs on Intracranial Self-Stimulation Responding in Rats

BRYON D. McCARTER AND LARRY KOKKINIDIS

Department of Psychology, University of Saskatchewan, Saskatoon, Saskatchewan S7N 0W0, Canada

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McCARTER, B. D. AND L. KOKKINIDIS. *The effects of long-term administration of antidepressant drugs on intracranial self-stimulation responding in rats.* PHARMACOL BIOCHEM BEHAV 31(2) 243–247, 1988.—A discrimination procedure employing a two hole nose-poke technique was used to evaluate the effects of chronic administration of desipramine, amitriptyline, bupropion, nomifensine and zimelidine on intracranial self-stimulation (ICSS). Analysis of ICSS as a function of descending and ascending current presentation revealed that long-term exposure to desipramine significantly facilitated rates of responding from the medial forebrain bundle, and resulted in a shift to the left of the rate-intensity functions. The use of a discrimination paradigm allowed for the assessment of incorrect responses which proved to be a sensitive measure of the motor activating properties associated with electrical brain stimulation. These data indicated that the positive reinforcing effects of desipramine were not accompanied by concomitant increases in motor arousal. No changes in ICSS responding were evident after long-term treatment with amitriptyline, or the atypical antidepressants, bupropion, nomifensine and zimelidine. The implications of these findings were discussed in terms of the effects of these drugs on reward processes and the role of dopamine in the therapeutic efficacy of antidepressant drugs.

Intracranial self-stimulation Antidepressant drugs Reward processes Dopamine (DA) Depression

IN agreement with clinical theories that depressive syndromes reflect a reduced capacity to experience pleasure (5, 11, 19), data derived from animal experiments indicate that manipulations used to model depression influence central reward processes [reviewed in (29)]. This conclusion is based on several lines of research assessing changes in performance in an ICSS paradigm. It is well documented, for example, that exposure to uncontrollable stress decreased rates of ICSS responding (31), indicating that the behavioral deficits associated with stress may involve alterations in the rewarding impact of electrical brain stimulation. An alternative approach utilized in this laboratory has shown a pronounced and sustained depression of ICSS responding following withdrawal from long-term amphetamine exposure (13,14). The finding that the decreased rates of ICSS were accompanied by increased reward thresholds (3,16), provides further support for the position that depressive symptoms associated with amphetamine abuse (4, 21, 22, 28), may involve decreased reward system functioning [for review see (21)].

With respect to the postamphetamine depression of ICSS, it was demonstrated that chronic tricyclic antidepressant treatment mitigated the observed deficits in ICSS responding (15). These findings are of particular interest since desipramine was shown to have therapeutic effects on depression related to stimulant withdrawal in humans (10). In light of these observations, it might be expected that administration of antidepressant drugs would have positive effects on ICSS. Yet the literature concerning the acute effects of antidepressants on ICSS is equivocal, with studies showing increases (9), decreases (26), and no effects on ICSS (1, 2, 25). Consistent with the delayed therapeutic onset of antidepressant treatment, however, Fibiger and Phillips (7) found chronic exposure to desipramine to facilitate ICSS responding, suggesting that long-term antidepressant treatment can have specific effects on central reward systems.

Since DA is an important modulator of ICSS (6,30), this behavioral observation has important implications concerning the role of DA in the therapeutic efficacy of antidepressant treatment. It was therefore worthwhile to determine whether the long-term administration of other antidepressant agents would have a positive effect on ICSS similar to that observed with desipramine. The purpose of the present study was to a) replicate earlier observations concerning the effects of desipramine on ICSS and b) to assess the effects of another tricyclic antidepressant, amitriptyline, as well as the atypical antidepressants nomifensine, bupropion and zimelidine on ICSS. In this way it would be possible to determine whether antidepressant drugs with

varying degrees of potency on monoamine uptake systems, when administered acutely, will exert common effects on ICSS after chronic administration.

METHOD

Subjects

Forty-eight male Wistar rats obtained from the Canadian Breeding Farms and Laboratories, Quebec, Canada served as subjects. Rats weighed approximately 300 g at the start of the experiment. Subjects were housed individually and were allowed free access to food and water. Animals were maintained on a regular 12 hr light/dark cycle and were tested during the light portion of the cycle.

Apparatus

The apparatus consisted of four identical black Plexiglas boxes (60 cm in length × 50 cm in width × 35 cm height) with a black Plexiglas floor. Two holes, 4 cm in diameter and 10 cm apart, were located in the center of the floor of each box. Each hole was surrounded by a ring of lights embedded in the Plexiglas floor with an opaque cover (2 cm in width). Three photobeam units were mounted in the Plexiglas of each hole 0.5 cm from the top, and disruption of the photobeams by a nose-poke response resulted in electrical brain stimulation. Brain stimulation was delivered from a constant current stimulator (Schnabel Electronics, Saskatoon, Canada), and consisted of a monophasic square wave with a pulse duration of 0.1 msec and a 100 Hz pulse frequency. Once initiated by a correct nose-poke response, the stimulation had a duration of 0.5 sec. All boxes were interfaced to a Commodore 64 computer whose software controlled the presentation of electrical stimulation, the discrimination procedure which involved alternating the onset of lights around each hole at specified intervals, as well as the recording of the number of nose-poke responses in each hole during behavioral testing.

Procedure

Surgery. Subjects were anesthetized with sodium pentobarbital (Somnotol, 60 mg/kg) and were stereotaxically implanted with bipolar 0.010-inch diameter electrodes (MS-303/1, Plastic Products Co.) in the medial forebrain at the level of the lateral hypothalamus. Electrodes had 0.5 mm of the tips scraped and electrode tips were separated by 0.5 mm. The coordinates for electrode placement were anterior-posterior −1.5 mm from bregma, lateral 1.5 mm from the midline suture and ventral −8.5 mm from the skull surface. Electrodes were implanted perpendicular to the horizontal plane and the incisor bar was adjusted for each animal such that the horizontal plane was level for posterior and anterior portions of the skull.

ICSS training. Training was initiated 7 days after recovery from surgery. Animals were placed in the ICSS boxes and were allowed to self-stimulate at a current level which engendered the highest rate of responding. During the training session the light surrounding one of the holes was on and a nose-poke into this hole resulted in electrical brain stimulation, whereas responding into the unlit hole was of no behavioral consequence. After stable rates of responding were established the discrimination procedure was initiated. The light was programmed to alternate between holes every 30 sec for a trial period of 5 min in duration. When animals responded correctly on at least 90% of the total responses made the alternation time was reduced to 20 sec and the trial duration to 4 min. This procedure was continued until the alternation time was 10 sec with a trial duration of 2 min. Animals readily learned this discrimination task and at their optimal current level responded 96–99% of the time to the correct hole.

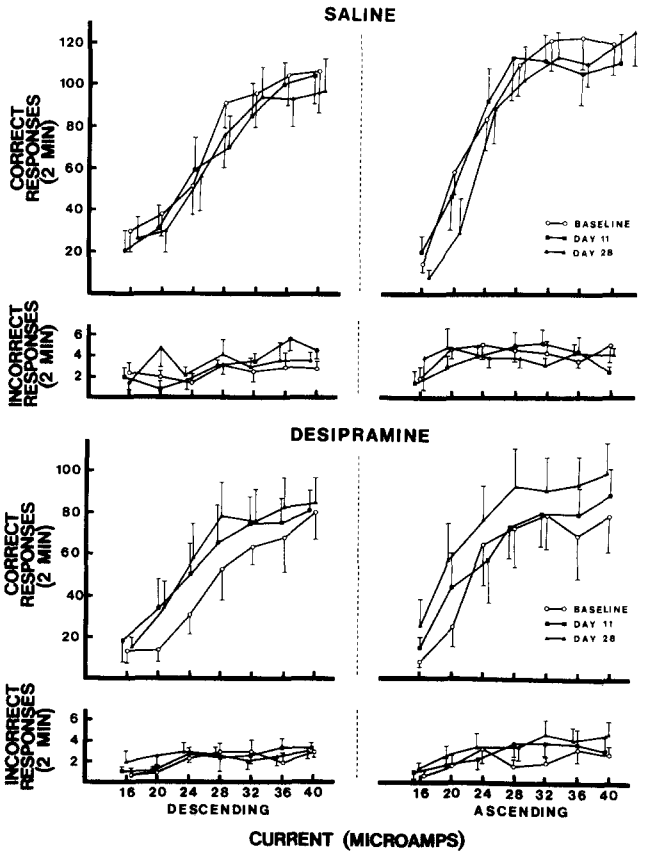

FIG. 1. Mean number of correct and incorrect responses (S.E.M.) as a function of descending and ascending current presentation and drug treatment. The top panel shows baseline response rates and ICSS responding after 11 and 28 days of repeated saline treatment (N=8). The bottom panel depicts baseline responding and performance after 11 and 28 days of chronic desipramine treatment (N=8).

Current-response baseline. Following discrimination training baseline rates of responding were established as a function of descending and ascending current presentation. When first placed in the apparatus animals were allowed a 5 min session at their individual optimal current intensities. The current was set at 40 μA (RMS) and was decreased by 10% in a stepwise fashion. Animals were tested for 2 min at each current level. The number of correct and incorrect responses were recorded at 40, 36, 32, 28, 24, 20 and 16 μA. After completion of the descending phase of the test session current was increased by 10% for 7 steps and the number of correct and incorrect responses were recorded as a function of ascending current presentation. Once current-response rates stabilized the baseline for each animal was determined using the mean rate of responding at each current level of the last 3 days of ICSS testing.

Drug treatment. Animals were placed into 6 groups (N=8/group) and were injected (IP) daily with either desipramine (10 mg/kg), amitriptyline (10 mg/kg), bupropion (20

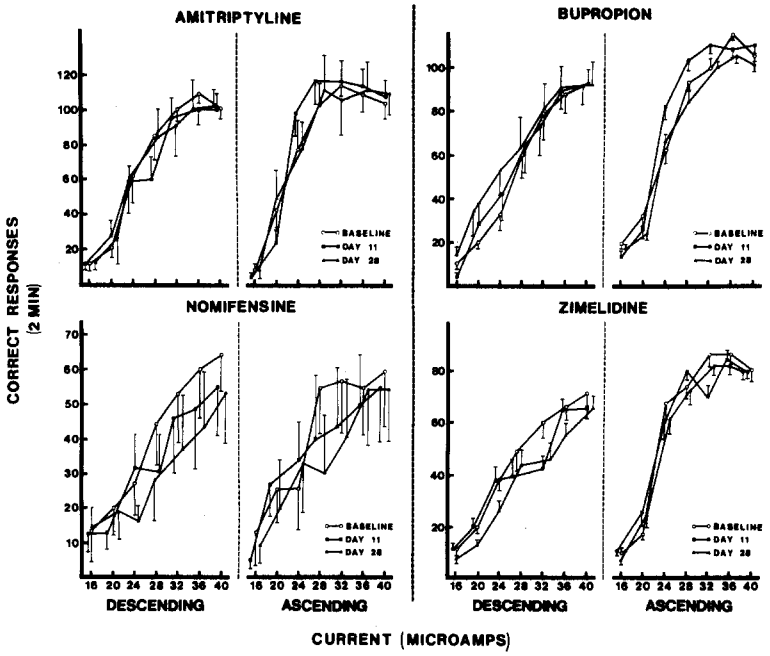

FIG. 2. Mean number of correct responses (S.E.M.) as a function descending and ascending current presentation and chronic drug treatment; amitriptyline (N=7), bupropion (N=7), nomifensine (N=8) and zimelidine (N=7). Baseline rates and ICSS responding after 11 and 28 days of drug treatment are depicted.

mg/kg), nomifensine (20 mg/kg), zimelidine (20 mg/kg) or saline for 28 consecutive days. During the chronic drug administration period animals were tested for ICSS three times weekly on Mondays, Wednesdays and Fridays. On ICSS test days, drug injections were administered immediately after the test session and animals were always tested 24 hr after the last drug injection.

RESULTS

At the termination of the experiment rats were overdosed with sodium pentobarbital and perfused intracardially with 0.9% saline followed by 10% Formalin. In those animals that completed the experiment, histological examination of electrode sites confirmed that placements were in the region of the lateral hypothalamus. Three animals did not complete the experiment due to head cap loss.

Since baseline response rates of the different drug groups were not equal, analysis of variance with repeated measures on current presentation and ICSS test days was carried out separately for each drug treatment using baseline response rates as the control variable. In addition, scores obtained from the descending and ascending presentation of current were analyzed separately for both correct and incorrect responses.

The number of correct and incorrect responses made as a function of descending and ascending current presentation and repeated ICSS testing after chronic saline and desipramine treatment are depicted in Fig. 1. In the case of saline, analysis of variance yielded a significant main effect for Current with respect to the number of correct responses made during descending current presentation, $F(6,42)=8.91$, $p<0.0001$, and ascending current presentation, $F(6,42)=32.02$, $p<0.0001$. While animals showed facilitated response rates as a function of increased current intensity there were no significant differences after repeated ICSS testing, F's(12, 84)=0.66 and 1.33, $p>0.05$ (for descending and ascending modes), and as is evident in Fig. 1, ICSS responding after 28 days of saline treatment was comparable to baseline rates.

Analysis of variance of the incorrect response scores also yielded a significant main effect for Current, F's(6,42)=3.90 and 6.36, $p<0.004$ for descending and ascending current presentation, respectively. The increase in errors seen as function of current intensity probably reflects enhanced arousal levels and the associated motor activating properties of electrical brain stimulation. Consistent with the ICSS data, however, there were no significant effects with respect to the number of incorrect responses after repeated ICSS testing, F's(12,84)=0.35 and 0.78, $p>0.05$.

Chronic desipramine administration significantly facilitated ICSS. With respect to the correct response scores, analysis of variance showed significant main effects for Current, F's(6,42)=2.53, $p<0.007$ and 22.27, $p<0.0001$ (for descending and ascending presentation, respectively), and Test Day, F's(12,84)=2.53, and 2.70, $p<0.007$. As is evident in Fig. 1, rates of responding were significantly higher relative to baseline rates after 11 and 28 days of desipramine treatment during the descending current mode, and a facilitating effect on ICSS was observed after 28 days of drug treatment during ascending current presentation. The absence of an effect on Day 11 in the ascending mode is, in all likelihood, the result of the rather rapid increase in ICSS rates at the lower current intensities. The increased slope of the current-response curve as a function of ascending current presentation probably reflects an anticipatory effect related to the reinforcing value associated with the expectant presentation of higher current levels. The higher response rates at these current intensities may have masked any re-

sponse increases that might have resulted from chronic desipramine treatment. In any event, the enhanced ICSS rates after desipramine were not paralleled by drug-induced increases in incorrect responses. Specifically, significant main effects for Current, F's(6,42)=2.32, $p<0.05$, and 9.44, $p<0.0001$ (for descending and ascending current presentation) were observed, with no significant effects for Test Day, F's(12,84)=1.58 and 1.11, $p>0.05$.

The number of correct responses after chronic treatment with amitriptyline, bupropion, nomifensine and zimelidine after ascending and descending current presentation are depicted in Fig. 2. Analysis of variance yielded significant main effects for Current with respect to amitriptyline, F's(6,36)= 49.46 and 36.62, $p<0.0001$; bupropion, F's(6,36)=35.98 and 32.73, $p<0.0001$; nomifensine, F's(6,42)=9.00 and 9.43, $p<0.001$; and zimelidine, F's(6,36)=12.96 and 35.28, $p<0.001$ (for descending and ascending current presentation, respectively). As can be seen in Fig. 2, no significant effects were observed after long-term treatment with amitriptyline and the atypical antidepressants. While a trend to decreased responding was evident after nomifensine administration, this effect was not statistically significant, F's(12,84)=0.48 and 0.50, $p>0.05$ (for ascending and descending modes).

DISCUSSION

Rats when given the opportunity to nose-poke for electrical brain stimulation showed typical current-response functions after descending and ascending current presentation. The use of a discrimination procedure allowed for the evaluation of correct and incorrect responding in the ICSS paradigm. An important finding in this study was that the facilitated ICSS rates associated with increased current levels were paralleled by enhanced responding to the incorrect hole. These data suggest that the discrimination procedure is sufficiently sensitive to the arousal and motor activating properties of electrical brain stimulation, and may prove useful in future research with respect to dissociating the motor consequences of drug treatments from effects on reinforcement.

Chronic administration of desipramine was found to have pronounced effects on ICSS significantly facilitating rates of responding. These findings essentially replicate previous reports involving the chronic effects of desipramine on ICSS (7). However, while in the Fibiger and Phillips study response enhancement was evident only during the ascending portion of the experiment, we observed increased responding and a shift to the left of the current-response function in both the descending and ascending modes. There are several procedural differences between experiments that can account for this variation including site of electrode placement, response type (nose-poke vs. bar press), chronic drug schedule and differences concerning the presentation of current. In the earlier study, response increases were evident when electrodes were situated in the ventral tegmental area. Since in this experiment the ICSS facilitation was observed from the medial forebrain bundle, it might well be the case that this brain region which contains a number of ascending monoaminergic fibers may be more sensitive to the response enhancing effects of desipramine.

Given the importance of DA in modulating ICSS (6,30), the results concerning desipramine confirm previous suggestions that chronic exposure to this tricyclic facilitates the neuronal efficacy of DA dynamics (7,23). In addition, the finding that long-term antidepressant treatment did not modify the number of incorrect responses made during ICSS testing in both the descending and ascending current modes, indicates that this tricyclic had specific effects on reward processes and did not involve a drug-induced motor bias. This observation is important since withdrawal hyperactivity after antidepressant administration has been reported (18), and animals are more sensitive to the motor activating properties of amphetamine after desipramine withdrawal (23).

Although a shift to the left of the current-response function was evident after desipramine, a similar effect on ICSS was not observed after long-term administration of the other antidepressants. Specifically, chronic administration of amitriptyline did not modify ICSS and long-term exposure to the atypical antidepressants bupropion, zimelidine and nomifensine were without influence on ICSS, as well. The lack of an effect with zimelidine is in agreement with previous reports indicating that this antidepressant does not alter other DA-mediated behaviors following chronic exposure (17). Moreover, it should be noted that a trend towards a response depression was evident after repeated nomifensine administration. While this effect was not statistically significant, the decrease in ICSS responding resembles the postamphetamine depression of ICSS seen after amphetamine withdrawal (12), and is interesting since, like amphetamine, nomifensine is readily self-administered by rats (24). Perhaps further work utilizing multiple daily injections might prove beneficial in determining the significance of this observation.

The finding in this study that chronic administration of desipramine enhanced ICSS, whereas similar exposure to bupropion and nomifensine was without influence in this respect, indicates that these antidepressants did not exert congruent effects on DA systems after chronic drug treatment. Moreover, it is clear from data of this nature that the long-term consequences of these antidepressants cannot be predicted from their acute effects. Since nomifensine and bupropion are potent inhibitors of DA reuptake (8,27), it would be expected that chronic administration of these atypical antidepressants should have enhanced ICSS responding. On the other hand, desipramine which has only weak effects on DA uptake (8,27), was observed to facilitate ICSS after long-term exposure.

A behavioral distinction was also evident between desipramine and the other tricyclic compound, amitriptyline. Since amitriptyline treatment did not modify ICSS, it would appear that this drug also had minimal effects on DA activity after chronic exposure. It is not certain whether the absence of a behavioral effect to repeated amitriptyline treatment reflects metabolic factors (20), however it should be pointed out that under different experimental conditions we have found this tricyclic to facilitate DA neuronal processes. Specifically, while amitriptyline did not influence ICSS in the present experiment, chronic exposure to this drug attenuated the ICSS depression that typically develops after amphetamine withdrawal (15); an effect thought to involve DA hypoactivity (12). Consistent with this observation, chronic imipramine administration also did not increase ICSS, but evoked a robust antidepressant action when administered to animals during amphetamine withdrawal (15).

On the basis of these data it would appear that amitriptyline can influence ICSS, however, this effect may become apparent only when reward systems are in a depressed state. Taken together, these findings suggest that modification of the neural substrate modulating reward processes is not limited to desipramine, but rather the ability of this tricyclic to facilitate ICSS after chronic administration may reflect a

more potent effect on DA systems. At this time, the available evidence implicating specific effects on ICSS rates and thresholds after chronic antidepressant administration is limited to the tricyclic compounds, and further work involving the postamphetamine depression of ICSS may prove useful in identifying and classifying antidepressant drugs whose therapeutic effects involve improved reward system functioning.

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