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Acute and Chronic Desipramine Treatment Effects on Rewarding Electrical Stimulation of the Lateral Hypothalamus[1]

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HALL, F. S., J. R. STELLAR AND A. E. KELLEY. *Acute and chronic desipramine treatment effects on rewarding electrical stimulation of the lateral hypothalamus.* PHARMACOL BIOCHEM BEHAV **37**(2) 277–281, 1990.—Two weeks of chronic desipramine HCl (DMI) (10 mg/kg, IP) treatment did not alter reward or motor/performance components of intracranial self-stimulation (ICSS) as assessed with the rate-frequency method. Acute DMI treatment produced an ICSS reward decrement relative to saline control treatment, which was similar in size on Day 1 and Day 15 of chronic testing. The failure to find a chronic DMI effect on ICSS reward suggests that ICSS in normal rats may not be a valid animal model of depression. A better paradigm may be to test the ability of antidepressants to reverse a chronic reduction in ICSS reward function that is first produced by some other method.

Self-stimulation reward Desipramine Dopamine

INTRACRANIAL self-stimulation (ICSS) of the lateral hypothalamus has been suggested to be a valid approach for studying the rewarding effects produced by antidepressant drugs (36). This has been proposed despite the fact that ICSS LH reward may depend upon dopamine (8, 10, 28, 37, 38), particularly in the nucleus accumbens (12,26); whereas antidepressants are believed to act primarily on noradrenergic and serotonergic systems (2, 21, 22, 31). A resolution of this problem may lie in interactions between the monoamines. For instance, chronic but not acute, antidepressant treatment decreases norepinephrine's inhibitory modulation of dopamine release in nucleus accumbens tissue slices (32). In any case, antidepressants have been widely tested in a variety of ICSS paradigms with varying results (1, 4, 7, 11, 14, 15, 19, 20, 24, 25, 34). These results are reviewed more extensively in the Discussion section.

A technical problem with the ICSS-antidepressant literature is that few studies of the effects of antidepressants on ICSS have employed reward-specific methods [cf. (13,28)]. For example, some antidepressant-ICSS experiments [e.g., (1, 20, 24)] were conducted with methods such as simple rate-of-response that do not separate drug effects on reward versus motor/performance components of ICSS behavior (29). Other studies have used so-called rate-free methods (13,29) such as set-reset (25), increasing fixed-ratios of reinforcement (4), ON-OFF (11,13), shuttle box (20), and rate-intensity curve-shift (7). However, all of these methods have methodological problems, concerning the independent measurement of reward and motor effects, that have been extensively reviewed elsewhere (13,29). Perhaps the best of these methods is the rate-intensity curve-shift approach because, to a first approximation, it allows a quantitative scaling [cf. (9)] of the size of the drug effect on ICSS reward (5, 10, 28). Nevertheless, even with this method, behavioral interpretation is somewhat

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complicated by the expanding stimulation field which recruits new axons that may produce new behavioral effects, e.g., aversiveness. To the best of our knowledge no antidepressant-ICSS study has utilized the rate-frequency method.

This study employed the rate-frequency version of the curve-shift method to test acute and chronic effects of the antidepressant, desipramine HCl, on ICSS reward. In addition to the advantages of a curve-shift approach without varying stimulation current, the rate-frequency method has a history of validation experiments [cf. (6, 10, 16, 30)] and has been widely used in ICSS studies to assess and scale a variety of drug effects [e.g., (5, 6, 8, 16, 28)].

METHOD

Subjects

All subjects (N = 11) were male Sprague-Dawley rats which, under Nembutal anaesthesia (55 mg/kg), were implanted with monopolar electrodes (Plastic Products Co.) in the lateral hypothalamus. The level-skull electrode coordinates were: AP −3.0 from bregma, ML ±1.7 from the midsagittal sinus, DV −7.5 from cortex. A ground wire was attached to stainless steel screws implanted in the skull and the entire construction was covered with dental acrylic anchoring the electrode to the skull. Subjects were housed in plastic tubs in a temperature- and humidity-controlled colony that was day-night reversed with a 12:12-hour light-dark cycle.

Behavioral Testing

After a one-week period of postoperative recovery, all rats were trained to lever-press in a standard operant chamber for a 1.0-second burst of 0.1-millisecond square-wave monophasic constant-current pulses of brain stimulation. The electrode and skull screws were electronically connected via a switching network between all stimulation pulses to prevent build-up of charge at the electrode tip. A reinforcement light situated next to the response lever signaled the delivery of brain stimulation and a house light was illuminated when the lever was active. During initial self-stimulation training the current was varied and the optimal current was found, i.e., that current which yielded the highest rate of responding and the fewest signs of aversiveness (such as retreat from the lever, defecation, vocalization or forced movements). Control of the lights, stimulation, and monitoring of responses in four operant chambers was conducted by four Basicon Co. microcontroller systems with Stimtek Co. stimulator interfaces, linked to a single IBM PC which served as a terminal and enabled disk storage of programs.

Rats were first trained on a continuous reinforcement schedule and then switched to a Variable Interval (VI) 3-second schedule. In this schedule, during stimulation delivery, no behavioral data were collected and the VI schedule was stopped to prevent stimulation-elicited motor effects from distorting the measure of operant responding. The stimulation current was again adjusted for each animal so that high rates of responding were obtained for a 63-Hz stimulation burst. Animals were then given extinction/reacquisition training in which the stimulation frequency alternated between 1 and 63 Hz. Finally, to complete the training, the animals were given an ascending rate-frequency curve with a warm-up condition of 63 Hz, extinction of 1 Hz, and increasing frequency conditions in 0.2 log unit steps ranging from 1.2 to 2.2 log Hz. Each frequency condition lasted for 3 continuous one-minute periods. Data from the first minute were discarded to allow the rat to adjust its responding and the average of the last 2 minutes was taken as the response rate for each stimulation frequency. Between each frequency there was a 30-second rest period in which the house light was turned off.

The resulting rate-frequency curve was analyzed for locus of rise (LOR) and asymptotic behavioral maximum (MAX) statistics according to the broken line method (5). LOR is defined as the stimulation frequency required to support one half the maximum level of responding. Rats were tested on the rate-frequency paradigm daily without drugs until the LOR was stable to within 0.1 log units of the previous test day and there were no upward or downward trends in either LOR or MAX over the last 5 days. After stability was achieved, drug testing began.

Drug Treatment

In the drug group, 6 animals were given daily injections of 10 mg/kg (IP) of desipramine HCl (DMI) dissolved in isotonic saline for 15 consecutive days. The control group consisted of 5 animals given equivolume injections of isotonic saline over the same period. Animals were always tested at the same time of the day. Acute test DMI injections were made 30 minutes prior to ICSS testing on Days 1 and 15. Chronic testing was conducted by giving the DMI injections just after ICSS testing on Days 2 through 14. The doses and administration schedule followed the protocol of Fibiger and Phillips (7).

In the drug data analysis, difference scores (dLOR, dMAX) were first constructed for each rat by subtracting LOR and MAX observed under DMI from their respective predrug baselines. Additionally, dMAX was expressed as a percent of baseline. All statistical analyses were performed upon these difference scores. Two-way analyses of variance (Treatment and Days as factors, with Days as repeated measures) also were performed on the dMAX and dLOR scores for the acute Days 1 and 15, and separately for five chronic days that had equal numbers of observations (Days 2, 3, 9, 13, and 14).

RESULTS

Figure 1 presents data collected under acute DMI testing conducted on Days 1 and 15 of chronic DMI treatment. It displays the effects on LOR and MAX expressed as the difference from baseline data collected prior to drug treatment. From Fig. 1 it can be seen that acute DMI increased LOR (decreased ICSS reward) more than saline vehicle control. In addition, for both DMI and saline groups, the LOR was lower on Day 15 than on Day 1. However, the difference between the LOR of saline and control groups on Day 1 was similar to that difference on Day 15. Thus, an ANOVA was significant for the comparison between LOR of saline and control groups for both Day 1 and 15, $F(1,9) = 5.09$, $p<0.05$, was significant for the decrease in LOR from Day 1 to 15, $F(1,9) = 6.33$, $p<0.03$, but was not significant for an interaction, i.e., the change in LOR difference across test days, $F(1,9) = 0.08$, $p<0.78$. The absence of a significant interaction indicates that chronic DMI treatment did not specifically decrease the ability of acute DMI to produce a LOR increase (an ICSS reward depression).

Similar results were found for MAX (presented in Fig. 1). The decrease in MAX in the acute DMI group is significant compared to the saline-control group, $F(1,9) = 39.22$, $p<0.0001$. However, the difference in MAX between Days 1 and 15 just missed statistical significance, $F(1,9) = 4.67$, $p<0.06$. Again, as with LOR, the interaction was not significant, $F(1,9) = 1.80$, $p<0.21$.

The effects of chronic DMI treatment on LOR and MAX, excluding acute testing days, are presented in Fig. 2. An ANOVA revealed no significant differences between DMI and saline-control treatment groups for either LOR, $F(1,9) = 0.02$, $p<0.890$, or MAX, $F(1,9) = 2.36$, $p<0.16$. As Fig. 2 shows, for LOR, the chronic saline and DMI curves lie virtually on top of each other,

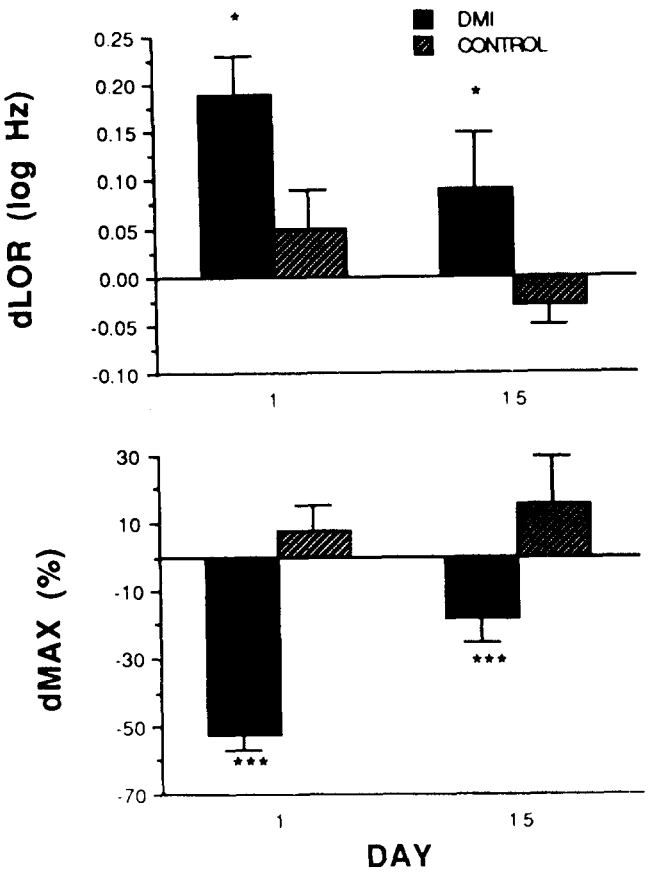

FIG. 1. The effects of acute treatment with 10 mg/kg DMI or saline on LH self-stimulation dLOR and dMAX scores (see text) on Day 1 and Day 15 of chronic DMI (10 mg/kg per day). There were significant differences in both dLOR and dMAX between groups. This difference in dLOR between DMI- and saline-treated groups was similar on Day 1 and Day 15 (0.14 vs. 0.12 log units). For dMAX the difference was 59.8% on Day 1 and 33.6% on Day 15. ($\star p<0.05$, $\star\star\star p<0.0001$ refer to overall treatment effects for DMI.)

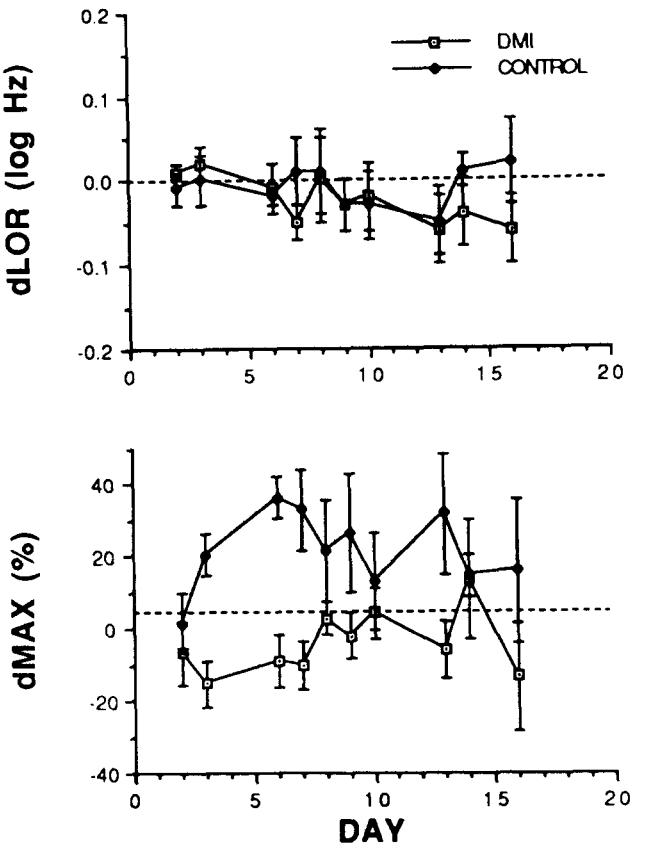

FIG. 2. The effects of chronic treatment with 10 mg/kg DMI administered daily immediately after testing on LOR and MAX statistics of the rate-frequency curve testing of ICSS in the lateral hypothalamus. Results are expressed as a difference from pre-DMI baseline (horizontal dashed line), and error bars represent 1 standard error.

while there appears to be some difference in MAX between saline and DMI curves, especially in the early part of the curve. The insignificance of the MAX results in the ANOVA may be attributed to high intragroup variance in the saline condition where 3 of 6 animals gradually increased their MAX over the 3-week testing period. Such increases are an occasional occurrence in our laboratory even after extended ICSS practice, but were not seen in the DMI-treated group. All other comparisons for the chronically treated groups were also insignificant.

DISCUSSION

This study found that acute DMI administration produced a small ICSS reward decrement (i.e., <0.15 log unit LOR increase) as judged by the difference between the averages of the two groups, even after 15 days of chronic DMI exposure (Fig. 1). Acutely, DMI also appeared to produce a decrement in ICSS motor/performance function, which might be attributable to the acute sedative properties of DMI.

The literature on the ICSS effects of acute antidepressants is marked by varied results. Studies with compounds similar to DMI have found increases (24), and also decreases (34), in ICSS rate-of-response. More reward-specific methods appear to have demonstrated increases in ICSS reward (25) or no effect on ICSS reward (4,7). Monoamine oxidase inhibitors (MAOI) have also been found to increase ICSS simple rate-of-response (19), although decreases in rate-of-response (24), and no effect on rate-of-response (1) have also been observed. In one study, using a more reward-specific method, MAOIs were found to increase ICSS reward (20). Atypical antidepressants have produced similarly equivocal results. Bupropion was reported to increase ICSS reward with the ON-OFF method (14), while mianserin decreased ICSS reward in an experiment using a similar method (11). It is interesting to note here that bupropion is a weak dopamine reuptake blocker with acute behavioral activating properties and mianserin is a serotonin reuptake blocker with sedative properties (18).

As stated previously, an advantage of the rate-frequency method employed in the present study is that it has been experimentally validated to separate ICSS reward effects from effects on operant motor/performance capacity. This is important for studies using antidepressants that block histamine (21), thereby producing acute sedative effects that could masquerade as ICSS reward depression in other ICSS methods. Additionally, some atypical antidepressants appear to act as psychomotor stimulants (18) and thus may produce nonspecific increases in operant response rate that could similarly masquerade as ICSS reward increases. For a

review of the validity of various ICSS methods with regard to reward/performance separation, see (13) or (28).

From a therapeutic perspective, the chronic DMI treatment effects on ICSS reward are the most interesting. This study found that chronic DMI treatment over 15 days did not alter ICSS reward. If chronic DMI did anything to ICSS, it seemed to produce some suppression in the operant motor/performance capacity relative to the saline control group tested over the same period (Fig. 2). This chronic DMI result is not in agreement with the fairly small chronic ICSS-antidepressant literature. For example, clorgyline was shown to increase simple ICSS rate-of-responding (1). In addition, two studies using the more specific rate-intensity curve-shift method found small increases in ICSS reward with DMI (7,15).

Three basic arguments can be offered as to why the two rate-intensity studies on DMI (7,15) found apparently different results from those reported here. First, one study (7) found an increase in reward after 2 weeks of treatment with DMI using an ascending but not descending order of frequency presentation, a finding attributed to positive contrast effects (13). The other study (15) did not find reward increases with other antidepressants such as amitriptyline, bupropion, nomifensine, and zimelidine. Second, both of these studies employed an analysis of variance that averaged raw rate-intensity curves to analyze drug effects. It has been suggested that such averaging of raw data before analysis into LOR and MAX statistics may cloud the reward − motor/performance distinction and possibly lead to misinterpretations (3). However, one of the studies (7) did do the proper analysis [cf. (3)] and still found that DMI induced an increase in ICSS reward. Third, standard curve-shift analysis [cf. (28)] indicates that chronic DMI increased ICSS reward only slightly in these two studies (7,15). For example, in one study (7), DMI decreased the rate-intensity curve 0.11 log μA which was less than the current range over which this curve rose from no behavior to maximal behavior. In the rate-frequency paradigm, large reward shifts typically move the curve so that the rising portions do not overlap [cf. (8)].

Although our findings indicate that over the range tested there are little or no chronic DMI effects on ICSS reward, it is not proper to conclude that antidepressants have no relationship to ICSS reward because the correct paradigm may not yet have been employed. The possibility remains that chronic ICSS reward increasing effects of antidepressants may only occur following some manipulation that first produces a sustained decrease in ICSS reward.

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