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Chronic DMI Reduces Thresholds for Brain Stimulation Reward in the Rat

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VALENTINO, D. A., A. J. RICCITELLI AND R. L. DUFRESNE. *Chronic DMI reduces thresholds for brain stimulation reward in the rat.* PHARMACOL BIOCHEM BEHAV **39**(1) 1–4, 1991.—The authors sought a demonstration of the validity of brain stimulation reward (BSR) models of depression. It was predicted that chronic, but not acute antidepressant treatment would enhance BSR responding. Rats with medial forebrain bundle electrodes were separated into 4 groups that received either saline or desmethylimipramine at 5, 10, or 20 mg/kg daily. A rate-free, threshold measure that has not previously been employed in studies of BSR and antidepressants was used. BSR thresholds were monitored every 3rd day over a 9-day baseline period and an 18-day drug treatment period, and after 12 days of drug withdrawal. Groups did not differ from one another till the 15th and 18th day of drug treatment. The greatest effects were seen in the 10 and 20 mg groups. The 20 mg group returned to baseline after drug withdrawal, but the 10 mg group did not. The absolute size of the effect was considered to be small, leading the authors to speculate that antidepressants act on homeostatic mechanisms that stabilize BSR substrates, only indirectly enhancing transmission of the reward signal.

Animal models Antidepressant Depression Desmethylimipramine Self-stimulation

IN his paper on animal models of depression, Paul Willner (17) judged BSR models to be among the most valid of the 18 types he reviewed. BSR models are based on measures of animals' responses to pleasurable brain stimulation. They are founded on the observation that a central symptom of depression is a decreased capacity to experience pleasure (1, 6, 13). Their common, underlying assumption is that the primary organic deficit in depression exists in brain systems that are responsible for pleasure. They also assume that such deficits can be measured as a decrease in responding for BSR relative to a previous, normal baseline or to nontreated, control animals.

Researchers exploring BSR models of depression have tested two predictions: that interventions that cause symptoms of depression in humans will cause deficits in BSR responding in animals, and that interventions that relieve symptoms of depression, e.g., antidepressant drugs, will cause enhanced responding. There are several examples of experiments that test the first prediction [e.g., (2, 7, 10, 14–16, 19)]. The results of these experiments have consistently supported the model. Results of experiments testing the second prediction have not been so consistent.

The prediction that procedures used to treat depression should facilitate BSR responding has a corollary, especially in regard to antidepressant drug treatment: effects should occur with chronic, but not acute drug administration, as is true in humans. Results of studies that use chronic treatment are mixed. Kokkinidis et al. (8) showed that the antidepressants imipramine and amitriptyline would reverse amphetamine-induced decreases in responding in rats, but reversal occurred in just two days after treatment began. Further, their no-amphetamine control group did not show enhanced responding after 14 days on the imipramine. Zacharko et al. (18) showed that chronic DMI prevented the disruptive effect of inescable shock on BSR in mice. On the other hand, though the authors do not specifically report whether the 17-day drug trial had any effect upon preshock response rates, the baseline data shown in their Fig. 2 indicate there were no differences between drug and saline groups until after the shock. After 2 weeks of DMI treatment, Hall et al. (5) found a decrement or no effect on BSR responding depending upon whether drug was administered prior to or after BSR testing. Fibiger and Phillips (3) and McCarter and Kokkinidis (12) did show that chronic DMI can improve responding over predrug baseline levels, although other antidepressant drugs used in the latter experiment had no effect.

One aspect of the Fibiger and Phillips and the McCarter and Kokkinidis studies that differentiates them from the others is that they used a current (intensity)-response (rate) measure of BSR. BSR measures can be confounded by performance variables. For instance, responding for BSR could be increased by a drug because the drug causes motor activation rather than because it increases an animal's capacity to experience reward. Current-response measures get around this problem by measuring the rate of BSR response at various stimulation intensities [and in one case (12) by adding a separate measure of motor effects]. [However, the measure does not entirely avoid the confound: see (5, 11, 17).] In the process, especially when brain stimulation is well below levels that elicit maximal responding, the current-response procedure may measure a different quality of BSR than other measures.

In the present experiment, in order to further explore the role of the BSR measure on the detection of antidepressant drug effects, we chose an adaptation of the rate-free, threshold technique of Kornetsky et al. (9). Because it measures the lowest current at which animals will begin to respond for brain stimulation, it may capitalize on the advantages of the current-response

measure. Its validity as a measure of susceptibility to reward is attested to by Kornetsky's observation that drugs with a high reward value, such as cocaine, morphine and amphetamine, cause dramatic reductions in BSR thresholds (9). In addition, in this study the threshold sensitivity of brain reward systems is observed every 3 days during an 18-day period of daily administration of 3 doses of DMI. Thus we could explore the time course of a drug effect and the dose-response relationship, two variables that have not been carefully reported in previous studies. We also retested animals 12 days after their last DMI administration to further confirm whether any observed BSR changes during drug treatment were actually drug related.

METHOD

Subjects

Subjects were 28 male Sprague-Dawley rats obtained from Charles River Breeding Laboratories and weighing between 250 and 300 g at the time of surgery. They were housed singly, provided with ad lib food and water, and maintained on an 18-h light/6-h dark cycle.

Surgery

Bipolar stainless steel electrodes (0.20 mm, Plastic One, Inc., Roanoke, VA) were stereotaxically implanted in rats anesthetized with sodium pentobarbital, 50 mg/kg. Electrodes were aimed at the MFB at the level of the lateral hypothalamus. Coordinates were 2.5 mm posterior to bregma, 1.8 mm lateral from the midline suture, and 8.3 mm ventral from the skull surface, with the top of the skull level.

Apparatus

Interval timing was accomplished using Coulbourn Instruments, Inc. modular hardware. A Grass S48 stimulator was used to deliver the stimulus. The stimulus consisted of a 0.5 s train of monophasic square waves of 4 ms duration, 60 pps. Amplitudes were expressed as μA.

Training

Not less than one week after surgery, rats were trained to lever press for BSR on a continuous reinforcement schedule. Rats that learned this task were next trained on a schedule in which a noncontingent (free) brain stimulation signaled the availability of BSR at the lever. A trial began with a free stimulation. If rats pressed the lever once within the following 10 s they received a second, contingent stimulation of equal intensity. After this lever press (or after the 10-s period if no lever press occurred), there was a 20-s intertrial interval. Lever presses during the intertrial interval postponed the next trial for 20 s. When fully trained, and tested at moderate stimulus levels, rats typically waited beside the lever for the free stimulus, pressed the lever within 4 seconds after receiving it, and rarely pressed the lever during the intertrial interval.

Threshold Determination

Once rats learned to lever press on this schedule the procedure was modified in order to determine the threshold value of the brain stimulus required to maintain lever pressing. At the beginning of any threshold test, rats received stimuli that were approximately 20 μA greater than their threshold amperage (estimated the first time a rat is ever tested). They received 10 trials at this amperage. If they lever pressed correctly 5 or more times, stimulus intensity was reduced by 2 μA for the next block of 10 trials. This process continued until stimulus levels were reached that failed to elicit 5 or more responses (descending threshold). After 3 consecutive blocks with fewer than 5 responses, stimulus intensity began to ascend in 2 μA increments after every 10-trial block. When rats began lever pressing again, making 5 or more responses (ascending threshold) for two consecutive blocks, the test ended. An entire test session lasted from 70 to 100 minutes. Threshold score on any given test day was defined as the mean of the descending and ascending thresholds.

This procedure requires limited motor responding from the rat, about 1 lever press every 22 seconds. Response stability is such that rats that have not been tested for up to 9 months immediately go on-task without error when they are reintroduced into the testing chambers.

Procedure

Once three stable baseline thresholds were obtained, the rats were randomly divided into one of four groups of 7 rats each: saline, 1 cc/kg; 5 mg/kg DMI; 10 mg/kg DMI; 20 mg/kg DMI. Animals were then orally administered either saline or the DMI daily for 18 consecutive days. BSR testing began two days after the first day of drug/saline and then every third day until the end of the 18-day period, for a total of 6 test days. Testing on these days began approximately 60 minutes after drug/saline administration. Upon completion of the 18-day testing period, each animal underwent a 12-day washout period, after which they were given a final threshold test.

RESULTS

Table 1 shows mean threshold scores and standard errors for each group at each BSR test day. F_{max} tests for homogeneity of variance were not significant. A mixed model, 4 (groups, between) × 8 (trials, within) ANOVA through the last drug trial resulted in a significant effect for the Group × Trial interaction, $F(24,192)=1.75$, $p=0.02$.

Simple main effects tests exploring the interaction approached significance at day 12 ($p=0.06$) and reached significance at day 15, $F(3,23)=2.95$, $p=0.05$, and day 18, $F(3,23)=3.46$, $p=0.03$. Tukey tests revealed that on day 15 the 10 and 20 mg groups differed from the saline group and on day 18 they differed from both the 5 mg and the saline group ($p<0.05$). No other comparisons were significant.

Planned comparison of groups on the washout day, 12 days after the last administration of DMI, was significant, $F(3,23)=3.58$, $p=0.03$. Tukey tests revealed that the 10 mg group remained different from the saline and 5 mg groups on this day ($p<0.05$), while the 20 mg group threshold had increased, and was no longer different from that of other groups.

Initial baseline differences between groups obscures some of the present findings. In order to aid in a clearer interpretation of the experimental results, we constructed Fig. 1, which shows the data adjusted for the mean score for all animals on all baseline days.

Inspection of Fig. 1 shows that thresholds of the saline group drifted upward during the 3-week testing period. Post hoc analysis showed that this was not a statistically significant trend, but it may account for the fact that drug group scores do not continuously decrease throughout the 18-day drug trial. Thresholds for the 10 and 20 mg/kg groups declined through the first 6 to 9 days on DMI, when they were significantly different from the first baseline day (post hoc analysis). Then they began to increase at a slope similar to that of the saline group, indicating that all groups were being acted upon by the same factor.

TABLE 1

MEAN BSR THRESHOLDS (μA) AND STANDARD ERRORS FOR SALINE- AND DMI-TREATED RATS ON 3 BASELINE DAYS (B), 18 DRUG DAYS, AND AFTER 12 DAYS OF DRUG WASHOUT (DAY 30)

	Day									
	B1	B2	B3	3	6*	9*	12	15†	18‡	30§
Saline	15.7(1.7)	16.7(1.9)	16.6(1.9)	16.7(2.3)	16.9(2.3)	16.6(2.6)	18.1(2.4)	18.3(2.9)	18.4(2.8)	18.9(2.8)
5 mg	19.1(3.8)	17.3(3.5)	18.6(3.4)	18.4(3.4)	17.3(3.0)	18.1(3.3)	18.4(2.9)	16.6(3.1)	19.1(3.3)	20.3(3.4)
10 mg	15.6(1.3)	15.3(1.0)	15.3(1.2)	14.7(1.1)	12.9(1.2)	13.0(1.1)	13.7(0.5)	14.3(0.6)	14.1(1.2)	14.1(1.2)
20 mg	16.7(1.4)	16.4(2.1)	16.6(1.8)	16.0(1.9)	14.7(2.6)	14.1(2.7)	16.2(2.0)	15.1(1.6)	14.9(1.8)	17.0(2.2)

*Significantly different from first baseline day, $p \leq 0.02$.
†Ten and 20 mg significantly lower than saline, $p < 0.05$.
‡Ten and 20 mg significantly lower than saline and 5 mg, $p < 0.05$.
§Ten mg significantly lower than saline and 5 mg, $p < 0.05$

DISCUSSION

The DMI did not cause group thresholds to be significantly different from one another until days 15 and 18. Differences in drug dose were not strictly related to drug effect at those times, though the 10 and 20 mg groups were different from saline at both trials and from the 5 mg group as well on day 18. Thresholds for the 20 mg/kg group returned to control levels 12 days after the drug was discontinued, as expected, but they did not do so for the 10 mg group.

The present finding that DMI lowers BSR thresholds supports the validity of BSR models of depression. The results are especially important not only because BSR responding is enhanced, but also because the enhancement occurs with chronic but not acute drug treatment, and because the threshold method of BSR measurement we used avoids the confounds that occur with the use of rate measures.

The absolute size of the threshold changes induced by DMI were relatively small. After 18 days, 20 mg/kg of DMI only reduced thresholds by 3.5 μA in comparison to saline. In contrast, the authors have observed decreases in threshold of 20 μA in response to an acute dose of morphine (personal observation). This perhaps explains why morphine and other drugs that lower BSR thresholds are euphorigenic and are abused (9) while antidepressants have neither of these properties.

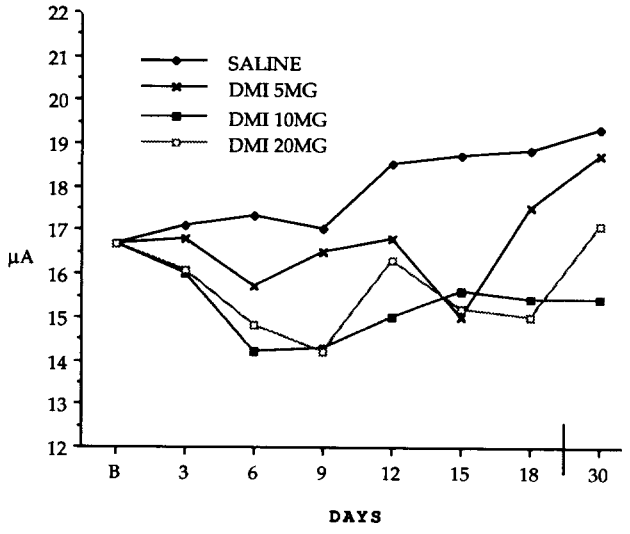

FIG. 1. Mean BSR thresholds (adjusted for a common baseline, B) over 18 DMI days and after 12 days of DMI washout (day 30).

Some expectations of the model were not well supported by the present experiment. Response to DMI was not strictly related to dose, and only the 20 mg group showed the expected rebound in thresholds following withdrawal of drug. These observations, together with the small size of the effects we observed and the fact that previous researchers have so often failed to find a measurable effect of chronic antidepressants on BSR in otherwise untreated animals, may have implications concerning the mechanisms of action of antidepressants.

One possibility is that antidepressants amplify neural transmission of the reward signal, as many researchers suspect, but they do so by correcting an initial deficit in transmission which is present during depression itself. (In fact, according to this line of reasoning the prediction that antidepressants should increase BSR responding in normal animals is unwarranted.) Since our rats presumably did not suffer from such a deficit the drug would have exhibited minimal effects. This possibility is discussed by Hall et al. (5), and is consistent with the results of Kokkinidis and Zacharko (7), who showed that antidepressants restored deficits in BSR responding that were caused by chronic amphetamine pretreatments, but did not cause measurable changes in saline-pretreated rats.

A second possibility is that antidepressants do not directly amplify neural transmission of the reward signal, but instead act on mechanisms that stabilize BSR substrates [e.g., (4)]. This possibility is consistent with the findings of Zacharko et al. (18) who showed that chronic antidepressant pretreatments protected BSR responses from decrements caused by stress, but did not measurably alter BSR responding prior to stress. In this case, the effect of antidepressants on normal animals would only be observed close to threshold since, for them, the drug might only serve to clarify detection of signal from noise. The threshold technique used in the present experiment is ideally suited to explore such a drug effect.

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