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Effect of Lithium Upon Desipramine Enhanced Shock-Elicited Fighting in Rats

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PRASAD, V. AND M. H. SHEARD. *Effect of lithium upon desipramine enhanced shock-elicited fighting in rats.* PHARMAC. BIOCHEM. BEHAV. 17(2) 377–378, 1982.—Rats were tested for changes in shock-elicited fighting (SEF) following the chronic administration of saline (IP); lithium (Li^+) (20 mEq./l tap water) + saline (IP); desipramine (DMI) (15 mg/kg, IP); and DMI + Li^+ for 14 days. The repeated test trials indicated a significant decrease in SEF in Li^+-saline group ($p<0.05$), a significant increase ($p<$p.05) in the DMI group, but no difference in the DMI + Li^+ group in comparison to saline controls. Combined treatment with DMI + Li^+ significantly reduced ($p<0.05$) SEF in comprison to the DMI group. These results suggest that enhanced aggressivity resulting from chronic DMI administration and measured by SEF can be a useful behavioral model to study the action of lithium.

Shock-elicited aggression Desipramine Lithium

THE chronic, but not acute, administration of a variety of antidepressant drugs result in enhanced aggressive behavior in animals [1, 3, 9]. Moreover, acute administration of antidepressants actually antagonized the excitatory effect of LSD on shock-elicited aggression [8]. This is particularly the case with irritable aggression induced by foot shocks in rats. Lithium, an antimanic and antidepressant agent, has been shown to have an antiaggressive effect in many animal models of aggression [7]. In particular, irritable aggression induced by footshock is inhibited by lithium [2,4].

These findings provide a rationale for the notion that lithium can be expected to inhibit the enhanced aggressive behavior resulting from chronic desipramine (DMI) administration. In the present study, we investigated the role of lithium, DMI, and the combination of lithium and DMI in a behavioral model of irritable aggression, shock-elicited fighting, in rats.

METHOD

Forty-eight male Sprague-Dawley rats weighing between 360–420 g at the time of the experiment were paired on the basis of weight. Rats were housed three to a cage of nonfighting members in a colony room maintained on a 12:12 light-dark (7 a.m.–7 p.m.) cycle.

The shock-elicited fighting (SEF) apparatus has been described previously [8]. Essentially, it consisted of a Plexiglas box (30×28×24 cm) with a grid floor of 0.5 mm parallel bars. This cage was housed in a dimly lighted LeHigh Valley sound attenuated chamber. Fighting was observed through a window from a darkened room. A LeHigh Valley shocker and scrambler delivered 30 shocks, at 1.5 mA, 0.5 sec duration and the intershock interval was 7 sec.

Animals received daily intraperitoneal (IP) injections of DMI (15 mg/kg) (USV Pharmaceutical Corp., Tuckahoe, NY) or control injections of 0.9% saline for 14 days. DMI was dissolved in 0.9% saline (injection volume 1 ml/kg). Lithium chloride (20 mEq./l) was dissolved in tap water and given in normal drinking bottle. Prior to drug treatment, 48 rats were paired and pretested to determine the baseline levels of SEF. Based on total number of fights, rats were divided into four matched groups of 6 pairs each having similar mean levels of SEF. Pretesting, as well as subsequent testing was always carried out between 10.00–13.00 hours. Injections of saline or DMI, started the same day as the pretest, were given between 15.00–16.00 hours.

Six pairs of rats received saline and 6 pairs DMI (15 mg/kg) by IP injection once every day for 14 days. These two groups received tap water for drinking. A third group of 6 pairs received saline (IP) and fourth group of 6 pairs received DMI (15 mg/kg) IP once every day for 14 days. These two groups received lithium chloride (20 mEq./l) in drinking tap water. All rats were retested after 1 week and after 2 weeks, approximately 18 hours after the last injection. All rats were weighed regularly and the amount of water containing lithium consumed per cage was recorded. Following the completion of the experiment rats on lithium were sacrificed. Blood was collected in heparinized syringes, centrifuged and plasma stored at −20°C. Lithium levels were determined by atomic absorption spectrophotometry.

RESULTS

Rats receiving lithium did not gain weight during the first week, and showed much slower weight gain during the second week in comparison to controls. During the first week of treatment, the DMI and Lithium + DMI groups of rats lost 11% and 15% weight, respectively. However, no further de-

crease in body weight was observed during the second week of treatment. Despite the slight weight loss, these rats did not appear unhealthy, were normal in appearance, and their fur was in good condition.

To assess the statistical reliability of the results, the data were analyzed with a two-way factor analysis of variance with drug treatments as a between subject factor and repeated test trails as a within subject factor. There was a significant between group effect, $F(3,20)=3.19$, $p<0.05$, indicating an overall drug effect on SEF. There was also a highly significant Drug by test interval interaction $F(2,20)=3.66$, $p<0.05$. This interaction reflected the fact that these drugs altered the SEF after repeated test trials.

One way analysis for repeated measure for each drug treatment indicated no significant effect of saline on SEF. However, DMI treatment enhanced SEF significantly $F(2,10)=6.91$, $p<0.005$. Subsequent individual comparisons by Dunnett's test showed a highly significant effect of DMI after 1 week, $t(1,10)=2.72$, $p<0.025$ and after 2 weeks $t(1,10)=3.57$, $p<0.005$. Over all there was a significant depression of fighting in Lithium treated rats $F(2,10)=4.44$, $p<0.05$. Subsequent individual comparison by Dunnett's test showed a significant effect of lithium after 1 week $t(1,10)=1.94$, $p<0.05$, whereas combined treatment of Lithium + DMI failed to alter SEF in rats in comparison to its pretest level.

The mean serum lithium level of the lithium-saline group was 0.34±0.01 mEq./l and the Lithium + DMI group was 0.28±0.04 mEq./l.

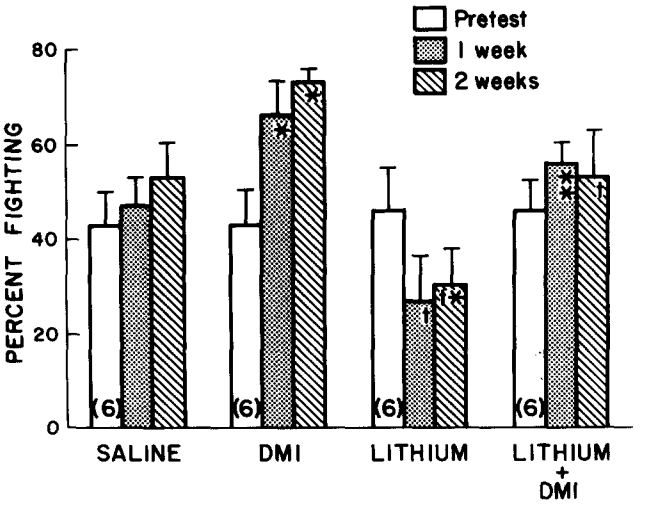

FIG. 1. Bar graph of percent fighting 1 week and 2 weeks after saline (IP); lithium (20 mEq./l tap water); DMI (15 mg/kg, IP) and DMI + Lithium. Numbers of pairs used for each treatment are given in parenthesis. The levels of significance was determined by independent t-test. $*p<0.05$, in comparison to saline; $\dagger p<0.05$, in comparison to DMI group; $**p<0.01$, in comparison to lithium controls.

DISCUSSION

The results of this experiment demonstrate a significant increase in shock-elicited fighting with chronic desmethylimipramine (DMI) administration (Fig. 1). This finding is in agreement with previous work [1,3].

The results also show clearly that chronic administration of lithium can block the increased irritable aggression resulting from chronic DMI administration. A comparison of the effect of lithium in saline controls and DMI treated groups suggests a more potent effect on the fighting behavior in the DMI group, particularly when the lower mean serum lithium level in the DMI group (0.28 mEq./l) is taken into account.

The greater effect on enhanced fighting is another example of lithium having a more potent effect on exaggerated states than normal states. For example, lithium's ability to inhibit manic states in man is remarkable, in view of its relatively small effects in normals [5,6].

A comparison between the SEF of saline controls and lithium treated rats showed an insignificant decrease in shock-elicited fighting in lithium treated control rats after 1 week, whereas a significant decrease was observed after 2 weeks. The absence of a significant decrease in SEF after 1 week is most likely due to the low dose of lithium used in this study reflected in low serum lithium levels (0.34 mEq./l). It is low in comparison to the findings of a previous study [2] where serum lithium levels were maintained closer to the usual therapeutic level in man.

This study suggests that enhanced aggressivity measured by SEF, resulting from chronic antidepressant administration, can be a useful behavioral model for studying the action of lithium.

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