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Effects of Lithium Chloride on Muricidal Behavior in Rats

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RUSH, J. AND J. MENDELS. *Effects of lithium chloride on muricidal behavior in rats.* PHARMAC. BIOCHEM. BEHAV. 3(5) 795–797, 1975. – Lithium chloride at two different doses (1 mEq/kg and 2 mEq/kg) IP BID for 10 days failed to inhibit muricidal behavior in rats. Lithium chloride at the higher dose caused neurotoxicity in 6 of 11 rats as measured by the rotorod. These dosages generated serum levels of 0.70 and 1.00 mEq/L respectively. The same behavior was blocked by imipramine HCl at an ED_{50} of 8.5 mg/kg 45 min following a single IP injection without evidence of neurotoxicity by the rotorod method. These results indiciate that lithium chloride is unlike the tricyclic agents in the muricide test. Therefore, if its clinical antidepressant activity is substantial, it may be most effective in a neurochemically different class of depressives than the tricyclics.

Lithium Muricide Depression Antidepressant Drugs

ANTIDEPRESSANT drugs, as well as some antihistamines and stimulants [1,3], inhibit muricide (mouse killing by rats) at doses which do not cause neurotoxicity, e.g. as measured by the rotorod performance [10]. In contrast, drugs that are not effective in the treatment of depression (e.g. sedative hypnotics and major tranquilizers) inhibit muricide only at doses which also produce neurotoxicity [10]. For these reasons, selective inhibition of muricide has been suggested as one test for predicting possible clinical antidepressant activity of new drugs [11].

While the role of lithium in the treatment of clinical depression remains controversial, there is evidence that it may act as an antidepressant in a subgroup of depressed patients [4, 9, 15, 17, 19].

The effect of lithium on muricide is uncertain. Sheard [23] has reported that a relatively high dose (5 mEq/kg) of lithium blocks para-chlorophenylalanine induced muricide. It is possible that this dose of lithium may cause significant neurotoxicity, but this effect was not examined for. Eichelman and Thoa [5] reported that lithium (0.8 mEq/kg for 14 consecutive days) failed to block muricidal behavior in Long Evans rats but did not report specific data, including serum lithium levels or evaluation of neurotoxicity.

The current experiment was undertaken to determine the effect of clinically equivalent doses of lithium on muricidal behavior.

METHOD

Animals and Procedure

Muricidal behavior was induced in individually housed Sprague-Dawley (Holtzman) male rats by a modification of the method of food limitation ([20] and Paul, personal communication).

Initially, the animals were given ad lib access to food and water for 10 days. Each animal was then allowed access to 10 g of Purina Rat Chow for 1 hr each day for 10 consecutive days. On each of the next 5 days, while food limitation continued, each animal was given 2 exposures to a mouse. The exposures were separated by 30 min and lasted for a maximum of 5 min if the rat failed to kill. If the rat killed, the mouse was removed from the cage within 15 sec of the kill. A muricidal rat was defined as one which killed mice on the last 5 consecutive exposures. The rats were given ad lib access to food and water for the remainder of the experiment. Their weights returned to baseline values after 10 days. On the tenth day following return to ad lib food, two additional exposures to mice were allowed. Rats which killed both mice were designated as muricidal. These rats were then divided into 2 equal sized groups and were used for the study.

Two groups of rats receiving different doses of lithium chloride were studied. The initial weight for the rats in Group 1 was 398 ± 6.2 g. (mean ± S D) and for the rats in Group 2 was 284 ± 8.7 g. (mean ± S D). The first group of 7 muricidal rats received 1 mEq/kg LiCl IP b.i.d. for 10 consecutive days. A control group (N = 7) received an equivalent volume of normal saline IP b.i.d. over the same time period. The second group of muricidal rats received 2 mEq/kg LiCl IP b.i.d. for 10 days. Eleven control animals received the same volume of saline. No rat was exposed to mice during the injection period.

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Two hours following the last (20th) injection, each animal was exposed to 1 mouse for 5 min, and the percentage of killers for each group was calculated. Subsequently, the rats were tested on the rotorod for 3 min following a 2 min acclimatization period [2,10]. Rats which fell more than 3 times were labelled neurotoxic. The animals were then guillotined and blood was collected for measurement of serum lithium concentration [6].

RESULTS

Food limitation induced muricidal behavior in 48 percent of the animals by the end of the food limitation period. After 10 days of their receiving food ad lib, 36 percent of the original group continued to be muricidal. Every killer rat exhibited muricidal behavior within 2 min following exposure to a mouse, even after return to ad lib food access. During the food limitation procedure 22 percent of the animals died.

These results compare favorably with those of Paul *et al.* [20]. Using a similar procedure with Sprague-Dawley rats, they reported a 43 percent muricide induction rate at the end of the food limitation period. At the conclusion of re-exposure to ad lib food, the muricide rate was 38 percent. The death rate in their study was 32 percent.

The serum lithium level obtained for the group treated with 1 mEq/kg LiCl b.i.d. was 0.70 ± 0.02 (mean ± S D) mEq/L. For the group given 2 mEq/kg LiCl b.i.d. the serum lithium level was 1.00 ± 0.11 mEq/L. Although a diuresis and increased water consumption was observed in the lithium treated animals, there were no deaths in either the lithium or saline treated groups during or following the injection period.

The effect of the two dosage schedules of lithium on muricidal behavior and rotorod performance is shown in Table 1. There was no alteration in either behavior in the animals who received 1 mEq/kg LiCl or saline. In the group receiving 2 mEq/kg LiCl b.i.d., there was a disappearance of muricidal behavior in 3 of 11 rats. Two of these animals, as well as 4 which continued to exhibit muricidal activity, were neurotoxic according to the rotorod test. One saline treated animal failed to display muricide following the injections.

Thus, LiCl 2 mEq/kg b.i.d. produced serum levels equivalent to clinically therapeutic levels. At this dose, a significant reduction in rotorod performance was found ($p<0.05$, Fishers Exact Probability Test) compared to the control group. However, there was no significant selective inhibition of muricide other than that accounted for by neurotoxicity.

A second brief experiment was conducted to ensure that the muricidal behavior produced by our experimental procedure was indeed susceptible to tricyclic antidepressant inhibition [10]. For this purpose, 4 muricidal rats were tested for rotorod performance and muricidal behavior 45 min following a single IP injection of imipramine hydrochloride. Since the reported ED_{50} for imipramine HCl was 8.0 mg/kg, 2 dosages were tested for, namely 7.0 mg/kg and 10.0 mg/kg. At the lower dose no inhibition of muricide or alteration in rotorod performance was noted. At the higher dose, all 4 animals failed to display muricidal behavior without a decrement in rotorod performance. The ED_{50} of 8.5 mg/kg is compatible with that reported elsewhere [10].

DISCUSSION

Although the effectiveness of lithium as an antidepressant remains controversial, recent reviews [15, 16, 17] suggest that a specific subgroup of depressed patients do respond to lithium. In addition, in a crossover study we found that 9 depressed patients who failed to respond to either lithium or desmethylimipramine did respond to the other drug [19]. The results of this and related studies suggest that a search for neurochemical differences between tricyclic and lithium responding depressed patients might be of value.

Our findings indicate that lithium does not act like the tricyclic antidepressants [10,11] or electroconvulsive therapy [25] in inhibiting muricidal behavior at non-neurotoxic doses. Further, at doses equivalent to those known to be therapeutic in humans, [18,22], no selective inhibition of muricide occurs.

These results support the findings of Eichelman and Thoa [5] who reported that lithium at 0.8 mEq/kg for 14 days was ineffective in blocking muricide in Long-Evans rats. However, it is likely from our data that the dose they

TABLE 1

THE EFFECT OF TWO DIFFERENT DOSES OF LITHIUM CHLORIDE ON MURICIDAL AND ROTOROD BEHAVIORS

Group	N	Serum Li*	Muricide Inhibited	Neurotoxic†
1 mEq/kg LiCl	7	0.70 ± 0.02	0	0
Saline Control	7	0.00	0	0
2 mEq/kg LiCl	11	1.00 ± 0.11	3	6
Saline Control	11	0.00	1	1

*$\bar{X}$ ± S.D. †Neurotoxicity was determined by rotorod performance

used failed to generate serum levels equivalent to those known to be therapeutic in man. The lack of agreement with Sheard [23] may be due to the high dose (5 mEq/kg) he used to inhibit PCPA-induced muricide. This dose is likely to be neurotoxic by the rotorod.

Our findings are consistent with those of Geyer *et al.* [7] who reported the failure of lithium to potentiate the behavioral and cardiovascular effects of yohimbine in conscious dogs at plasma concentrations of 1.29–1.54 mEq/L. This effect of yohimbine potentiation has been reported to be characteristic of clinically useful tricyclic antidepressants or monoamine oxidase inhibitors [13,21]. Using a different approach, Goldstein and his associates have shown that lithium and several tricyclic antidepressants all potentiated the inhibitory effect of norepinephrine on evoked postganglionic potentials in the superior cervical ganglion of the cat [14,24].

An alternative conclusion suggested by the data is that the muricide model is a limited predictor of antidepressant activity in general. For example, some investigators have suggested that thioridazine has antidepressant activity in some neurotic depressed outpatient populations [12]. However, in doses up to 40 mg/kg IP in rats, this drug failed to inhibit muricide without causing neurotoxicity [8].

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