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Inhibition of Fighting in Isolated Mice Following Repeated Administration of Lithium Chloride

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MALICK, J. B. *Inhibition of fighting in isolated mice following repeated administration of lithium chloride.* PHARMAC. BIOCHEM. BEHAV. 8(5) 579–581, 1978. – Lithium was found to be a selective (i.e., it antagonized aggression at doses that did not produce concurrent neuromuscular impairment) antagonist of isolation-induced aggressive behavior in mice following repeated (subacute) administration for five days. Acute (single dose) administration of lithium failed to inhibit aggression. At antiaggressive doses, lithium did not produce ataxia as measured by the inclined-screen or rotarod procedures. The mechanism of this action is discussed in terms of a possible influence on serotonergic mechanisms.

Chronic administration Isolation-induced aggression Lithium chloride Rotarod

LITHIUM is effective in the treatment of mania [6,16] and in the prophylaxis of both manic and depressive states [1,3]. Lithium has also been shown to be effective in the management of aggressive behavior in man [10, 21, 22].

In animal models of aggression, lithium has been shown to significantly decrease footshock-induced aggression in rats [5, 13, 19], fighting in Siamese fish [23], and intraspecific aggression in mice and hamsters [23]; lithium also prevented the induction of muricidal behavior that is usually observed following parachlorophenylalanine, a serotonin depletor [20]. In contrast, lithium failed to significantly inhibit septal lesion-induced aggression in rats [12] or spontaneous muricidal (mouse-killing) behavior in rats [12,15] and has even been observed to produce an increase in aggressive behavior in rats in one study [17]. The differences observed in the effects of lithium on the various models of aggression are not surprising since Moyer [11] has postulated that there are several physiologically distinctive forms of aggression in animals.

Since lithium has been shown to be an effective antagonist of only certain forms of aggression in animals, the present studies were designed to determine the effects of acute (single-dose) and subacute (multiple-dose) administration of lithium on isolation-induced aggression in mice.

METHOD

Isolation-induced aggression in mice was produced by a modification of the method of Yen and coworkers [24] and has been reported previously [2]. Briefly, CF No. 1-S male mice (18–22 g) were isolated for a period of four weeks and then tested for aggression by placing an isolated mouse into the home cage of another isolate. Pairs of mice were observed for 3 min, and presence or absence of fighting was recorded. All pairs of mice were tested for aggression for several days and only those which were consistent fighters were used in this study. All mice received either vehicle (physiological saline) or lithium (40, 80, 160, 240 or 300 mg/kg) intraperitoneally (IP) at the same time of day (two p.m.) on each of five consecutive days and were tested for aggression 30 min after drug administration on Day 1 and again on Day 5 of the study. Since most authors express the dosage of lithium chloride in terms of milliequivalents (1 mEq of LiCl = 42.4 mg), the doses used in this study were approximately equal to 1, 2, 4, 6 and 7.5 mEq/kg, respectively. Immediately following the aggression test, the mice were checked for neuromuscular impairment by gently placing them on a 45° inclined-screen; any mouse that exhibited impaired performance was scored as being ataxic.

Lithium chloride was dissolved in distilled water and administered in a volume of 10 ml/kg, IP. The ED50, that dose of chronically administered lithium which prevented fighting in 50% of the pairs when tested on Day 5, and the 95% fiducial limits were calculated by the method of Litchfield and Wilcoxon [8].

Although all of the isolated mice were tested for neuromuscular impairment (ataxia) on an inclined-screen immediately after the aggression test, the effect of lithium on muscular coordination was tested further using a rotarod [7]. Mice were trained to maintain themselves on a rotating rod (6 rpm); only mice that stayed on the rod for the entire 60 sec period in two consecutive trials spaced 1 hr apart were used in these studies. Of the 124 mice screened, only 41 met the aforementioned criteria; they were divided into three treatment groups and received either saline or lithium (100 or 300 mg/kg) IP for five consecutive days. The mice were then retested for rotarod performance 30 min after

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TABLE 1

EFFECTS OF ACUTE AND CHRONIC ADMINISTRATION OF LITHIUM ON ISOLATION-INDUCED AGGRESSION IN MICE

Treatment	Dose (mg/kg, IP)[a]	N[b]	% Inhibition of Fighting Day 1	% Inhibition of Fighting Day 5	% Ataxic[c] Day 1	% Ataxic[c] Day 5
Saline	–	20	0	0	0	0
Lithium	40	20	0	35	0	0
	80	20	0	45	0	0
	160	10	0	60	0	0
	240	10	0	70	0	0
	300	10	0	100	0	0

[a]Mice tested for aggression 30 min post drug
[b]Number of pairs of mice tested
[c]Percentage of mice exhibiting impairment of inclined-screen performance (ataxia)

the last injection; the length of time spent on the rod (60 sec cut-off time) was recorded for each mouse.

RESULTS

The effects of lithium administration on isolation-induced aggression in mice are summarized on Table 1. Lithium failed to inhibit aggression following acute (single dose) administration in any of the mice tested over a wide range of doses (40–300 mg/kg, IP). However, following repeated (subacute) administration for five days, lithium exhibited a dose-related inhibition of fighting behavior (see Table 1); lithium exhibited an ED50 of 80.9 (31.9–126.6) mg/kg, IP (approximately 2 mEq/kg) when administered repeatedly for five days.

The antiaggressive activity of lithium was selective in that impairment of inclined-screen performance (ataxia) was not observed in any of the isolated mice tested following either acute or repeated administration (see Table 1). Furthermore, the results of the rotarod study, summarized on Table 2, indicate that repeated administration of lithium for five days failed to produce significant ($p>0.05$; Student's t test) impairment of neuromuscular coordination in mice at either of the doses tested (100 or 300 mg/kg, IP).

DISCUSSION

Subacute administration of lithium was shown to produce a dose-related inhibition of fighting in isolated

TABLE 2

EFFECTS OF CHRONIC LITHIUM ADMINISTRATION ON ROTAROD PERFORMANCE IN MICE

Treatment	Dose (mg/kg, IP)[a]	N[b]	Rotarod Performance: % Failing to Reach Criteria[c]	Rotarod Performance: $\bar{X}$ Latency (sec) on Rod ± SEM[d]	p Value[e]
Saline	–	14	21.4	55.9 ± 2.6	–
Lithium	100	13	15.3	55.0 ± 3.7	>0.05
Lithium	300[f]	14	35.7	46.8 ± 5.3	>0.05

[a]Mice dosed once a day for 5 days and tested 30 min post last injection
[b]Number of mice tested
[c]Number of mice failing to stay on rod for full 60 sec test; all of mice that failed to stay on the rod in this study appeared to jump from the rod and none of the animals appeared ataxic.
[d]Mean ± SEM
[e]Student's t test comparing mean latency on rod for lithium-treated groups to saline-treated control group
[f]All of the mice receiving this dose exhibited slight diarrhea.

mice. This antiaggressive effect was selective in that lithium did not induce concurrent neuromuscular incoordination (ataxia) at antiaggressive doses as measured by the inclined-screen or rotarod procedures.

Numerous neurochemical evaluations have been made in both rats and mice following subacute lithium administration; however, the majority of the studies have been performed in rats and there appears to be marked species differences in neurochemical alterations following subacute lithium between rats and mice [18]. Oksenkrug and Kiseleva [14] administered lithium to mice repeatedly for seven days (100 mg/kg) and studied its influence on serotonergic (5-HT) mechanisms; although there was no significant alteration in the concentration of 5-HT in brain, subacute lithium prevented the rise in 5-HT observed after the administration of 5-hydroxytryptophan (5-HTP). The authors concluded that the lithium enhanced the catabolism of 5-HT. In this laboratory (unpublished results) subacute administration of lithium (120 and 300 mg/kg, IP/day for five days) significantly antagonized the 5-HTP induced head-twitch response [4,9] in mice.

Since repeated lithium administration in mice has been shown to produce significant alterations in response to administration of 5-HTP, the serotonin precursor, it may be that either 5-HT is catabolized more rapidly under the influence of lithium or some other alteration in serotonergic mechanisms is involved. Since serotonergic pathways have been shown to be at least partially responsible for the regulation of isolation-induced aggression in mice [9], lithium may, at least in part, be affecting this behavior via some alteration in serotonergic mechanisms. However, in addition to the possible involvement of serotonergic pathways in the mechanism of action of lithium, alterations in dopaminergic and noradrenergic mechanisms also have been observed following subacute administration of lithium (see [18] for review). Thus, until further evidence as to lithium's mechanism of action in isolation-induced aggression is accrued, due consideration must be given to the possibility that other amines, in addition to serotonin, may be involved.

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