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# Lithium Increases Selective Attention in Rats[1]

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CAPPELIEZ, P. AND N. WHITE. *Lithium increases selective attention in rats.* PHARMAC. BIOCHEM. BEHAV. **15**(1) 81–88, 1981.—Both 0.15 and 1.50 mEq/kg lithium chloride were found to increase inspective exploration (i.e. behaviors directed at the close examination of discrete stimuli in a new environment) in rats. In addition, 1.50 mEq/kg LiCl decreased general activity, irrespective of the characteristics of the experimental situation. The dose-independent increase in inspective exploration was interpreted as increased selective attention to salient stimuli which provide information about the environment. This hypothesis predicts that both doses of lithium should decrease distractibility by irrelevant stimuli. This prediction was confirmed in a second experiment, in which the ability of a tone to suppress drinking by thirsty rats was reduced by both doses of lithium. A two-factor model of lithium's action in rats is proposed. Lithium produces a dose-independent improvement of selective attention to stimuli which provide detailed information about the environment. In addition, lithium exerts dose-related effects on activity levels: a mild increase in activity with doses in the 0.15–0.20 mEq/kg range and a decrease in activity with doses of 0.50 mEq/kg and higher.

Lithium chloride  Inquisitive exploration  Inspective exploration  Distractability  Activity levels  Selective attention

THE effect of lithium on rats' reactivity to environmental stimulation has been investigated within the context of changes in exploratory behavior with controversial results. Some authors [14, 15, 20, 24] concluded that lithium chloride (1 mEq/kg and higher) reduced responsiveness to the environment on the basis that it decreased rearing without affecting ambulation in small tubular open fields. In contrast, it has been shown [9] that lithium chloride (2 mEq/kg) made rats more aware of environmental changes. When lithium-treated rats faced such stress-inducing conditions as a white light or a foot shock, they showed greater reduction of open field activity, particularly rearing, than control animals. Our recent suggestion [3] that lithium-induced changes in responsiveness to the environment might be dose-related did little to resolve the controversy. We demonstrated that a low dose of lithium chloride (0.15 mEq/kg) produces selective increases in rearing and cage-directed behaviors in the open field, and that a high dose (1.50 mEq/kg) produces a general depression of activity.

A major difficulty with these studies is that exploratory behavior was assessed in the open field, an experimental situation which does not allow for a clear distinction to be drawn between exploratory behavior and simple spontaneous locomotion [5].

Four other studies made valuable attempts to circumvent this methodological problem by measuring locomotor activity and exploratory behavior separately and/or by manipulating exploration eliciting variables. However no clear picutre of the effect of lithium on exploration emerges from these studies either. It has been reported that lithium (2 mEq/kg LiCl), while decreasing locomotor activity, increased time devoted to the investigation of novel objects [10]. Similarly it has been found that lithium (2 mEq/kg LiCl), while decreasing activity, increased the duration of investigation of discrete stimuli [1]. In another study lithium (3 mEq/kg LiCl), while again decreasing activity, did not significantly affect exploration of an entirely novel environment [22]. Lithium (5 mEq/kg LiCl) has also been demonstrated to reduce exploration of the stimulus section of a large environment [19].

A valuable concept for understanding the behavior exhibited by rats in an open field is provided by the distinction between "inquisitive" and "inspective" exploration [2]. Inquisitive exploration ("looking for") brings the organism into contact with distant stimuli and comprises behaviors which provide information about the environment at large: walking, rearing, and sniffing the cage. Inspective exploration ("looking at") is behavior directed at the investigation of proximal stimuli, and involves the close examination of specific objects located in the environment, i.e. sniffing, gnawing, licking, and touching them. In the present experiment this distinction was applied to the effect of lithium on exploratory behavior in the rat. For this purpose a double exploration box paradigm was used [4, 6, 11, 12, 13].

The effect of 0.15 mEq/kg LiCl on components of ex-

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ploratory behavior was of most interest because of the suggestion that this dose increases responsiveness to the environment [3]. 1.50 mEq/kg LiCl was also tested since it has been shown to produce a clear reduction of open field activity [3]. For purposes of comparison with the two doses of lithium, two doses of ethanol were also included. 0.4 g/kg ETOH produces an increase in open field activity very similar in magnitude to the one obtained with 0.15 mEq/kg LiCl [3]. Pilot data indicated that acute administration of 1.6 g/kg ETOH produced a decrease in open field activity which was very similar in magnitude to the one obtained with 1.50 mEq/kg LiCl.

## EXPERIMENT 1

### METHOD

*Subjects*

Sixty male Wistar rats weighing 240–260 g upon arrival at the laboratory were used. They were housed in groups of 2 or 3 in clear plastic cages in a temperature-controlled room (23°C) on a 12 hr light-dark cycle (light on at 7:00 a.m.). Food and water were freely available.

*Apparatus*

The apparatus consisted of a 45.6 by 91.2 cm rectangular box with sides 30.4 cm high. The box had an open top, 3 unpainted wooden walls, a Plexiglas front, and a wire mesh floor. It was divided into 2 halves by a wooden wall with a 10 cm wide guillotine door in the middle. The testing room was dimly lit and kept at 23°C. Both sides had one wall painted with 3.5 cm wide black stripes. In one side, the stripes were vertical, in the other side, the stripes were horizontal. Both sides contained 4 identical small, red wooden beads, one in each corner.

*Drugs*

The two doses of lithium chloride were: 0.15 (low lithium) and 1.50 mEq/kg (high lithium), administered in volumes of 1 ml/kg. Lithium chloride was dissolved in 0.9 percent saline. The 2 doses of ethanol were: 0.4 (low ethanol) and 1.6 g/kg (high ethanol) of 100 percent ethanol, administered as a v/v 20 percent ethanol solution in distilled water. Control injections were 0.9 percent saline, administered in volumes of 1 ml/kg. All drugs were injected intraperitoneally. In the case of daily injections of lithium or saline, the side of the peritoneum on which the injection was given was alternated from day to day.

*Behavioral Measures*

The categories used for recording behavior are described in Table 1. These categories were considered mutually exclusive. The nature of each rat's behavior and the side of the box on which it occurred were recorded every 3 seconds during 5 minute tests. These raw data served as the basis for computing the following derived measures. The total number of crossovers from one side of the box to the other gave the measure of locomotor activity. The total number of responses made on the novel side gave the measure of preference for novelty. The sum of walking, rearing, and sniffing the box, according to the side of the box on which it occurred, gave measures of inquisitive exploration in the familiar and novel sides. The sum of sniffing, gnawing, and manipulating the objects, according to the side of the box, gave measures of inspective exploration in the familiar and novel sides.

TABLE 1

CATEGORIES FOR BEHAVIORAL OBSERVATION IN EXPERIMENT 1

| | |
|---|---|
| Walking | Rat walks or shifts position so as to involve all four limbs; usually accompanied by sniffing |
| Rearing | Rat lifts both forepaws off the floor; usually accompanied by sniffing |
| Grooming | Rat licks, scratches or cleans any part of its body |
| Sitting | Rat sits relaxed and motionless, tail on surface of floor without sniffing |
| Sniffing the cage | Rat stays motionless, sniffs around any feature of the box or pokes its nose in the wire mesh floor |
| Sniffing objects | Rat stays motionless and sniffs wooden objects |
| Gnawing objects | Rat stays motionless and bites or gnaws wooden objects |
| Manipulating objects | Rat pushes or carries wooden objects in its mouth |

*Procedure*

The 60 rats were randomly divided into 5 groups. For three consecutive days half the rats in each group were allowed to explore one side, and the other half were allowed to explore the other side of the box for 15 minutes, with the door between the 2 sides closed. The side explored by each rat on these 3 days became its "familiar" side; the other side became its "novel" side. Behavior recordings were made during the first 5 minutes of the 15 minute exposure on Days 1 and 3. Drug treatments began on Day 4 for all rats. All subjects received single daily "chronic" injections of saline or lithium for 6 days, and single "acute" injections of saline or ethanol on the test days (Days 1 and 6 of chronic treatment). The injections received by the rats in each particular group were:

| Chronic | Acute |
|---|---|
| saline | saline |
| saline | low ethanol |
| saline | high ethanol |
| low lithium | saline |
| high lithium | saline |

The saline-saline group had 20 subjects, each of the other 4 groups had 10 subjects. On Day 4, each rat received its chronic treatment. Thirty minutes later, it received its acute injection. Ten minutes later, the rat was placed into the observation apparatus for 5 minutes. Half the rats in each group were placed into their familiar side and the other half were placed in their novel side. On Days 5, 6, and 7, the rats received chronic treatments and remained in their home cages. On Day 8 (i.e. the fifth day of chronic treatment), the rats received their chronic treatments and were re-exposed for 15 minutes to their respective familiar sides. On Day 9 (i.e. the sixth day of chronic treatment), the procedure of Day 4 was repeated. Testing was conducted between 10:00

a.m. and 4:00 p.m. The order of testing for the groups was randomly assigned. Objects and box were wiped clean with a 50 percent ethanol solution after each subject to minimize odor cues.

*Statistical Analysis*

To analyse the frequencies of inquisitive and inspective behaviors on Days 1 and 3, when the animals were pre-exposed to only one side of the box, two separate 6 (Group) by 2 (Day) analyses of variance with repeated measures on the Day factor were used. For drug treatment Days 4 and 8, number of crossovers and total number of responses in the novel side were analyzed with separate 5 (Treatment) by 2 (Day) analyses of variance with repeated measures on the Day factor. Inquisitive and inspective exploration scores were analyzed with separate 5 (Treatment) by 2 (Day) by 2 (Side) analyses of variance with repeated measures on Day and Side factors. In all cases, the unweighted means method was used to control for unequal sample size. When a significant treatment effect was found, Dunnett's tests were used to assess the significance of the difference between each of the experimental groups and the saline-saline control group.

## RESULTS

On Days 1 and 3 of the pre-exposure (familiarization) phase of the experiment, no significant differences were found among the 5 groups in frequencies of inquisitive, $F(5,54)=0.16$, $p>0.05$, or inspective exploration, $F(5,54)=2.15$, $p>0.05$, a finding which supports the contention that all groups entered the drug phase with equivalent inquisitive and inspective activity baselines. The highly significant day effect found for inquisitive exploration, $F(1,54)=47.60$, $p<0.01$, was attributable to a marked decrease in this behavior shown by all groups over the 3 days of exposure to the same side of the box. In contrast, repeated exposure had no apparent effect on the levels of inspective exploration, $F(1,54)=3.53$, $p>0.05$. These findings indicate that, when rats are repeatedly exposed to the same complex environment, their inquisitive exploration levels drop while their inspective exploration levels remain stable, as predicted by Berlyne [2]. These differences between inquisitive and inspective exploration support the idea that these measures detected different aspects of the rats' exploratory behavior.

Figure 1 shows the frequencies of crossovers made by the rats in each of the 5 treatment groups on the 2 drug test days. Both high lithium and high ethanol treatments produced a marked decrease in the frequency of crossovers. The non-significant treatment by day interaction, $F(4,55)=2.08$, $p>0.05$, and day effect, $F(1,55)=2.71$, $p>0.05$, underscore that there was no change over days for any of the treatment groups. The significant treatment effect, $F(4,55)=33.84$, $p<0.01$, was attributable to the decrease in crossovers produced by high lithium, $F(1,55)=57.62$, $p<0.01$, and high ethanol, $F(1,55)=76.71$, $p<0.01$, as compared to the saline control group. In contrast, low lithium, $F(1,55)=0.80$, $p>0.05$, and low ethanol, $F(1,55)=1.36$, $p>0.05$, did not produce significantly different numbers of crossovers compared to the saline control group. These results indicate that both high lithium and high ethanol markedly decreased locomotor activity.

The total number of responses made in the novel side was unaffected by either the drug treatments, $F(4,55)=1.99$, $p>0.05$, or the repetition of exposure, $F(1,55)=0.23$, $p>0.05$.

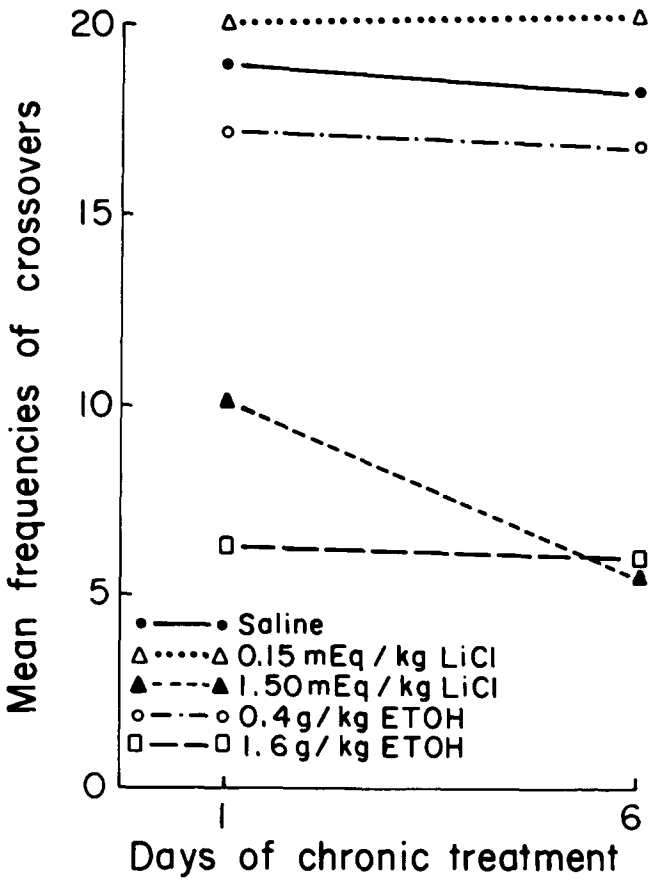


FIG. 1. Mean frequencies of crossovers from one side of the exploration box to the other for the 5 treatment groups.

These findings show the limitation of a measure of exploration which considers simply the amount of time spent on the 2 sides of the box without taking into account the nature of the responses made.

Figure 2 shows the levels of inquisitive exploration observed in the 5 treatment groups. All treatment groups except high ethanol displayed more inquisitive activity in the novel than in the familiar side. All groups, except low ethanol, displayed slightly less inquisitive exploration on the second than on the first exposure. The two high dose treatments produced a decrease in the levels of inquisitive exploration in both the familiar and the novel sides. The non-significant treatment by day by side, $F(4,55)=1.08$, $p>0.05$, and treatment by day interactions, $F(4,55)=0.71$, $p>0.05$, and the significant day main effect, $F(1,55)=16.16$, $p<0.01$, support the conclusion that inquisitive exploration levels decreased with repeated exposure in both familiar and novel sides for all treatment groups. The treatment effect, $F(4,55)=20.82$, $p<0.01$, and the side effect, $F(1,55)=55.65$, $p<0.01$, were significant. Analysis of simple main effects of the significant treatment by side interaction, $F(4,55)=2.64$, $p<0.05$, revealed that the interaction was entirely attributable to the effect of high ethanol treatment: it was the only group in which activity levels were not differentially affected by the novelty factor, $F(1,55)=1.27$, $p<0.05$. All other

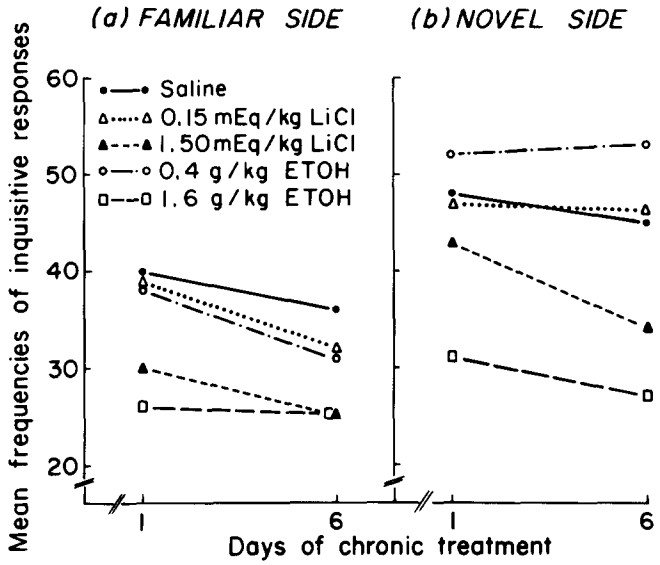


FIG. 2. Mean frequencies of inquisitive responses in (a) the familiar and (b) the novel sides of the exploration box for the 5 treatment groups.

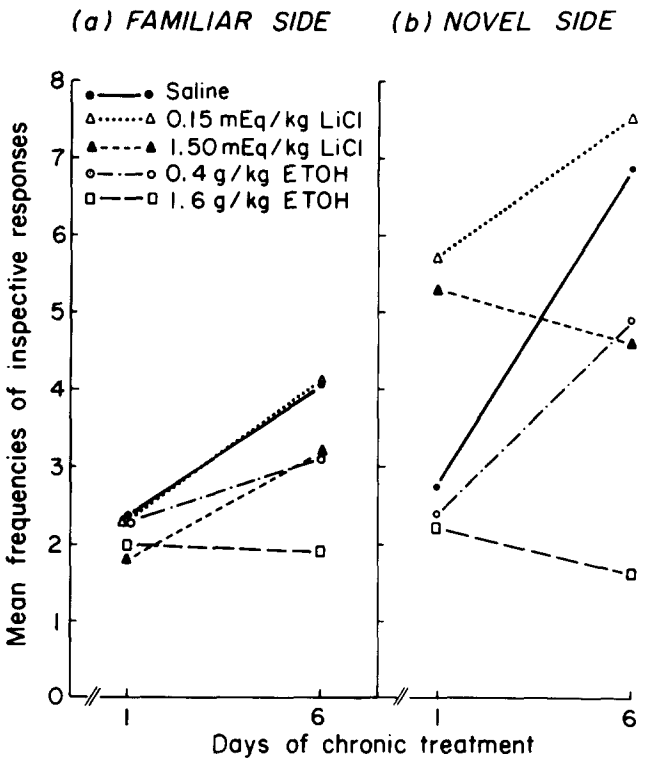


FIG. 3. Mean frequencies of inspective responses in (a) the familiar and (b) the novel sides of the exploration box for the 5 treatment groups.

treatments produced significantly more inquisitive exploration in the novel than in the familiar side (saline, $F(1,55)=6.80$, $p<0.05$; low lithium, $F(1,55)=11.05$, $p<0.01$; low ethanol, $F(1,55)=29.13$, $p<0.01$; high lithium, $F(1,55)=11.45$, $p<0.01$). Further analysis of the significant treatment main effect, $F(4,55)=20.82$, $p<0.01$, indicated that, as compared to the saline group, both high lithium, $F(1,55)=22.85$, $p<0.01$, and high ethanol, $F(1,55)=57.29$, $p<0.01$, decreased inquisitive exploration levels, while low lithium, $F(1,55)=0.39$, $p>0.05$, and low ethanol, $F(1,55)=0.30$, $p>0.05$, produced no change.

Figure 3 shows the levels of inspective exploration observed in the 5 treatment groups. In the familiar side, there were no significant differences among levels of inspective exploration of the various treatment groups. In the novel side, on the first exposure, low and high lithium treatments produced an increase in inspective exploration. On the second exposure, the high lithium and both ethanol treatments produced decreased levels of inspective exploration. The non-significant treatment by day by side, $F(4,55)=1.74$, $p>0.05$, and treatment by day interactions, $F(4,55)=2.14$, $p>0.05$, and the significant day effect, $F(1,55)=10.55$, $p<0.01$, support the contention that, across treatments, inspective responses increased with repetition of exposure. The presence of a significant treatment by side interaction, $F(4,55)=2.88$, $p<0.05$, treatment effect, $F(4,55)=5.71$, $p<0.01$, and side effect, $F(1,55)=22.64$, $p<0.01$, prompted an analysis of simple main effects of the interaction. It showed that significantly increased inspective exploration levels were found on the novel side in the low and high lithium treatment groups. Low lithium, $F(1,55)=12.29$, $p<0.01$, and high lithium, $F(1,55)=6.38$, $p<0.05$, induced more inspective exploration in the novel than in the familiar side. In contrast, with saline, $F(1,55)=2.72$, $p>0.05$, low ethanol, $F(1,55)=0.96$, $p>0.05$, and high ethanol, $F(1,55)=0.00$, $p>0.05$, there was no significant difference in levels of inspective exploration in one side compared to the other. There was no significant treatment effect in the familiar side, $F(4,55)=1.48$, $p>0.05$, but there was a significant treatment effect in the novel side, $F(4,55)=5.74$, $p<0.01$. This treatment effect was significant on both the first, $F(4,55)=3.73$, $p<0.01$, and the second exposure, $F(4,55)=4.83$, $p<0.01$. On first exposure to the novel side, low lithium, $F(1,55)=14.31$, $p<0.01$, and high lithium, $F(1,55)=10.69$, $p<0.01$, significantly increased the levels of inspective exploration as compared to saline. In contrast, low ethanol, $F(1,55)=0.20$, $p>0.05$, and high ethanol, $F(1,55)=0.49$, $p>0.05$, had no significant influence. On the second exposure, low ethanol, $F(1,55)=4.16$, $p<0.05$, high ethanol, $F(1,55)=30.15$, $p<0.01$, and high lithium, $F(1,55)=4.16$, $p<0.05$, decreased inspective exploration, as compared with saline treatment. Low lithium, $F(1,55)=0.46$, $p>0.05$, did not have such an effect.

## DISCUSSION

Rats treated with 1.50 mEq/kg lithium chloride showed clear deficits in crossovers and in inquisitive activity. These changes occurred in the familiar and novel environments. These results, taken together with those previously reported [3], indicate that this dose of lithium produces a reliable and generalized decrease in rats' activity levels, which is not influenced by the characteristics of the environment.

The present experiment failed to confirm that 0.15 mEq/kg LiCl significantly increases locomotor activity, as

previously suggested [3]. A possible explanation for this discrepancy is that an open field of the type used in that initial experiment may not elicit behaviors other than horizontal and vertical displacements. This might have given undue importance to these behaviors as reflections of the effect of low lithium. The finding that this activity increasing effect does not occur in an experimental situation which allows other behaviors to be demonstrated indicates that this dose does not have a general effect on rats' activity levels.

In contrast to their dissimilar effects on locomotor activity both low and high lithium treatments were found to promote an increase in the frequency of inspective responses in a new environment, particularly on the first exposure. While this effect might have been predicted for low lithium treatment on the basis of our previous results [3], its parallel occurrence with the high lithium treatment was unexpected. The finding that both the high and the low doses of lithium increase certain parameters of exploratory behavior, even though the high dose reduces overall activity is of particular interest. This finding may suggest that lithium, over a range of doses, has the property of enhancing rats' capacity to direct and maintain attention to stimuli which provide detailed information about the environment.

Two recent studies on rats have provided additional evidence that lithium chloride (2.0 mEq/kg), despite reducing locomotion, increases the duration of contact with discrete objects the first time they are encountered. This was demonstrated both after a single administration [1] and after 15 days of treatment [10]. Both reports might be taken as suggesting that lithium increases rats' reactivity to environmental stimulation. The present research demonstrates that this effect is not restricted to high doses of lithium, and suggests further that lithium may facilitate extraction of detailed information about the environment through a mechanism of selective attention.

The finding that high lithium failed to maintain increased levels of inspective exploration in the novel side on the second exposure apparently conflicts with the hypothesis that both doses of lithium affected inspective exploration in similar ways. However, it is reasonable to assume that these behaviors might have been indirectly affected by the overall decrease in activity produced by the high dose of lithium, an effect which might be cumulative with repeated administration [3].

A possible alternative explanation for this dose-independent effect of lithium is that it decreased the initial level of fear, so that the animals more readily engaged in object inspection. While this hypothesis could account for the increased levels of inspection in the novel side on the first exposure, it cannot account for the fact that changes occurred exclusively in inspective behavior and not in inquisitive responses. Furthermore, it was found that the acute low ethanol treatment, whose potential as an anxiolytic is better documented than that of lithium [7,8] had no influence on inspection. In fact, low ethanol had few effects on any of the behavioral measures in this experiment. Such effects as were observed appeared to represent a trend towards the disinhibition of inquisitive exploration in the novel environment, an effect totally absent with both doses of lithium.

Another alternative hypothesis to explain the lithium-induced increases in inspective exploration is that rats were made thirsty by lithium and that this behavior was motivated by an increased search for water. However, there is experimental evidence that a single administration of lithium chloride, even in doses larger than the ones used in this experiment, does not result in any significant polydipsia in rats [23]. It would therefore be difficult to explain the lithium-induced increase in inspective responses after a single administration on the basis of increased thirst.

The argument that the decreased activity observed after high lithium treatment could have been secondary to some generally deleterious consequences of lithium administration is contradicted by the demonstration that this high dose is also capable of increasing inspective exploration. There is no obvious reason to assume that some aspects of active behavior would be more resistant than others to disruption by lithium sickness, let alone to suppose that they would be affected in opposite ways.

High ethanol induced a generalized sedative effect, which indiscriminately affected all types of activity. This treatment produced decreases in locomotor activity and in inquisitive and inspective exploration in both the familiar and novel environments. This finding is in agreement with observations of other workers on the dose-related biphasic action of ethanol on rats' activity levels (for a review, see [21]). Because of its pervasive nature, this depressant effect on behavior stands in sharp contrast to the one observed with a high dose of lithium. With lithium, a clear dissociation was found between a decreasing effect on locomotor and inquisitive activities and an increasing effect on parameters of inspective exploration.

## EXPERIMENT 2

Experiment 1 presented evidence suggesting that administration of lithium at both the low and high doses tested might facilitate attention to cues which provide specific information about the environment. However, some doubts might be raised as to the validity of this conclusion given that the data on which it is based consisted of observational measures.

A prediction that can be derived from this hypothesis is that, in situations involving exposure to distracting stimuli, lithium should increase the animals' ability to detect the irrelevance of the stimuli and thereby help them to focus on the salient aspects of the situation. That is, lithium should decrease distractability.

The purpose of this experiment was to investigate the effects of 0.15 and 1.50 mEq/kg lithium chloride on the suppression of drinking induced by a novel, irrelevant tone. The dependent variable in this experiment (licking a drinking tube) was measured by automatic equipment. Since this task is relatively unaffected by locomotor impairment, it was predicted that the effects of a high dose of lithium after single and repeated administrations would be similar to each other, and that both of these would be similar to both the acute and chronic effects of a low dose of lithium.

### METHOD

*Subjects*

Sixty male Wistar rats weighing 220–240 g at the start of the experiment were used. They were housed individually in metal cages in a temperature-controlled room (23°C) on a 12 hr light-dark cycle, and provided free access to food. Water was also continuously available, except for the 12 hr period preceding the experiment.

*Drugs*

The two doses of lithium chloride were 0.15 and 1.50

mEq/kg and 0.9 percent saline administration constituted the control treatment. Volumes and route of administration were identical to the ones described in the previous experiment.

*Apparatus*

The test chamber was a black 20.5 by 20.5 by 25 cm box with a clear Plexiglas front, located in a dimly lit, sound-attenuating enclosure. The floor, made of stainless steel rods, was connected to a drinkometer circuit together with a stainless steel drinking tube which protruded from a side wall. The drinking tube was covered with a Plexiglas shield so that only its tip could be contacted. A high frequency-response speaker was fixed to the wall just above the drinking tube and set to deliver a 12 kHz tone at approximately 72 dB.

*Procedure*

*Single dose.* All subjects were deprived of water for 12 hours. Thirty to forty-five minutes before each subject's testing, 3 groups of 10 rats each received single intraperitoneal injections of either saline, 0.15 and 1.50 mEq/kg LiCl, respectively. Each rat was placed into the test chamber and allowed to drink freely until a period of 5 seconds had elapsed with no pauses of more than 1 second between consecutive licks. At the end of such a 5 second-period, the tone came on for 5 seconds, and the full 10 second-period was defined as a trial. The next trial was initiated when the rat licked continuously for another 5 seconds. Each rat was given 12 trials. Licking during the tone-off and tone-on periods was recorded by a counter as the number of half second-periods during which the rat contacted the drinking tube at least once. A suppression ratio was calculated for each trial by dividing the number of counts made during the 5 second-period when the tone was on by the total number of counts made during the entire 10 second-trial.

*Six doses.* Three groups of 10 rats each received daily intraperitoneal injections of either saline, 0.15 or 1.50 mEq/kg LiCl, respectively, for 6 days. On Day 6, the rats were deprived of water for 12 hours. Thirty to forty-five minutes after each rat's injection and 12 hours after the water bottles were removed, each rat was placed into the test chamber and tested according to the procedure described for a single injection. After testing, each rat was given free access to water in its home cage. The amount of water consumed over a 24 hr period was recorded.

*Statistical Analysis*

The suppression ratios for the 12 trials for each animal were grouped into 4 blocks of 3 successive trials. A 3 (Dose) by 2 (Number of injections) by 4 (Block of trials) analysis of variance with repeated measures on the Block factor was used to assess the significance of the results. One way-analysis of variance for 3 independent groups was used to assess the significance of the water intake data. Newman-Keuls tests were performed to evaluate the significance of the difference between each dose group.

## RESULTS

Figure 4 shows the mean suppression ratios for all groups in the experiment. Acute or chronic treatment with either 0.15 or 1.50 mEq/kg LiCl decreased the tone-induced suppression of licking in similar fashion. All three dose groups, after both single and repeated injections, also showed a gradual habituation to the tone over trials.

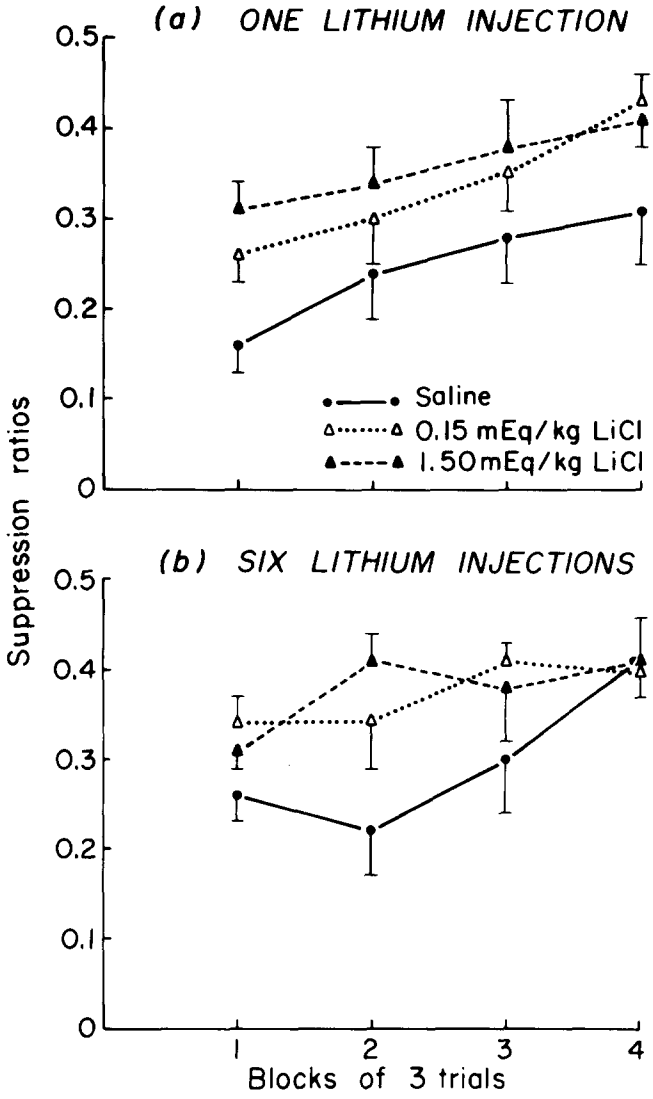


FIG. 4. Mean licking suppression ratios of the 3 lithium groups after (a) one lithium injection and (b) six lithium injections.

None of the interactions was significant: dose by number of injections by block of trials, $F(6,162)=1.07$, $p>0.05$; dose by number of injections, $F(2,54)=0.17$, $p>0.05$; dose by block of trials, $F(6,162)=0.61$, $p>0.05$; number of injections by block of trials, $F(3,162)=0.32$, $p>0.05$. The non-significant interactions and the significant block of trials effect, $F(3,162)=10.46$, $p<0.01$, underscore that all three groups reacted in the same way to repetition of exposure by gradually habituating to the tone. There was no difference between the groups that received one single injection and those that received repeated administration, $F(1,54)=2.74$, $p>0.05$. Further analysis of the significant dose main effect, $F(2,54)=8.71$, $p<0.01$, revealed that, as compared to 0.00 mEq/kg, both 0.15 ($p<0.01$) and 1.50 mEq/kg LiCl ($p<0.01$) significantly decreased tone-induced suppression of licking.

The effects of 0.15 and 1.50 mEq/kg LiCl did not differ from each other.

Suppression ratios on the first trial of block 1 were compared to assess the hypothesis that lithium treatment altered sensory threshold or stimulus salience. Data of the 0.15 and 1.50 mEq/kg LiCl groups were pooled, on the basis that there was no significant difference between these two dose groups in the overall analysis. There was no difference between the saline and the lithium group, neither after a single injection, $t(28)=0.39$, $p>0.05$, nor after repeated administration, $t(28)=0.15$, $p>0.05$.

The mean volumes of water consumed by the 3 groups during the 24 hr period which followed the sixth day of lithium administration were 32, 35 and 45 ml, for 0.00, 0.15, and 1.50 mEq/kg LiCl group, respectively. 1.50 mEq/kg LiCl, but not 0.15 mEq/kg LiCl, significantly increased water intake above control level ($p<0.05$). Water intake levels of 0.15 and 1.50 mEq/kg LiCl were not different from each other.

### DISCUSSION

These findings indicate that administration of lithium reduces tone-induced suppression of drinking in rats. This effect was demonstrated both after a single and after six daily administrations of either 0.15 or 1.50 mEq/kg lithium chloride.

These results fit the prediction that lithium, independent of the dose and administration regimen used in the present study (acute/chronic), would reduce a rat's susceptibility to interference by irrelevant stimuli. A specific mechanism was postulated to underly this effect, in terms of a lithium-induced facilitation of the process of extraction of specific information about the situation.

The hypothesis that the drinking of the lithium-treated rats was less suppressed because they experienced greater thirst has difficulty in reconciling all the findings. First, evidence has been mentioned in Experiment 1 that a single intraperitoneal administration of lithium chloride does not produce increased drinking in rats [23]. The present experiment showed that repeated administration of 1.50 mEq/kg LiCl increased water intake, but no significant increase in water intake was found with chronic administration of 0.15 mEq/kg LiCl. However, both of these doses, after both acute and chronic administrations, produced approximately equal alterations of suppression. These considerations make the explanation of these effects by the single hypothesis of increased thirst unlikely.

It is also difficult to attribute these findings to a lithium-induced decrease in reactivity to the tone. Saline and lithium treated animals responded in the same fashion to the initial presentation of the tone. These unaffected initial suppression ratios make it unlikely that lithium altered sensory thresholds or stimulus salience.

## GENERAL DISCUSSION

We documented earlier, for the first time, that lithium's dose-response effect on rats' activity levels is not monotonic [3]. At relatively low doses, in the 0.15–0.20 mEq/kg range, lithium produced an increase in activity and, with further increases in dosage, produced a decreasing effect on activity. In the same report the suggestion was made that the excitatory effect seen with lower doses of lithium could be best interpreted as reflecting an enhanced responsiveness towards the environment.

Experiment 1 was designed to investigate this hypothesis. This experiment provided additional evidence that a high dose of lithium produces a decrease in general activity, since it decreased both locomotor activity and inquisitive exploration, irrespective of the characteristics of the experimental situation. In contrast, low lithium did not influence these behavioral indicies. This finding led to the conclusion that the increase in activity produced by this low dose of lithium tends to disappear when the experimental situation allows for behaviors other than simple, large displacement in an open field. In addition, it was found that both low and high lithium increased rats' readiness to engage in inspective exploration of a novel environment, and it was suggested that this effect might be due to an increase in selective attention to the stimuli most likely to provide detailed and relevant information about the environment. This hypothesis led to the prediction that lithium would decrease distractability and this idea was supported at both lithium doses in Experiment 2.

Taken together the results of Experiments 1 and 2 are difficult to reconcile with an hypothesis of lithium's action formulated in terms of change in reactivity to stimulation. The finding that both doses of lithium increased rats' readiness to engage in inspective exploration of a novel environment contradicts the hypothesis that lithium reduces the significance attached to stimuli [16,17]. The converse hypothesis, i.e. that lithium increases reactivity to stimulation, is also difficult to sustain, in view of the finding that lithium-induced increases were restricted to inspection of discrete stimuli and did not extend to grosser measures of reactivity to stimulation, such as preference for novelty. Rather it seems that, under the influence of lithium rats are more ready to engage in search strategies aimed at acquiring precise knowledge of the environment. The experiment on distractibility supported and extended this conclusion by showing that lithium increases rats' readiness to disregard interfering stimulation and to focus on stimuli relevant to their current motivational state. The absence of a change in response to the tone on the initial presentation indicates that lithium did not simply alter the animals' reactivity to the auditory stimulation. It could still be argued that this last finding does not rule out entirely the possibility that subsequent tone presentations produced lesser interference in the lithium-treated rats because the drug treatment reduced the significance attached to this stimulation [16,17]. However this hypothesis further specifies that lithium's reduction of responsiveness only applies to stimulation which is near-threshold level or otherwise relatively low in perceptual salience [18]. Clearly the auditory stimulation used in Experiment 2 dose not meet these qualifications. Rather it appears that lithium facilitates the processing of information leading to a ready classification of the auditory stimulus as irrelevant.

These results lead to the formulation of an hypothesis for the understanding of the effects of lithium on the behaviour of rats, which involves two independent components. First, it is proposed that lithium facilitates the process by which rats acquire relevant information about their environment. This effect is probably independent of dose (within the range tested) and therefore, of any influence a particular dose might have on activity levels. In addition to its dose-independent effect on selective attention, lithium appears to exert a genuine, dose-related, bimodal effect on locomotor activity levels. Doses of lithium in 0.15–0.20 mEq/kg range produce a mild increase in rats' activity. In contrast, doses of 0.50 mEq/kg and higher induce a decrease in activity which becomes more pronounced with increased dosage.

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