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Lithium Effects on Position Learning With Exploratory and Aversive Goal-Box Conditions[1]

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HINES, G. *Lithium effects on position learning with exploratory and aversive goal-box conditions.* PHARMACOL BIOCHEM BEHAV 22(5) 695–698, 1985.—Under conflict conditions in which reinforcement occurred within mildly aversive white goal-boxes, the chronic administration of lithium chloride (20 meq/l, in drinking water) to rats, while reducing avoidance of the goal boxes, impaired acquisition of an exploration-reinforced position discrimination. These results were interpreted as supporting the concept that lithium salts reduce the individual's reaction to general environmental stimulation—an effect which may account for its therapeutic action in the treatment of manic disorders.

Lithium Position learning Exploration Goal-aversion Passive avoidance

SINCE Cade's [3] early observation that the administration of lithium salts produced both a decrease in responsiveness to stimulation by guinea pigs and a measure of control over manic symptomology in humans, the efficacy of lithium in the treatment of manic disorders has become well established [15]. Consequently, considerable research has been performed in an attempt to determine the behavioral mechanisms underlying lithium's therapeutic action.

The administration of lithium has consistently been observed to produce a reduction in both spontaneous and exploratory activity [5, 10, 16, 17]. This reduction is greater during exploratory than spontaneous responding [7], and is greatest when differences between novel and familiar stimuli are minimal [9]. Other findings include reduced environmental responsiveness [18], and an attenuation of the orienting response to novel stimulation [2]. Thus, lithium's primary behavioral influence may be on those aspects of activity which represent responses occurring at or near threshold levels of stimulation, producing a reduction in "stimulus significance" [7]—possibly as a result of alterations sensory analysis processes [8].

One exception to the production of reduced exploratory activity following lithium administration was noted by Harrison-Read [5], who observed that lithium produced an increase in the exploration of a novel, white goal-box. This increase in exploratory activity was interpreted as resulting from an attenuation of the aversive qualities of the white goal, since control animals exhibited a tendency to avoid white-goal entry.

Katz and Carroll [11], using a conflict between feeding behavior and shock, and Hines and Poling [6] using dark-preference and shock, have both demonstrated a reduction in passive avoidance behavior following chronic lithium administration. In the latter study, a reduction in the subjects' reactions to shock-delivery was felt to account for the decrease in avoidance, while Katz and Carroll interpreted their results in terms of a drug-induced reduction in conflict-induced anxiety.

In the present study, passive avoidance conditions were established by placing an exploratory incentive in an aversive white goal-box. Since both the reinforcer and the aversive stimulus represent relatively mild environmental conditions, it was felt that this paradigm might allow some further insight into the mechanisms involved in lithium's reduction in passive avoidance.

METHOD

Subjects

Twenty male, 100-day old Holtzman albino rats (Holtzman Company, Madison, WI), housed in standard suspended cages with free access to food and water, were used in this study. Temperature in the housing room was controlled (22±2°C), with 24-hour light-on conditions. Ten of the subjects received lithium chloride (20 meq/l) in their drinking water, while the remaining ten received tap water.

Apparatus

Testing was performed in a T-maze constructed of translucent gray Plexiglas, with white Plexiglas goals at the end of each arm. The start box, which measured 17 × 14 × 15 cm, opened by a manually-operated guillotine door onto a 50 × 14 × 15 cm runway. At the end of the runway were two 25 × 14 × 15 cm arms. At right angles to the end of each arm, and also utilizing manually-operated guillotine doors, were the 25 × 14 × 15 cm goal boxes.

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Reinforcement consisted of the opportunity to explore several "junk" items (a ping-pong ball, a 5 cm wooden cube, a hanging set of 7 keys, and a 5 × 10 cm hardware cloth cylinder) placed in the correct-choice goal box. The positioning of the items in the goal box was changed from one trial to the next.

Timing functions were controlled by manually switching to and from a BRS/Foringer Model Mv-45 Precision clock through BRS 100-series solid state programming units.

Procedure

Testing (using a blind coding of the subjects' treatment condition) was initiated after twenty days on the lithium solution, which allowed ample time for serum lithium levels to stabilize. Each subject was tested for six trials/day on a position-habit discrimination, with half of the subjects in each group receiving reinforcement for left-box responses, and half receiving reinforcement for right-box responses. Entry into the correct (reinforced) goal box was followed by 30 sec of junk-object exploration; if the incorrect goal box was entered, the subject remained in it for 30 sec prior to removal from the apparatus. Finally, if the subject failed to enter a goal box within 150 sec after a trial was initiated, it was removed from the apparatus, and the trial scored as a goal-entry failure. The subjects were tested sequentially in groups of ten, providing a 25-min intertrial interval for each subject.

Each subject was tested for 10 days (a total of 60 trials), at which point responding had clearly stabilized for all subjects. Data was collected on start times, goal-box entries (either box), and proportion of correct (object-box) goal entries. The results were collapsed to 10 session (6-trial) blocks, and analyzed using two-factor, mixed (repeated measures across sessions) Analysis of Variance tests of significance.

Due to the nature of measurements taken for each data collection condition, appropriate transformations [21] were made on the scored values prior to statistical analysis. Thus, start-time scores were subjected to a log transformation, goal-box entries to a square root transformation, and proportion correct goal entries to an arcsin transformation.

On the 11th day, each subject was sacrificed at its usual testing time, and serum lithium levels determined by Flame Photometry [1], using an IL Model 253 spectrophotometer.

RESULTS

Serum lithium levels for the experimental group ranged from 0.15–1.06 meq/l, with mean and S.D. equal to 0.68 meq/l and 0.24 meq/l, respectively. Thus, the serum levels were generally within the range used therapeutically in the treatment of manic disorders. While no formal analysis was performed, there was no apparent relationship between serum level and performance on any of the measures within the experimental group, although the subject at 0.15 meq/l did respond on all measures more similarly to the control subjects than to the other lithium animals.

Consistent with other work in our laboratory, the mean body weight for the LiCl group was somewhat lower than that for the control subjects (469 g vs. 486 g), although the difference was not statistically significant, $t(9)=1.87$, $p>0.05$. Informal assessments of coat conditions, respiration, eyes and nose, and fecal conditions failed to indicate any differences in health status for the two groups.

In the maze, both groups showed the expected decrease in start times across trial blocks (Fig. 1; $F(9,162)=12.84$, $p<0.001$), with lithium subjects producing significantly longer start latencies than did controls, $F(1,18)=12.0$, $p<0.001$.

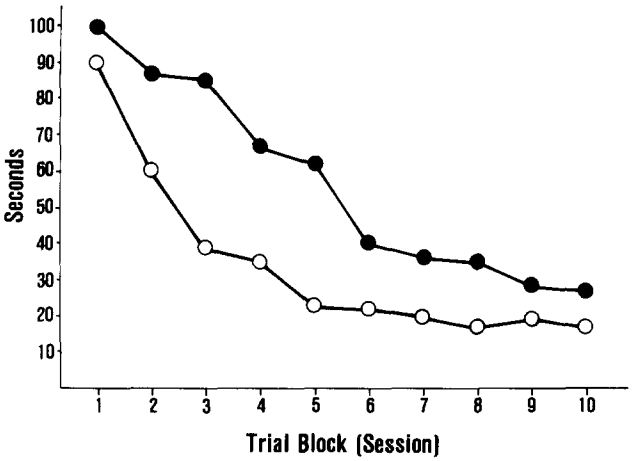

FIG. 1. Mean start times across sessions (6-trial blocks). Closed circles=lithium; open circles=tap water controls.

While both groups increased their frequency of goal-box entries across sessions (Fig.2; $F(9,162) + 8.67$, $p<0.001$), lithium subjects consistently entered the goal boxes more frequently than did controls, $F(1,18)=34.10$, $p<0.001$. Unlike controls, however, the lithium subjects showed no preference for the goal-box containing the junk objects (Fig. 3; $F(1,18)=6.44$, $p<0.05$) maintaining a random selection between the reinforced and non-reinforced goals. Control subjects, on the other hand, showed a gradual increase in exploration-goal entry across sessions, stabilizing at 63–68% entry of the reinforced goal. This behavior on the part of the controls produced a marginally significant Drug × Sessions interaction, $F(9,162)=2.01$, $p<0.05$. Due to a very slight decrease in object-goal entry from the first two sessions by the lithium subjects, the trials factor approached, but did not reach, significance at the 0.05 level.

DISCUSSION

In spite of the relative infrequency of goal entry by the control subjects, their results are consistent with earlier studies of exploration-reinforced position discrimination [12], indicating that these subjects did learn the discrimination in the face of the conflict produced by the aversive nature of the goal boxes. That they did not reach or stabilize at 100% object-goal selection is the result of a tendency to habituate to the novel stimuli. When this habituation is disrupted by scopolamine, 100% levels are reached and maintained [12].

Lithium subjects were less reactive to all aspects of the stimulus situation. They left the start box more slowly, entered the goal-boxes more frequently, and showed no preference for the reinforced goal over the empty one. While the lack of preference may represent a learning deficit, the results of other investigations suggest that this is not the case. Hines and Poling [6] found no effect of lithium on acquisition of a cued-avoidance response, and reported data suggesting that the delayed acquisition of the passive avoidance response was due to a decreased reaction to the relatively low shock level utilized, rather than to learning

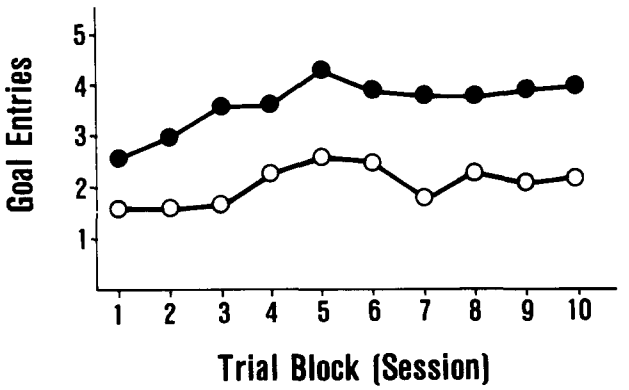

FIG. 2. Mean number of goal-entries (reinforced and non-reinforced goals). Closed circles=lithium; open circles=tap water.

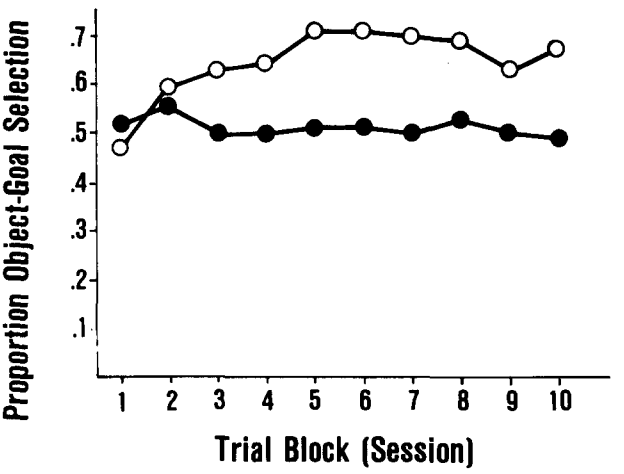

FIG. 3. Mean proportion of goal entries that were the correct (exploratory-reinforced) box. Closed circles=lithium; open circles=tap water.

deficits. Further, Wittrig *et al.* [22] concluded that chronic lithium administration had no influence on maze learning. Thus, these results are most consistent with the concept that lithium's effects on passive avoidance, and on responding in general, are the results of a reduction in the subjects' reaction to environmental stimulation, whether that stimulation be midly aversive (as indicated by the greater frequency of goal-box entry) or exploratory (as indicated by the longer start latencies and the lack of preference for the exploration-reinforced goal box).

Such a reduction in the tendency to respond to environmental stimuli could, at least in part, account for the effectiveness of lithium salts in the treatment of manic disorders. The increasing psychomotor acceleration, flight of ideas, disorientation, impulsivity, distractability, and impairment of concentration and attention that characterizes progress through the manic stages could all result from an increase in the individual's tendency to respond to low-intensity stimulation. Such an increase in responsivity could be produced in either (or both) of two ways. First, the sensitivity of the individual to stimulation (d') might be altered, producing a change in the ability to distinguish those stimulus events which represent meaningful signals from general background stimulation ("noise"). In signal detection terms, the manic individual might be experiencing an elevation of the "noise" distribution to near-signal levels. The resultant decrease in signal-to-noise ratio would then produce an increase in the number of false alarm responses, or responses to "noise" stimuli that are misinterpreted as signals [4]. As a result, the manic individual would show an increase in the frequency, diversity and intensity of behavior due to the increase in the number and variety of response-producing stimuli that would, under normal conditions, be neither noticed nor responded to. Lithium, by normalizing the individual's sensitivity to low-intensity stimulation, would produce an increase in the signal-to-noise ratio, and reduce the number and diversity of response-inducing stimuli. Warburton [20] has determined that just such a mechanism is involved in the activity of the cholinesterase inhibitor, physostigmine, a drug which has also found partial effectiveness in the treatment of manic disorders [13].

Alternatively, increases in reactivity to stimulation by the manic individual could be produced by changes in the individual's response criterion (β), which represents that collection of factors (including, among others, motivation, perceived gains and losses associated with responding, and estimates of the liklihood that particular responses will be followed by specific stimuli) which influence the subject's moment-by-moment decisions about whether or not to respond. Decreases in β produce decreased response inhibition, thereby increasing responding. Lithium, by producing an increase in β, would lower responding to more normal levels. Preliminary results in this laboratory suggest that β is elevated in rats under conditions of chronic intake. Whether this result is a reliable one, and whether it is accompanied by an alteration in d', awaits further clarification.

Finally, it should be noted that the serum lithium levels obtained in this study are not consistent with earlier findings utilizing the same drinking water concentrations. Trautner *et al.* [19] found that a drinking water concentration of 20 meq/l lithium chloride produced serum levels of 1.5–2.0 meq/l, while Prasad and Sheard [14] obtained lower serum levels (0.34 meq/l) than those observed in this study. While variations in age, sex, strain and testing conditions may account for the differences, it is clear that there is a need for further investigation of the parameters determining terminal serum concentrations in free-consuming subjects.

REFERENCES

1. Amidgen, A. Serum lithium determination for clinical use. *J Clin Lab Invest* **20**: 104–108, 1967.
2. Barratt, E. S., D. L. Creson and G. Russell. The effects of lithium salts on brain activity in the cat. *Am J Psychiatry* **125**: 530–536, 1968.
3. Cade, J. F. T. Lithium salts in the treatment of psychotic excitement. *Med J Aust* **36**: 349–352, 1949.
4. Engen, T. Psychophysics: I. Discrimination and detection. In: *Woodworth & Scholsberg's Experimental Psychology (3rd Ed.). vol 1: Sensation and Perception*, edited by J. W. Kling and L. A. Riggs. New York: Holt, Rinehart and Winston, Inc., 1972, pp. 11–46.

5. Harrison-Read, P. E. Models of lithium action based on behavioral studies using animals. In: *Lithium in Medical Practice*, edited by F. N. Johnson and S. Johnson. Baltimore: University Park Press, 1977, pp. 289–303.
6. Hines, G. and T. Poling. Lithium effects on active and passive avoidance behavior in the rat. *Psychopharmacology (Berlin)* **82:** 78–82, 1984.
7. Johnson, F. N. Chlorpromazine and lithium: Effects on stimulus significance. *Dis Nerv Syst* **33:** 235–241, 1972.
8. Johnson, F. N. On the relevance of animal studies on lithium to the understanding of lithium therapy. *Compr Psychiatry* **17:** 591–599, 1976.
9. Johnson, F. N. Effects of lithium chloride on response to salient and *nonsalient stimuli in Carassius Auratus*. *Int J Neurosci* **9:** 185–190, 1979.
10. Johnson, F. N. and S. Wormington. Effects of lithium on rearing activity in rats. *Nature* **235:** 159–160, 1972.
11. Katz, R. J. and B. J. Carroll. Effects of chronic lithium and rubidium administration upon experimentally induced conflict behavior. *Prog Neuropsychopharmacol* **1:** 285–288, 1977.
12. Leaton, R. N. Effects of scopolamine and eserine on position discrimination learning with an exploratory incentive. *Psychon Sci* **12:** 181–182, 1968.
13. Murphy, D. L. Animal models for mania. In: *Animal Models in Psychiatry and Neurology*, edited by I. Hanin and E. Usdin. New York: Permagon Press, 1977, pp. 211–222.
14. Prasad, V. and M. H. Sheard. Effect of lithium upon desipramine enhanced shock-elicited fighting in rats. *Pharmacol Biochem Behav* **17:** 377–378, 1972.
15. Schou, M. J. Lithium in psychiatric therapy and prophylaxis. *J Psychiatr Res* **6:** 67–95, 1968.
16. Smith, D. F. Biogenic amines and the effect of short-term lithium administration on open-field activity in rats. *Psychopharmacologia* **41:** 295–300, 1975.
17. Smith, D. F. and H. B. Smith. The effect of prolonged lithium administration on activity, reactivity, and endurance in the rat. *Psychopharmacologia* **30:** 83–88, 1973.
18. Syme, L. A. and G. J. Syme. The role of sex and novelty in determining the social response to lithium chloride. *Psychopharmacologia* **40:** 91–99, 1974.
19. Trautner, E. M., P. R. Pennycuik, R. J. H. Morris, S. Gershon and K. H. Shankly. The effects of prolonged sub-toxic lithium ingestion on pregnancy in rats. *Aust J Exp Biol Med Sci* **36:** 305–322, 1958.
20. Warburton, D. M. The cholinergic control of internal inhibition. In: *Inhibition and Learning*, edited by R. A. Boakes and M. S. Halliday. New York: Academic Press, 1972, pp. 431–460.
21. Winer, B. J. *Statistical Principles in Experimental Design*. New York: McGraw-Hill Book Company, 1962.
22. Wittrig, J., A. E. Woods and E. J. Anthony. Mechanisms of lithium action. *Dis Nerv Syst* **30:**767–771, 1970.