The Effect of Lithium on Motivation and Learning in the Rat

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Abstract

Recent research has suggested that lithium (Li) may increase cholinergic activity with a resulting increase in cholinergically mediated behavior. Li toxicity, however, poses serious methodolgical problems for researchers in this area. In Experiment I, daily i.p. injections of 1.4 mEq/kg LiCl were found to cause only minor motivational changes as indicated by a computer system which continuously monitored activity, eating, and drinking. Using this dosage in Experiment II, Li and control animals were taught to run in a radial arm maze for a food reward in two learning tasks, spatial and cue. Results indicated that while there were no significant learning differences between the Li and control groups, running times were increased for the Li animals. Although the Li administered animals did not demonstrate the expected facilitation in learning, the careful quantification of Li induced behavioral changes should prove of value in future research.

Key words: lithium - lithium toxicity - motivation
activity, eating, and drinking
maze learning - acetylcholine
distractability - cognitive processing

The Effect of Lithium on Motivation and Learning in the Rat*

It has been well documented that lithium (Li) influences the adrenergic - serotonergic balance in the brain (Schildkraut 1973; Shou 1976; Maggi and Enna 1980). Less well understood is Li's possible role in increasing brain acetylcholine (ACh) levels. While a number of studies have suggested that Li does increase ACh levels (Janowsky et al. 1972a; Jope 1979; Miyauchi et al. 1980; Russell et al. 1981), the extent and importance of this effect is still not clear. The notion that Li, the drug of choice for antimanic therapy, may have a cholinergic component is supported by the observation that physostigmine, a powerful acetylcholinesterase inhibitor, is also therapeutic in the treatment of mania (Janowsky et al. 1972b; Janowsky et al. 1973). Further, physostigmine has been shown to cause other significant behavioral changes similar to those of Li (Simpson 1974; Samples et al. 1977). A particularly interesting effect of physostigmine, which has been demonstrated in both animal and man, is that of a learning facilitation (Davis et al. 1978; Bratus 1979). If both physostigmine and Li work through a common cholinergic mechanism, Li administered subjects may show a similar increase in this cholinergically induced behavior.

In another line of research, various investigators have found Li to decrease distractability, reduce emotional reactivity, and increase exploratory behavior (Cappeliez and White 1981; Russell et al. 1981). These findings are consistant with Li's antimanic effects (Davies 1974) and further support the hypothesis

that Li may facilitate learning.

The major methodological problem of Li toxicity, however, complicates research in this area. Li causes significant behavioral changes at toxic levels which can influence a subject's motivational levels and confound the interpretation of experimental results. To be maximally effective in behavioral studies, the dosage which the subjects receive should be just below that which would generate significant changes in motivation. The determination of such a dose is difficult, especially in animal research. For this reason, all research involving Li should be viewed with suspicion unless the motivational effects generated by the particular dosages used have been carefully evaluated (Smith 1977a, 1977b).

The present study is divided into two parts. In the first experiment, the activity, eating, and drinking behavior of Li administered rats was compared to that of control animals in order to evaluate the motivational effects of this drug and determine an effective dosage. This would be the dose where the animal does not experience significant behavioral changes but, given a slightly increased dose, would. Once this effective dose was determined, it was used in the second experiment, a learning one, where Li and control animals were taught to run in a complex radial arm maze task. It was hypothesized that Li administered animals, given a dosage which does not significantly influence motivation, would learn the maze more quickly and with fewer errors than would control animals

Experiment I

Materials and Methods

In order to evaluate the effects of Li on behavior, eight naive male rats derived from the Sprague-Dawley strain were placed in individual cages (38.5 X 23 X 17.5 cm) in which activity, eating, and drinking were continuously monitored by a computer system (Ohio Scientific C4P). The cages were located in a shielded room where a white noise generator provided further sound masking. A timer regulated 12 hour day/night cycles with lights on at 6:00 A.M. At 9:30 A.M. each day, the rats were weighed, food and water were replaced, and the trays beneath the cages were cleaned. Ultrasonic sound transducers recorded activity while eating and drinking behavior was recorded when the rat made contact with the feeder or the drinking tube. Daily weighing of the feeders provided data on the quantity of food consumed and graduated drinking tubes were used to determine water consumption.

After four weeks of familiarization in these cages, data were collected for a five-day period to establish baseline behavioral levels. These data included the quantity of food and water consumed, frequency of eating and drinking, and activity levels. The rats were allowed free access to food and water throughout this experiment. At the time of the aquisition of the baseline data, they weighed between 450 and 526 g.

Once the baseline data had been established, five rats received daily i.p. injections of lithium chloride (LiCl) (Fisher Co.) at a dosage of 1.4 mEq/kg administered in volumes of 1 ml/kg.

The LiCl was dissolved in 0.9 percent saline. Control animals received injections of 0.9 percent saline, administered in volumes of 1 ml/kg. The experimental dosage was selected, after reviewing the literature, as an approximation of a dose which while having demonstrated behavioral effects, does not cause significant changes in motivation (Gray et al. 1976; Cappeliez and White 1981). The animals continued receiving daily injections for a 16-day period. On day 17, the Li animals' dose was increased to 2.0 mEq/kg. Data were then collected for 10 additional days.

Results and Discussion

The results of this experiment were averaged into 2-day blocks (except for the first block which consisted of the base-line averages) for frequency of activity, eating, and drinking, as well as amount of food and water consumed. Analysis of variance of activity levels revealed a significant Day • Night effect, F (1,6) = 519.80, $p < .001$, with greater activity at night for both the Li and control groups. No significant difference, however, was found between Li and control groups for this effect, F (1,6) = 2.09, $p > .05$. A Group X Block interaction was also found, F (13,78) = 2.42, $p < .01$, where further analysis showed this effect to be attributable to the Li group, F (13,78) = 2.79, $p < .01$. To understand this interaction scheffé contrasts were computed, and they revealed no significant difference between the baseline and other blocks until block 10 (4 days after the increase in drug dosage to 2.0 mEq/kg) at which time activity levels decreased, $p < .01$.

Insert Figure 1. about here →

Analysis of variance revealed a significant Group X Block interaction where the frequency of eating differed for groups over time, F (13,78) = 3.65, $p < .001$. This effect was attributed to the Li group, F (13,52) = 8.67, $p < .001$, where Scheffé contrasts indicated that significant increases in the frequency of eating began after the second day of the 1.4 mEq/kg LiCl injections, $p < .01$. Although the frequency of eating began to diminish after the start of the 2.0 mEq/kg injections (block 12), $p < .05$, it was still elevated significantly higher than the baseline levels, $p < .05$. A Day • Night effect was found for eating frequencies where both groups ate more at night, F (1,6) = 12.99, $p < .05$. There were no significant differences between Li and control groups for this effect, F (1,6) = .078, $p < .05$. Analysis of food consumption revealed a significant Group X Block interaction, F (13,78) = 4.11, $p < .001$. The Li group was found to be responsable for this effect showing a significant decrease in food consumption over blocks, F (13,52) = 6.90, $p < .001$. Scheffé contrasts, however, revealed no significant differences between the Li and control groups for food consumption until the fourth day of the 2.0 mEq/kg injections, $p < .01$. Thus, while both the low (1.4 mEq/kg) and high (2.0 mEq/kg) drug dosages increased the frequency of eating, food consumption was affected only at the higher dosage level (see Figure 1).

Concerning drinking behavior (see Figure 2), a significant Day • Night effect was found for both Li and control groups, F (1,6)

= 6.35, $p < .001$, where the frequency of drinking was increased at night. Further, a Group X Day • Night interaction was also noted, F (1,6) = 7.43, $p < .05$, and was attributed to the Li group which showed markedly increased frequency of night drinking, F (1,6) = 119.30, $p < .01$. A Group X Block interaction was found, F (13,78) = 4.77, $p < .001$, and further analysis indicated that the Li group was responsable for this effect, F (13,52) = 10.63, $p < .001$. Scheffé contrasts showed increased frequency of drinking for both the high and low drug dosages across all blocks, $p < .01$. With respect to water consumption, a significant Group X Block interaction was noted, F (13,78) = 21.53, $p < .001$, and analysis showed the Li group to have consumed significantly more water than controls, F (13,52) = 42.03, $p < .001$. Through Scheffé contrasts, it was found that while there was significantly increased water consumption from the very beginning of the 1.4 mEq/kg injections, $p < .01$, water consumption drastically increased at the higher drug dosage, $p < .01$

Insert Figure 2 about here →

The results of the present experiment indicate that for Li administered animals (a) there are no changes in home cage activity at the low drug dosage while at the higher dosage level there was a decrease in night activity; (b) the frequency of eating was increased at both drug levels and at the higher level, food consumption was decreased; and (c) water consumption and the frequency of drinking were increased by both drug levels, with very large increases at the higher dosage.

A close inspection of the Scheffé contrasts for these changes in activity, eating, and drinking reveals a general pattern of

behavioral effects which plateau at approximately the eighth day (block 5) of the 1.4 mEq/kg injections and the sixth day (block 12) of the 2.0 mEq/kg injections. Once these high and low plateaus were reached, they were constant over the time they were monitored in this experiment. In addition to the presence of these behavioral plateaus, one should note the general increase in the frequency of activity, eating, and drinking at night for both Li and control animals. The increased frequency of these behaviors reflects the nocturnal nature of the subjects. Also, it should be noted that the subjects maintained a constant body weight throughout the experiment despite the behavioral changes described above, $F < 1$.

The results of this experiment are generally supported by those of previous researchers (see Smith 1977c) and based upon them it was concluded that while minimal changes in behavior occur at the dose of 1.4 mEq/kg, substantial changes in behavior occur at 2.0 mEq/kg LiCl. Li administration with the lower dose of 1.4 mEq/kg was therefore assumed not to significantly effect motivational levels. Thus, this lower dosage was used in Experiment II.

Experiment II

Materials and Methods

In the learning experiment, 12 individually housed naive male rats (274-350 g) were the subjects. The maze consisted of eight arms each 97 cm long and 9 cm wide connected to an octag-

onal center platform 34 cm in diameter. On either side of each arm were clear 5.8 cm high plexiglass walls. The reinforcement was placed in holes 1.3 cm wide and 0.6 cm deep located at the distal end of each arm. The maze was elevated 76 cm above the floor. Throughout the experiment, food intake was restricted so that the animals were maintained at 85 percent of their free-feeding body weight. Water was continuously available in the home cages. After maze familiarization, seven experimental animals received daily i.p. injections of 1.4 mEq/kg LiCl while five control animals received saline. These injections were given six hours before testing to minimize any peripheral effects, especially a learned taste aversion (Smith 1980), and were continued for eight days so that the behavioral effects of the Li would stabilize.

Beginning on the ninth day of injections, the animals were taught to run to four baited arms of the eight arm maze for a food reward (97 mg Noyes pellets) in two learning tasks, spatial and cue. In the spatial task, the same four maze arms were baited for any one animal in every trial. Therefore, the animals must use extramaze (spatial) cues in order to successfully navigate their way to the four correct arms and the food reward. The room in which the maze was located had many prominent spatial cues such as overhead lights, heating pipes, cabinets, and a door. The cue task consisted of placing removable textured inserts in the arms of the maze with the same four inserts consistently baited for any one animal. These inserts were made of different materials (sandpaper, chickenwire, cloth, screen, tin, wood,

ceiling tile, and carpet) and served as intramaze cues. The position of the inserts was randomly varied over trials. To minimize the animals' use of extramaze cues, the only illumination in the cue task was a 100-watt light suspended in a shade 52 cm above the maze. Food was used as the reinforcement in these tasks because it had been demonstrated in the previous experiment that 1.4 mEq/kg LiCl had only a very minor effect on eating behavior.

The animals received two trials a day in both the spatial and cue tasks with the order of testing reversed between the two tasks over days. A trial consisted of entering the four baited arms, entering 16 arms, or five minutes, whichever occurred first. After each animal had received 50 trials on each learning task, they were run in a reversal condition where the previously unbaited arms (and cues) became baited and the baited arms (and cues) became unbaited. Testing in this reversal condition continued for another 50 trials. Both the arms entered and the running times were recorded. Two types of memory errors were evaluated. A reference memory error occurred when the animal entered an unbaited arm, indicating a failure of long term memory. Working memory errors were committed when the animal reentered an arm previously visited in the same trial. This type of error reflects a failure of short term memory (see Honig 1978). The data collected in both the aquisition and reversal conditions were analyzed with respect to these two error types.

Results and Discussion

Insert Figure 3 about here →

The error analyses revealed that overall preformance of the Li and control groups was similar in both learning tasks (spatial and cue), $F < 1$. These results are summarized in Figure 3. Although there were no differences in choice accuracy, $p > .05$, running times in the two learning tasks were significantly increased for the Li animals. The average time per arm summed across all initial aquisition trials was 22.0 seconds for the Li group and 18.6 seconds for the controls, which is a highly significant difference, F (1,10) = 23.87, $p < .001$. In the reversal condition, the average time per arm summed across all trials was 19.7 seconds for the Li group and 13.5 seconds for the control animals, which is also highly significant, F (1,10) = 14.06, $p < .01$. The Li animals were observed to spend long amounts of time at the distal end of both baited and unbaited maze arms. When the animals did move to another arm, they did so quickly and without apparent difficulty. These latter observations, however, were not quantified. The results of this experiment indicate that while the Li and control groups learned the maze at approximately the same rate, the Li animals took significantly longer to run each arm.

General Discussion

The major findings of the present study are (a) the lower dosage of 1.4 mEq/kg causes only minor changes in behavior while the higher dose of 2.0 mEq/kg causes considerable behavioral disruption; (b) when the lower dosage was used in the learning experiment, no changes were found for the rate of maze learning;

and (c) running times for Li animals were increased.

While the behavioral data from Experiment I are consistant with previous research, they are considerably more complete and accurate quantifications of the effects of Li than has been previously reported. Although the lower drug dosage generated only minor changes in behavior (and thus motivation), it was near the borderline of considerable behavioral disruption. It is probably the case that one could not use a higher dosage in behavioral research without the possibility that the results may be confounded by Li toxicity. For this reason, the low dosage seemed appropiate for use in the learning experiment. With the effects of LiCl carefully quantified, it was felt that considerable confidence could be placed in the accuracy of the results from Experiment II.

The increased running times observed in the learning experiment are consistant with previous research which has shown that Li decreases open field activity (Smith 1975; Gray et al. 1976; Mukherjee, Baily, and Pudhan 1977; Cappeliez and White 1981). While open field activity was suppressed by the dosage of LiCl used in Experiment II, the same dose had no significant effect on home cage activity (as demonstrated in the first experiment). This finding supports the current belief in a dichotomy between home cage and open field activity (Leyland et al. 1976).

The spatial and cue tasks used in Experiment II are very sensitive to changes in learning and have been used successfully to evaluate learning in other drug research (Okaichi and Jarrard in press). Despite the use in the present experiment of as

high a dose as possible without probable motivational confounding, maze learning was not affected by the Li. The rates of learning for the experimental and control groups were, in fact, very similar to those of control animals from other studies run on the same tasks (Jarrard unpublished results). The major implications of this finding include the following: (a) either Li does not result in a significant increase in cholinergic activity as does physostimine, or cholinergic levels are not important in learning; or (b) the drug dosage used in Experiment II was too low to facilitate learning. It should be noted that numerous researchers have used doses as low, or lower, than the 1.4 mEq/kg used in the learning experiment and yet they still found various significant behavioral effects (Gray et al. 1976; Cappeliez and White 1981). The increased running times indicate that that the drug was having an effect on the animals. Therefore, the dosage used in Experiment II seemed large enough to facilitate learning if a Li facilitation were possible. It seems, then, that the lack of significance of the data from the learning experiment must be due to factors other than too low a drug dosage.

In addition to the lack of support for the cholinergic hypothesis of Li action, the results of this study also suggest that while Li may decrease distractability, reduce emotional reactivity, and increase exploratiry behavior (Cappeliez and White 1981; Russell et al. 1981), these effects may not significantly influence complex maze learning.

Finally, a third line of research has suggested that Li

may reduce exploratory behavior by limiting the central analysis of sensory information (Johnson 1972, Judd et al. 1977a, 1977b). Although the learning experiment was not intentionally designed to test this hypothesis, one would think that decreased cognitive processing would result in slower rates of learning in tasks as sensitive as those used in Experiment II. Since there was no decrease in choice accuracy or the rate of learning, it seems that the hypothesis of decreased cognitive functioning under Li administration is not applicable to complex maze learning tasks.

It seems, then, that the results of the present study are contrary to predictions based on several different theories implicating Li in learning. The minimal effect of a carefully evaluated Li dose makes it reasonably safe to accept the null hypothesis that Li plays an insignificant role in radial arm maze learning.

Now that the motivational effects of Li have been quantified at two important dosage levels, it is hoped that this information will be used in further research in this area. It is only with such information that one can discount confounding motivational changes which have complicated Li research in the past.

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Footnotes

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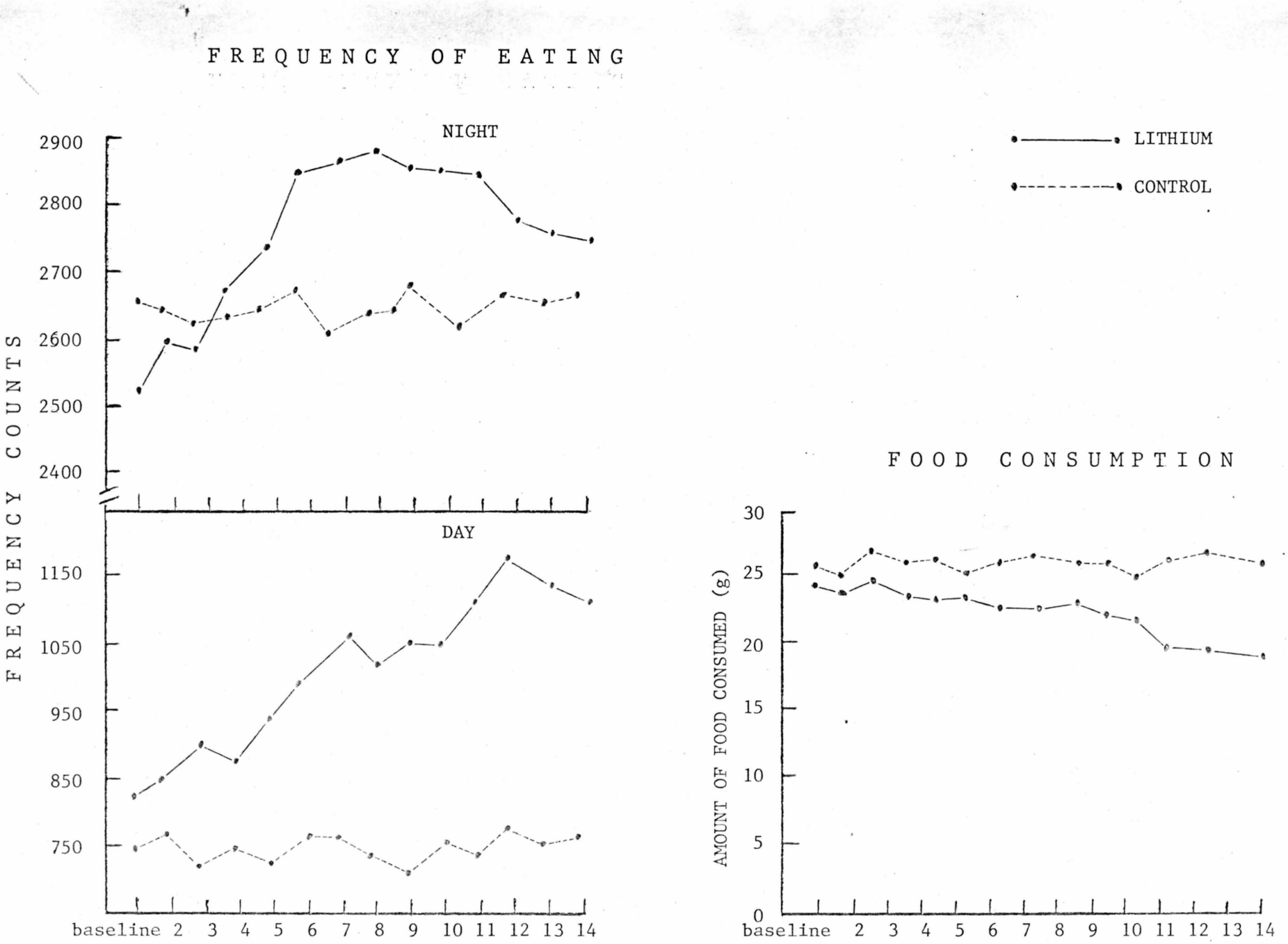
Legend

Figure 1. A summary of the effects of 1.4 mEq/kg and 2.0 mEq/kg LiCl on eating behavior.

Figure 2. A summary of the effects of 1.4 mEq/kg and 2.0 mEq/kg LiCl on drinking behavior.

Figure 3. Mean percent correct responses on the spatial and cue tasks in both aquisition and reversal conditions as a function of blocks of 10 trials.


FREQUENCY OF EATING
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750
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2 DAY BLOCKS
FOOD CONSUMPTION
AMOUNT OF FOOD CONSUMED (g)
30
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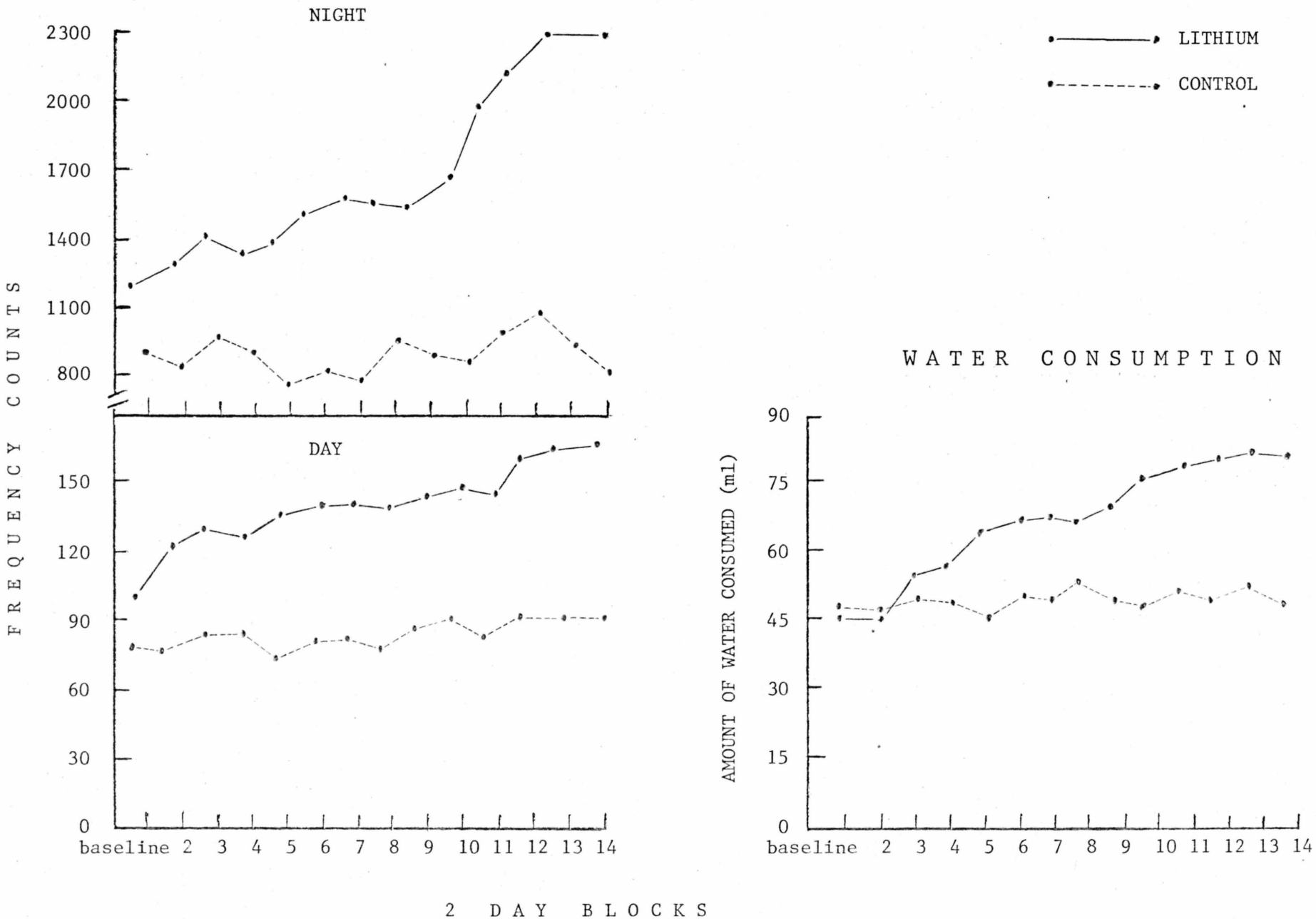
FREQUENCY OF DRINKING
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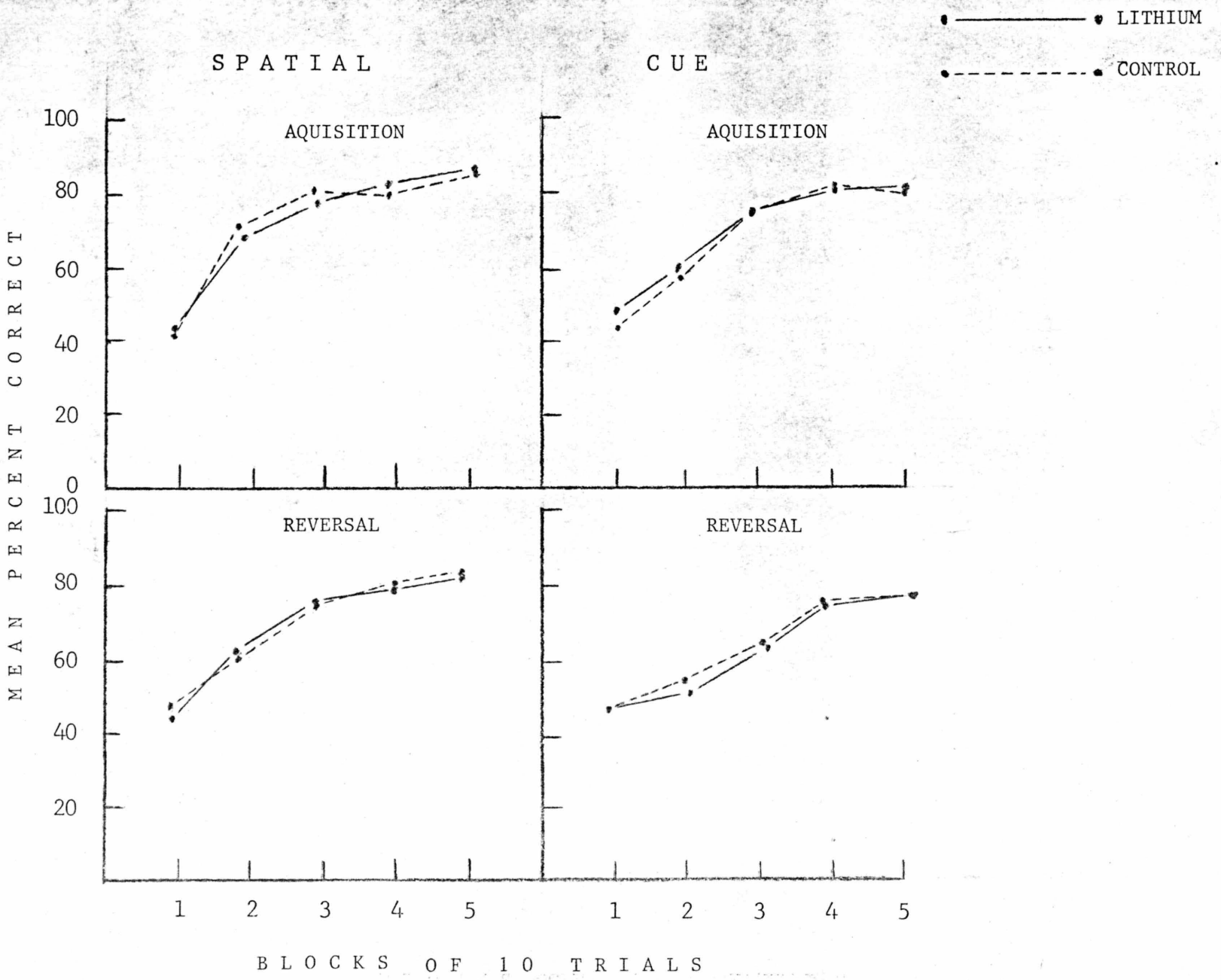
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BLOCKS OF 10 TRIALS