Physiology and Behavior, Vol. 10, pp. 73–78, Brain Research Publications Inc., 1973. Printed in U.S.A.

Learned Taste Aversions in Rats as a Function of Dosage, Concentration, and Route of Administration of LiCl

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(Received 19 May 1972)

NACHMAN, M. AND J. H. ASHE. *Learned taste aversions in rats as a function of dosage, concentration, and route of administration of LiCl.* PHYSIOL. BEHAV. **10**(1) 73–78, 1973.–Rats drank a 15% sucrose solution for 10 min and were then injected intraperitoneally with various volumes of 0.15 M LiCl to produce a learned taste aversion to the sucrose. A dose response curve was obtained between the volume of 0.15 M LiCl injected and the degree of aversion. With additional groups, the LiCl concentration was varied inversely with volume injected and it was found that the aversion was dependent on the absolute quantity of LiCl and not on the concentration or volume of solution. LiCl was also found to be equally effective in producing learned aversions whether administered intraperitoneally, subcutaneously, or by stomach tube. The dose-response curve indicated that a very strong aversion occurs at a dose of 3.0 mEq/kg and that the threshold dose for producing an aversion is approximately 0.15 mEq/kg. The threshold dose was discussed in relation to the amount normally given to human patients as a therapeutic dose. It was concluded that the rat is highly sensitive to learning a taste aversion with LiCl.

Lithium Learned aversions Dosage Illness Injection route

A VARIETY of toxic substances and aversive treatments, such as arsenic [28], apomorphine [9], cyclophosphamide [10], and radiation [33] have been used to produce learned taste aversions in rats. More recently, an increasing number of studies have used lithium chloride (LiCl) which has several advantages such as ease of administration, availability, safety, and a sickness onset which is rapid but not long lasting. In addition, it has become apparent that LiCl is one of the most effective substances for producing learned taste aversions in a single trial [11, 21, 25].

The first experiments utilizing LiCl to produce learned taste aversions used a concentration of 0.12 M LiCl [18, 19]. These experiments had been concerned with comparisons of oral intake of NaCl and LiCl solutions and it was therefore necessary to use concentrations which are acceptable orally to the rat. Since 0.12 M NaCl is near the peak of the NaCl preference - aversion curve, this concentration of NaCl and the same concentration of LiCl were used as test solutions. Several other investigators have also used the concentration of 0.12 M LiCl [5, 12, 32] although, to our knowledge, there is no advantage to such a concentration when the LiCl is given other than by oral intake. For injections, we have used a 0.15 M LiCl solution because it is approximately isotonic with serum NaCl concentration and, in contrast to hypertonic solutions, it does not produce pain when injected. However, hypertonic concentrations of 0.3M [17] and 0.4M [15] LiCl have also been used and, in addition, LiCl has been used in 0.1 M concentration [35] and has been added to diets [7, 27].

The choice of various concentrations and amounts of LiCl used by different investigators has often been done arbitrarily and nonsystematically. For this reason, a parametric study was undertaken to determine the effects of various concentrations and amounts of LiCl as well as to examine the effects of administering the LiCl by different routes. Preliminary results of dose response curves with LiCl have been presented verbally at meetings [8, 20], and learned aversions have been shown to vary with strength of treatment using radiation [24, 33] and cyclophosphamide [6, 38].

In Experiment 1, a dose response curve was obtained using various volumes of 0.15 M LiCl and in addition, the effects of hypertonic LiCl concentrations were studied. Experiment 2 investigated the effects of route of administration of hypertonic LiCl.

EXPERIMENT 1

Method

Animals. The animals were 90, 60-day old Sprague-Dawley male rats weighing 250–350 g. The rats were housed in wire mesh cages where Purina Lab Chow was available ad lib. During the course of the experiment, the rats received no water in their home cages and their total fluid intake was restricted to daily 10-min tests which were administered in wooden test boxes.

Procedure. The procedure and apparatus for producing learned aversions have been previously described [21]. Briefly, daily 10-min single bottle drinking tests with tap

water or test solution were given in individual drinking boxes 30 x 17 x 17 cm which had a guillotine door that was raised to start the drinking period. Each day the rats were adapted to the boxes for 2–4 min before the doors were raised. The amount drunk at the end of 10 min was recorded from 25 ml graduated cylinders equipped with stainless steel spouts.

The rats were water deprived for one day, and beginning the next day were given 10 min of access to water in the drinking boxes for 4 successive days. On Day 5, the treatment day, 15% sucrose (w/v) was used as the drinking test solution; the rats were then randomly divided into 15 injection treatment groups, with an N of 6 each, as summarized in Table 1. Group 1 served as a noninjection control and Groups 2–8 received 0.15 M LiCl which was administered in increasing volumes to result in a dosage range of 0–3.0 mEq/kg. Group 9 served as an injection control for the largest volume delivered and was injected with isotonic NaCl.

The remaining six groups (Groups 10–12 and 13–15) were used to test the effectiveness of hypertonic LiCl solutions of 0.24 M, 0.40 M, and 0.65 M at two dosage levels of LiCl. For these groups, the volume was varied inversely with concentration to result in constant amounts of LiCl. For Groups 10–12, the total LiCl dosage was 3.0 mEq/kg which was the amount given to Group 8 using 0.15 M. For Groups 13-15, the total LiCl dosage was 1.8 mEq/kg which was the amount given to Group 6 using 0.15 M.

All injections were given intraperitoneally with solutions which had been maintained at 37°C. The injections were given within 2–5 min after the end of the 10-min drinking test, and the rats were immediately returned to their home cages. Food was removed for one hr after injection to minimize any possible interfering effects of eating while the sickness developed.

On Days 6 and 7, all animals were given water during their regular 10 min drinking period. These two post-sickness days allowed recovery from any possible residual sickness effects and also were used to determine if there was any generalized avoidance to drinking water in the drinking boxes. On Day 8, test day, 15% sucrose was once again given to all animals and the amounts drunk in 10 min were recorded. The sucrose solutions given on Days 5 and 8 were prepared the day prior to being used. Statistical analyses of the data were performed using the Kruskal-Wallis H-test and the Mann-Whitney U-test [30]. All U-test probabilities are one-tailed.

TABLE 1

TREATMENT GROUPS IN EXPERIMENT 1

Group	Dosage mEq/kg	Volume ml/kg	Solution
1	0	0	---
2	0.15	1.00	0.15 M LiCl
3	0.3	2.00	0.15 M LiCl
4	0.6	4.00	0.15 M LiCl
5	1.2	8.00	0.15 M LiCl
6	1.8	12.00	0.15 M LiCl
7	2.4	16.00	0.15 M LiCl
8	3.0	20.00	0.15 M LiCl
9	3.0	20.00	0.15 M NaCl
10	3.0	12.50	0.24 M LiCl
11	3.0	7.50	0.40 M LiCl
12	3.0	4.61	0.65 M LiCl
13	1.8	7.50	0.24 M LiCl
14	1.8	4.50	0.40 M LiCl
15	1.8	2.77	0.65 M LiCl

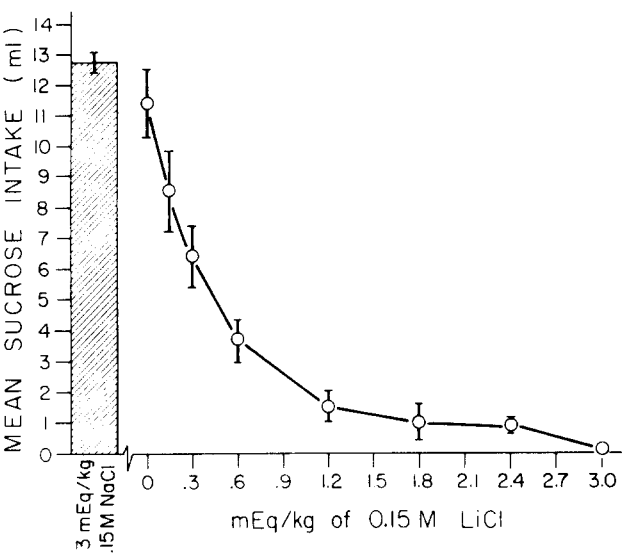

FIG. 1. Mean sucrose intake (±1 S.E.M.) in the test for learned aversion as a function of the quantity of LiCl (mEq/kg) injected on the treatment day. The group receiving a control injection of NaCl is included for comparison. For all groups, N=6.

Results

Figure 1 presents the mean sucrose intake for each group on the test day as a function of the amount of 0.15 M LiCl injected on the treatment day. As can be readily seen, there is a systematic effect of dose with a maximal aversion appearing at the strongest dose of 3.0 mEq/kg. The control injection of 3.0 mEq/kg of isotonic NaCl was without effect and this group did not differ from the control group which had not received any injection ($p>0.2$, U-test). Finally, it is noteworthy that even the smallest dose of 0.15 mEq/kg appeared to produce some aversion. This group drank significantly less than the isotonic NaCl group ($p<0.05$, U-test) although the difference between it and the control group only approached significance ($p<0.1$, U-test). At the next dose of 0.3 mEq/kg the rats clearly showed an aversion and drank less than controls ($p<0.001$, U-test). It is of interest to note that these lower two dose levels are approximately at the dose range given to patients with manic symptoms as initial therapeutic doses [13, 29].

While there was a systematic relationship between the amount of LiCl injected and learned aversion, there was no effect of the concentration of LiCl on the learned aversion when the amount of LiCl was held constant and the volume varied. Figure 2 contains the mean intake for Groups 8, 10, 11, 12 and 6, 13, 14, 15; at both the 3.0 mEq/kg and the 1.8 mEq/kg dose levels, the concentration of the LiCl solution injected had no effect on the degree of aversion

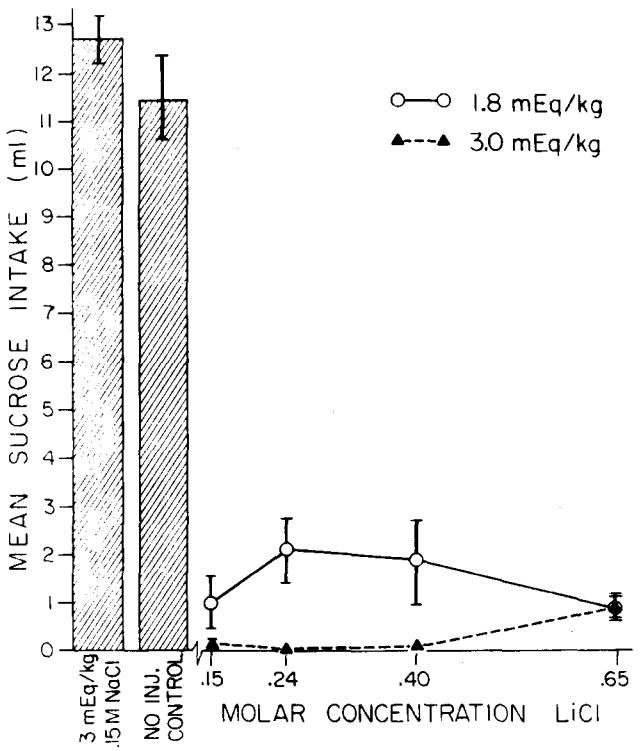

FIG. 2. Mean sucrose intake (±1 S.E.M.) in the test for learned aversion as a function of the concentration of LiCl solution injected. At both the 1.8 mEq/kg and 3.0 mEq/kg dosage levels, the volume injected was varied inversely with concentration to give a constant quantity of LiCl. The NaCl and no injection control groups are included for comparison. For all groups, N=6.

(both p's>0.2, H-tests). As expected, the total amount of LiCl injected did have an effect and the 4 groups receiving the higher dose of 3.0 mEq/kg drank significantly less than the 4 groups receiving the lower dose of 1.8 mEq/kg ($p<0.01$, U-test).

All differences between groups on the sucrose test day were specific to that day indicating that the differences in intake were reflections of learned aversion to sucrose and were not generalized to water nor were there any residual effects of sickness on drinking. Thus, there were no significant differences among the 15 groups in sucrose intake on the treatment day, before the LiCl injections, ($p>0.2$, H-test) nor were there any significant differences in intake on the two water days intervening between the treatment day and test day (p's>0.2, H-test). On the treatment day, the mean sucrose intake for all 90 rats was 10.7 ml and on the two posttreatment water days the mean intakes were 12.2 ml and 14.7 ml respectively.

The dose response curve of Fig. 1 shows that the amount of learned aversion is a function of the volume of 0.15 M LiCl injected. The results shown in Fig. 2 suggest that it is the total amount of LiCl and not the specific volume or concentration which is responsible for the aversion. However, it is possible that the various hypertonic LiCl groups were equally effective in producing the learned aversion, not because they involved the same amount of LiCl, but because the hypertonicity may have produced pain and gastrointestinal disturbances. When these injections are administered to the rat, it is clear that the 0.15 M injection can be given without any sign of rat discomfort and often with no indication whatsoever that the rat feels the injection or the fluid being injected even at the large volume injections of 20.0 ml/kg. In contrast, when hypertonic LiCl solutions are given IP, particularly at the higher concentrations, the rat reacts usually within a few sec after the injection by bodily movements involving extension of the abdominal wall. With a higher volume of hypertonic solution such as 20.0 ml/kg, there are obviously more pronounced responses indicating pain such as squeeling, biting, and gross bodily contortions. Thus, it is possible that the various hypertonic LiCl solutions were equally effective in producing aversions because of the discomforting aspects of the injections and not because they were equated in the amount of LiCl given to groups receiving 0.15 M LiCl.

EXPERIMENT 2

Experiment 2 was designed to further test the effects of hypertonic LiCl in two ways: (a) by comparing the effects of three routes of administering the 0.65 M LiCl, intraperitoneally, subcutaneously, and via stomach tube; and (b) by comparing the effectiveness of 0.65 M LiCl with 0.65 M NaCl solutions in producing learned aversions. Hypertonic NaCl solutions have been used in our laboratory as well as in others to produce learned aversions [14, 25]. Stomach tubing of 0.12 M LiCl has also been shown to be effective in producing learned aversions [20,31] while control stomach tubing of 0.12 M NaCl was without effect [20].

Method

Animals. The animals were 36 male Sprague-Dawley rats, 250–350 g, 70 days of age. Food and water conditions were identical to those in Experiment 1.

Procedure. The test procedure was the same as in Experiment 1. For the first 4 days, the rats were given 10 min of water daily in the drinking boxes and on Day 5, the treatment day, they were given 10 min of 15% sucrose. All treatments were administered 2–5 min after the 10-min sucrose intake. The 36 rats were randomly assigned to 6 treatment groups with an N of 6 each, as summarized in Table 2. For all treatments the solutions were maintained at 37°C. For the stomach loads, the rat's mouth was held open with a speculum and a No. 8 French rubber catheter was passed down the esophagus into the stomach. For the subcutaneous injections the site was the middle back region, dorsal to the rib cage. As can be seen in Table 2, Group 1 was not injected, Groups 4–6 were given 4.61 ml/kg of 0.65 M LiCl by different routes, Group 2 was given 4.61 ml/kg of 0.65 M NaCl and Group 3 was given the larger dose of 20.0 ml/kg of 0.65 M NaCl. The larger dose of hypertonic NaCl was clearly more painful to the rat and was included because preliminary work indicated it was effective in producing a learned aversion.

On Days 6 and 7, all rats were given a 10-min test with water and on Day 8, the test day, the animals were once again given 10 min of 15% sucrose to test for aversion.

Results

The mean sucrose intake of each group on the test day is presented in Fig. 3. All three LiCl groups, whether administered the LiCl subcutaneously, intraperitoneally, or by stomach tube, showed a strong aversion to the sucrose

TABLE 2

TREATMENT GROUPS IN EXPERIMENT 2

Group	Dosage mEq/kg	Volume ml/kg	Solution	Route
1	0	0	--	--
2	3.0	4.61	0.65 M NaCl	IP
3	13.0	20.00	0.65 M NaCl	IP
4	3.0	4.61	0.65 M LiCl	IP
5	3.0	4.61	0.65 M LiCl	stom. tube
6	3.0	4.61	0.65 M LiCl	subcut.

and there were no significant differences among these groups ($p>0.2$, H-test). In contrast, the rats receiving 4.61 ml/kg of 0.65 M NaCl did not show an appreciable aversion and did not differ significantly in intake from controls ($p>0.2$, U-test). Group 3, which received the larger volume (20.0 ml/kg) of 0.65 M NaCl, did show a significant aversion when compared with controls ($p<0.01$, U-test) but they still were less aversive to sucrose than were the three LiCl groups ($p<0.01$, U-test).

All differences between the six groups were restricted to the test day and there were no significant differences between groups in sucrose intake on treatment day or in water intake on Days 6 and 7 (all p's>0.1, U-tests). The mean intake of sucrose on Day 5, for all rats, was 11.9 ml and the mean intake of water on Days 6 and 7 was 11.7 ml and 13.9 ml, respectively.

DISCUSSION

Lithium chloride is clearly an effective substance for producing learned taste aversions in rats and a simple monotonic relationship exists between the amount of LiCl injected in a single trial and the degree of learned aversion. When a dose such as 3.0 mEq/kg is administered, all rats without exception show a strong aversion to the conditioned taste stimulus.

The results in Experiments 1 and 2 were consistent in showing that the aversion was determined by the amount of lithium delivered and not by the route of administration or concentration of solution employed. The dose of 3.0 mEq/kg of LiCl produced a uniformly strong aversive effect with the four concentrations used and with the three routes of administration. While intraperitoneal injections of hypertonic lithium solutions may have also produced painful gastrointestinal effects, the hypertonicity was presumably not responsible for the aversion since comparable NaCl injections were without effect. The stomach tubed group was of particular interest in also showing that the quantity of lithium and not the concentration was important, since for this group, the 0.65 M LiCl was undoubtedly diluted by being added to the stomach a few minutes after the animal had finished drinking sucrose.

It is difficult to compare the effectiveness of various toxic substances used in different experiments since the experimental procedures have also varied. Nevertheless, the evidence seems to indicate that LiCl is more effective than some other agents which are commonly used. While we have invariably observed strong aversion in all rats after one

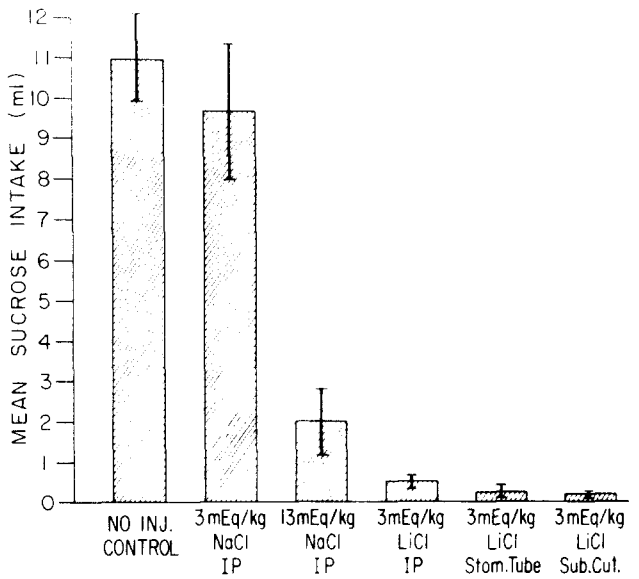

FIG. 3. Mean sucrose intake (±1 S.E.M.) in the test for learned aversion for each treatment group in Experiment 2. To give the quantity of 3 mEq/kg, the dosage was 4.61 ml/kg of a 0.65 M solution, and to give 13 mEq/kg, the dosage was 20.0 ml/kg of a 0.65 M solution. For all groups, N=6.

trial with 3.0 mEq/kg LiCl, studies using cyclophosphamide and apomorphine for example, often use multiple trials before strong aversions are seen [2, 10, 11]. This of course may be in part, a result of the dosages which have been employed in those studies since with high dosages strong aversions may be seen in a single trial [10].

Why lithium chloride should be particularly effective as an aversive stimulus is an important question for which there is no clear answer at present. The most obvious behavioral symptom of high dosage LiCl in the rat is that the rat will be relatively inactive and will tend to lie quietly on the floor of the cage. In addition, and perhaps more significantly, diarrhea is often present, indicative of gastrointestinal disturbance. Gastrointestinal symptoms such as nausea and vomiting are also reported as possible adverse reactions to lithium treatments in human patients. However, because lithium does affect catecholamine metabolism and does alter sodium transport in nerve and muscle cells, its effects are undoubtedly widespread and a large range of potential side effects have been reported in the clinical use of lithium with human patients [13, 29].

The fact that lithium chloride, radiation, apomorphine and cyclophosphamide are all known to produce nausea and gastrointestinal sickness suggests that it is this syndrome which makes them all effective as treatments in producing learned taste aversions. However, this evidence is certainly not conclusive particularly since each of these treatments has other widespread effects and also because there does not seem to be a good correlation between the effectiveness of a treatment in producing a learned aversion and the degree of sickness which it produces. Radiation, for example appears to produce learned aversions at dosages which are too low to elicit any observable symptoms of illness [33] whereas apomorphine appears to make a rat exceedingly sick while producing a less pronounced aversion [25]. Furthermore, many other treatments have been

reported to produce learned aversions in recent years, and it is certainly not evident that these various treatments have specific influences on nausea or gastrointestinal sickness. The treatments used have been diverse and have included amphetamine and mescaline [4], ethanol [16], p-chlorophenylalanine, n-butyraldoxime, and pyrazole [22], anesthetics [3], actinomycin-D [36], physostigmine [34], formalin [37], and even IV isotonic saline [26].

An examination of the dose response curve in Fig. 1 gives an indication of the sensitivity of the rat to developing a learned taste aversion in response to lithium. The threshold dose to produce an aversion is approximately 0.15 mEq/kg and at this dose, the rat does not show any obvious signs of sickness. That this dose is relatively mild, is further suggested by the fact that it is less than the dose routinely administered as a therapeutic treatment for manic symptoms. A typical starting dose for treating patients in the manic phase of manic-depressive psychosis is 600 mg lithium carbonate given orally three times a day and maintenance dosages are approximately half that amount [23]. Assuming a patient weighs 70 kg, this initial dose is approximately 0.23 mEq/kg of lithium. Thus, patients receive three times a day, a dose which is about 1½ times the dose necessary to produce a learned aversion in rats. The dose for patients is clearly near the threshold for producing gastrointestinal sickness as this effect is a frequently reported side reaction and may lead to a reduction in the prescribed dosage. When volunteers were given a single large experimental dose of 30–40 mEq (equal to about 0.50 mEq/kg assuming 70 kg subjects) most of the subjects experienced slight to moderate discomfort with symptoms such as nausea, vomiting, and abdominal pain lasting about one hr [1]. Thus, the evidence seems to be that at 0.50 mEq/kg, people feel clear discomfort and that 0.23 mEq/kg is probably near the threshold for feeling any effect. Assuming that the responses of the rat to LiCl are similar to those in man, it can be inferred that the low dose of 0.15 mEq/kg used in the present study produced only slight, if any, discomfort. The fact that rats show evidence of learning to such a dose suggests a highly sensitive mechanism for learning taste aversions.

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