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VOLUNTARY LITHIUM INTAKE, 'ANTIDOTAL THIRST' AND CONCURRENT BEHAVIOUR OF RATS

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1 Voluntary intake of various pair combinations of fluids (100 mM, 10 mM LiCl, 10 mM NaCl, water) and body weight was measured daily in rats.

2 More lithium was consumed when water was available.

3 When offered a lithium-sodium choice the rats did not consume significantly more saline than water on the previous trial. While saline consumption increased over the two days, lithium decreased slightly.

4 Following the lithium-only trial, water and saline were provided. Marked polydipsia was observed on the first day and the rats drank more water than saline. On the second day there was a significant drop in saline intake while water consumption returned to baseline levels.

5 Behavioural measurements overall confirmed the depressant effect of lithium: decreased ambulation and rearing and increased time spent immobile/grooming.

6 These findings are discussed with reference to lithium toxicity, which may be a confounding variable in studies concerned with the effects of this salt on the behaviour of laboratory rodents. Behavioural irritability such as aggression reported in situations using long-term lithium treatment may be reduced by provision for voluntary saline consumption.

Introduction

Voluntary ingestion of lithium and sodium salts by laboratory rats has been the subject of two separate areas of investigation. Firstly, the ability of these animals to discriminate between chloride solutions has provided a useful paradigm for neuro-physiological (e.g., Beidler, 1953) and learning (e.g., Strom, Lingenfelter & Brody, 1970) theorists. Secondly, the use of lithium as a prophylactic for manic-depressive states has prompted examination of electrolyte metabolism, since sodium levels may influence the renal excretion of lithium and thus its therapeutic efficacy (Thomsen, 1973).

One side effect of prolonged treatment with lithium salts in rats is the development of polydipsia and polyuria. The causal sequence of these symptoms, however, is unclear although their similarity to those of diabetes insipidus has been attributed to the reversible inhibition of anti-diuretic hormone in the rat kidney (Harris & Jenner, 1968).

Smith, Balagura & Lubran (1970) suggest that rats exhibit 'antidotal thirst' for water which acts, through the renal system, to rid the body of toxic lithium ions. Evidence has since emerged to show that high doses of lithium can impair conservation of sodium, so that rats administered lithium in food choose to drink saline rather than water, thus minimizing lithium toxicity (Schreiber & Roháčová, 1971; Thomsen, Jensen & Olesen,

1974). Furthermore, an inverse relationship between the intake of lithium and of sodium chloride solutions has been noted (Strom *et al.*, 1970; Ellman & Gan, 1973).

The present work examines the voluntary consumption of the two salts (LiCl, NaCl) and water by rats, using a two-bottle choice situation and baseline water intake measures. This procedure differs from those used in earlier studies of lithium toxicity in that administration of the salt is neither masked in food (e.g., Thomsen *et al.*, 1974) nor introduced directly to the stomach (e.g., Smith *et al.*, 1970). Also, no previous designs have incorporated a water/saline choice following short-term voluntary intake of small amounts of lithium in the drinking water.

Since lithium has been reported to depress the activity of laboratory rats (Johnson & Wormington, 1972; Smith & Smith, 1973; Syme & Syme, 1973, 1974) the non-directed behaviour of individual subjects was observed daily in an open field to determine any gross effects of the experimental manipulations.

Methods

Male hooded rats (67-168 g) were housed singly and measures of water intake and body weight were obtained for 10 days. Each cage measured 25 x 27 x 13 cm and two water bottles were situated 3.5 cm from the edge and in the middle of the front wall. Standard laboratory food was freely available in hoppers attached to the side wall. Details of solutions presented, including the 10-day baseline water measures, are shown in Table 1. Pairs were switched on alternate days to avoid position preferences for particular bottles. The solutions were diluted to 10 mM after the first trial (days 11-12) since the experimental error involved in volume measurements (± 0.5 ml) precluded accurate assessment of the amount consumed, this being about 1 ml of 0.1 M LiCl solution.

Table 1 Details of the experimental procedure

Days	*Solution (distilled water)*	
	A (100 ml)	*B (100 ml)*
1-10	Water	Water
11-12	Water	100 mM LiCl
13-14	Water	Water
15-16	10 mM LiCl	10 mM NaCl
17-18	Water	Water
19-20	10 mM LiCl	10 mM LiCl
21-22	10 mM NaCl	Water
23-30	Water	Water

The rats were observed alone for 10 min daily at normal room illumination in a circular arena (diam. 1 m, walls 40 cm) which was painted black and the floor divided into 21 segments by white painted lines. Behaviour recorded included the number of segments crossed, the number of times each animal reared up on the hind legs, and the time spent immobile/grooming. On days 13-14 the animals were not tested since they were disturbed for cage cleaning. A random test order was adopted.

Results

Individual fluid consumption, body weights and behavioural measures were compared daily with the previous day's figures using a Wilcoxon Matched-pairs signed-ranks test. The results are shown in Table 2 and Figure 1. Treatment days refer to the time at which intake was measured, so that behaviour observed on day 11, for example, corresponds with the consequences of lithium consumption between days 10 and 11.

There was a high correlation between mean body weight and baseline water intake ($r = 0.79$, $P < 0.001$); both increased as the study progressed.

On the first treatment (days 11-12, 100 mM LiCl) the rats consumed between 1 and 2 mM LiCl, while there was no change in water intake from previous levels. Although the corresponding behavioural measures showed a significant increase in time spent immobile/grooming there was no difference in locomotor activity or rearing frequency.

When the rats were provided with a choice between two 10 mM salt solutions for the second treatment (days 15-16) they drank between 0.1 and 0.5 mM LiCl and 0.5 to 4.8 mM NaCl. The volume of NaCl consumed was similar to the baseline water measures; although it increased on the second day, this was not significant. Behavioural measurements again demonstrated a significant increase in time spent immobile/grooming; also a significant decrease in the distance travelled and rearing frequency.

When 10 mM LiCl was offered in both bottles for the third treatment (days 19-20) the mean volume consumed increased, while the intake (0.3-0.9 mM) was actually less than for the first trial (days 11-12) when the rats could drink either a more concentrated solution of LiCl (100 mM) or water. Similar behavioural changes occurred to those seen in earlier trials, but only the decreased ambulation was significant (day 19) and there was little change between (days 19-20).

Following this LiCl presentation the rats drank

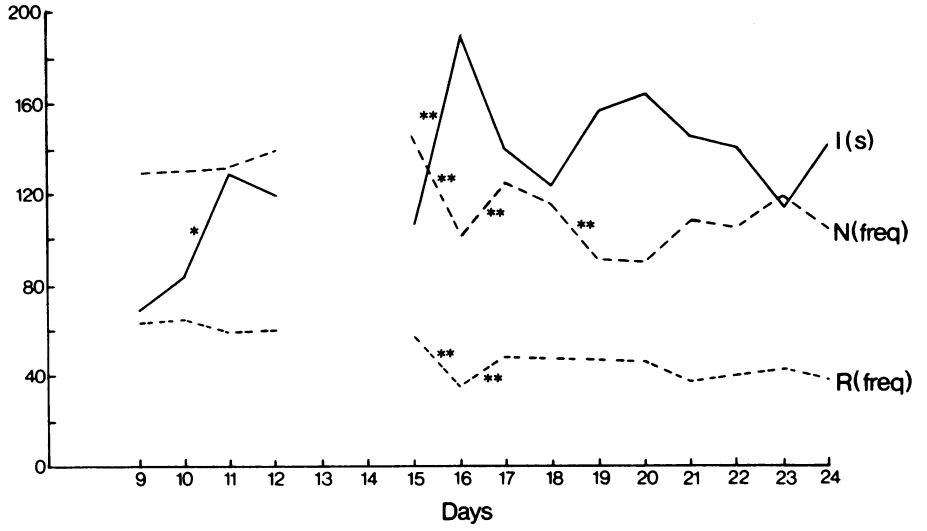

Figure 1 Median values of behaviour indices obtained between days 9-24. I = Time spent immobile; N = number of segments crossed; R = rearing frequency.
* $P < 0.02$, ** $P < 0.01$ (Differs from previous measure, Wilcoxon signed-ranks matched-pairs test, two-tailed).

Table 2 Details of fluid consumption and body weight measurements

Day	*Body weight (g)*	*Water (ml)*	*10 mM NaCl (ml)*	*10 mM LiCl (ml)*	*100 mM LiCl (ml)*
1	133.0 ± 9.4	34.3 ± 1.0			
2	137.2 ± 9.3	31.2 ± 1.3			
3	140.5 ± 8.9	33.6 ± 1.2			
4	144.8 ± 9.1	34.5 ± 1.1			
5	149.1 ± 8.4	29.3 ± 1.5			
6	153.9 ± 8.8	33.1 ± 0.9			
7	160.9 ± 8.3	32.8 ± 1.1			
8	162.5 ± 7.6	33.9 ± 1.3			
9	163.4 ± 8.0	33.9 ± 1.3			
10	167.8 ± 7.6	32.0 ± 0.9			
11	173.1 ± 7.6	33.3 ± 1.1			1.5 ± 0.2
12	175.5 ± 7.4	34.5 ± 1.1			1.5 ± 0.1
13	187.4 ± 7.9	32.4 ± 0.9			
14	188.7 ± 7.5	35.7 ± 1.1			
15	187.1 ± 7.3		33.1 ± 4.9	2.2 ± 0.4	
16	188.5 ± 7.6		38.6 ± 3.6	1.3 ± 0.3	
17	192.6 ± 7.1	36.1 ± 1.2			
18	196.8 ± 7.1	34.6 ± 1.7			
19	186.6 ± 6.7			6.4 ± 0.6	
20	177.4 ± 6.6			6.1 ± 0.4	
21	199.0 ± 6.8	31.2 ± 5.7	28.0 ± 6.7		
22	202.3 ± 7.0	36.1 ± 2.4	6.0 ± 2.4*		
23	207.0 ± 6.9	38.1 ± 1.0			
24	209.9 ± 7.0	44.2 ± 1.0			
25	219.6 ± 6.5	42.5 ± 1.5			
26	221.3 ± 6.9	39.3 ± 1.3			
27	225.1 ± 6.8	37.8 ± 1.1			
28	227.8 ± 6.4	41.8 ± 1.2			
29	229.2 ± 5.9	37.4 ± 1.1			
30	234.2 ± 5.9	41.1 ± 1.7			

Values expressed as mean with s.e. mean
* Differs from previous day's measure ($P < 0.02$)

a large quantity of fluid ($\bar{X}_{total}$ = 59.2 ml) which comprised slightly more water than NaCl. However, NaCl consumption dropped sharply on the second day while water intake returned to baseline levels. There was no significant change in the behavioural measure following the final LiCl presentation.

Discussion

The return to baseline levels for both water consumption and behaviour indicates that the effects were, in fact, discrete. While this is not unexpected for the physiological response it is interesting that any stable baseline behaviour was maintained. In this sort of apparatus, once the setting ceases to be 'novel' or aversive to the rat, a decrease in overall activity is generally observed with repeated testing (Archer, 1973). Thus any reaction to extraneous stimuli (e.g., drug administration) might well be lessened as the experiment progressed (Kršiak & Janků, 1971). In the present study a significant change was noted for each of the three trials on at least one index while no significant alterations in behaviour were recorded on the eight baseline water days.

Two explanations are possible for the greater lithium consumption when water was available. Lithium causes polydipsia which may act to increase renal activity and thus lithium excretion (Smith *et al.*, 1970). Alternatively, when water was not present the rats learned to avoid both bottles, whereas when water was available in one bottle this increased the probability of sampling the wrong bottle (i.e., lithium) since these were switched over each day.

Previous studies have used either water (Smith *et al.*, 1970) or saline (Thomsen *et al.*, 1974) for the investigation of lithium toxicity. The present work supports the view that both liquids act, presumably, to reduce the retention of lithium ions. Following the lithium-only presentation on days 19-20 the polydipsic response was composed almost equally of water and saline on day 21 while on day 22 saline consumption was significantly decreased. In view of previous findings that rats will consume enough saline to compensate for renal sodium losses (Thomsen *et al.*, 1974) the optimal saline concentration was voluntarily achieved. Further investigation of saline/water choices when lithium is chronically administered in food or by injection is planned.

Whilst saline and water both act to reduce lithium toxicity, both were ineffective in preventing the behavioural effects of the salt. In fact the greatest depressant effect was observed on the lithium/sodium trials (days 15-16) when the least lithium was consumed.

Provision for voluntary consumption of saline may be useful for behavioural studies since chronic administration of LiCl has been reported to reduce individual foot-shock 'jump response' thresholds in rats (Harrison-Read & Steinberg, 1971) and to increase aggression in the cage environment (Schreiber & Roháčová, 1971). This irritability may well account for different behaviours observed in laboratory rodents treated with lithium salts by different routes (injection, food, stomach load, drinking water) and over different periods, by removing a potential confounding variable. For example, we have noted that rats administered 3 mEq/kg LiCl (i.p.) and placed together in the home cage will often fight for several minutes (Syme & Syme, 1973). Observed physical discomfort (abdominal contractions) following injection, particularly in a social setting, may also be manifest as a 'depressant' effect of the salt.

The ability of rats to choose their own lithium intake might be applicable to studies using drug-induced 'manic' activity (Cox, Harrison-Read, Steinberg & Tomkiewicz, 1971). If rats can show an 'antidotal thirst' for water or saline to counteract lithium toxicity, they may also be able to monitor their consumption of lithium solutions to reduce an adverse drug response. Perhaps this would be best demonstrated in groups of caged mice, where such hyperactivity is associated (Chance, 1946) with high mortality.

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