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Alcohol Consumption in Rats Treated with Lithium Carbonate or Rubidium Chloride

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ALEXANDER, G. J. AND R. B. ALEXANDER. *Alcohol consumption in rats treated with lithium carbonate or rubidium chloride.* PHARMAC. BIOCHEM. BEHAV. 8(5) 533–536, 1978. – Wistar-NTRU rats, offered a free choice between tap water and a 10% ethanol solution (v/v) in the absence of reinforcement, were injected for five days with Li_2CO_3, RbCl or placebo. Lithium-treated group consumed 25% more liquid per day but chose to take 14.5% less alcohol than controls ($p<0.05$). By contrast, rubidium-treated animals consumed 15% less liquid but 70% more alcohol than control animals ($p<0.005$). Rubidium-treated rats were strikingly more active than the other two groups: their motility index was 60.0, as compared to 33.6 for lithium-treated and 29.4 for control rats. Serum glucose and urea nitrogen concentration were not significantly affected by the treatment but serum alcohol content was low in lithium-treated and high in rubidium-treated animals.

Ethanol Alcohol intake Lithium carbonate Rubidium chloride

CONTINUOUS oral ingestion of lithium salts, known modifiers of affective disorders [2,7], has been suggested as a possible treatment modality for chronic alcoholism [17]. Preliminary clinical results have been promising [9, 12, 17]. In addition, in a study of experimental animals, voluntary consumption of ethyl alcohol has been significantly reduced during treatment with lithium [14]. Salts of rubidium can apparently also serve as modifiers of mood and behavior [10], but their effects are likely to be opposite to those produced by lithium [3]. The only available study of alcohol intake after rubidium treatment in rats produced data indicating no significant changes in the amount of alcohol consumed, but a tantalizing possibility that an increase may have occurred 3–4 days after the start of treatment [13]. In this communication, we report that while treatment with lithium carbonate decreased, treatment with rubidium chloride increased alcohol preference in the laboratory rat.

METHOD

Thirty male albino Wistar-NTRU rats, 335 ± 20 g, were picked at random from our animal colony and placed individually in wire cages equipped with two drinking bottles, one containing tap water, the other 10% aqueous ethanol solution made from absolute ethanol (Commercial Solvents Corporation, Terre Haute, Ind.) with tap water. To minimize uncontrollable variables, drinking bottles and sippers were alternated daily in a random fashion. Location of the ethanol solution, the order of testing and the order of injections were also randomized. After 14 days of exposure, the rats in three matched groups were injected intraperitoneally at 11 A.M. for five consecutive days with Li_2CO_3 (22 mg/kg/day, 0.3 mEq/kg/day), RbCl (120 mg/kg/day, 1 mEq/kg/day) (both dissolved in 0.1% Tween-20) or vehicle (2 ml/kg/day). Water and ethanol intake were measured during the 48 hr interval between the third and fifth injection. Gross activity was tested at 9 A.M. on the last day with a Bel-Art Motility Tester, Model 80, and expressed as the average number of crossings from plate to plate during a 30 min period. Four hr after the fifth injection the animals were guillotined and bled. Serum glucose and urea nitrogen (BUN) were analyzed on a Technicon Autoanalyzer and serum alcohol was assayed by a modification of the enzymatic procedure, utilizing commercial alcohol dehydrogenase preparation (Calbiochem, La Jolla, CA) coupled to NAD reduction. The assay consisted of measuring the difference in UV absorbance of each specimen at 0 time and after 10 min of in vitro incubation.

RESULTS

Total fluid intake in placebo-treated rats during the third and fourth day averaged 41.4 ml/rat/day, of which 4.2 ml was 10% alcohol solution in tap water. Ethanol, therefore, comprised slightly more than 1% (v/v) of total fluid consumption (Table 1). Individual fluid intake ranged from a low of 35 ml to a high of 50 ml/rat/day (Fig. 1). Individual ethanol intake ranged from 1 ml to 10 ml/rat/day. Characteristically, several animals consistently refused to take more than minimal amounts of the alcohol solution, while others, with equal consistency, drank up to 10 ml (i.e., 1 ml of ethanol) per day. The average motility index of the placebo group was 29.4 crossings/30 min, serum glucose was 132.0 mg/100 ml, serum urea nitrogen

TABLE 1

VOLITIONAL INTAKE OF 10% ETHANOL SOLUTION AFTER PLACEBO, LITHIUM CARBONATE OR RUBIDIUM CHLORIDE INJECTIONS

Treatment	Dose mEq/kg/day	Average Fluid Intake (ml/kg/day) Water	10% Ethanol
Placebo	–	111.6 ± 4.2	12.6 ± 0.3
Li_2CO_3	0.3	144.0 ± 4.4*	10.8 ± 0.3*
RbCl	1.0	84.6 ± 16.1*	21.6 ± 2.4*

*Difference from placebo is statistically significant ($p<0.05$, Student's t test). Thirty rats in matched groups of 10 injected on five consecutive days with placebo, Li_2CO_3 or RbCl. The salts were dissolved in 0.1% Tween-20 vehicle. Fluid intake was measured during the last 48 hr.

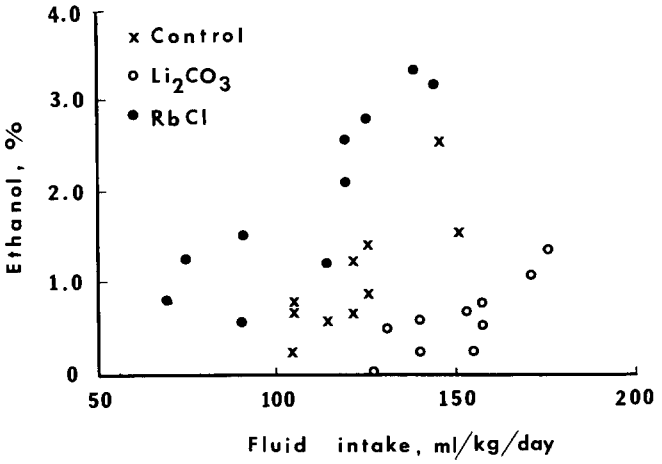

FIG. 1. Volitional ethanol intake in individual rats treated with placebo, Li_2CO_3 or RbCl. Each point denotes total fluid and ethanol intake of an individual animal from Table 1.

22.0 mg/100 ml and serum alcohol level 1.8 mg/100 ml (Table 2).

Rats treated with Li_2CO_3 drank 25% more total liquid (51.6 ml vs. 41.4 ml/rat/day in placebo-treated animals, $p<0.005$), but decreased their intake of the 10% alcohol solution from 4.2 ml to 3.6 ml/rat/day, i.e., from 1.01% of ethanol in the total fluid to 0.70% (v/v). In the lithium group individual fluid intake ranged from 40 ml to 60 ml/rat/day; intake of 10% alcohol solution from 0 to 6 m/rat/day. A slight increase in motility was observed but was not statistically significant, 33.6 compared to 29.4. No significant change in serum glucose or urea nitrogen was observed, but serum alcohol level was 0.5 mg/100 ml as opposed to 1.8 mg/100 ml in controls ($p<0.01$).

Treatment with RbCl had a largely opposite effect: the average total liquid intake dropped to 35 ml/rat/day; 10% alcohol intake increased to 7.2 ml/rat/day (i.e., from 1.01% to 2.03% ethanol (v/v) ($p<0.005$). Individual values ranged from 23 ml to 46 ml of total fluid/rat/day and 2 ml to 13 ml of 10% alcohol/rat/day. Motility rose sharply, to 60.0 ($p<0.05$), serum glucose or urea nitrogen did not change (127.7 mg% glucose; 20.0 mg% BUN) but serum alcohol level rose to 2.2 mg% ($p<0.05$).

DISCUSSION

Salts of lithium were proposed for treatment of alcoholism [6,17] on the basis of the observation that alcoholics are often depressed [17]. Results were encouraging [9, 12, 17] although the amelioration could not always be correlated with changes in the depressive state because in at least one case both lithium- and placebo-treated patients were less depressed after treatment than before [17]. Animal studies confirmed the effect of lithium salts while avoiding some of the difficulties inherent in studying a random patient population. Treatment with lithium carbonate or lithium chloride reduced volitional ethanol intake in rats offered a free choice of water or alcohol solution in the absence of any reinforcing schedules under most, if not all, experimental conditions [8,14].

Meltzer *et al.* have predicted that salts of rubidium may exert an effect on mood and affect opposite to that of lithium [10]. Animal data and exploratory human studies with rubidium chloride were not inconsistent with such a possibility [1, 3, 5, 11]. In the present investigation volitional alcohol intake by the laboratory rat was influenced in opposite ways by lithium carbonate and rubidium chloride treatment. Lithium salt increased water and decreased ethanol consumption, rubidium salt decreased water and increased ethanol consumption. Neither treatment affected serum glucose but both altered serum alcohol levels in a manner consistent with changes in intake. The only significant effect of one salt without a somewhat opposite effect of the other was the increase in the motility index in rubidium-treated rats.

Ethanol concentrations varying from 4–11% have been used in animal studies of the effect of alkali metal salts on alcohol intake [8, 13, 14]. In preparation for this work, therefore, we have tested whether 5% or 10% ethanol solution would be more effective and found a distinct advantage in the use of the more concentrated solution. Our animals did not consume appreciably higher volumes of the 5% than the 10% solution. As a consequence, their ethanol intake was higher with the latter.

TABLE 2

MOTILITY AND SERUM ALCOHOL, GLUCOSE AND UREA NITROGEN AFTER PLACEBO, LITHIUM OR RUBIDIUM TREATMENT

	Placebo	Li_2CO_3	RbCl
Serum (mg%)			
alcohol	1.8 ± 0.4	0.5 ± 0.1*	2.2 ± 0.2*
glucose	132.0 ± 5.1	138.0 ± 5.1	129.3 ± 2.9
urea nitrogen	22.0 ± 2.3	22.0 ± 2.7	20.0 ± 4.7
Motility (counts/30 min)	29.5 ± 14.1	33.6 ± 7.1	60.0 ± 23.9*

*Difference from placebo is statistically significant ($p<0.05$, Student's t test). Thirty rats in groups of 10 injected for five consecutive days were bled 4 hr after last injection. Motility was tested on the 5th day prior to the last injection.

Animals given a choice between water and 5% aqueous alcohol for two weeks and then switched to a choice between water and 10% solution did not decrease but slightly increased the volume of solution consumed, thereby sharply increasing their intake of ethanol. As a result of these and similar findings we have used the 10% aqueous alcohol solution throughout this work.

The results of the previously published study of alcohol preference in rats treated with RbCl were difficult for us to interpret. No statistically significant changes were observed in that study but "a slight reduction . . . during the initial 48 hr period" was noted and the available data are compatible with the possibility that a slight increase in ethanol consumption occurred after 48 hr [13]. These data, from only four rats, were obtained under conditions not comparable to those used in our work. A different strain of rats, a lower concentration of alcohol (5% as compared to 10%) and a higher dose of RbCl (3 mEq/kg/day as compared to 1 mEq/kg/day) were used [13]. In addition, prior to the study of the effect of RbCl, the experimental animals were made to accept an alcohol solution as the exclusive source of fluid and, perhaps as a result of that treatment, when offered a choice, they consumed more alcohol solution than water [13]. Our rats were always given a choice and they consistently consumed more water than alcohol solution even when their consumption of the solution increased as a result of treatment.

Treatment with lithium carbonate or rubidium chloride may have altered alcohol preference in our rats because it affected (a) the amount of gross activity and the need for energy which can be provided by alcohol, (b) the general awareness of smell and taste and the degree of aversion for alcohol solutions and/or (c) the Na/K ratio, regulating water balance. We are currently investigating the role of biogenic amines in these mechanisms.

Rubidium-treated animals showed an enhanced startle reflex and susceptibility to convulsive seizures [1]. They also were very active, strongly aggressive and agitated. Hence, they may have had the need for additional energy which could account for the increase in ethanol consumption. Lithium-treated animals, however, did not show reduced physical activity. Neither was increased or decreased energy utilization, if any, reflected in changes in serum glucose.

Changes in sensory acuity could also have accounted for our data. Lithium is known to decrease the intake not only of ethanol but also of other substances such as morphine [16]. An increase in sensory acuity has been postulated as the reason for the rejection of alcohol solutions prepared from 100% but not 95% ethanol by rats treated with the serotonin depletor *p*-chlorophenylalanine [4]. Our alcohol solutions were prepared with absolute alcohol and, therefore, may have had some residual benzene odor, but intake of solutions made from 95% ethanol has also been decreased by lithium treatment [8,14].

It is likely that the most critical factor controlling alcohol consumption in our treated rats involved Na/K balance. We have observed significant changes in water intake after both lithium carbonate and rubidium chloride treatment, but in the absence of data on daily food consumption and urine volume the significance of these findings remains to be ascertained. Both lithium and rubidium enter alkali ion pools which normally produce and maintain inter- and intracellular electrochemical potentials and osmotic pressures. Like sodium and potassium, lithium and rubidium enter along concentration gradients but, unlike sodium and potassium, are not easily removed [11,15]. Restoration of a balanced milieu may require, in part, compensatory changes in water distribution. Ethanol, even in small concentrations, can profoundly influence this system. While commonly included with drugs of abuse, ethanol is not a drug in the usual accepted sense of the word, but functions essentially as a solvent. Unlike other abused substances, it is fully miscible with water and can readily penetrate most body membranes and become part of the inter- and intra-cellular fluid milieu. As such it can affect osmotic pressures and surface tensions and lead to significant changes in the solubility and distribution of water and fat-soluble compounds of either endogeneous or exogeneous origin. Living

organisms have the ability to regulate alcohol consumption. It may prove worthwhile to investigate the possibility that they also possess the ability to utilize exogeneous alcohol when available, to control internal macro- and micro-environment, particularly after it has been altered by lithium or rubidium treatment.

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