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Cesium and Rubidium Salts: Effects on Voluntary Intake of Ethanol by the Rat

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MESSIHA, F. S. *Cesium and rubidium salts: Effects on voluntary intake of ethanol by the rat.* PHARMAC. BIOCHEM. BEHAV. 9(5) 647–651, 1978.—The effects of RbCl and CsCl on voluntary intake of ethanol solution by rats preferring ethanol solution 5% (w/w) over water as the drinking fluid was studied as a function of the dose given and the vehicle injected. Administration of RbCl or CsCl, 0.5 mEq/kg/day or 1.5 mEq/kg/day for three consecutive days, did not alter amounts of ethanol consumed. Repeated administration of RbCl or CsCl, 3.0 mEq/kg/day for three days, produced some moderate reduction in ethanol consumption. Simultaneous injection of RbCl (1.5 mEq/kg) and CsCl (1.5 mEq/kg) resulted in greater and profound lasting decrease in ethanol drinking. The later treatment did not alter specific activities of rat liver alcohol- and aldehyde dehydrogenase from saline treated controls. In general, dissolving the chloride salt of the alkali metals in saline resulted in greater effects on ethanol drinking than that determined after identical doses injected with water as the vehicle. The possible mechanism(s) underlying the effects of alkali metal salts used are suggested.

Alkali metals Cesium chloride Liver alcohol dehydrogenase Liver aldehyde dehydrogenase
Rubidium chloride Voluntary intake of ethanol

THE DISCOVERY of the therapeutic value of lithium carbonate in the management of manic states [4] led to probing into the biological activity of the other alkali metal salts, i.e., rubidium [12] and cesium [13]. This is based on the implicit assumption that differing physiological properties between Li^+ and the other alkali metal ions may be indicative of paradoxical effects on mood and behavior, thus, providing a unique sequentially logical rationale distinctly different from the common molecular modification approach employed in the development of novel psychoactive agents. The high incidence, 8–23%, of alcoholism in manic depressive populations [5, 11, 22, 26] suggests an interrelationship between compulsive drinking behavior and affect. The antidepressant properties of Rb- [12] and Cs-salts [18], their antagonisms to the depressant action of ethanol [14,15] and the possible implication of the sedative effect of ethanol (ET) as an incentive for alcohol drinking prompted the present study on the effects of RbCl and CsCl on voluntary intake of ET solution by the rat. The value of the enzymatic approach in studying the mechanistic concepts underlying certain drug action prompted the study of the effects of these alkali metal salts on the hepatic enzymes involved in the major metabolism of ET and acetaldehyde.

METHOD

Sprague-Dawley male rats weighing 350–400 g were obtained from Holtzman Farm, Inc., and maintained on Purina pellet food and water ad lib in a laboratory with 12 hr dark/12 hr light photo-period at 23–25°C. The animals were housed individually in 46×21×26 cm cages throughout the experiments. A 5% ET (w/w) solution, prepared from 95% ET, was offered as the sole drinking fluid for three consecutive weeks. This was followed by a three week period of free choice situation between water and ET. Animals preferring to consume at least 60% of their daily fluid requirement as the ET solution were selected for studying voluntary intake of ET using the two-way two-bottle method since it is more suitable [27] than the three-way bottle choice procedure. The drinking bottles were weighed and rotated once every 24 hr at 11–11:30 a.m. Amounts of food consumed and changes in body weights were determined every 24 hr and 48 hr, respectively. The chloride salts of the alkali metal ions used were individually dissolved in distilled water or saline and injected intraperitoneally (IP) at the daily doses indicated. The animals were divided into three groups of 5 rats each. Two groups were injected either RbCl or CsCl, dissolved in distilled water, in a gradual dose buildup as shown in Figs. 1 and 2 with four days drug free period between the various dose regimens. The third group was injected three times at 48 hr intervals with a combination of RbCl and CsCl, 1.5 mEq/kg, IP, dissolved in distilled water.

The animals of the third group and a corresponding water drinking control group receiving saline injections were sacrificed 72 hr after final drug or saline administration. Their livers were quickly removed and processed for the determinations of alcohol-(EC 1.1.1.1) and aldehyde dehydrogenase (EC: 1.2.1.3) after the fractionations of their liver into mitochondrial-(MIT), for the ALDH assay, [2] and cytoplasmic fraction (CYT), for the ADH assay [3], as described in detail elsewhere [20]. Hepatic ALDH was also measured in the CYT fraction and protein determinations were made according to the biuret procedure. The activities of the enzymes are expressed as specific activity, nMol/min/mg protein, measured at pH 9.6 and 30°C.

In a separate set of experiments, similar groups of rats were tested on the effects of two injections of saline, RbCl or

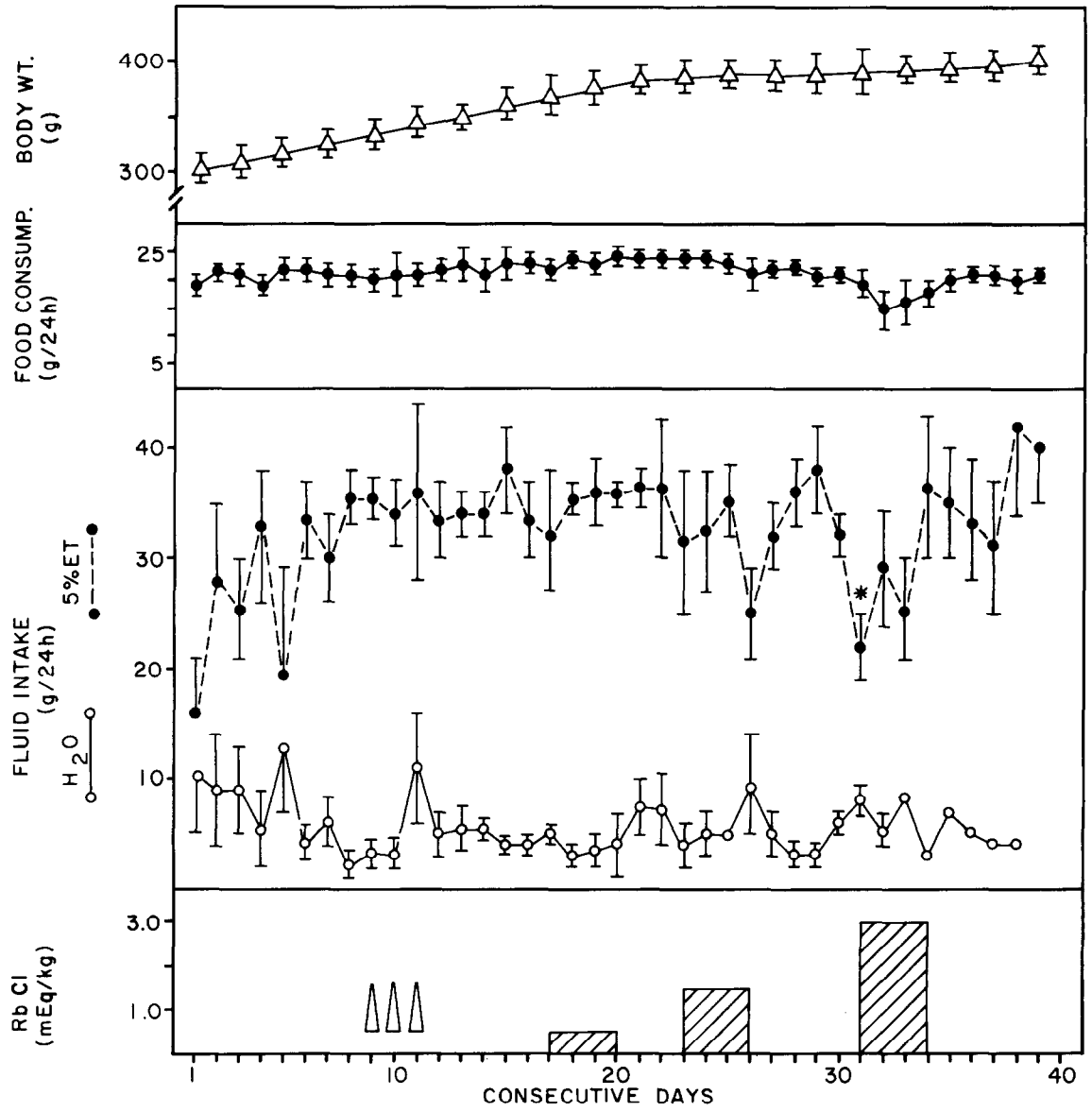

FIG. 1. The effect of graded daily doses of RbCl on voluntary intake of 5% ethanol (ET) solution by the rat. Means ± SE (n=5) of daily consumption of fluids and food (g/24 hr) and changes in body weights (g/48 hr) are plotted as function of time. Arrows indicate injection of saline. *$p<0.05$). Difference from mean base line value, obtained by averaging the daily intake of ET for the 4 day period preceding injection of RbCl (3.0 mEq/kg).

CsCl, dissolved in saline or water, 5.0 mEq/kg/day, for two days, on voluntary drinking of ET by the rat.

Student *t*-test for independent means was used for the statistical analyses of the results.

RESULTS

Figure 1 shows the relationships between RbCl dose and changes occurring in voluntary drinking of ET, water intake, food consumption and body weight of the animals. Administration of saline for three consecutive days, shown by the arrows, exerted little change on ET drinking by the rat. Repeated administration of RbCl, 0.5 mEq/kg/day for three days or 1.0 mEq/kg/day for three days, was not associated with marked changes in fluid and food consumption from predrug treatment period. Injection of RbCl, 3.0 mEq/kg, resulted in approximately 30% ($p<0.05$) reduction in ET intake from preceding treatment value. However, continued administration of this dose failed to maintain a significant decline in ET and food intake.

Figure 2 shows the effects of CsCl on voluntary intake of 5% ET solution by the rat. Saline injections, shown by the arrows, did not alter fluid or food consumption. Both initial doses of CsCl used, 0.5 mEq/kg and 1.0 mEq/kg, had no effects on the parameters measured. Administration of CsCl at 3.0 mEq/kg, IP, showed approximately the same degree of reduction in ET drinking as did the respective RbCl dose. However, this decrease was not statistically significant

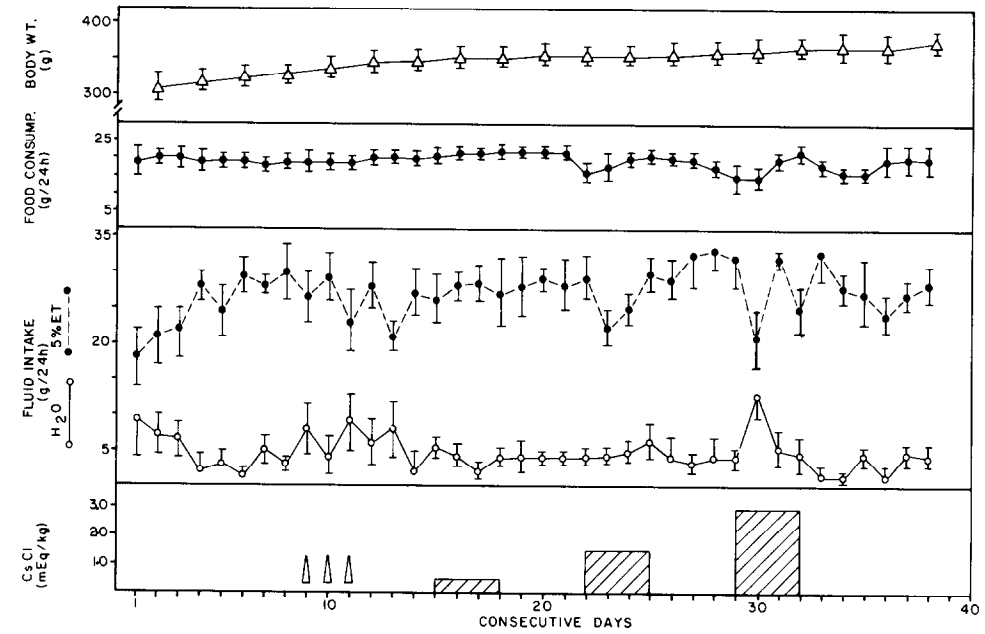

FIG. 2. The effects of graded daily doses of CsCl on voluntary intake of 5% ethanol (ET) solution by the rat. Means ± SE (n=5) of daily consumption of fluids and food (g/24 hr) and changes in body weights (g/48 hr) are plotted as function of time. Arrows indicate injection of saline.

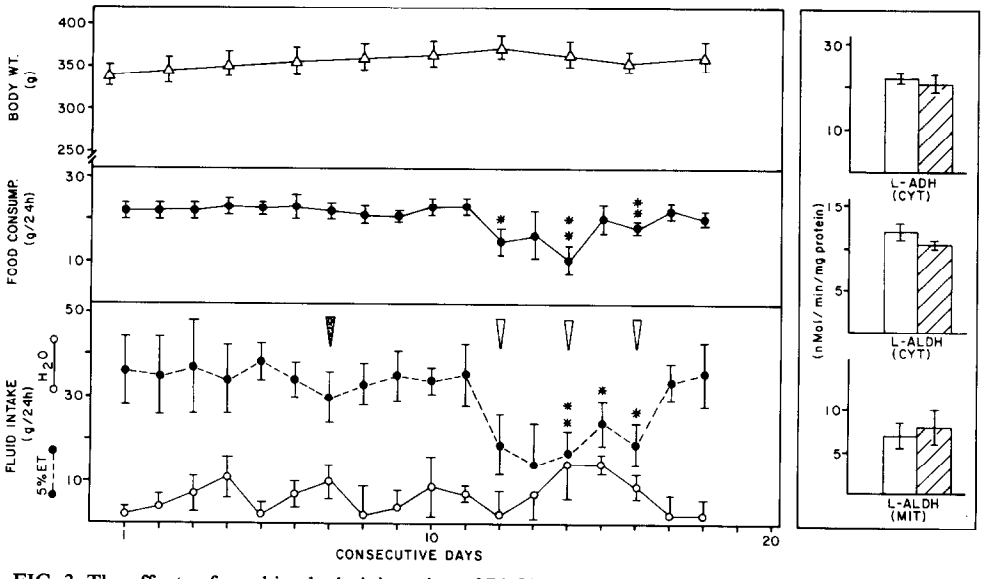

FIG. 3. The effects of combined administration of RbCl (1.5 mEq/kg, IP) and CsCl (1.5 mEq/kg, IP) on voluntary intake of 5% ethanol (ET) solution by the rat and their effects on specific activities of liver alcohol- (ADH) and aldehyde dehydrogenase (ALDH), nMol/min/mg protein. Means ± SE (n=5) of daily consumption of fluids and food (g/24 hr) and changes in body weights (g/48 hr) are plotted as function of time. Stippled arrow shows period of saline injection and open arrows indicate combined drug administration. The right panel shows the effects of combined administration of RbCl and CsCl on liver ADH, in the cytoplasmic (CYT) fraction, and ALDH, in the mitochondrial (MIT) and CYT fractions, derived from animals maintained on water □ or 5% ET ▨ as the drinking fluid. **($p<0.02$), *$p<0.05$). Differences from mean base line value, obtained by averaging 4 day period preceding combined drug trials.

TABLE 1

EFFECTS OF INJECTABLE VEHICLE ON RbCl- AND CsCl-PRODUCED ALTERATIONS ON 24 HR VOLUNTARY INTAKE OF ETHANOL (ET), WATER AND FOOD CONSUMPTION BY THE RAT

Injectable Vehicle	Drugs (5 mEq/kg)	% of base line (g/24 hr)* H_2O	ET	Food	(n)
Saline	RbCl	88.5 ± 15.2	78.2 ± 5.2†	72.7 ± 4.3†	(6)
	CsCl	97.0 ± 18.2	70.3 ± 4.3§	67.5 ± 3.2‡	(6)
Water	RbCl	89.7 ± 15.0	85.0 ± 9.2	92.0 ± 4.2	(5)
	CsCl	98.4 ± 12.3	80.1 ± 6.2†	91.0 ± 5.2†	(5)

*Results are for Mean ± SE of percent changes (g/24 hr) from baseline (=100%), obtained by averaging the daily intake of fluids and food consumptions for the 5 day period preceding drug trials. Alkali metals were dissolved in saline or distilled water and injected 5 mEq/kg, IP, once daily for two consecutive days. The results obtained for the 24 hr period following drug administration were compared with their respective base line values for the statistical evaluation of the data by Student *t* test for correlated means.

† ($p<0.1$).

‡ ($p<0.05$).

§ ($p<0.02$).

($p<0.1$). There was a moderate reduction in food intake without concomitant decrease in body weight during the 1 mEq/kg and the 3 mEq/kg dose regiments of CsCl.

Figure 3 summarizes the effects of combined administration of RbCl, 1.5 mEq/kg, IP, and CsCl, 1.5 mEq/kg, IP, on ET consumption and on hepatic ADH and ALDH activities in vivo. Saline injection, indicated by the stippled arrow on the left panel, was ineffective in altering the parameter measured. Combined administration of ineffective doses of Rb- and Cs-salts reduced ET intake by approximately 43% from pre-drug administration. A 51% ($p<0.02$) and 40% ($p<0.05$) reduction in ET drinking were evident after the second and third drug trials, respectively. Concomitantly, there was a marked and significant decrease in amounts of food consumed. There were no apparent changes in L-ALDH or ALDH as a consequence of simultaneous administration of RbCl and CsCl 72 hr post drug injection to rats maintained on water or ET.

Table 1 compares % changes in ET intake produced by alkali metal salts, 5 mEq/kg, IP, dissolved in saline with these changes occurring by identical doses of the corresponding salts but dissolved in water as the injectable vehicle. Administration of RbCl or CsCl, dissolved in salines was associated with a significant reduction in voluntary intake of ET for the 24 hr following drug administration compared to base line value. There was a marginal decrease in ET drinking following treatment with identical dose regimens of the salts used when distilled water was the injectable vehicle.

DISCUSSION

Indirect evidence suggests that electrolytes are involved in ET-produced alterations of neuronal cell membrane permeability and nerve-cell transmission which may be implicated in the mechanism of action of ET. Furthermore, it appears that Rb^+ and Cs^+ bear strong resemblance physiologically to K^+ and that there are metabolic interchangeabilities between Rb^+ and K^+ [1, 6, 7, 10, 24]. Alteration in extracellular ionic concentration of Cs^+ and Rb^+ also influence the resting potential in nerve and muscle preparation and the configuration of the electrocardiogram [23]. Thus, a relationship between Rb^+ and/or Cs^+ produced alteration in K^+ concentration in certain critical neuronal tissue and their effects on some of ET-mediated responses, is likely. It has been shown, that short-term administration of RbCl to mice resulted in the reduction of whole blood and brain [16,17] content of K^+. It seems likely, therefore, that the efficacy of Rb^+ and possibly Cs^+ in decreasing ET drinking may reside in their intracellular actions on K^+ and the resulting physiological alteration related to membrane excitability and/or in the regulation of Na^+ and K^+ pump, i.e., stimulation of neuronal K^+, Na^+-adenosine triphosphatase activity by Rb^+ and Cs^+ [25,29]. Furthermore, the potency of combined administration of ineffective separate doses of Rb- and Cs-salts in reducing voluntary intake of ET over water as the drinking fluid by the rat suggests a synergistic effect between Rb^+ and Cs^+ on the mechanism(s) underlying preference to ET drinking in the species studied. It should be noted, however, that administration of identical doses of alkali metal salts used resulted in variable potency on ET drinking depending on the vehicle used. For example, when saline used as the vehicle both RbCl and CsCl exerted greater effects than that produced by the same corresponding doses but with distilled water as the vehicle. Thus, suggesting of the relative importance of salt concentration as an experimental variable in this behavioral performance test. Furthermore, it remains to be determined if the observed reduction in food and fluid intake following administration of these salts may be indicative of their toxic manifestations.

There is little known on the precise mechanism of action of Cs^+. However, it is conceivable that the efficacy of Cs^+ in negating the ET effects studied may be ascribed to indirect cholinergic action. For example, cholinergic mechanism has been implicated in ET preference [9] and Cs^+, which appear to possess weak cholinergic property [30], increased ganglionic hyperpolarization produced by repetitive preganglionic stimulation which is attributed to acetylcholine release by Cs^+ from presynaptic nerve terminals [8].

In view of the renewed interest in Rb^+ and Cs^+ it is noteworthy that they may be associated with various disease states. For example, it has been reported that patients with rheumatoid arthritis [21] have elevated serum Cs^+ and re-

duced whole blood Cs^+ occurred in cancer patients from control subjects [31]. Furthermore, decreased serum Rb^+ and urinary Cs^+ excretion occurred 5 days after administration of chlorthalidone to hypertensive patients [28]. It is conceivable, therefore, that these alkali metal ions, particularly Cs^+, may provide a useful pharmacologic tool in probing into the managements of seemingly unrelated disorders, i.e., compulsive mood drinking behavior and extrapyramidal disorders. Recent preclinical results from our laboratory are suggestive for the unique pharmacologic properties of Cs^+ relative to tardive dyskinesia [19] and neuroleptics produced toxicity in experimental animals [18].

In conclusion, the present results strongly suggest the merit for further evaluation of Rb^+ and Cs^+ for their possible clinical trials in the management of and/or detoxification of the alcoholic patients especially these with recurrent affective disorders provided a shorter half lifetime and lower retention rate of Rb^+ and Cs^+ can be obtained.

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