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BRIEF COMMUNICATION

Alkali Metal Cations: Effects on Aggression and Adrenal Enzymes

BURR EICHELMAN, NGUYEN B. THOA AND JORGE PEREZ-CRUET

Division of Clinical and Behavioral Research, National Institute of Mental Health
9000 Rockville Pike, Bethesda, Maryland 20014

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EICHELMAN, B., N. B. THOA AND J. PEREZ-CRUET. *Alkali metal cations: effects on aggression and adrenal enzymes.* PHARMAC. BIOCHEM. BEHAV. 1(1) 121–123, 1973.–Alkali metal cations (lithium, sodium, potassium, rubidium and cesium) were given to rats on a chronic large dose schedule. Lithium depressed shock induced fighting, while potassium and rubidium facilitated this aggression. After chronic high doses of the alkali cations, all groups except the sodium treated group showed an elevation of the adrenal enzymes, tyrosine hydroxylase and phenylethanolamine-N-methyl transferase (PNMT).

Shock induced aggression Lithium Sodium Potassium Rubidium Cesium
Adrenal tyrosine hydroxylase Adrenal PNMT

THE ALKALI metal cations have long been implicated in neuronal metabolism and more recently in altering abnormal behavior. Proper sodium and potassium balance is essential for neuronal condition. Lithium has been used clinically to treat hypomanic states [10]. This study was designed to examine the effect of equal dose administration of the alkali metal cations on aggressive behavior in the rat. The behavioral model chosen was that of shock induced aggression. This model pairs two rats in a small enclosure and subjects them to inescapable footshock. The rats will attack each other by displaying species–specific aggressive and submissive postures. This is a form of irritable aggression [12] which has been previously used for neuroanatomical localization and pharmacological studies [6,8]. In this experiment, a high dose, chronic experiment, additional measurements of adrenal enzymes were made to evaluate the stress of the experimental paradigm and the similarity of an adrenal response to the changes in fighting behavior.

METHOD

The animals were 96 male Sprague-Dawley rats (200–250 g). The rats were housed separately with ad lib access to rat chow and water throughout the study. The shock induced fighting apparatus has been described previously [6]. Essentially it consisted of two Plexiglas boxes (32 x 25.5 x 30.5 cm) with stainless steel grid floors. Shock was delivered by a constant current source at 2 ma for a duration of 0.4 sec every 7.5 sec.

The rats were ear punched, randomly paired and then subjected to three days of testing for levels of shock induced aggression. Each test period consisted of delivering 50 footshocks to each pair of rats and counting the number of attack responses made. The criteria for an aggressive response have been previously described [6,8]. For each day an attack/shock percentage was calculated (the number of attacks divided by the number of shocks administered x 100). This daily percentage was then averaged over the three days to provide a baseline. Eight pairs served as naive controls and were not tested. Following the determination of the preinjection baseline level of fighting, the pairs were divided into five groups. Each group received twice daily (bid) IP injections of the chloride salt of one of the alkali metals in a concentration of 1.5 mEq/kg. Thus there were groups receiving respectively LiCl, NaCl, RbCl, and CsCl. The animals were tested intermittently from the third to the 26th day for levels of shock induced fighting. The four final tests (on the 16th, 18th, 23rd, and 26th days of injection) were averaged to provide a chronic drug mean level of shock induced aggression for each group. This was compared with the baseline levels, again by a matched pair *t*-test, two-tailed. The Rb treated group was tested for mouse killing during the third week of injections in a manner previously described [4,7]. At the termination of the experiment, the animals were injected with labeled tyrosine for brain amine studies reported in part elsewhere [9]. The adrenal glands were rapidly removed and the adrenal levels of tyrosine hydroxylase and PNMT were assayed according to the methods of Nagatsu, Levitt, and Udenfriend [13] and Axelrod [2].

RESULTS

The following numbers of pairs were eliminated from each group due to respiratory illness or death: Li-1; Na-1; K-2; Rb-2; and Cs-3. The rats in the lithium group had marked polydipsia, polyuria, and diarrhea. All except the Na group showed increased vocalizing and struggling when injected. Rats in both the K and Rb groups frequently developed ventricular fibrillation following injection which was usually reversed by transient chest massage. The Cs group developed alopecia and periodic bloody diarrhea. A marked increase in irritability occurred in the Rb treated group. After two days this group vocalized during injection more than the other groups. By the seventh day of injection, this group demonstrated a syndrome similar to the septal syndrome described by Brady and Nauta [3]. These rats would vocalize and overreact to external stimuli. They would jump from a partially opened cage, or jump in response to a puff of air. They would vigorously attempt to bite the handler or any foreign object which touched them. However, they did not begin to spontaneously kill mice, nor did they fight spontaneously when housed together. Further, this rage syndrome appeared a full week prior to the increase in shock induced aggression noted below.

Levels of shock induced aggression were altered in both directions. Lithium lowered fighting. Rubidium and, to a lesser degree, potassium facilitated shock induced fighting (Table 1). Cesium slightly depressed fighting, but the change was not statistically significant ($0.1>p>0.05$).

Both adrenal enzymes were markedly increased over naive controls in all groups except the Na treated group (Table 2). The Li, K, Rb, and Cs groups all had significantly elevated levels of adrenal tyrosine hydroxylase and PNMT. These levels increased regardless of whether shock induced aggression increased or decreased.

DISCUSSION

This study replicates the decrease in shock induced aggression after lithium salts as reported by Sheard [16]. That study, however, used a much higher, nearly toxic dose of 5 mEq/kg of LiCl. The same effect can be achieved by more moderate drug doses.

The increase in aggression with Rb replicates the study by Stolk *et al.* [18]. However, we utilized a higher dose and a more chronic dose schedule to elicit the behavioral changes. Once these developed, they were unequivocal.

The early onset in the Rb group of the hyperirritability which preceded the facilitation of shock induced aggression might argue that these behaviors are separate. This has been suggested previously by Ahmad and Harvey [1] regarding the septal syndrome and the facilitation of shock induced aggression after septal lesions, since the abatement of these two behaviors follows different time courses.

The lack of change in adrenal enzymes in the Na treated group compared with naive controls suggests that the experimental paradigm was not, in itself, stressful enough to induce adrenal enzyme changes, in contrast to such procedures as immobilization [11]. This also suggests that the hypertonicity of solutions was insufficient to induce adrenal enzyme changes. In contrast, all ions which altered behavior and general body ionic balance elicited an increase in adrenal enzymes. This increase was not correlated with changes in aggression.

As reported elsewhere, however, changes in brain amine turnover are differentially affected by the alkali metal cations [9]. Lithium appears to increase norepinephrine deamination and decrease the availability of functional norepinephrine [15] while rubidium increases norepinephrine turnover [9] facilitating norepinephrine's conversion to normetanephrine products [19]. Functionally, in terms of brain norepinephrine these two ions have converse biochemical effects. The behavioral effects on aggression are also converse. In contrast, cesium appears to alter serotonin metabolism [14] but does not alter shock induced aggression. This is also true with parachlorophenylalanine, which alters serotonin synthesis but fails to alter shock induced aggression [5,7]. Thus, the alkali metal cations appear to affect central catecholamine metabolism in differing ways and are correlated with differing behav-

TABLE 1

CHANGES IN ATTACK SCORE FOLLOWING ALKALI METAL CATIONS: CHRONIC DOSE

Drug (1.5 mEq/kg/bid)	Number of Pairs	Predrug M Days 1–3	Drug M After 15 Days	Difference in % Attacks
Li^+	7	36.9	29.9	−7.0*
Na^+	7	27.0	26.4	−0.6
K^+	6	30.3	41.7	+11.4*
Rb^+	6	17.4	40.4	+23.0†
Cs^+	5	20.0	12.3	−7.7

*$p<0.05$
†$p<0.01$

TABLE 2

EFFECT OF ALKALI METAL CATIONS ON ADRENAL ENZYMES

Group	Tyrosine Hydroxylase mμM DOPA/ Pair Adrenal Gland/Hr	%	PNMT mμM End Product/ Pair Adrenal Gland/Hr	%
Control (15)	219 ± 7.73	100	119 ± 3.11	100
Li^+ (14)	398 ± 16.70‡	182	146 ± 3.82‡	123
Na^+ (15)	236 ± 8.18 (N.S.)	108	126 ± 2.05 (N.S.)	106
K^+ (12)	302 ± 11.46‡	138	132 ± 3.59†	111
Rb^+ (11)	332 ± 11.79‡	152	142 ± 4.12‡	119
Cs^+ (4)	313 ± 23.43‡	143	135 ± 5.84*	113

*$p<0.05$ *t*-test experimental group vs control
†$p<0.02$
‡$p<0.001$
Note: Drug dose in all cases was 1.5 mEq/kg, bid, IP for 32 days of the chloride salt.

ioral characteristics, while their effect on adrenal medullary enzymes is uniform.

This study should add further support for clinical trials of lithium in aggressive states [17]. The clinical use of rubidium should be carefully weighed, in view of its effect on irritability and aggression and its risk of inducing cardiac arrest.

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