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BRIEF COMMUNICATION

Alkali Metal Cations: Effects on Isolation-Induced Aggression in the Mouse[1]

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EICHELMAN, B., E. SEAGRAVES AND J. BARCHAS. *Alkali metal cations: effects on isolation-induced aggression in the mouse.* PHARMAC. BIOCHEM. BEHAV. 7(4) 407–409, 1977. – Alkali metal cations were given in varying doses over 14 days to CF–1, male mice, isolated for 4 weeks prior to testing for isolation-induced fighting. Lithium and cesium in doses of 4.5 and 6.0 meq/kg reduced the duration of isolation-induced aggression in a 15 min test period when compared with controls. Toxicity was evident in the cesium-treated, but not the lithium-treated mice. No enhancement of aggression was seen in the rubidium-treated group.

Isolation-induced aggression Lithium Sodium Potassium Rubidium Cesium

LITHIUM and rubidium alter aggressive behavior in animals [3, 5, 6, 9] and man [7,11]. This study was carried out to observe the effect of the alkali metal cations on isolation-induced fighting in mice.

EXPERIMENT 1: ALKALI METAL CATIONS, 3 meq/kg/da

Method

Animals. The animals were 102 male CF–1 mice, 30 days old (Carworth Farms, NY). Upon arrival they were individually housed in cages (26 × 16 × 12 cm) with unlimited food and water.

Apparatus. At the time of behavioral testing, the mice were fought in cages of size identical with their home cages. However, the test cage for each pair was a fresh, clean cage different from either mouse's home cage.

Procedure. After 14 days of individual housing, the mice were randomly divided into five groups of ten pair each, plus one group of 11 pair. Each group was then treated for 14 days (1.5 meq/kg, IP, bid) with one of the following cation solutions: LiCl, KCl, RbCl, or CsCl. At the end of these 14 days, the mice were paired for 15 min in a test cage and the total time of isolation-induced fighting in the 15 min period was cumulatively recorded. Groups were compared by a one-way analysis of variance.

Results

Ten mice died during the injection period, particularly in the potassium-treated group, leaving group size as indicated in Table 1. These deaths occurred throughout the 14 days, usually following injection. These deaths appeared to be related to intra-abdominal venous injection of drug and consequent cardiac arrhythmia. Although there was a noticeable difference between groups, the variance of each group was extremely large. Consequently, analysis of variance between groups was not significant, $F(4,40) = 1.62$.

EXPERIMENT 2: LITHIUM, RUBIDIUM AND CESIUM – LARGER DOSES

Since previous studies in mice [10,13] had reported decreased fighting with lithium, and since rubidium facilitated shock-induced fighting in the rat [3, 5, 9], an enlarged dose curve was carried out with lithium, rubidium, and cesium, utilizing uninjected and sodium-injected mice as controls.

Method

Animals. The animals were 210 male CF–1 mice, 30 days old (Carworth Farms, NY), housed as in Experiment 1.

Apparatus. This was the same as in Experiment 1.

Procedure. Due to limitations of housing, this study was carried out in two parts. In the first portion of the study, 100 mice were isolated for 14 days, then randomly divided into treatment groups as follows: (1) uninjected; (2)

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TABLE 1

ISOLATION-INDUCED AGGRESSION IN MICE: ALKALI METAL CATIONS (1.5 meq, IP, bid × 14 DAYS)

Cation	N (pr)	Time Fought (in 15 min observation)
Li^+	9	8.8 ± 4.4 (s)
Na^+	9	35.8 ± 17.1 (s)
K^+	7	24.6 ± 9.7 (s)
Rb^+	11	51.1 ± 14.5 (s)
Cs^+	9	22.9 ± 12.7 (s)

NaCl-injected (3.0 meq/kg, bid; (3) LiCl-injected (1.5 meq/kg/da); (4) LiCl-injected (1.5 meq/kg, bid); (5) LiCl-injected (3.0 meq/kg, a.m. and 1.5 meq/kg, p.m.); and (6) LiCl-injected (3.0 meq/kg, bid). All injections were given IP for 14 days and were of equal volume. After the 14 days of treatment, the mice were paired and fought as in Experiment 1.

In the second portion of this experiment, 110 mice were isolated for 14 days and then divided into the following groups: (1) uninjected controls; (2) NaCl-injected (3.0 meq/kg, bid); (3) RbCl-injected (4.5 meq/kg/da); (4) RbCl-injected (3.0 meq/kg, bid); (5) CsCl-injected (4.5 meq/kg/da); and (6) CsCl-injected (3.0 meq/kg, bid). Again, injections were of equal volume and given IP for 14 days. After this treatment, the mice were weighed and fought as previously described.

Since there can be seasonal variability in biogenic amine levels in mice [12] which might alter control levels of fighting, the two halves of the uninjected and NaCl control groups were compared statistically. Following this, the uninjected and NaCl groups were compared statistically. Lastly, with the uninjected and NaCl group as controls, the data were evaluated by analysis of variance across all groups. Due to a six-month interval between Experiments 1 and 2, no attempts were made to pool data from these two experiments.

Results

Animal losses during the course of the study were evenly distributed across groups with the exception of the cesium-treated groups. Twelve of the 18 mice in the 4.5 meq/kg/da group survived and only six of the 18 mice in the 6.0 meq/kg/da group survived. The cesium-treated rats appeared toxic, with unkempt fur and some rectal bleeding. No other group appeared toxic. No group was significantly different from controls in body weight at the termination of the experiment.

There was no statistical difference by *t*-test between the uninjected groups or the NaCl-injected control groups of the first and second halves of the experiment. The combined mean fighting times of the two groups were 121.1 ± 13.5 s for the uninjected controls and 91.0 ± 18.2 for the NaCl controls. These values were not significantly different and were pooled as the control group. The mean control value of the combined groups was 102.2 ± 10.3. This control group, the four LiCl groups, the two RbCl groups and the two CsCl groups (see Table 2) were compared by one-way analysis of variance. There was a significant difference across groups in spite of the large group variances, $F(8,75) = 2.11$, $p<0.05$. Individual comparisons between treatment groups and the control groups demonstrated a significant decrease in fighting in the LiCl groups treated with 4.5 and 6.0 meq/kg/da (*t*-test, two-tailed, $p<0.02$). There was no significant difference in fighting time with the lower doses of LiCl or the RbCl groups. The CsCl groups showed decreased fighting times in both the 4.5 and 6.0 meq/kg/da groups ($p<0.05$ and 0.025, respectively).

DISCUSSION

This study appears to corroborate the reports of Weischer [13] and Tadano [10] showing that lithium inhibits aggression in the mouse. However, the doses required are higher than those which inhibit shock-induced fighting in the rat [3,5]. The effect of cesium cannot, in this study, be considered behavior-specific as the mice in these groups appeared toxic. There was no facilitation of aggression observed with rubidium. This is in marked contrast to the facilitation of irritability and shock-induced fighting observed in the rat [3, 5, 9]. Disparity in effects of drugs and brain lesions between the mouse and rat models of aggressive behavior has been observed before. Rats sustaining septal lesions demonstrate increased levels of

TABLE 2

CUMULATIVE SECONDS FOUGHT IN 15 MIN TEST

Dose	0 meq/kg	1.5 meq/kg	3.0 meq/kg	4.5 meq/kg	6.0 meq/kg
Group Control	106.6 ± 11.4 (n = 29)				
Li^+		87.9 ± 13.4 (n = 8)	93.4 ± 23.1 (n = 8)	44.7 ± 13.9† (n = 7)	43.9 ± 14.4† (n = 8)
Rb^+				97.4 ± 31.8 (n = 8)	84.8 ± 23.3 (n = 7)
Cs^+				47.8 ± 29.0* (n = 6)	19.5 ± 10.4* (n = 3)

*$p<0.05$ *t*-test, two-tailed comparison with control.
†$p<0.02$.

shock-induced fighting [2], while septal-lesioned mice show decreased isolation-induced fighting [8]. Rats treated with 6-hydroxydopamine, intraventricularly, show increased shock-induced fighting [4], while mice similarly treated show decreased fighting [1]. These contrasting effects strongly suggest that different neural systems may be critical in the facilitation or inhibition of these different aggressive paradigms in the rat and mouse.

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