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EFFECTS OF CHRONIC LITHIUM AND RUBIDIUM ADMINISTRATION UPON EXPERIMENTALLY INDUCED CONFLICT BEHAVIOR

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Abstract

1. Chronic treatment of rats with lithium chloride produced a significant reduction of shock induced suppression of feeding behavior (passive avoidance) in the rat.
2. Rubidium chloride, on the other hand, caused additional suppression of feeding under the same conditions.
3. These results suggest that two drugs may affect anxiety processes in opposite directions, and this may be of clinical significance.

Keywords: anxiety, lithium, passive avoidance, rubidium

Introduction

Salts of the alkali metal lithium (Li) have been shown to be of considerable therapeutic benefit both in the treatment of acute episodes of mania (Baldessarini and Lipinski, 1975; Bunney *et al.*, 1968; Johnson *et al.*, 1968; Platman, 1970) and in the prophylactic control of bipolar affective disorder (Angst *et al.*, 1970; Baastrup *et al.*, 1970; Prien *et al.*, 1974). Rubidium (Rb), a related ion of the same chemical series has been shown to have generally contrasting behavioral, biochemical, and neurophysiological effects in comparison to lithium (Bond and Jenner, 1974; Carroll and Sharp, 1971; Edelson *et al.*, 1976; Fieve *et al.*, 1973; Meltzer *et al.*, 1969; Tehrani *et al.*, 1974; Stolk *et al.*, 1970), and based largely upon the clinical efficacy of the latter, Rb has been proposed as a potentially useful antidepressant (Fieve *et al.*, 1973; Carroll, 1971).

Given the current and potential uses of Li and Rb in the treatment of affective disorders a full understanding of the effects of these drugs upon hedonic processes (i.e. reward and punishment) is of considerable practical and theoretical importance. The present report examines the effects of both lithium and rubidium upon behavior suppressed by punishment. The passive avoidance paradigm has been used extensively as a preliminary index of a drug's potential to alter anxiety states and drugs which reduce the suppressive effects of punishment, e.g. the benzodiazepines and other minor tranquilizers have been shown to be clinically effective anxiolytic agents (Cook and Sepinwall, 1975; Rech and Moore, 1971). For the above reason we tested the effects of both ions upon passive avoidance.

Methods

Subjects were thirty-six experimentally naive adult male Sprague Dawley rats (250–500 g), housed individually and maintained upon standard day/night cycles of 12 hr each. All subjects were initially exposed to a drinking tube containing sweetened milk (Borden's Eagle Brand, diluted 1 part milk to 2 parts tap water) in a standard plexiglass test chamber (Scientific Prototype A-100) for ten daily sessions of 15 min each. Based upon day 10 drinking latency (i.e. time from introduction into the apparatus until initial oral contact with the drinking tube) subjects were divided into four matched groups of nine subjects each. Groups 1 and 2 served as unshocked and shocked control groups, respectively, and received neither Li or Rb. Group 3 received Li in their food (as lithium chloride 120 mEq/kg Purina lab chow) and a supplement of sodium (as sodium chloride, 0.15 M in their drinking water) to minimize the sodium loss that normally occurs with prolonged Li administration (Olesen and Thomsen, 1974; Thomsen and Olesen, 1974). Group 4 received Rb (as rubidium chloride 0.02 M) in their drinking water. Drugs were administered for 7 days prior to the reinstitution of testing. During this time subjects were kept in their home cages without access to the milk reinforcement. On the eighth

day of drug administration all subjects were retested for drinking latency. All subjects, except group 1, the unshocked control, were allowed to consume 1 ml of sweetened milk and were then immediately shocked on their paws with a 3 sec 0.5 mA scrambled shock (Leaf and Muller, 1965; Masserman and Yum, 1946). All subjects were then removed from the apparatus and returned to their home cages (group 1 was also removed after the daily consumption of 1 ml of milk). Testing for drinking latency continued for 3 days, with the shock contingency and drug regimens in effect throughout. If a subject failed to consume 1 ml in 15 min it was returned to its home cage unshocked, and a latency of 900 sec was recorded for the daily session. At the conclusion of testing all subjects were sacrificed by decapitation and their blood collected and immediately centrifuged for determination of serum Li and Rb levels, on a Perkin Elmer 305B Atomic Absorption Spectrophotometer.

Results

Unshocked subjects showed essentially stable performance, while in comparison shocked control rats showed an expected increase in drinking latency. Day 1 performance for this group was 23 ± 0.4 sec and this increased to 445 ± 115.0 sec by day 4. The group receiving Li showed attenuated passive avoidance in comparison with the shocked controls, while the Rb-treated group showed increased conflict in this same task (Fig. 1). Since visual inspection revealed a trend for group means to vary with their respective standard deviations all scores were log transformed to more nearly equate variances prior to any analysis of the data (Dixon and Massey, 1969). All scores were then subjected to a 2 factor mixed-design repeated measures analysis of variance (Dixon and Massey, 1969; Brunning and Kintz, 1968). F scores from this analysis revealed significant effects of trials ($F_{3,96} = 21.1$; $p < 0.01$), conditions ($F_{3,32} = 19.5$; $p < 0.01$) and interaction ($F_{9,96} = 4.48$; $p < 0.01$). In addition, Duncan's Multiple Range tests revealed significant differences between both drug treatments and the shocked control group (ranges for Li and Rb = 2.2 and 2.1 respectively, critical range - 2.0 at $p < 0.05$). Li did not differ significantly from an unshocked control with this same test (range = 0.7, $p > 0.05$). At the close of the experiment average serum Li concentrations were 0.45 ± 0.04 mEq/l and serum Rb concentrations were 1.3 ± 0.1 mEq/l.

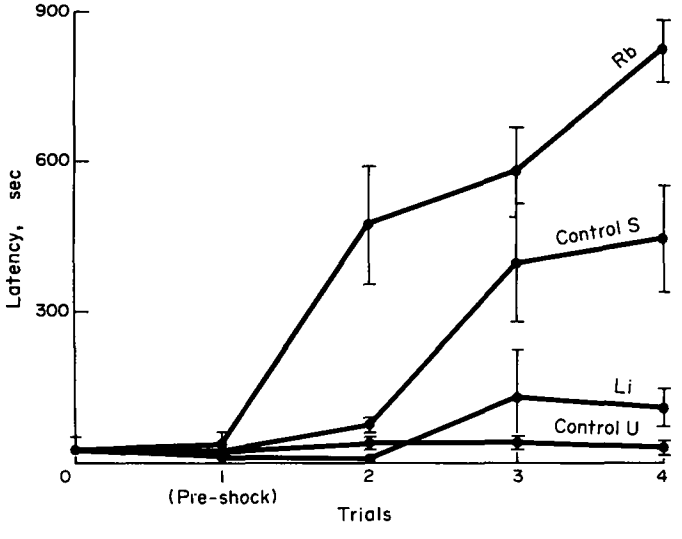

Fig. 1. Effects of Lithium and Rubidium upon experimentally induced conflict behavior (all results as means ± standard errors). Rb = Rubidium; S = Shocked Control; Li = Lithium; U = Unshocked Control.

Discussion

The present findings indicate potentially important effects for both Li and Rb at a clinical level. On the one hand, Li has benzodiazepine-like conflict reducing capacity that may point to a fundamental anxiolytic potential for this drug. Although few clinical data are available regarding this point it is our clinical impression that prolonged Li does reduce subjective anxiety in patients suffering from manic-depressive illness. While some apparently variant data have been reported (Lackroy and Van Praag, 1971) these data were based upon an acute administration schedule and the assessment of state (acute) rather than trait anxiety. Either of the latter two circumstances might contribute towards negative findings.

Finally, it might also be noted that chronic Rb produced increased conflict in the present design. The fact that Rb produced an effect opposite to that of Li is consistent with other studies in which these two ions also acted in a manner opposite to each other (Bond and Jenner, 1974; Carroll and Sharp, 1971; Edelson *et al.*, 1976; Fieve *et al.*, 1973; Meltzer *et al.*, 1969; Tehrani *et al.*, 1975; Stolk *et al.*, 1970). Given lithium's clinical efficacy in the control of manic states it is possible that Rb may be a useful antidepressant. Since the antidepressant drug combination of a monoamine oxidase inhibitor with 5-hydroxytryptophan (Carroll, 1971; Glassman, 1969) is reported to have the same effect as rubidium on passive avoidance behavior (Wise *et al.*, 1970), this lends further support to the possible antidepressant potential of rubidium.

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