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Lithium reduces preference for ethanol induced by hypothalamic stimulation

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Ho & Tsai (1975) have reported that treatment with lithium reduced the preference for dilute solutions of ethanol displayed by rats that had limited experience with ethanol. Lithium would be valuable clinically if it could reduce the consumption of ethanol by organisms with a history of persistent self-administration. We therefore decided to examine the effects of lithium on the chronic preference for concentrated solutions of ethanol established by hypothalamic stimulation in rats (Amit, Stern & Wise, 1970; Amit & Stern, 1971; Corcoran & Amit, 1974).

Eighteen adult male Wistar rats (Canadian Breeding Farms) with a monopolar stainless steel electrode implanted in the left lateral hypothalamus were housed individually in stainless steel cages with free access to food. Fluids were available in two calibrated glass Richter tubes (Kimax), containing either tap water or varying concentrations of 95 % ethanol diluted with tap water to form solutions of the desired concentration (v/v). The positions of the tubes containing water and ethanol were alternated to prevent the development of a position habit. The aversive cutoff concentration of ethanol was determined for each rat with the method of Amit & others (1970); these concentrations ranged from 10 to 19 % (v/v) in different rats, with a mean of 13·7 %. Following the procedure of Amit & others (1970), ethanol solutions were available on even-numbered days, with water available at all times. For the first 30 days of the experiment, ten of the rats received 30 min of daily hypothalamic stimulation according to Amit & Stern (1971). The schedule of stimulation was discontinued on day 31 and the ethanol intake of all rats was examined without further intervention until day 170. Beginning on day 171, a day in which only water was available, all rats received twice-daily intraperitoneal injections of lithium chloride at a dosage of 0·3 m equiv kg^{-1} (Ho & Tsai, 1975); according to Ho & Tsai, this dosage of lithium results in plasma concentrations of approximately 0·2 m equiv $litre^{-1}$. The injections were given at 12 h intervals. After 10 days (5 days of ethanol presentation), the dosage of lithium was raised to 0·6 mequiv kg^{-1}, which was administered for 6 additional days (3 ethanol days). To control for the possibility that the effects of lithium on ethanol consumption were due to the stress of the injections rather than to the lithium itself, a control group of 8 additional rats was prepared after the original experiment was completed. These rats had developed a preference for ethanol after a schedule of hypothalamic stimulation, and were treated in the same manner as above except that they received twice-daily injections of isotonic saline instead of lithium chloride. The data were analysed with one-way analysis of variance for repeated measures and, when post-hoc comparisons were justified, the Scheffe test (Ferguson, 1966).

For the purposes of this experiment, preference for ethanol was defined as intake greater than 65 % of total in a choice with water. At the time injections of lithium began, 10 of 10 rats subjected to hypothalamic stimulation had developed a consistent preference for ethanol, whereas 4 of 8 non-stimulated rats preferred ethanol to water. Administration of lithium produced a significant reduction ($P < 0.05$) in intake of ethanol, as shown in Fig. 1A and B. The reduction in ethanol intake was evident with the lower dosage of lithium (0·3 m equiv kg^{-1}), and subsequent doubling of the dosage of lithium not only failed to produce a further reduction in intake of ethanol, but actually seemed to result in a slight increase in intake. As can be seen in Fig. 1A, the reduction in intake of ethanol was not due to a nonspecific depression of drinking, because it was compensated for by a significant increase in intake of water. Repeated intraperitoneal injections of saline had no effect on the control group's intake of ethanol, indicating that the effects of the lithium injections were not due to the stress of the injections *per se*.

There were marked individual differences in the responses of the rats to lithium, in that the rats with a long-standing preference for ethanol were least affected by lithium, whereas a greater depression of intake was observed in the rats that did not prefer ethanol or had developed a preference only recently. For example, the 10 rats most affected by lithium (i.e., a significant reduction in intake of ethanol on at least 5 of the 8 drug sessions) had preferred ethanol for a mean of 20·6 of the 50 sessions preceding treatment with lithium, whereas the 8 least-affected rats had preferred ethanol

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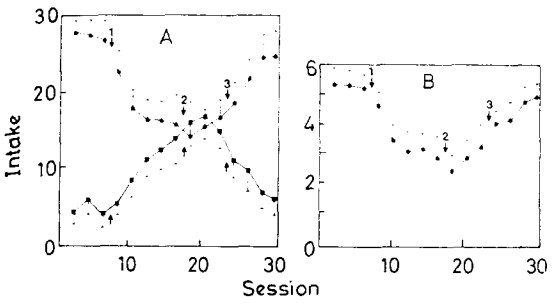

FIG. 1.A. The effect of administration of lithium on the mean oral intake (ml) of ethanol and water. Vertical bars represent s.e.m. The first arrow indicates the start of twice-daily lithium chloride injections (0·3 m equiv kg^{-1}, i.p.): the second arrow indicates a doubling of the dose (0·6 m equiv kg^{-1}); and the third arrow indicates the termination of the lithium chloride treatment. ●—● Ethanol, ■—■ water.

B. The effect of lithium treatment on the mean absolute intake (g kg^{-1}) of ethanol. The significance of arrows is as explained in A.

for a mean of 40·2 of the previous 50 sessions. This difference between the groups was significant ($P < 0.05$). The rapid recovery of ethanol intake that occurred after termination of the injections of lithium (Fig. 1) indicates that the effects of lithium were not the result of a learned avoidance of ethanol due to the association of its taste with the punishing or illness-producing effects of lithium (e.g., Garcia & Ervin, 1968; Nachman, 1970), because a learned aversion would persist even in the absence of the drug.

These results are consistent with the report of Ho & Tsai (1975) that parenteral treatment with lithium reduces the oral intake of ethanol in rats, and that cessation of treatment with lithium is followed by a rapid recovery of intake to pretreatment levels. It may be significant, however, that the magnitude of the reduction we observed was considerably less marked than that reported by Ho & Tsai (1975). Several factors could account for this difference: For example, most of our rats displayed a strong preference for concentrated ethanol solutions; the subjects of Ho and Tsai (1975) on the other hand, were in general offered weaker concentrations of ethanol, and did not consistently prefer ethanol to water (see Fig. 1A of Ho & Tsai, 1975). Another difference between the studies is that many of our rats developed a preference for ethanol after a schedule of hypothalamic stimulation, which may have made them more resistant to the effects of lithium. A third possibility is that the advanced age of our rats or their long experience with ethanol may have attenuated the effects of lithium; in contrast to our study, Ho & Tsai (1975) used younger rats that were exposed to ethanol for a short time. We favour the possibility that the duration of the preference for ethanol is an important variable, because we observed the most marked effects of lithium in the rats that either did not prefer ethanol or had only begun doing so shortly before the period of treatment with lithium. If chronic consumption of ethanol can attenuate the effects of lithium upon ethanol consumption, the value of lithium as a therapeutic agent for clinically treating chronic alcoholism may require further investigation.

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