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Lithium Effects on Adjunctive Alcohol Consumption. I: Comparison With Adjunctive Water Consumption

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HINES, G. *Lithium effects on adjunctive alcohol consumption. I: Comparison with adjunctive water consumption.* PHARMACOL BIOCHEM BEHAV **25**(6) 1159–1162, 1986.—Chronic administration of lithium chloride (20 mEq/l, in drinking water) produced an earlier onset of the adjunctive consumption of both water and alcohol. Terminal consumption levels, however, were unaffected by either lithium or the liquid available for consumption. The rate of increase, once drinking was initiated, was slower for lithium subjects than it was for controls. Under extinction conditions, adjunctive alcohol consumption showed no evidence of decline for either lithium or control subjects. Water consumption by control subjects did decrease considerably as a result of extinction. Subjects receiving lithium, however, maintained their intake of water at terminal adjunctive drinking levels.

Lithium Alcohol Water Adjunctive drinking Acquisition Extinction

THE administration of lithium salts has been found to have some efficacy in the treatment of alcoholism [12, 14, 20]. Investigations of the effects of lithium administration on voluntary alcohol intake by animals have generally supported this finding. Specifically, lithium reduces alcohol intake under free-choice conditions [1], even when the alcohol concentration used is one which is ordinarily preferred over water [18]. Perhaps more relevantly, lithium administration produces a reduction in alcohol consumption by subjects who have developed a chronic dependence on alcohol [9].

Not yet investigated is the degree to which the chronic administration of lithium might influence the initial acquisition of alcohol consumptive behaviors, a question of some importance in light of lithium's effectiveness in the treatment of manic disorders [16], conditions which are often accompanied by high levels of alcohol consumption [19]. One method of producing alcohol self-administration in rats is through the use of adjunctive, or schedule-induced, procedures [5]. This procedure establishes alcohol as a relatively potent reinforcer [13], and can result in alcohol intake levels that are sufficient to produce physical dependence [5].

Initial attempts (Hines, unpublished results) to compare lithium's effects on the acquisition of adjunctive alcohol consumption under conditions in which both water and alcohol were concurrently available to the subject were largely unproductive, since the adjunctive drinking that occurred in all instances involved water consumption. The selectivity of the adjunctive drinking behavior occurred even with those subjects who had shown a clear initial preference for the alcohol solution offered as an alternative to the available water. The present experiment, then, was designed to assess lithium's effect on adjunctive alcohol consumption under conditions in which no choice was offered to the subject. These results were then compared with lithium's effects on adjunctive water consumption.

METHOD

Subjects

Twenty-eight male Holtzman albino rats, approximately 90 days of age, were randomly assigned to one of four groups (N=7). All subjects were housed in standard (24 cm long × 18 cm wide × 18 cm high) suspended cages, with free access to water and access to food (Purina Laboratory Chow) sufficiently limited to produce 85% free-feeding body weights. Fourteen of the subjects (Groups Li/Et and Li/TW) received lithium chloride (LiCl) in their home cage drinking water, at a concentration of 20 mEq/l. The remaining 14 subjects (Groups C/Et and C/TW) received tap water in their home cages. An 0700–1900 hours light-on schedule was operating in the housing room.

Apparatus

Testing was performed in a Grason-Stadler Model 1111 rat operant chamber, with the levers and stimulus lights removed, and the spaces covered with stainless steel. The operant chamber was housed in a Grason-Stadler Model 1101 research chest, with an exhaust fan providing 67dB masking noise. A water bottle was mounted on the entry door, with the drinking spout protruding at a right angle to the food magazine, 12.5 cm to the right of the magazine and 6 cm above the floor. For subjects in the Li/Et and C/Et groups,

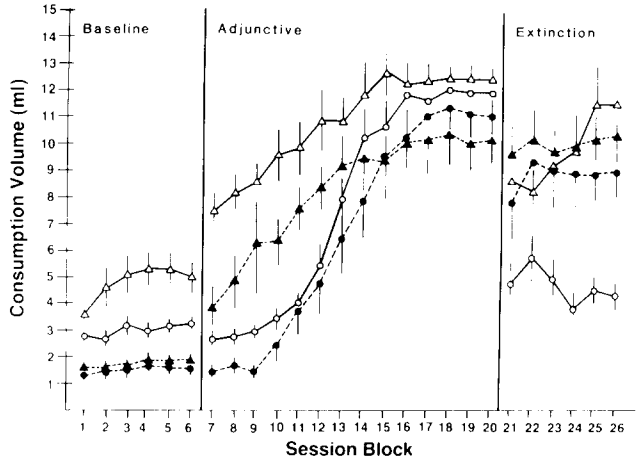

FIG. 1. Mean volume (ml) solution consumed across session blocks. Open triangles=Li/TW; open circles=C/TW; closed triangles=Li/Et; closed circles=C/Et.

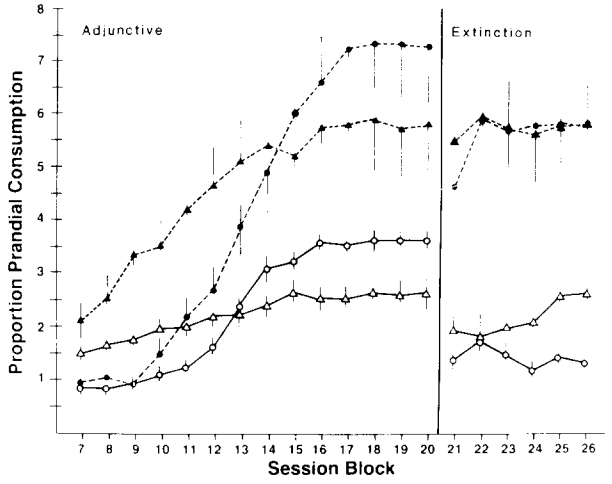

FIG. 2. Proportion of prandial consumption levels: adjunctive acquisition and extinction phases. Open triangles=Li/TW; open circles=C/TW; closed triangles=Li/Et; closed circles=C/Et.

the bottle contained a 10% (v/v, mixed from 95% ethanol) alcohol solution; for the subjects in the Li/TW and C/TW groups, the bottle contained tap water.

Procedure

Testing was initiated after the subjects had been exposed to the lithium and deprivation schedules for 15 days. For the first nine sessions (sessions occurred daily, and were 42 min in duration) the subjects were placed in the chamber with the appropriate liquid present, but food was neither present nor delivered—a procedure which allowed for determination of baseline consumption levels. Next, to determine the effects of prandial thirst on consumption, there were nine sessions in which 28 food pellets (45 mg Noyes) were placed in the food magazine at the start of the session. For the next 42 sessions, one 45 mg food pellet was delivered to the organism every 90 sec, independently of the organism's behavior (an FT90 sec schedule). Finally, there were 18 sessions in which the liquid was available, but food pellets were not delivered. This last, procedure allowed an analysis of the degree to which the drug and/or the adjunctive consumption liquid used influenced the extinction of an established drinking pattern.

At the termination of the study, each subject was sacrificed at its usual testing time, and its serum lithium determined by flame photometry [2] using an IL Model 253 spectrophotometer.

The results for each subject (ml consumed per session) were collapsed into means of three-day blocks, and statistically analysed using a Drug × Liquid × Sessions mixed design ANOVA. Additionally, the results for the adjunctive acquisition and extinction sessions were plotted as a percent of prandial consumption levels (test volume/mean prandial volume). This latter data was not statistically analysed, but was used illustratively.

RESULTS

Subjects in the two lithium groups consumed approximately 80% of the daily volume of lithium solution available in their home cages (33±7 ml), relative to the water volume consumption by control group subjects (41±2 ml). This difference in liquid consumption produced treatment subjects whose body weights (404±56 g) were approximately 85% of Control subject weights (487±19 g). Serum lithium levels for Group Li/TW ranged from 0.20–0.99 mEq/l, with the mean and S.D. equal to 0.72 and 0.27 mEq/l, respectively. For Group Li/Et, the range was 0.24–1.02 mEq/l, with the mean and S.D. equal to 0.68 and 0.29 mEq/l, respectively. These values are consistent with other values obtained in this laboratory using similar administration procedures [6], and are predominantly at the low end of the concentration range recommended for therapeutic use in humans [3].

Figure 1 shows the volume of liquid consumed under each of the three experimental conditions (baseline/prandial; adjunctive acquisition; and extinction). Under baseline/prandial test conditions, there was a significant Drug effect, $F(1,24)=9.67$, $p<0.01$, with lithium subjects engaging in more overall consumption than did controls; a significant Liquid effect, $F(1,24)=47.80$, $p<0.01$, indicating that the subjects consumed more water than they did alcohol; and a significant Drug × Liquid interaction, $F(1,24)=5.71$, $p<0.05$, with the significant consumption differences occurring between Li/TW and C/TW, while the Li/Et and C/Et groups consumed equivalent levels of alcohol. All F's involving sessions were also statistically significant, $F(5,120)=10.44$ for the Sessions effect; $F(5,120)=2.67$ for Drug × Session; $F(5,120)=3.44$ for Liquid × Session; and $F(5,120)=2.89$ for Drugs × Liquid × Sessions, at values ranging from 0.05 to 0.001. To summarize these results, there was a tendencey for consumption to be greater at the end of the 18 baseline/prandial sessions than it was at the beginning; this increase was greater for the Li/TW and C/TW groups than for the C/Et and Li/Et subjects; and the increase was almost entirely due to the increase in consumption by the subjects in the Li/TW group.

When the results of the next 14 (adjunctive acquisition) session blocks were subjected to statistical analysis, a significant, $F(13,312)=133.53$, $p<0.001$, increase in consumption across sessions was observed, along with a significant Drug effect [Li subjects consumed more, overall, than did con-

trols: $F(1,24)=8.52$, $p<0.01$] and a significant Liquid effect [more water was consumed than alcohol: $F(1,24)=5.57$, $p<0.05$]. The only other outcome that was statistically significant was the Drug × Sessions interaction, $F(13,312)=19.18$, $p<0.001$. Examination of Figs. 1 and 2 indicates that the subjects receiving lithium had generally shallower slopes to their acquisition curves than did the control respective subjects.

Separate analysis of the first four and of the last four session blocks of the acquisition phase indicated that, while initial consumption levels were greater for the Li groups than they were for controls, $F(1,24)=59.28$, $p<0.001$, by the end of the acquisition sessions these differences had disappeared, $F(1,24)<1$. The Li subjects' greater overall water consumption that was present during the early sessions, $F(1,24)=13.33$, $p>0.01$, was also lost by the end of the acquisition phase, $F(1,24)=2.85$, $p<0.05$. While the greater consumption by the lithium subjects may have simply reflected the greater initial consumption during baseline/prandial sessions by the Li/TW group, Fig. 1 indicates a greater consumption by the Li/Et subjects, as well. Further, Fig. 2 indicates an increase over baseline levels for both Li/TW and Li/Et in the first session block, with the greater proportional increase made by the Li/Et subjects. Both figures also indicate a steady increase in consumption by the Li groups across the first four session blocks, while the control groups did not begin to increase their intake until the fourth block. This observation is supported by the significiant, $F(3,72)=21.05$, $p<0.001$, Sessions effect, with a significant, $F(3,72)=5.57$, $p<0.01$, Drugs × Sessions interaction.

Analysis of the extinction sessions indicated that alcohol consumption was less likely to decline in the absence of the FT schedule than was water consumption, $F(1,24)=4.75$, $p<0.05$, although this difference was primarily due to the decline in consumption by the C/TW group. In general, the lithium subjects consumed more than did the controls, $F(1,24)=9.90$, $p<0.01$, and there were significant Drug × Session, $F(5,120)=3.54$, $p<0.01$, and Drug × Liquid × Session, $F(5,120)=3.15$, $p<0.05$, interactions, indicative of the tendency for Li subjects to increase their consumption across extinction sessions, with a large increase by subjects in the Li/TW group, and an actual across-sessions decline in consumption by the subjects in the C/TW group.

DISCUSSION

Terminal consumption levels under these conditions appear to be almost entirely determined by the nature of the FT schedule controlling the intake behavior, with (as the failure to obtain any statistically significant results for the analysis of the last four session blocks indicates) neither the drug administration nor the available liquid exerting an influence on the outcome. Equally, the impact of lithium on schedule-induced alcohol consumption does not appear to be qualitatively different than its impact on the adjunctive intake of water, and may simply reflect lithium's effect on schedule-induced behaviors as a general class. In terms of the acquisition of schedule-induced behaviors, lithium appears to increase the subject's sensitivity to those factors in the FT schedule which control adjunctive drinking behaviors. This increase shows itself in the degree to which the Li subjects show an immediate increase in consumption with the initiation of the FT schedule, while control subjects failed to increase their intake until 10–12 sessions had elapsed. On the other hand, the rate of acquisition was markedly slower for the Li subjects than it was for controls.

While the earlier intake increases might possibly have resulted from lithium's polydipsic effect [4], as indicated by the higher baseline/prandial level of water consumption, three lines of evidence argue against this interpretation. First, the relative increase (Fig. 2) was both greater initially and more rapid throughout for the Li/Et subjects than it was for the Li/TW subjects, while baseline/prandial measures showed no impact of lithium-induced thirst on alcohol consumption. Second, the observed attenuation of the rate of consumption increase produced by Li for both TW and Et conditions is not consistent with an explanation couched in terms of increased thirst. Finally, and perhaps most importantly, Roper and Posadas-Andrews [15] have indicated that adjunctive drinking is not affected by variations in thirst motivation.

Johnson [10] has suggested that lithium's primary behavioral effect results from a decrease in the subject's sensitivity to low-intensity stimulation. If adjunctive behaviors are emitted because they provide interval-mediating response-produced stimuli [17], both the earlier initiation of schedule-induced drinking and the failure to produce terminal intake level differences are readily explained. To the degree that Li subjects are less responsive to low-intensity environmental stimuli, they would be expected to become more active in seeking out stimuli that could be utilized in the mediation of the FT interval. This would translate into an earlier acquisition of the adjunctive (response-cue producing) drinking behavior. On the other hand, terminal intake levels would not be expected to be appreciably affected by lithium administration, since these are under the relatively strong control of the inducing schedule in operation.

The decrease in the rate of acquisition of the drinking behavior, once adjunctive drinking is begun, is less readily explained. It is clear from examination of Figs. 1 and 2 that the decreased slope is not an artifact of the Li subjects reaching terminal levels first (having, in the case of the Li/TW subjects, started from a higher baseline), and flattening out thereafter. Clearly, the attenuated slopes represent a deficit in the acquisition process that is differentiable from the initiation of adjunctive drinking. Lithium does, however, retard the acquisition of a passive-avoidance response [8,11] and a cue-stimulus-free CER [7], so the lower acquisition obtained here may simply represent an attenuation of basic associative processes. In any case, it is clear that the factors influencing the initiation of adjunctive drinking and the factors influencing the rate of increase once adjunctive drinking had begun represent different processes, and are differentially influenced by lithium.

Two aspects of the extinction results stand out clearly. First, the consumption of alcohol, as established through the use of adjunctive procedures, does not extinguish. Consumption levels were as high after 18 extinction sessions as they were at the termination of the adjunctive acquisition phase. Furthermore, lithium does not influence the amount of alcohol consumed under these conditions. When water is the available liquid, however, intake is greatly reduced in the absence of the controlling FT schedule, although Group C/TW did appear to stabilize at water consumption levels that were somewhat higher than their baseline/prandial levels. Lithium did exert a considerable influence on this process, producing intake levels at the end of the extinction sessions which were again equivalent to those obtained at the end of the acquisition phase. While this result may to

some degree have resulted from a greater tendency to drink water as a result of increased levels of thirst brought about by the chronic lithium regimen, the terminal levels of intake were considerably higher than those observed at the end of the baseline/prandial sessions (which represented 33 days of lithium intake). Again, it is more likely that lithium influences more basic processes related to response extinction; and in that regard these results are consistent with earlier findings [7] of a decrease in the rate of extinction of the suppression of activity produced by response-independent (adventitious) shock.

While the results obtained here do not appear to be consistent with earlier findings in terms of lithium's effects on voluntary alcohol consumption, the differences appear to relate to the degree of control exerted by adjunctive procedures on consummatory behavior. In that regard, it is unlikely that these procedures will prove to represent an adequate animal model for human alcohol-consumption behavior, since the control exerted over intake by the scehedule-induced paradigm is in all likelihood so great that it will override attempts to moderate intake through therapeutic-level chemical intervention.

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