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Lithium Effects on Adjunctive Alcohol Consumption. II: Effects of Adding Concurrent Shock

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HINES, G. *Lithium effects on adjunctive alcohol consumption. II: Effects of adding concurrent shock.* PHARMACOL BIOCHEM BEHAV **25**(6) 1163–1167, 1986.—Rats receiving chronic administration of lithium chloride (20 mEq/l) in their drinking water were tested for adjunctive alcohol (10% v/v) consumption in which temporally scheduled, noncontingent shock delivery was added following the establishment of food delivery-based adjunctive alcohol intake. The addition of shock to the eliciting schedule produced an initial reduction in alcohol consumption (Lithium subjects took longer to reach maximal suppression of drinking than did Controls), with a subsequent return to preshock levels for both groups. The reduction in alcohol consumption seen in control subjects following the discontinuation of food and shock delivery (extinction) was interpreted as suggesting that adding conflict/stress to established drinking conditions may facilitate subsequent extinction of that drinking behavior. Lithium subjects produced an initial suppression of drinking, with alcohol consumption returning to adjunctive levels by the end of the extinction series, suggesting that lithium decreases conflict/stress effects, that it impairs extinction processes, that it increases the reinforcing value of alcohol, or that it produces a combination of the three outcomes.

Lithium Alcohol Adjunctive drinking Shock Extinction Aversion conditioning

SHOCK-INDUCED stress has consistently been found to produce an elevation in alcohol consumption by rats. Shock intensities ranging from 200 μA to 1.0 mA, delivered under a wide variety of schedule conditions, have all resulted in an increase in alcohol consumption during the stress period [2, 6, 7, 10, 25, 29]. While Mills *et al.* [24] did fail to obtain an elevation in alcohol intake during the shock-stress period, it is possible that the shock intensity utilized (1.5 mA) may have produced responses that were incompatible with the drinking behaviors. Measures of post-stress alcohol consumption have produced more varied results. When tests were made in the stress environment, alcohol consumption was generally found to decrease [2, 6, 24], although in the Caplan and Puglisi study [6], terminal intake did not return fully to prestress baseline levels. On the other hand, Volpicelli *et al.* [29] and Freed [10] found an increase in post-stress alcohol consumption, and Casey [7] found alcohol intake to increase following stress for 16 days, after which consumption declined. Results have been a bit more consistent when post-stress testing was performed in an environment that had not been associated with the shock. Volpicelli *et al.* [29] found a further increase in alcohol consumption under these conditions; Powell *et al.* [25] found alcohol intake to remain at its elevated, stress-induced level; and, while Caplan and Puglisi [6] obtained a decrease in alcohol consumption, intake was again maintained at higher levels than were obtained during prestress baseline tests.

The above studies have all been concerned with the effects of shock-stress on animals that did not ordinarily drink alcohol. That is, the measurements were taken relative to very low pre-stress levels of alcohol consumption. An alternative approach would be to establish high levels of alcohol intake prior to the introduction of shock, and to measure subsequent changes in consumption. Such an approach might be of particular interest in studies of lithium's effects on alcohol consumption, in light of the substance's established efficacy in the treatment of alcoholism [18, 23, 30]. The addition of shock to the drinking regimen might be considered generally analogous to aversive conditioning procedures, which are also utilized in the treatment of substance-abuse problems [28].

One method of inducing high levels of alcohol consumption by rats involves the use of adjunctive, or schedule-induced, drinking [9, 19, 22]. While lithium's effect on adjunctive alcohol consumption are complex, involving earlier initiation of drinking along with a slower rate of consumption increases once adjunctive drinking along with a slower rate of consumption increases once adjunctive drinking has begun, terminal levels of intake are comparable to those obtained with untreated controls [13].

The present study, then, applied to shock to an established, high level of adjunctive alcohol consumption. Intake measures were taken during the adjunctive and the adjunctive + shock sessions, as well as during extinction sessions (when neither shock nor the inducing food schedule were operative). This approach allowed the assessment not only of the immediate (stress-session) effects of shock on elevated consumption, but also upon drinking behavior, in the previ-

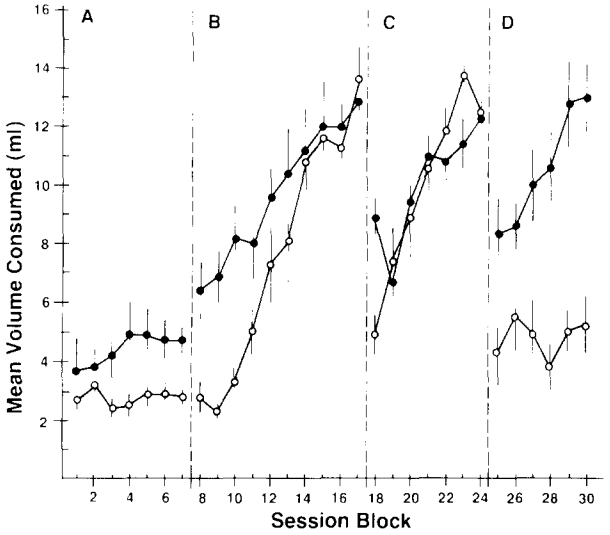

FIG. 1. Mean volume (±SEM) of alcohol solution consumed across 3-session blocks. A=Baseline/Prandial; B=FT_f; C=FT_{fs}; D=Extinction. Solid circles represent the lithium means, open circles represent control values.

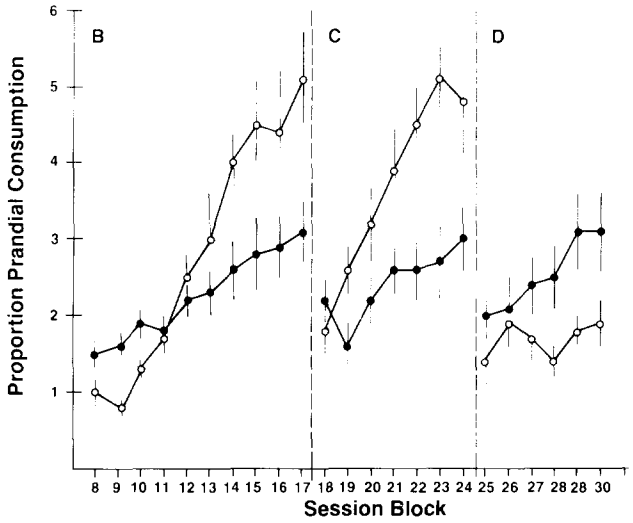

FIG. 2. Adjunctive alcohol consumption as proportion (±SEM) Baseline/Prandial consumption (volume consumed ÷ Baseline/Prandial consumption). B=FT_f; C=FT_{fs}; D=Extinction. Solid circles represent lithium values, open circles represent control values.

ously stressed environment, under conditions in which both the eliciting conditions and the stress-inducing conditions have been terminated.

METHOD

Subject

Twelve male, Holtzman albino rats, 90 days old at the start of the experiment, were used. The subjects were divided into two groups (N=6), and maintained at 85% of their projected free-feeding growth curves by controlled feeding at the end of each day's session. One group of subjects (Li) received 20 mEq/l lithium chloride in their drinking water, while the other group (Control) received plain tap water. All subjects were housed in standard individual stainless steel suspended cages, with an 0700–1900 hour light-on cycle.

Apparatus

Testing was performed in a Grason-Stadler Model 1111 operant chamber, housed in a Model 1101 research chest. An exhaust fan provided 67 dB masking noise. The two response levers were removed from the chamber, and the spaces were covered with stainless steel plates. A water bottle was mounted on the door of the chamber, 12.5 cm to the right of the food magazine, with the nozzle extending to 6.0 cm above the floor. Food pellet delivery (45 mg Noyes) was controlled by BRS 100-series solid-state control modules; and shock delivered to the chamber's grid floor by Lafayette Models 82401 constant current shocker and 82501 grid scrambler.

Procedure

Subjects were assigned to treatment groups by a weight-matching procedure, to ensure equivalent body weights throughout the study. Thereafter, the subjects were maintained at 85% growth rate (relative to initially weight-matched subjects maintained under free-feeding conditions) by controlled feeding at the end of each day's test session. Testing was begun 20 days after deprivation conditions were initiated, a time interval sufficient to allow both serum lithium levels and growth rates to stabilize.

For the first 12 days (45 min sessions) alcohol (10% v/v, mixed from 95% ethanol) was available to the subjects in the operant chamber, but food was neither present nor delivered. This procedure produced baseline measures of alcohol consumption. In order to determine the degree to which prandial drinking would influence consumption levels, this was followed by nine sessions in which 30 food pellets were placed in the food magazine at the start of each session. Following baseline and prandial determinations, food pellets were delivered to the subjects on a noncontingent basis, every 90 sec (FT 90 sec, hereafter referred to as FT_f). FT_f was maintained for 30 sessions, after which a concurrent schedule of inescapable, unavoidable shock delivery (0.75 mA, 250 msec duration) was initiated. Under this condition (FT_{fs}) shock occurred on a FT 180 sec schedule, with the shocks timed to occur with every other food pellet delivery. FT_{fs} was maintained for 21 sessions, and was followed by 18 "extinction" sessions, during which time alcohol was available, but neither food not shock-delivery occurred.

Following the extinction sessions, each subject was sacrificed at its usual testing times, and serum lithium levels determined by flame photometry [1], using an IL Model 253 spectrophotometer.

The results were collapsed into mean consumption levels (ml) for successive 3-session blocks. Additionally, FT_f, FT_{fs}, and extinction blocks were calculated as proportion of baseline sessions (Test Measure/mean baseline measure). Drug × Sessions mixed-design ANOVAs were used on the Baseline/Prandial, FT_f, FT_{fs}, and extinction consumption data. The proportion baseline results were not analyzed statistically, but were used to provide illustrative support.

RESULTS

Subjects in the lithium group consumed the lithium solu-

tion available in their home cages at a mean volume (34.5±5.5 ml) that was approximately 83% of the average daily water volume consumed by the control subjects (41.5±3 ml). As a result, lithium subjects' body weights (416±39 g) were approximately 85% of the weights of non-deprived, non-tested control subjects (496±22 g). Serum lithium levels for the experimental group ranged from 0.20–0.94 mEq/l, with mean and S.D. equal to 0.61 mEq/l and 0.19 mEq/l, respectively. These values are generally at the low end of the 0.6–1.2 mEq/l established as the therapeutic maintenance level for lithium [5]. While no formal analysis was performed, there was no apparent relationship between serum level and consumption in any of the four experimental phases.

Analysis of the Baseline/Prandial results (Fig. 1) indicated no significant sessions effect, $F(6,60)=1.08$, or Drug × Sessions interaction, $F(6,60)=1.39$, and a Drug effect that approached, but did not reach, the 0.05 level of significance, $F(1,10)=3.92$, $p<0.10$. A similar result was obtained for the Drug factor under FT_f conditions, $F(1,10)=4.18$, $0.10>p>0.05$, although both the Sessions factor and the Drug × Sessions interactions were statistically significant, $F(9,90)=34.46$, $p>0.001$; and $F(9,90)=2.90$, $p<0.01$, respectively.

With the introduction of shock (FT_{fs}) both groups evidenced an initial reduction in their levels of alcohol consumption, followed by a gradual return to FT_f consumption levels. Statistical analysis indicated that the Drug factor was again nonsignificant, $F(1,10)<1.00$, while both the Sessions factor, $F(6,60)=27.55$, and the Drug × Sessions interaction, $F(6,60)=4.93$, were significant at $p<0.001$. It is worth noting that five of the six control subjects showed their maximum suppression of alcohol consumption during the first block of three sessions, while five of the six Li subjects showed greater suppression during the second block of sessions than they did during the first block. In the latter group, the sixth subject showed the same level of alcohol consumption during both the first and the second three-session blocks.

The most striking effects occurred during the extinction sessions. While both groups showed an initial decline in alcohol consumption, the decline was greater for the control group than it was for the subjects receiving lithium. Furthermore, the Li group recovered its alcohol consumption to FT_f levels across sessions, while the control group did not. The control group did, however, maintain alcohol consumption at levels above those seen during Baseline/Prandial sessions. The ANOVA supported these observations, with the Drug factor significant at $p<0.01$, $F(1,10)=17.46$, and the Sessions factor and Drug × Sessions interaction significant at the 0.001 level, $F(5,55)=7.59$ and $F(5,55)=6.20$, respectively.

DISCUSSION

While the Baseline/Prandial analysis suggests the possibility of influence by lithium-induced thirst, the failure to produce significant increases in consumption of alcohol are consistent with other findings in this lab [13] that there is virtually no difference in the consumption of alcohol produced by lithium under these administration conditions. Furthermore, since variations in thirst motivation have not been found to influence adjunctive drinking [26], it is unlikely that any contribution to initial alcohol consumption made by lithium-induced polydipsic effects would have contributed to the subsequent findings. Nevertheless, FT_f, FT_{fs}, and extinction results were replotted (Fig. 2) in terms of proportion Prandial consumption. While this data was not analyzed statistically, the figure does emphasize the results noted earlier in the paper, and discussed below.

Lithium produced two major effects on the acquisition of adjunctive alcohol consumption. First, Li subjects responded to the factors that induce drinking behaviors earlier in training than did the control subjects. Increased alcohol consumption was apparent in the first block of sessions for Li subjects, while control subjects required more extensive exposure to the FT_f before alcohol consumption increased, with significant increases in alcohol consumption not apparent until the fourth session block (Figs. 1 and 2). Second, lithium treatment slowed the rate at which acquisition of adjunctive drinking occurred. Thus, the overall picture is of an "almost significant" drug effect (consumption is higher for Li in the early sessions, and no different from that seen with control subjects in the middle and late sessions), a significant Sessions effect (consumption increased across blocks for both groups), and a significant Drugs × Sessions interaction (the slope of the increase function is much steeper for the control subjects than it is for the Li subjects). When the change in consumption is plotted relative to prandial drinking levels (Fig. 2), this interaction is even more strikingly apparent. While there was a 50% increase in alcohol consumption by Li subjects during the first session block, their terminal consumption was only approximately 3× their prandial levels, as compared with a 5× increase noted for the control subjects. These results are similar to other findings on lithium's effects on adjunctive consumption of both alcohol and water [13], and suggest that sensitivity to the factors that induce adjunctive behaviors is separable from the actual rate of acquisition of those behaviors.

The presentation of shock led to an initial suppression of adjunctive alcohol consumption. Under these circumstances, shock would be considered uncued, and the suppression consistent with that observed by Kinney and Schmidt [13]. In that study, uncued shock was found to suppress alcohol consumption under free-drinking conditions, while cued shock produced an increase in alcohol intake. That lithium subjects took longer to reach maximal suppression of alcohol consumption than did controls is consistent with Johnson's [15] hypothesized reduction in reactivity to environmental stimulation, and with Hines' observation [12] that lithium produces a reduction in the degree of activity suppression seen prior to the administration of inescapable shock.

As the FT_{fs} sessions continued, the fixed-time nature of the shock delivery imparted a "cued" status, and alcohol consumption recovered. That it did not exceed FT_f valued (i.e., that cued shock did not produce an increase in the previously established consumption levels) may be due to the strength of the food-delivery schedule as a determining factor in adjunctive consumption, to the relatively weak cue-stimulus property of the FT 180 sec schedule of shock delivery, to the limits placed on alcohol volume consumption by the nature of the organism involved, or to a combination of those three factors.

While terminal consumption levels for lithium and control subjects did not differ under FT_f and FT_{fs} conditions, there were striking differences with respect to alcohol consumption under extinction conditions. Both groups showed an initial suppression alcohol consumption, but the magnitude

of the decrease (both in terms of volume and of proportion prandial consumption measures) was greater for controls than it was for the lithium subjects. Further, alcohol consumption by lithium subjects recovered to FT_f and FT_{fs} levels, while control drinking did not. The results for the control subjects conflict with the findings of Volpicelli *et al.* [29], and of Mills *et al.* [24], who indicated an increase in alcohol consumption following the termination of shock-induced stress. They also conflict with Casey's [7] observation that alcohol consumption increased for 16 days post-stress, and only then declined, and with Caplan and Puglisi's [6] observation that, following conflict-stress conditions, alcohol consumption maintained the increases obtained during the conflict-induced sessions. They are, however, consistent with the latter study's observation of decrease in alcohol consumption following shock-induced stress when conflict is not present. It is worth noting that in neither this study nor Caplan and Puglisi's did post-stress consumption return completely to baseline levels, a finding that is consistent with the observation [11] that, while subjects who received direct aversive conditioning did report a greater dislike for the taste of alcohol that did control subjects, differences in physiological responses or in 4-month follow-up sobriety between aversively conditioned subjects and controls were lacking. Further, Blake [3,4] found a lower efficacy for electrical-aversion therapy alone than for aversive conditioning combined with relaxation therapy. The present data thus supports the view that, while pairing shock with established drinking behavior may produce a subsequent decrease in alcohol consumption after the conditions inducing the drinking and the shock are subsequently removed (thereby producing "room" in the behavioral repertoire for the establishment of behaviors that are incompatible with drinking), there is still sufficient suprabaseline consumption to maintain a basis for subsequent recidivism if aversive conditioning is the only procedure utilized. It is also clear that the effects of shock-induced stress on alcohol consumption will vary as a function of the level of drinking that occurred prior to the introduction of shock. The present study indicates a clear reduction in extinction drinking behavior by controls when high levels of alcohol consumption are established prior to shock administration, while the earlier studies [6, 7, 24, 29] indicated that alcohol consumption during extinction will tend to increase or to be maintained when no elevation in baseline levels of drinking were established prior to the initiation of the shock-induced stress.

That the lithium subjects returned to their FT_f and FT_{fs} levels of drinking suggests that lithium reduces the level of reaction to the shock utilized, that lithium reduces conflict (and thereby its subsequent effects) that lithium reduces the subject's response to extinction process, or that lithium increases the reinforcing properties of alcohol consumption. All four interpretations have received some support in the literature. Hines and Poling [14] suggested that their subjects were less responsive to shock during the acquisition of a passive avoidance task, while Katz and Carrol [16] indicated that a lithium-produced reduction in conflict could account for the reduced latencies to approach a reinforcement source that had been paired with shock. With respect to extinction processes, Hines [12] has observed that recovery by lithium by lithium subjects of open-field activity following the termination of a series of test sessions in which activity was suppressed by the delivery of inescapable shock was significantly delayed relative to the recovery seen in control subjects. Finally, Marcucella *et al.* [20] report that restricting access to alcohol produced increased consumption relative to that observed under conditions of unrestricted access; and Sinclair [29] reported that lithium increased alcohol consumption under similar conditions. Since restricted access to behaviors has been found to increase their "value" [21], the Sinclair result also suggests that lithium may increase the reinforcing properties of alcohol consumption. In any case, the results clearly indicate that the use of lithium as an adjunct to aversive conditioning would be counter-productive in the treatment of alcoholism.

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