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Taste Aversion Disruption by Drug Pretreatment: Dissociative and Drug-Specific Effects[1]

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CANNON, D. S., T. B. BAKER, AND R. F. BERMAN. *Taste aversion disruption by drug pretreatment: dissociative and drug-specific effects.* PHARMAC. BIOCHEM. BEHAV. 6(1) 93–100, 1977. — Disruption of taste aversion learning following the administration of the same drug prior to and during conditioning (intra-agent disruption) was shown to be greater than disruption following the administration of one drug prior to conditioning and another during conditioning (inter-agent disruption). Comparable dosages of ethanol and lithium chloride served as unconditioned stimuli. Inter-agent disruptions are attributed to a dissociation of conditioned and unconditioned stimuli, while intra-agent disruptions are attributed to both a dissociative effect and drug-specific effects. Intra-agent disruption was correlated with an independent measure of tolerance, suggesting tolerance constitutes at least a portion of the drug-specific effects.

Taste aversion Ethanol Lithium chloride Taste aversion disruption Tolerance

PRECONDITIONING experience with a drug has been demonstrated to impede the conditioning of taste aversions [2–9, 11, 13, 16, 18, 21, 29]. One of the more frequently proposed explanations of this effect is that tolerance to the unconditioned stimulus (UCS) acquired during preconditioning experience attenuates UCS aversiveness during conditioning [2, 7, 8, 9, 13, 17, 23]. (Tolerance has been defined in these studies in the general sense of the decreased effect of a given dosage with repeated administration.) However, Cappell *et al.* [8], Goudie and Thornton [13], LeBlanc and Cappell [17], and Riley *et al.* [23] present no evidence of UCS tolerance other than attenuated taste aversions. Instead, they offer tolerance as the explanation with the fewest empirical challenges. Cappell and LeBlanc [7], in separate experiments using amphetamine as the UCS, varied the number of preconditioning trials and the interval between a constant amount of preconditioning experience and the first conditioning trial. They concluded, "Although alternative explanations are possible, the time intervals required for the acquisition and loss of the effectiveness of prior treatment are consistent with the hypothesis that tolerance is the mechanism underlying the observed effects" (p. 157). Only minimal support for tolerance as a possible explanation is found in Berman and Cannon's [2] report of a decreased incidence (not statistically significant) of unconsciousness among ethanol (EtOH) pretreated animals following the initial EtOH conditioning dose.

A number of studies either have failed to find evidence of UCS tolerance or have shown that tolerance is not a necessary condition of the preconditioning disruption effect. Brookshire and Brackbill [5] reported that preconditioning experience with apomorphine hydrochloride disrupts apomorphine-induced taste aversions, but they found no evidence of apomorphine tolerance in their study. Vogel [29] found that while pretreatment with amobarbital greatly interfered with taste aversion learning with that agent, it had only a modest effect on sleeping time. He argued from these data that preconditioning taste aversion disruption is based on something other than tolerance per se. Studies by Braveman [3], Cappell *et al.* [8], Goudie and Thornton [13], and Vogel [29] show that preconditioning experience with one drug can disrupt taste aversion learning with a secong drug even though the two drugs are not known to produce cross-tolerance. Braveman [3] has also demonstrated that rotation-induced taste aversions can be attenuated by drug pretreatment. Cannon *et al.* [6] report the attenuation of lithium chloride (LiCl)-induced aversions by a single preconditioning dose of LiCl, even though two consecutive daily LiCl doses resulted in greater illness than did one dose.

Braveman [4] states, in contradistinction to the UCS tolerance hypothesis, that "the preexposure effect is indifferent to the types of treatments that are used during preexposure and training" (p. 31). He postulates a single aversive element (i.e., the adrenocorticotropic hormone

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[ACTH] stress response) common to all stimuli which produce conditioned taste aversions. He suggests that the preexposure effect occurs because this common aversive elements elicits "opponent processes" [27,28] during preconditioning UCS exposure which are conditioned to environmental cues and which interfere with the aversiveness of the common element during conditioning.

Another frequently discussed hypothesis is that the preconditioning disruption effect is due to dissociation of the conditioned stimulus (CS) and UCS [5, 6; cf. 3, 4, 8, 17]. The conditioning dissociation hypothesis advanced by Cannon *et al.* [6] states that the acquisition of taste aversions may be a function of the differential probability of the UCS following the CS. Illness effects common to even dissimilar UCS's would not be associated with the CS since their occurrence is no more likely following the CS than at other times. Their theory further states that the ability of pretreatment to disrupt aversion acquisition is time limited, the effective duration being a function of such factors as amount of pretreatment and the preconditioning and conditioning dosages. Other interpretations somewhat akin to a simple dissociative hypothesis include latent inhibition and learned helplessness [3,4].

Rather than being mutually exclusive, it is possible that both tolerance effects, or at least drug-specific effects, and dissociative effects contribute to the preconditioning disruption effect under certain conditions. This paper reports the results of two studies which examine the possible contribution of drug-specific effects such as tolerance to preconditioning taste aversion disruption. Further, the relationship between amount of aversion and an independent measure of UCS tolerance is assessed as a test of the possibility that at least a portion of the drug-specific effect is due to UCS tolerance.

EXPERIMENT 1

One test of the possible contribution of drug-specific effects to the disruption effect is to compare the degree of attenuation produced by administering the same drug prior to and during conditioning (intra-agent disruption) with the degree of attenuation produced by administering one drug prior to and another during conditioning (inter-agent disruption). Greater intra-agent than inter-agent disruption would suggest that drug-specific effects do contribute to the disruptive effect of preconditioning UCS experience. As mentioned above, inter-agent disruption has been previously reported by Braveman [3,4], Cappell *et al.* [8], Goudie and Thornton [13], and Vogel [29]. However, these studies did not compare the magnitude of intra-agent and inter-agent disruption, and so do not reveal whether drug-specific effects contribute measurably to the disruptive effect of preconditioning UCS experience.

A pilot study conducted in this laboratory showed that inter-agent preconditioning disruption is a negative function of conditioning dosage. A similar dosage effect has been found in intra-agent disruption [6]. Therefore, if intra- and inter-agent disruptions are to be compared, it is essential that equivalent drug dosages be employed. If the dosages are comparable, inter- and intra-agent disruption should produce equivalent levels of taste aversion disruption, unless drug-specific effects are operative. The dosages of the two drugs used in this study produced comparable levels of taste aversions in naive animals in pilot studies, and their comparability was reassessed in this study.

TABLE 1

PRECONDITIONING AND CONDITIONING DRUG ADMINISTRATION SEQUENCES: EXPERIMENT 1

Group	Preconditioning Drug*	Conditioning Drug*
1	LiCl	LiCl
2	EtOH	LiCl
3	NaCl	LiCl
4	LiCl	EtOH
5	EtOH	EtOH
6	NaCl	EtOH
7	NaCl	NaCl

*The EtOH dosage was 5 g/kg/day (37.5% EtOH, v/v), the LiCl dosage was 0.02 ml/g/day of 0.10 M LiCl, and the NaCl dosage was 5 ml of normal saline (0.9%).

Method

Animals. Fifty-eight naive male Long-Evans rats initially weighing 280–365 g were used.

Procedure. Rats were adapted to a 23½ hr/day water deprivation schedule for 8 days and then were assigned to one of seven groups of equal mean weight. On Days 9–12 rats were intubated immediately following the drinking period according to the schedule shown in Table 1. Groups 1 and 4 (n = 9 each) were intubated with 0.02 ml/g of 0.10 M LiCl; Groups 2 (n = 9) and 5 (n = 7) with 5 g/kg of EtOH (37.5%, v/v); and Groups 3, 6, and 7 (n = 8 each) with 5 ml of 0.9%NaCL. The water drinking period was not followed by intubation on Days 13–15 to insure that differences in fluid consumption and thirst which may have developed during drug preexposure would dissipate prior to conditioning. On Days 16, 19 and 22 rats were presented with a 0.1% (w/v) saccharin solution in lieu of water for 30 min. Immediately following the removal of the saccharin on Days 16 and 19, rats were given the following treatments: Groups 1, 2, and 3 were intubated with 0.02 ml/g of 0.10 M LiCl; Groups 4, 5 and 6 with 5 g/kg of EtOH (37.5%, v/v); and Group 7 with 5 ml of 0.9% NaCl. Thus, Groups 1 and 5 were intra-agent conditioning groups, Groups 2 and 4 were inter-agent conditioning groups, Groups 3 and 6 were naive conditioning groups, and Group 7 was a control group.

Results

Mean water consumption per day prior to saccharin conditioning is shown in Fig. 1. The water consumption data of animals treated similarly during preconditioning were combined; i.e., Groups 1 and 4 (LiCl preconditioning groups) were combined, as were Groups 2 and 5 (EtOH preconditioning groups), and Groups 3, 6 and 7 (NaCl preconditioning groups). Water consumption on Days 10–13 was analyzed with a 3 × 4 (preconditioning drug × days) repeated measures analysis of variance [31]. There was a significant preconditioning drug by day interaction, $F(6,165) = 3.7$, $p < 0.01$. (This result, as well as all other significant within-subjects effects in all analyses of variance with more than two repeated measures, was significant with the conservative Greenhouse-Geisser degree of freedom correction for heterogeneous covariance [31]. This indicates that within-subjects effects would have remained

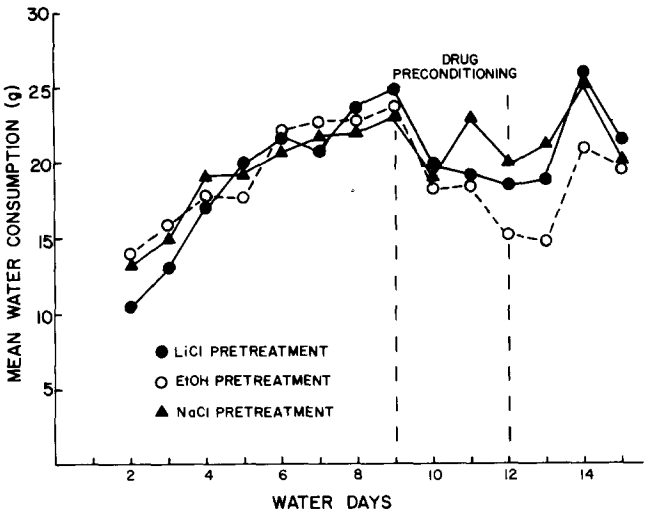

FIG. 1. Mean preconditioning water consumption of animals given 0.02 ml/g of 0.10 M LiCl, 5 g/kg of 37.5% EtOH, and 5 ml of normal saline on Days 9–12 of Experiment 1.

significant with an exact degree of freedom correction (ϵ). This strategy for protecting against spurious significance due to heterogeneous covariance was recommended by Greenhouse and Geisser [15].) Tests of simple drug effects for each day revealed no differences among groups on Day 10, but there were reliable differences on Days 11, 12 and 13 ($p < 0.01$). Newman-Keuls a posteriori tests indicated animals given EtOH drank less water on each of those three days than did the animals given NaCl ($p < 0.01$). Water consumption by animals given LiCl was intermediate, being reliably less than that of NaCl animals on Day 11 ($p < 0.01$) and greater than that of EtOH animals on Days 12 and 13 ($p < 0.01$).

Mean saccharin consumption per group is shown in Fig. 2. The data of Group 7 are shown in Fig. 2 for comparative purposes but were not included in the statistical analyses. There was no difference among groups in saccharin consumption on Day 16 (i.e., prior to the first conditioning UCS presentation). To test the equivalence of the LiCl and EtOH dosages, the saccharin consumption of the naive conditioning groups (i.e., Groups 3 and 6) and the intra-agent groups (i.e., Groups 1 and 5) was analyzed with a 2 × 2 × 2 (i.e., UCS × preconditioning × days) repeated measures analysis of variance across Days 19 and 22. This analysis did not indicate the UCS dosages were dissimilar as there was neither a UCS effect nor a UCS × experience interaction.

Saccharin consumption of Groups 1–6 over Days 19 and 22 was reanalyzed to test the hypothesis that intra-agent disruption is comparable to inter-agent disruption. In this 3 × 2 analysis with repeated measures across days, inter-agent disruption (i.e., Groups 2 and 4), intra-agent disruption (i.e., Groups 1 and 5), and no disruption (i.e., Groups 3 and 6) were considered to be three levels of one treatment variable. These data are shown in Fig. 3. This analysis indicated a reliable treatment effect, $F(2,47) = 9.3$, $p < 0.01$, and a day effect, $F(1,47) = 14.1$, $p < 0.01$. There was no treatment by day interaction. Newman-Keuls a posteriori tests indicated that both intra- and inter-agent conditions resulted in reliable disruption in comparison with the naive conditioning groups ($p < 0.05$), but that

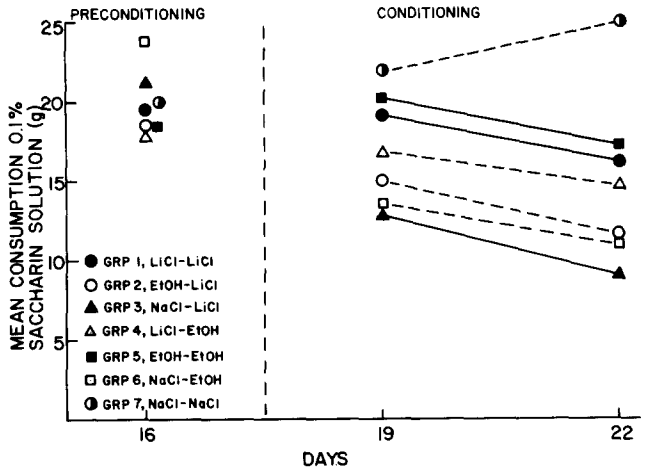

FIG. 2. Mean saccharin consumption per group in Experiment 1. (Group 1 was given LiCl on Days 9–12, i.e., prior to conditioning, and on Days 16 and 19, i.e., during conditioning. Group 2 was given EtOH prior to LiCl conditioning; Group 3, normal saline prior to LiCl conditioning; Group 4, LiCl prior to EtOH conditioning; Group 5, EtOH prior to EtOH conditioning; and Group 6, normal saline prior to EtOH conditioning. Group 7 was given normal saline prior to and during conditioning. Dosages were 0.02 ml/g of 0.10 M LiCl, 5 g/kg of 37.5% EtOH, and 5 ml of normal saline.)

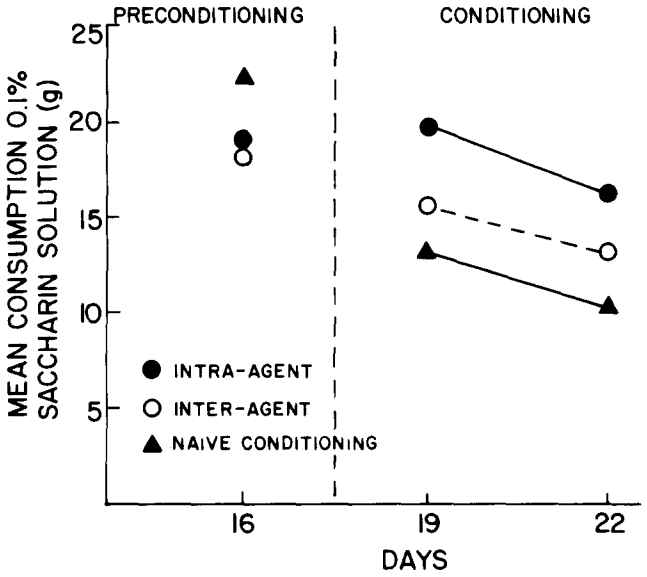

FIG. 3. Mean saccharin consumption of intra-agent groups (Groups 1 and 4), inter-agent groups (Groups 2 and 5), and naive conditioning groups (Groups 3 and 6) in Experiment 1.

intra-agent disruption was significantly greater than inter-agent disruption ($p < 0.05$).

Discussion

The finding of major interest in Experiment 1 is that intra-agent preconditioning experience results in greater attenuation of learning than does inter-agent experience. Thus, the results suggest drug-specific effects do contribute to intra-agent disruptions. The presence of reliable inter-agent disruptions is consistent with earlier reports [3, 4, 8, 13, 29] and supports the conclusion that drug-specific

effects are not necessary to attenuate taste aversion learning [3, 4, 6]. However, Braveman's [4] contention that disruption is indifferent to drug-specific effects is refuted by the comparison of intra- and inter-agent disruptions. The nature of the relevant drug-specific effects cannot be identified on the basis of Experiment 1.

Previous studies of inter-agent disruption [8, 11, 13, 29] report instances in which one drug disrupted aversions produced by a different drug, but the second drug did not disrupt aversions produced by the first. There are three possible reasons for such instances of asymmetrical disruptions. One, noted by Braveman [4] and consistent with the findings of Cannon *et al.* [6] with intra-agent disruptions, is that previous researchers may not have used comparable dosages of the drugs involved. Neither Vogel [29], Goudie and Thornton [13], nor Cappell *et al.* [8] investigated whether different preconditioning and conditioning dosages could have produced symmetrical disruption. The experiments by Goudie and Thornton [13] and Vogel [29] seem to be particularly susceptible to this explanation. Goudie and Thornton [13] showed that fenfluramine pretreatment disrupted amphetamine conditioning, but the opposite was not true. However, their data seem to indicate that, at the dosages used, fenfluramine was a more effective conditioning agent than amphetamine (a statistical comparison of the fenfluamine and amphetamine naive conditioning groups was not presented). (In a report published since submission of this paper for publication, Goudie *et al.* [14] demonstrate and discuss the significance of dosage effects on inter-agent disruptions.) In the Vogel study [29], a ceiling effect on the dependent measure makes it impossible to evaluate the relative effectiveness of the conditioning dosages used. In Experiment 1 of this series, dosages of LiCl and EtOH were used which produced comparable aversions in naive animals and comparable levels of intra-agent disruption. At these dosages, these two dissimilar agents produced symmetrical inter-agent disruptions. Thus, indirect support of the dosage-effect explanation of inter-agent asymmetry is provided. A second possible explanation of the asymmetrical disruptions found in earlier studies is that the lengthy preconditioning drug exposures in those studies may have allowed animals to more effectively discriminate between the different drugs. Both Cappell *et al.* [8] and Goudie and Thornton [13] used extensive drug pretreatment experience (22 and 9 days respectively). In Experiment 1 there were only 4 preconditioning trials and 2 conditioning trials. A final explanation of asymmetrical disruptions, suggested by Cappell *et al.* [8], is that drug synergies might affect inter-agent disruption. That is, drug interactions could interfere with symmetrical disruption. While such drug synergies might exist, they should be considered only after inter-agent dosage effects have been ruled out.

While some other investigators have reported that no water or food aversions developed during drug pretreatment [6, 8, 17], there was a decrease in water consumption in Experiment 1. Whether this decreased water intake was due to taste aversion conditioning or to the adipsic effects of prolonged LiCl and EtOH illness is unknown. In a similar instance, Goudie and Thornton [13] attributed the decreased food intake of fenfluramine treated animals to the anorexic effects of that drug.

The main findings of Experiment 1, i.e., that intra-agent disruption is greater than inter-agent disruption and that inter-agent disruption is symmetrical, have been systematically replicated in another study in our laboratory. In that study, LiCl and EtOH were given in slightly different dosages (i.e., 0.02 ml/g of 0.12 M LiCl and 4 g/kg of 30% EtOH, v/v). There was only one preconditioning trial, scheduled just 24 hr prior to the first conditioning trial. The smaller EtOH dosage (relative to the EtOH dosage in Experiment 1) produced a weaker aversion in naive animals than did the relatively greater LiCl dosage, and EtOH was not quite as effective in disrupting LiCl aversions as vice versa. The drug dosages used in Experiment 1 produced a more symmetrical cross-disruption.

EXPERIMENT 2

The results of Experiment 1 suggest that drug-specific effects do contribute to the disruption of the acquisition of taste aversions following preconditioning UCS experience but do not indicate whether the drug-specific effects are due to tolerance. The demonstration of a relationship between CS consumption and an independent measure of UCS tolerance would lend support to the tolerance interpretation. As mentioned above, there has been scant evidence for such a relationship [2, 7, 29], and there has been at least one failure to find such evidence [5].

In Experiment 2, preconditioning EtOH doses were administered in a fashion shown to produce optimal EtOH tolerance [18], and sufficient EtOH was used during taste aversion conditioning to maintain high tolerance levels. The day following the last CS presentation, animals with preconditioning and conditioning EtOH experience, animals with only conditioning EtOH experience, and EtOH-naive animals were given an EtOH tolerance test [10]. Tolerance scores of EtOH animals with no LiCl experience were then correlated with CS consumption on the previous day. This procedure represents a conservative test of the tolerance hypothesis because the animals receiving EtOH during conditioning would be expected to develop some EtOH tolerance during that phase of the study, thus attenuating differences between that group and the group with preconditioning EtOH experience. Therefore, a substantial tolerance effect would have to be present to be detectable.

A greater number of preconditioning and conditioning trials were used in this experiment, permitting a test of whether increased preconditioning and conditioning UCS experience decrease inter-agent disruption by making the UCS's more discriminable.

To reduce the possibility of conditioning water aversions during drug pretreatment, a 7 hr water consumption-drug administration interval was used as in Cappell *et al.* [8].

Method

Subjects. Fifty-seven naive male Long-Evans rats initially weighing 250–410 g were used.

Apparatus. A rotating rod (rotarod) was used to measure tolerance [10]. The rotarod was made of Plexiglas covered with Armstrong Armaflex insulation hose (3.0 cm o.d.) and was turned at a constant speed (2.4 rpm) by an AC motor (Barcol Speed Reducer, Barber Coleman Co., 115 V, 60 cycle). The rod was mounted 45 cm above the floor of a transparent Plexiglas enclosure (30 × 60 × 70 cm).

Procedure. All rats were adapted to a 23½ hr/day water deprivation schedule for 7 days and then were assigned to one of six groups of equal mean weight. Throughout the study, drinking sessions were scheduled from 0800–0830 hr daily. On Days 8–21 at 1600 hr, Groups 1 (n = 9) and 2 (n = 10) were intubated with EtOH, Groups 3 (n = 10) and

4 (n = 9) with LiCl, and Groups 5 (n = 9) and 6 (n = 10 with NaCl (cf. Table 2). On Days 8–10 the EtOH dosage was 3 g/kg (22.5%, v/v), while the LiCl dosage was 0.02 ml/g of 0.06 M LiCl. On Days 11–21 the EtOH dosage was 6 g/kg (45%, v/v), and the LiCl dosage was 0.02 ml/g of 0.12 M LiCl. No drugs were administered on Day 22, and conditioning began on Day 23. At that time all rats received a 0.1% (w/v) saccharin solution from 0800–0830 hr and were intubated with either 5 g/kg of a 37.5% (v/v) EtOH solution (Groups 1, 3, and 5) or 0.02 ml/g of 0.10 M LiCl (Groups 2, 4, and 6) immediately after the saccharin drinking period (cf. Table 2). There were six conditioning trials, scheduled at 3-day intervals (i.e., Days 23, 26, 29, 32, 35, and 38), with water presented on the intervening days.

On Day 39, the day after the final conditioning trial, Groups 1, 3, 5 and 6 were intubated with 2 g/kg EtOH (25%, v/v). Each rat was placed on the rotarod exactly 30 min after its EtOH dose, and the time it remained on the rotarod was recorded. Each rat was given two temporally contiguous trials, and the longer one was used as the measure of tolerance. (The average of the two trials was not used as the tolerance measure since animals frequently fell off the rod immediately on the first trial. Thus, the longer trial was taken to be a more valid measure of ability.) The order of testing was counterbalanced across groups.

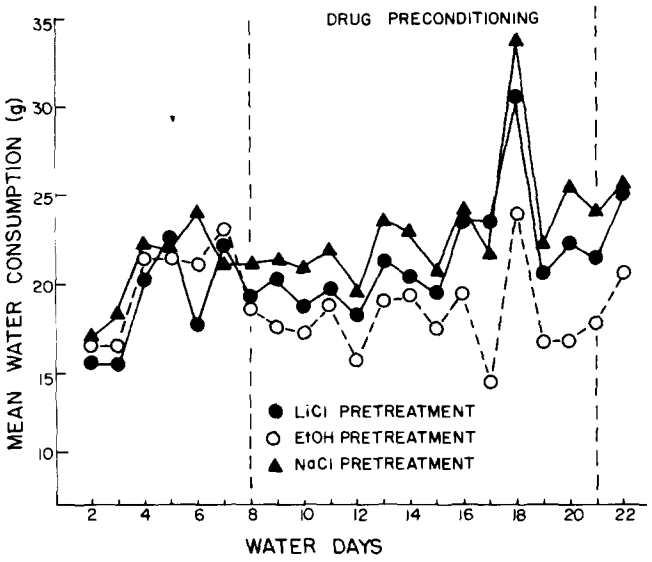

FIG. 4. Mean preconditioning water consumption of animals given LiCl, EtOH and normal saline prior to conditioning in Experiment 2. (On Days 8–10, dosages were 0.02 ml/g of 0.06 M LiCl and 3 G/kg of 22.5% EtOH. On Days 11–21, dosages were 0.02 ml/g of 0.12 M LiCl and 6 g/kg of 45% EtOH. The saline dosage was 5 ml.)

Results

Water consumption across Days 2–22 is shown in Fig. 4. The data of groups receiving NaCl at 1600 hr (i.e., Groups 5 and 6) are combined, as are the data of groups receiving EtOH (Groups 1 and 2) and LiCl (Groups 3 and 4). The figure indicates fairly stable consumption across days, after initial adaptation to the deprivation schedule on Days 2–4, except for Day 18. The increased consumption on Day 18 was due to the water bottles inadvertently being left on the cages too long. From Day 9, the day after the first preconditioning trial, the water consumption of the EtOH

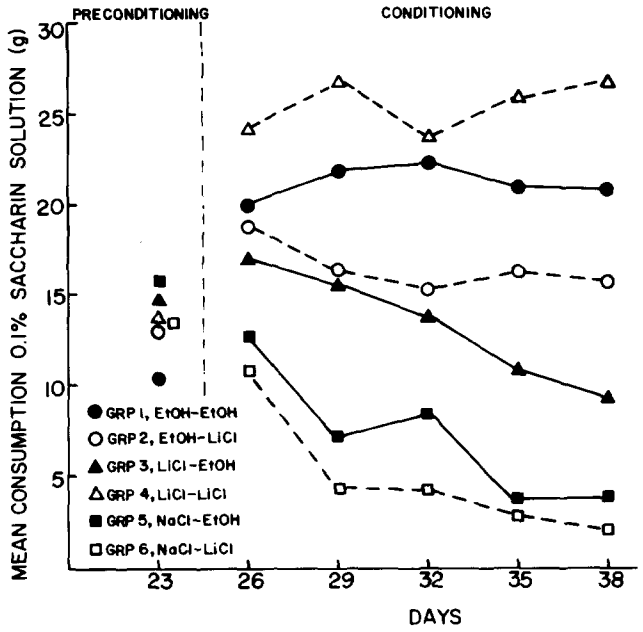

FIG. 5. Mean saccharin consumption per group in Experiment 2. (Group 1 was given EtOH on Days 8–21, i.e., prior to and during conditioning. Group 2 was given EtOH prior to LiCl conditioning; Group 3, LiCl prior to EtOH conditioning; Group 4, LiCl prior to LiCl conditioning; Group 5, normal saline prior to EtOH conditioning; and Group 6, normal saline prior to LiCl conditioning.)

animals was lower than that of the other animals. An analysis of variance of water consumption on Day 22 indicated a treatment effect, $F(2,54) = 10.1$, $p < 0.01$. Newman-Keuls a posteriori tests demonstrate the EtOH animals drank less than either the LiCl or NaCl animals ($p < 0.01$) but that the latter groups did not differ from each other.

Mean saccharin consumption per group across Days 23–38 is shown in Fig. 5. There was not a reliable difference in saccharin consumption on Day 23, i.e., prior to the first conditioning dose. As in Experiment 1, the equivalence of UCS dosages was tested by analyzing the consumption of naive conditioning and intra-agent groups with a UCS x preconditioning experience x days repeated measures analysis of variance. This analysis did not indicate a dissimilarity of UCS dosages as there was neither a UCS effect nor a UCS x experience interaction. Thus, the data of the inter-agent groups (i.e., Groups 2 and 3) were combined, as were the data of intra-agent groups (i.e., Groups 1 and 4) and naive conditioning groups (i.e., Groups 5 and 6). These regrouped data, shown in Fig. 6, were analyzed with a 3 x 5 (treatment x days) repeated measures analysis of variance. This analysis indicated a significant treatment effect, $F(2,54) = 72.5$, $p < 0.01$, a day effect $F(1,54) = 22.6$, $p < 0.01$, and a treatment x day interaction, $F(2,54) = 12.2$, $p < 0.01$. Tests of simple main effects indicated the interaction was due to the fact that there was no day effect for the intra-agent groups, while there were day effects for both the inter-agent and naive groups ($p < 0.01$). There was a treatment effect on each of the 5 days ($p < 0.01$). Newman-Keuls a posteriori analyses computed separately for each day indicated that each group differed reliably from the other two every day ($p < 0.05$).

The mean time per group spent on the rotarod is shown

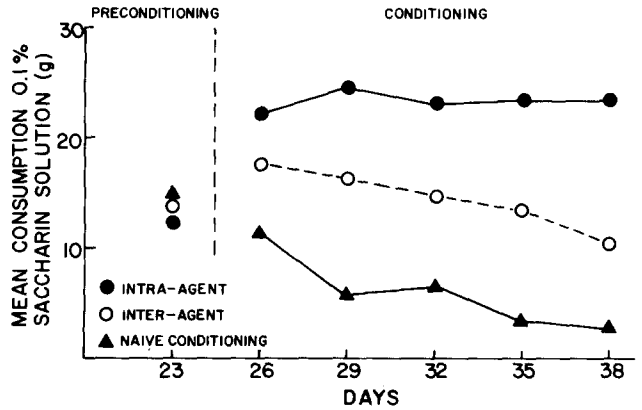

FIG. 6. Mean saccharin consumption of intra-agent groups (Groups 1 and 4), inter-agent groups (Groups 2 and 3), and naive conditioning groups (Groups 5 and 6) in Experiment 2.

in Table 2. An analysis of variance across the 4 groups receiving the rotarod test (i.e., Groups 1, 3, 5 and 6) indicated a significant treatment effect, $F(3,33) = 3.29$, $p<0.05$. Newman-Keuls a posteriori tests showed that Group 6, the EtOH-naive group, spent less time on the rotarod than any of the other groups ($p < 0.01$). the differences between the three EtOH-experienced groups were not statistically reliable. The correlation between saccharin consumption on Day 38 and amount of time on the rotarod on Day 39 computed across Groups 1 and 5, the EtOH groups with no LiCl experience, was statistically significant, $r(15) = .54$, $p < 0.05$.

Discussion

Experiment 2 systematically replicates the major finding of Experiment 1 that intra-agent preconditioning experience results in greater attenuation of learning than does inter-agent experience. Therefore, the conclusion that drug-specific effects enhance intra-agent disruptions is given additional support.

The correlation between the tolerance test and saccharin consumption across the intra-agent (i.e., Group 1) and naive conditioning (i.e., Group 5) EtOH groups suggests that at least part of the drug-specific effect of preconditioning experience may be due to tolerance. Gibbins *et al.* [12] describe the rotarod test as a relatively insensitive measure of tolerance in rats, but it did differentiate EtOH-naive animals (i.e., Group 6) from EtOH-experienced animals (i.e., Groups 1, 3, and 5) in this study. Thus, the correlation across Groups 1 and 5 is a valid indication of a relationship between UCS tolerance and the attenuation of taste aversion learning. That there was a reliable relationship between the two variables is impressive given that the rotarod may be a relatively insensitive tolerance measure and that the test was administered after differences in tolerance due to preconditioning treatment had been diminished by UCS exposure during conditioning.

As in Experiment 1, inter-agent disruptions were found to be symmetrical when comparable dosages were used, thus providing additional indirect support for the hypothesis that asymmetrical inter-agent disruptions are the consequence of dosage effects. The results of Experiment 2 do not support the hypothesis that previous failures to find symmetrical inter-agent disruptions [8,13] are due to the increased discriminability of the drugs following more extensive preconditioning and conditioning experience.

Since Cappell *et al.* [8] reported no water aversions using a similar procedure (i.e., a 7 hr water-drug interval) with different drugs, the decrease in water consumption of EtOH animals over Days 9–22 is probably due to pharmacologic effects of EtOH rather than the development of water aversions.

TABLE 2

PRECONDITIONING AND CONDITIONING DRUG ADMINISTRATION SEQUENCES AND ROTAROD SCORES: EXPERIMENT 2

Group	Preconditioning Drug*	Conditioning Drug†	Rotarod Scores (sec)
1	EtOH	EtOH	25.6
2	EtOH	LiCl	‡
3	LiCl	EtOH	18.6
4	LiCl	LiCl	‡
5	NaCl	EtOH	18.5
6	NaCl	LiCl	5.0

*The preconditioning EtOH dosage was 3 g/kg/day (22.5% EtOH, v/v) on Days 8–10, and 6 g/kg/day (45% EtOH, v/v) on Days 11–21. The preconditioning LiCl dosage was 0.02 ml/g/day of 0.06 M LiCl on Days 8–10, and 0.02 ml/g/day of .12 M LiCl on Days 11–21. Preconditioning NaCl was normal saline (0.9%).

†The conditioning dosage for EtOH was 5 g/kg (37.5%, v/v) and for LiCl was 0.02 ml/g of 0.10 M LiCl.

‡Groups 2 and 4 were not given the rotarod test.

GENERAL DISCUSSION

As noted earlier, two of the most frequently proposed explanations of the attenuation of learned taste aversions following preconditioning UCS experience have been UCS tolerance and CS-UCS dissociation. It is apparent from the results of the present studies that neither hypothesis provides a comprehensive account of the data and that both hypotheses require further specificity. The inter-agent disruptions observed in these studies are consistent with the growing body of data which indicates that neither tolerance nor other drug-specific effects are necessary for preconditioning treatment to attenuate taste aversion learning [e.g., 3, 4, 6]. On the other hand, the comparison of intra- and inter-agent disruptions indicates that drug-specific effects do enhance disruptions produced by preexposure to the UCS. The results of the present studies therefore support Cappell and LeBlanc's [7] contention that "very likely, no single hypothesis will be able to embrace all of the data in this general area" (p. 161). It is probable that effects not drug-specific (i.e., general effects) are operative in both intra- and inter-agent disruptions, and that both general and drug-specific effects are operative in intra-agent disruptions. Thus, the distinction between intra- and inter-agent disruptions is critical in theoretical analyses. Braveman [4] did not make this distinction when he stated that the magnitude of aversion disruption is "indifferent" to the types of preconditioning and conditioning treatment used. His assertion is undoubtedly correct that treatment-specific effects such as tolerance do not provide an adequate account of inter-agent disruption, but it does not follow that treatment-specific effects do not contribute to preconditioning disruptions under certain conditions (e.g., intra-agent disruptions).

The precise nature of the general effect(s) remains to be delineated. As mentioned previously, CS-UCS dissociation has been a frequently discussed possibility [5, 6; cf. 3, 4, 8, 17]. This hypothesis, as presented by Cannon *et al.* [6], posits that a CS-UCS association is not made following preconditioning treatment because the CS simply is not a good predictor of the occurrence of aversive consequences. Aversion-producing effects common to even dissimilar agents in inter-agent paradigms would not be associated with the CS for the same reason aversion-producing UCS effects are not assiciated with the CS in intra-agent paradigms.

Braveman's [4] opponent process hypothesis can be considered to be an alternative explanation of inter-agent disruptions and of that portion of intra-agent disruption which is independent of treatment-specific effects. However, no independent evidence has been produced either for the existence of opponent processes elicited during preconditioning or for the association of these putative processes with environmental cues. Indeed, Cannon *et al.* [6] have shown that giving preconditioning UCS experience in one environment and conditioning trials in another does not alleviate the disruption effect. Thus it does not seem that the association of either the UCS or UCS-elicited opponent processes with exteroceptive stimuli during preconditioning affects subsequent learning of the CS-UCS association. Furthermore, both Cannon *et al.* [6] and Revusky *et al.* [21] have presented data which indicate that pairing a UCS with one CS during preconditioning enhances, rather than retards, the subsequent development of an aversion to a second CS. This, of course, raises the question of why opponent processes would not be operating when preconditioning treatment is paired with a novel flavor other than the CS.

Braveman [4] and Riley *et al.* [23] have recently discussed the hypothesis that the ACTH stress response is the aversive element common to all aversion-producing stimuli. While such efforts to delineate the nature of the aversive stimuli in taste aversion learning are laudable, confirmation of the ACTH hypothesis would not necessarily support Braveman's opponent process theory. Regardless of the nature of the common aversive stimuli involved, a simple dissociative model seems a more parsimonious explanation than the opponent process model for that portion of taste aversion disruption not attributable to drug-specific effects. It should be observed that neither the dissociative hypothesis, the opponent process hypothesis, nor the ACTH hypothesis can account for the fact that intra-agent disruptions are of greater magnitude than inter-agent disruptions.

The nature of the drug-specific effects which enhance intra-agent disruptions also requires further delineation. Tolerance, of course, has been the most frequently proposed drug-specific effect [2, 7, 8, 9, 13, 17]. The correlation in Experiment 2 between saccharin consumption and rotarod performance is the first time a tolerance measure procedurally independent of CS consumption has been shown to covary with CS consumption and thus is the best evidence to date of a relationship between degree of aversion and tolerance.

Tolerance usually has been defined in taste aversion studies as the decreased effect of a given drug dosage following previous exposure(s) to that drug. However, this general concept of tolerance can be further differentiated by distinguishing between behavioral or functional tolerance and metabolic or dispositional tolerance [cf. 16]. Behavioral tolerance is the adaptation to a given level of a drug in the body such that that level of the drug has less behavioral effect. Metabolic tolerance is the increased rate of drug metabolism or clearance. Although both types of tolerance may contribute to intra-agent disruption, some evidence suggests that behavioral tolerance may be prepotent. For instance, while the difference between intra- and inter-agent disruption was as great for LiCl as for EtOH, it is dubious that metabolic tolerance contributes to intra-agent disruption with LiCl. Li is excreted rather than metabolized, and there is no evidence that this process is accelerated by repeated exposure [24,25]. Segal *et al.* [26] have shown neurochemical and behavioral adaptation to Li, however, while Schou [25] reports adaptation to Li side effects (e.g., nausea, abdominal pain, and diarrhea) in its clinical use.

Another drug-specific effect which has been suggested as a source of the preconditioning disruption effect is novelty [1, cf. 11]. This hypothesis states that the novelty of a drug's effects are aversive, and preconditioning drug experience attenuates taste aversion learning by reducing novelty. Both theoretically and procedurally, it is difficult to differentiate the diminution of novelty from the development of behavioral tolerance. Indeed, diminution of novelty may be thought of as a contributing factor to behavioral tolerance. Thus, this hypothesis does little to add to our understanding of the disruption effect.

Some of the original interest in the attenuation of learned taste aversions by drug preexposure was motivated by the hope that the degree of attenuation would be a useful index of changes in a drug's reinforcing properties following the development of tolerance [e. g., 2]. It now appears that hope was ill-founded. Tolerance effects have proven to be quite difficult to extricate from both other drug-specific effects and general dissociative effects. The taste aversion disruption phenomenon could conceivably be used to measure tolerance if it could be proven that the difference between intra-agent and inter-agent disruption was due entirely to tolerance. This difference would, in effect, represent the level of tolerance acquired during pretreatment.

Although of limited value as a measure of tolerance, the disruption effect may nevertheless prove to be a useful tool to the psychopharmacologist. It is possible that the extent to which preexposure to one drug disrupts conditioning with another drug is determined by the similarity of the psychopharmacological effects of the two agents. If this similarity hypothesis is valid, pharmacologically similar agents such as alcohol and barbiturates should produce more inter-agent disruption (and a smaller difference between inter- and intra-agent disruption) than dissimilar agents such as morphine and amphetamine [cf. 8]. This strategy might be useful in evaluating the similarity of the effects of new drugs to those of agents with known properties. Further research is necessary to determine if this proposal has merit.

It was suggested above that the decreased preconditioning water consumption observed in these studies was due to drug-induced adipsia rather than conditioned water aversions. The long water-drug interval in Experiment 2 and the relative difficulty of conditioning aversions to familiar flavors [e.g., 20,30] support this conclusion. It should be noted, however, that the existence of a conditioned water aversion would not jeopardize our ex-

planation of taste aversion disruption. The attenuation of a saccharin aversion cannot be attributed to a competing water-UCS association. As noted earlier, if a UCS is paired with a flavor other than the CS during preconditioning, subsequent conditioning is more rapid than if the UCS had been unpaired [6,21]. Thus, the only consequence of a water-drug association, if it did occur, would be to facilitate, rather than retard, the learning of a saccharin aversion. Such a consequence would merely reduce the magnitude of both inter- and intra-agent disruptions but would not invalidate our conclusions regarding the sources of those disruptions.

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