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Paradoxical Aversive Conditioning with Ethanol[1]

CHRISTOPHER L. CUNNINGHAM AND JAMES G. LINAKIS

University of Oregon Health Sciences Center, Portland, OR 97201

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CUNNINGHAM, C. L. AND J. G. LINAKIS. *Paradoxical aversive conditioning with ethanol.* PHARMAC. BIOCHEM. BEHAV. 12(3) 337–341, 1980.—In three experiments with hooded rats, paired injections of ethanol and lithium chloride produced an aversion to the taste of ethanol, yet reduced ethanol's potency as an unconditioned stimulus during subsequent taste aversion conditioning with saccharin (i.e., saccharin→ethanol). Two of the experiments were designed to test an associative "blocking" account of the latter finding. In each of these experiments, an attempt was made to extinguish the aversion conditioned to a potential blocking stimulus after ethanol-lithium pairings, but before saccharin-ethanol conditioning. Nonreinforced exposure to intraperitoneally mediated ethanol taste cues did not eliminate the detrimental effect of ethanol-lithium pairings on subsequent saccharin-ethanol conditioning (Experiment 2), whereas nonreinforced exposure to handling-injection cues did (Experiment 3), thus providing support for the associative blocking interpretation. Implications of these findings for chemical aversion therapy are discussed.

Ethanol Lithium chloride Taste aversion conditioning Blocking Second-order conditioning Aversion therapy

PAIRED injections of ethanol and lithium chloride have been found unexpectedly to decrease the subsequent ability of ethanol to serve as a reinforcer for conditioning aversion to a novel flavor solution [11]. These investigators had set out to determine whether pairing the ethanol state with lithium-induced illness might not prove to be a desirable extension of chemical aversion therapy for alcoholism, which typically involves pairing only the sight, smell and taste of alcohol with an illness-inducing agent. However, the result of their experiment suggested that such treatment might actually be countertherapeutic inasmuch as it appeared to render the ethanol state less aversive. The authors were at a loss to provide an account of this effect in terms of conventional conditioning principles. They simply labelled the effect Avfail (Aversion failure), and suggested that it represented a specialized adaptation of the feeding system.

The experiments reported here, which were conducted without knowledge of the findings of Revusky *et al.* [11], show a similar effect using somewhat different conditioning and test procedures. The initial impetus for these studies, however, was quite different from that described above, and our research has suggested at least one conventional account of the Avfail phenomenon. Our original reason for pairing ethanol injection with lithium injection was to see whether an aversion could be established to the flavor of ethanol injected intraperitoneally. An earlier series of studies had provided indirect evidence that ethanol injection produces a taste capable of interacting with the tastes of orally ingested substances [5], and the present experiments began as an attempt to provide more direct evidence for the existence of such a taste.

In each of the experiments described below and in several others, the pairing procedure was found to produce a significant level of aversion to a mild solution of ethanol presented orally, confirming the existence of an intraperitoneally-mediated taste cue. However, in every instance, the magnitude of the aversion was rather small and tended to dissipate over the course of a relatively short test period, despite the use of what would normally be considered a relatively intensive taste aversion conditioning regime (five trials using a high dose of lithium chloride as the unconditioned stimulus).

It seemed likely that features of ethanol injection other than its taste were also being conditioned, and we chose the procedure of pairing a novel flavor solution (saccharin) with injection of ethanol as an alternative means of assessing ethanol-lithium conditioning. The rationale for this procedure was similar to that described by Revusky *et al.* [11] and our expectations were similar. That is, saccharin-ethanol conditioning was viewed as a second-order conditioning test of first-order ethanol-lithium conditioning. Presumably, successful first-order conditioning of an ethanol aversion would be revealed by stronger second-order conditioning of a flavor aversion to saccharin paired with ethanol. However, the outcome of that test was contrary to expectation, and like the study of Revusky *et al.*, [11] indicated that ethanol-lithium pairings actually retarded subsequent saccharin-ethanol conditioning.

The first experiment documents this paradoxical effect, showing that the same conditioning procedure establishes an aversion to the taste of ethanol yet reduces its ability to induce an aversion to a paired flavor stimulus. The second

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and third experiments replicate this finding and, in addition, provide tests of an associative blocking account of the Avfail phenomenon.

EXPERIMENT 1

This experiment had two purposes: (1) To determine whether several pairings of ethanol injection with lithium injection would condition an aversion to the taste of ethanol, and (2) To examine the impact of such conditioning on the subsequent effectiveness of injection of ethanol as a reinforcer for conditioning an aversion to a novel flavor solution. Accordingly, two groups of fluid-deprived rats were exposed to ethanol injections and to lithium injections separated either by 2.5 min (Paired Group) or by 24 hr (Unpaired Group). The choice of a relatively short interstimulus interval (in contrast to the 30-min interval used by Revusky *et al.*) [11] reflected a desire especially to promote conditioning to the hypothesized ethanol taste cues which were assumed to be mediated vascularly, and hence, to be most salient shortly after injection when blood-drug levels are near their peak (cf. [9]). Both groups then received a common test procedure that involved consumption of an oral solution of ethanol followed by a series of saccharin-ethanol conditioning trials.

METHOD

Subjects and Apparatus

The subjects were 13 female Simonsen hooded rats, weighing an average of 282 g. They had previously served in a classical heart-rate conditioning experiment in which they had been exposed to tones, light, shock and a single intraperitoneal (IP) injection of saline or ethanol (1 or 2 g/kg, 10 ml/kg). Assignment to groups in the present experiment was done randomly with respect to previous experimental history.

The rats were individually housed in wire-mesh cages with free access to lab chow throughout the experiment. Water and flavor solutions were presented at room temperature in Nalgene test tubes fitted with stainless steel drinking spouts inserted through the front of the home cage. All fluid measurements were made in the middle of the light portion of a normal 12-hr light-dark cycle.

Procedure

A fluid-deprivation schedule was initiated 7 days before the first conditioning trial. Thirty-min access to tap water was allowed on the first day, with 20-min per day thereafter. Two groups were then formed, matched on the basis of weight and average water consumption.

Table 1 outlines the procedure used for the rest of Experiment 1. During Phase 1, the experimental, Paired (P) group (n=7) received a total of five ethanol-lithium (EtOH-LiCl) conditioning trials on odd-numbered days over a 10-day period. These trials began 40 min after the end of the daily drinking period. On each trial, each rat was given a 0.6 g/kg IP injection of ethanol in normal saline (30.4%, v/v, 2.5 ml/kg) followed 2.5 min later by an IP injection of lithium chloride (0.6 M, 5 ml/kg). The rats were returned to their home cages during the interval between injections. Rats in the Unpaired (U) control group (n=6) also received two injections on odd-numbered days during this phase. However, the ethanol injection was followed 2.5 min later by a placebo injection (normal saline, 5 ml/kg) (EtOH-Sal). In order to equate groups for exposure to each drug, the Unpaired group received a single injection of lithium 24 hr later, 40 min after drinking. The Paired group received a single injection of saline at that time.

The conditioning phase was followed by two recovery days on which all rats were given their usual 20 min access to tap water. A test for aversion to the taste of ethanol was given on the next day. This test consisted of two 5-min periods of access to a 4.75% (v/v) solution of ethanol in tap water separated by 2 min. Short test periods were used in order to make an alternative interpretation of the outcome less plausible. Specifically, one might argue that Paired-group rats suppressed drinking, not because the taste of ethanol had been associated with lithium toxicosis, but because intoxication or some other feature of ethanol (which gradually became stronger as the rat consumed ethanol during the test) had been associated with lithium. The taste interpretation would be more strongly supported if a group difference appeared early in the test, before very high blood-ethanol levels could be reached.

The final phase of the experiment provided a different assessment of the effects of ethanol-lithium pairings. After a single water-recovery day, all rats were exposed to a series of six taste-aversion conditioning trials in which 10-min access to a sodium saccharin solution (0.1%, w/v) was followed within 10 min by an IP injection of ethanol (1.8 g/kg, 30.4%, v/v). The ethanol dosage was increased over the level used earlier so that the absolute level of taste aversion produced during this phase would be in a range that might be more sensitive to any effects of prior ethanol-lithium conditioning (see Revusky *et al.*, [11], p. 185, for a discussion of floor and ceiling effects in this context). Thus, the results of this procedure reflect the simultaneous contributions of the primary aversive effects of ethanol and whatever effects were acquired as a result of Phase-1 conditioning.

The saccharin conditioning trials were given on alternate days over a 12-day period; twenty-min access to tap water was permitted on the days between each conditioning day.

RESULTS AND DISCUSSION

Table 1 shows the average amount of 4.75% ethanol drunk during the oral aversion test and the average amount of saccharin consumed over the six saccharin-ethanol conditioning trials. These data indicate that whereas the Paired Group consumed less ethanol (i.e., showed a greater aversion to ethanol's taste), it also consumed more saccharin (i.e., showed a greater resistance to taste-aversion conditioning with an ethanol reinforcer). Statistical analysis confirmed the reliability of the difference between groups obtained during the first 5 min of the ethanol test (Mann-Whitney U (6,7)=5, $p<0.03$), but not for the 10-min totals (U=12). Analysis of average saccharin consumption also yielded a significant difference (U=2, $p<0.01$).

Thus, despite many differences in parametric detail, Experiment 1 yielded an effect very similar to the Avfail phenomenon reported by Revusky *et al.* [11]. Moreover, the fact that the paired injections produced an aversion to ethanol's taste, while simultaneously rendering ethanol a less effective reinforcer for subsequent conditioning seems to underscore the puzzling nature of the latter finding. However, as will be seen, the development of an aversion to at least one of ethanol's features provided an important clue for the analysis which follows.

TABLE 1
EXPERIMENTAL DESIGNS AND AMOUNTS OF ETHANOL AND SACCHARIN CONSUMED DURING TESTING

Group	Phase 1 Odd days; even days	Phase 2	Oral ethanol test* (mean ml ± SEM) 1st 5 min	10-min total	Saccharin → ethanol conditioning (mean ml/trial ± SEM)
Experiment 1					
P (n=7)	EtOH → LiCl; Sal†	—	6.8 (± 1.1)	11.4 (± 1.6)	12.6 (± 1.0)
U (n=6)	EtOH → Sal; LiCl	—	9.9 (± 0.6)	13.0 (± 0.5)	6.9 (± 1.1)
Experiment 2					
P-NE (n=9)	EtOH → LiCl; Sal	Sal	8.9 (± 0.5)	12.1 (± 0.7)	10.5 (± 0.8)
P-E (n=9)	EtOH → LiCl; Sal	EtOH	9.3 (± 0.6)	13.6 (± 0.8)	9.9 (± 0.4)
U (n=9)	EtOH → Sal; LiCl	Sal	11.6 (± 0.7)	15.2 (± 1.0)	7.2 (± 1.2)
Experiment 3					
P-NI (n=8)	EtOH → LiCl; Sal	—	5.9 (± 1.1)	—	14.6 (± 0.9)
P-I (n=6)	EtOH → LiCl; Sal	Sal	5.8 (± 1.3)	—	11.9 (± 1.2)
U (n=9)	EtOH → Sal; LiCl	—	10.2 (± 0.5)	—	11.6 (± 0.7)

*In Experiment 3 only, the oral ethanol test intervened between Phases 1 and 2.
†EtOH=ethanol; LiCl=lithium chloride; Sal=normal saline.

EXPERIMENT 2

Superficially, there appeared to be a resemblance between the effect observed in Experiment 1 and a rather familiar phenomenon in the gustatory aversion conditioning literature—namely, the unconditioned-stimulus (US)-preexposure effect (cf. [1,6]). In both instances, a preconditioning treatment retards subsequent taste-aversion learning. However, it is clear that the ethanol-lithium treatment cannot be reduced simply to an instance of US pre-exposure without additional assumptions, because both the Paired and Unpaired groups received an equal number of each kind of injection. First of all, one would have to argue that the Paired Group received a stronger or different US pre-exposure than the Unpaired group because of the close temporal relation between the injection of each drug. Moreover, it would be necessary to assume that pre-exposure to one of these drugs is able to affect aversion conditioning based on the other, for which evidence is already available [2]. It should be noted, however, that reducing the ethanol-lithium treatment to a special instance of US pre-exposure would not entirely explain the effect, inasmuch as there remain several alternative accounts of the US pre-exposure effect itself (cf. [1, 4, 6, 10]). At best, this approach only points to a group of explanations that might be considered.

It seemed that the outcome of Experiment 1 might be explained by either of two alternative accounts of a US preexposure effect: (1) enhanced development of tolerance (or habituation) to the drug, or (2) associative blocking. According to the first account, it might be assumed that the Paired Group actually received a more intense US pre-exposure treatment because the overlap of ethanol with lithium potentiated lithium's toxic consequences (cf. [8]), and led to more rapid development of tolerance to the drug effect which normally induces flavor aversion. Greater retardation of subsequent taste aversion learning would be consistent with other reports of an inverse relation between intensity of US pre-exposure and the subsequent potency of the US (e.g., [3]). The second explanation relies on the possibility that as a result of being paired with lithium toxicosis, certain features of ethanol (or its administration) acquired the ability to block subsequent learning of the relation between saccharin and the aversive consequences of ethanol intoxication. Although the blocking phenomenon was originally studied in conditioned suppression experiments (cf. [7]), recent experiments have shown its role in determining US pre-exposure effects on taste-aversion learning [4,10]. Experiment 1 provided direct evidence that at least one of ethanol's features—its taste—had become aversive as a result of ethanol-lithium pairings. Possibly, the taste of ethanol blocked conditioning to the taste of saccharin.

An implication of the blocking interpretation (or any other account that posits an ethanol-lithium association) which distinguishes it from the pharmacological account is that it should be possible to eliminate blocking by extinguishing the aversion to the alleged interfering feature before saccharin-ethanol conditioning [10]. Thus, according to the associative account, a Paired Group which has received such an extinction treatment would be expected to develop saccharin aversion more readily than a Paired Group which has not received extinction. Experiment 2 was designed to test this analysis based on blocking by intraperitoneally-mediated ethanol taste cues.

METHOD

Subjects and Apparatus

Twenty-seven female Simonsen hooded rats were used (average weight=334 g). Their experimental history and maintenance conditions were identical to those of subjects in Experiment 1.

Procedure

All rats were first placed on the fluid-deprivation schedule described earlier. The procedure for the rest of Experiment 2

is outlined in Table 1. Phase 1 conditioning was identical to that used in Experiment 1, with two groups receiving paired ethanol-lithium injections and a third group receiving unpaired injections (n=9/group). Unlike Experiment 1, however, a 10-day extinction period (Phase 2) intervened between Phase-1 conditioning and testing. On each of these 10 days, each rat received an IP injection 40 min after the end of the daily 20-min drinking period. Rats in the Paired-Extinction (P-E) group received injections of ethanol in the same dose as used during Phase 1 (0.6 g/kg) in an attempt to extinguish the aversion conditioned to ethanol's taste. Rats in the Paired-No Extinction (P-NE) group and in the Unpaired (U) control group received saline injections of the same volume (2.5 ml/kg).

The oral ethanol test and saccharin-ethanol conditioning trials were conducted as in Experiment 1 with two exceptions: (1) saccharin trials were given at 72-hr intervals and (2) only five saccharin trials were given.

RESULTS AND DISCUSSION

Table 1 lists the amounts of ethanol and saccharin consumed during testing. As in the first experiment, the Paired groups drank less ethanol, but more saccharin than the Unpaired group. Although the differences between the Paired groups were in the direction predicted by the blocking analysis, they were quite small. Analysis of amount consumed during the first 5 min of the ethanol test indicated that the Paired groups did not differ, but that each drank significantly less than the Unpaired control group (both $Us \leq 17$, $p<0.05$). After 10 min, only the difference between Groups P-NE and U was reliable ($U=19$, $p<0.05$, one-tail). Thus, this experiment replicated the finding that ethanol-lithium pairings produced an ethanol taste aversion, but provided only weak evidence that additional ethanol injections without lithium extinguished that aversion.

Statistical analysis of saccharin consumption scores revealed no difference between the Paired Groups, although each group drank significantly more than the Unpaired control (both $Us \leq 17$, $p<0.05$). A trial-by-trial analysis of saccharin consumption also failed to yield differences between the Paired Groups.

Thus, Experiment 2 replicated the main findings of Experiment 1, but did not provide evidence to support an interpretation of the taste-aversion retardation effect based on blocking by ethanol taste cues. Given the failure to find strong, direct evidence that the ethanol taste aversion had been extinguished, it is possible that the extinction treatment was simply not carried out long enough. Alternatively, it may be that blocking is not involved, or that blocking is mediated by some cue other than ethanol taste. The next experiment assessed the last possibility.

EXPERIMENT 3

It seemed possible that both paired groups in Experiment 2 might have received a treatment that extinguished aversion to a potential blocking stimulus. One aspect of the treatments that was common to both groups could have played such a role—specifically, the cues provided by handling and injection. There is growing evidence that associations between handling-injection cues and certain drugs may contribute to the interference produced by US pre-exposure [4,10]. If, in Experiments 1 and 2, handling-injection cues were made more aversive during the conditioning phase by the Paired trials than by Unpaired trials, then one could predict blocking of subsequent conditioning by those cues, as well as a reduction in that interference after a series of handling-injection extinction trials. Examination of the procedures used in these studies suggests that handling-injection could have been more aversive in Paired Groups either because the combined action of ethanol and lithium constituted a more potent US than either drug alone or because the double handling-injection of ethanol-lithium trials enhanced the salience of handling-injection cues.

Experiment 3 was designed to assess an interpretation of the retardation effect based on blocking by handling-injection cues. Three groups of rats received treatments generally comparable to those given in Experiment 2, except for the Phase-2 extinction treatment. In this case, extinction consisted simply of several injections of saline, whereas no-extinction and control animals were not handled at all.

METHOD

Subjects and Apparatus

The subjects were 23 naive male Simonsen hooded rats (mean weight=392 g) maintained as in the previous experiments.

Procedure

Three groups of rats were first exposed to the fluid-deprivation and Phase 1 conditioning procedures used in Experiment 2. A single water-recovery day preceded a 5-min ethanol taste test (4.75%, v/v), which intervened between Phases 1 and 2 in this experiment. Ten-min access to water was permitted 90 min after the taste test. Another water-recovery day preceded the beginning of the handling-injection extinction treatment. For the three days before, and throughout saccharin-ethanol conditioning, rats in the Paired-Injection group (P-I; n=6) received four double injections of saline (two 0.25 ml injections separated by 2.5 min) at 90-min intervals beginning 90 min before the end of the daily drinking period, except when an ethanol injection was scheduled. This treatment was intended to extinguish any aversion conditioned to handling-injection cues during Phase 1. Rats in the Paired-No-Injection group (P-NI; n=8) and in the Unpaired group (U; n=9) were not handled at these times. All groups then received six saccharin-ethanol conditioning trials at 72-hr intervals using the parameters described earlier.

RESULTS AND DISCUSSION

Average ethanol and saccharin consumption during testing is shown in Table 1. As can be seen, Group P-NI drank less ethanol but more saccharin than Group U, replicating again the main findings of the previous experiments. However, the level of saccharin aversion shown by Group P-I was greater than that of Group P-NI and nearly the same as that of Group U. Statistical analysis confirmed these observations, indicating that both Paired groups drank less ethanol than Group U (both $Us \leq 7$, $ps<0.05$). The analysis of saccharin consumption yielded differences between Group P-NI and each of the other groups (P-NI vs P-I: $U(8,6)=10.5$, $p<0.05$, one tail; P-NI vs U: $U(8,9)=13.5$, $p<0.05$), but no difference between Groups P-I and U.

In summary, Experiment 3 replicated the main findings of the earlier experiments, and, in addition, suggested that the taste-aversion retardation effect is due, at least in part, to blocking by conditioned aversive handling-injection cues.

This is supported by the finding that extinction of handling-injection cues in Group P-I eliminated the otherwise retarding effects of ethanol-lithium pairings.

GENERAL DISCUSSION

All three of the experiments reported here show that paired injections of ethanol and lithium chloride induce an aversion to the taste of ethanol yet reduce the subsequent potency of ethanol as a US. It was suggested that the apparent reduction in ethanol's potency as a US might be produced by associative blocking in much the same way that associative blocking has been found to contribute to the US pre-exposure effect in gustatory conditioning [4,10]. According to this account, certain of the features of ethanol (e.g., taste, intoxication) or its administration (e.g., handling, injection) are presumed to become relatively more aversive in animals receiving paired ethanol-lithium injections than in animals receiving unpaired injections. When these cues are later presented in conjunction with a novel flavor cue during aversive conditioning, there is a greater tendency for overshadowing of the flavor cue in paired-group animals, leading to relatively greater consumption of the flavor solution. Experiment 3 provided support for this analysis by showing that extinction of the aversion conditioned to a potential blocking stimulus (handling-injection cues) reinstated ethanol's potency as a US.

The results of these experiments do not clearly indicate that conditioning of any of ethanol's *intrinsic* features during Phase 1 mediated the subsequent retardation effect. One extreme implication of this is that IP injection of *any* substance before lithium in Phase 1 might be expected to retard saccharin-ethanol conditioning. On the other hand, these experiments do not preclude the possibility that features of ethanol injection other than handling and injection also contribute to the blocking of saccharin-aversion conditioning. Experiment 2, for example, leaves open the possibility that ethanol's taste is involved, although the available data suggest that it is not a very strong component of the blocking stimulus complex. It may be that the use of different parameters during ethanol-lithium conditioning would differentially affect the strengths of potential blocking stimuli. For instance, the longer inter-injection interval (30 min) used by Revusky *et al.* [11] may have especially promoted conditioning of the drug state (intoxication), which in turn, blocked later conditioning of saccharin. It should be noted, however, that because Revusky *et al.*'s [11] control group (a backward pairings group) was not handled as much as their paired group before each lithium injection, the possibility remains that their Avfail phenomenon reflected blocking by conditioned aversive handling-injection cues as in the present experiments.

The full implications of the findings reported here for chemical aversion therapy will ultimately depend on a more complete identification of potential blocking stimuli. In general, however, the phenomenon described here suggests that if, after aversion therapy, the patient drinks in the presence of such stimuli, any new behavior(s) or event(s) which accompanies these cues might be relatively immune to any negative effects of alcohol ingestion. Unfortunately, these new behaviors may be the very ones in which the individual engaged to circumvent the effects of aversion therapy. According to the present analysis, one of the procedures often used to improve the effectiveness of aversion therapy—attempting to increase the similarity between the treatment environment and the patient's normal drinking environment—also increases the likelihood that a potential blocking stimulus will be present if a relapse occurs.

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