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Nicotine and Ethanol Interaction on Conditioned Taste Aversions Induced by Both Drugs

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KUNIN, D., B. R. SMITH AND Z. AMIT. *Nicotine and ethanol interaction on conditioned taste aversions induced by both drugs.* PHARMACOL BIOCHEM BEHAV **62**(2) 215–221, 1999.—The present study was designed to explore the interactive effects of nicotine and ethanol in the pretreatment and preexposure conditioned taste aversion (CTA) paradigm. The first experiment examined the effects of ethanol pretreatment on a nicotine induced CTA. The second experiment examined the effects of nicotine pretreatment on an ethanol CTA. The results of these two experiments revealed an asymmetrical interaction between ethanol and nicotine. Although nicotine pretreatment blocked an ethanol induced CTA, ethanol pretreatment merely attenuated a nicotine-induced CTA. These findings demonstrated that ethanol and nicotine interact pharmacologically in a unidirectional fashion, suggesting some unique and unshared pharmacological properties of each agent. The third experiment of this study examined the effects of preexposure with ethanol on a nicotine-induced CTA, while the fourth experiment examined the effects of preexposure with nicotine on an ethanol-induced CTA. These results revealed a symmetrical interaction between ethanol and nicotine in that both agents equally blocked CTA to one and the other. In contrast to the pretreatment CTA paradigm, these results suggested that both ethanol and nicotine appear to be functionally related and share common stimulus properties. Taken together, the present study demonstrates that while ethanol and nicotine are functionally related, they may also be endowed with unique unshared properties. © 1999 Elsevier Science Inc.

Conditioned taste aversion (CTA) Ethanol Nicotine Rats

MULTIPLE drug use is an increasingly common phenomenon (25). Ethanol and nicotine in the form of alcoholic beverages and tobacco cigarettes are two frequently combined psychoactive substances (38). In humans, a strong positive relationship has been suggested between cigarette smoking and alcohol use (38). A number of studies have demonstrated that alcohol pretreatment can increase cigarette intake (15,19,20). In addition, several studies on the effects of ethanol and nicotine consumed separately or jointly have demonstrated that nicotine can counteract specific detrimental effects of ethanol on cognitive skills such as reduction in alertness and speed of decision making (28–30).

The interactive effects between ethanol and nicotine have also been examined in laboratory animals. In a study which assessed the effects of continuously administered psychoactive agents on ethanol consumption, it was found that chronically infused nicotine potentiated the oral intake of a 10% ethanol solution in rats (32). More recently, it was reported that rats given nicotine (0.35 mg/kg SC) daily increased their ethanol intake (3). It has also been demonstrated that short-term treatment with nicotine can result in the development of crosstolerance to some of the effects of ethanol, and that short-term treatment with ethanol can result in the development of crosstolerance to some of nicotine's effects in mice (7,10). Finally, the effects of ethanol and nicotine have also been compared in the drug discrimination paradigm. Nicotine has been shown to potentiate ethanol discrimination in rats (33). In addition, alcohol-preferring (P) rats have been shown to be more sensitive to the ethanol-like effects of nicotine compared to nonpreferring (NP) rats (16).

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The present study was an attempt to further explore the interactive effects between ethanol and nicotine using the conditioned taste aversion (CTA) paradigm. Both ethanol (8) and nicotine (14,23,26) have been shown to produce a CTA on their own, but their interactive effects have never been examined in the CTA paradigm. In the traditional CTA paradigm, an animal will typically ingest a novel tasting fluid (e.g., saccharin) or food and then immediately after receive a treatment consisting of a drug injection. On a later occasion, the animal is presented once again with the same fluid, which under these circumstances, results in an avoidance of this fluid. This reduced preference or intake of the once novel tasting fluid is taken as evidence of a conditioned taste aversion (17,21).

Traditionally it was believed that this reduction of fluid intake as reflected in the CTA procedure was due to the association between the novel taste of a substance and some aversive property of the treatment. It was subsequently demonstrated, however, that a wide variety of drugs including those with positive reinforcing properties could produce CTAs within dose ranges that were known to be self-administered (2). The finding that a reinforcing drug can produce a CTA within dose ranges that are self-administered has been called "paradoxical" (17,21).

Essentially this "paradox" implied that a given drug can be both rewarding, as reflected in self-administration, and "aversive," as reflected in the CTA. In fact, this paradoxical phenomenon was shown for almost all self-administered drugs, i.e., morphine (8), amphetamine (12), cocaine (18), and ethanol (8). The evidence from the animal literature seems to support the view that the seemingly "aversive" and positive reinforcing properties of self-administered drugs are, nevertheless, functionally related, and involve common discriminative characteristics (17). This view is based on two sets of evidence. The first set of evidence is obtained from research that has demonstrated that the same injection of morphine and or amphetamine can act simultaneously both as a positive reinforcer and CTA-inducing agent in the same animal (36,37). The second set of evidence is obtained from research that has shown that the same neurochemical mechanisms can mediate both self-administration of and CTA to the same given drug (21).

The first experiment of this study examined the effects of pretreatment with ethanol on a nicotine-induced CTA. The second experiment of this study assessed the effect of pretreatment with nicotine on an ethanol-induced CTA. In the pretreatment CTA paradigm, a pretreatment drug is typically administered to the animal prior to conditioning with another drug treatment but in close temporal proximity (e.g., 60–90 min) to permit a pharmacological interaction between the pretreatment and conditioning agent. The pretreatment procedure permits one to assess whether one drug directly alters the pharmacological effects of a subsequent drug administration (i.e., unconditioned stimulus) thereby altering the latter's association with a novel flavor (i.e., conditioned stimulus). It has been shown that pretreatment with a variety of neurochemical altering agents may differentially effect taste aversion learning to a variety of self-administered drugs (21).

The third experiment of this study was designed to assess the interaction between ethanol and nicotine in the preexposure conditioned taste-aversion paradigm. This experiment examined the effect of preexposure to ethanol on the formation of a nicotine-induced CTA. The fourth experiment of this study, assessed the effect of nicotine preexposure on the formation of a ethanol-induced CTA. In the preexposure paradigm, animals typically receive exposure to a drug on one or more occasions prior to the onset of taste-aversion learning. In this paradigm, unlike the pretreatment variant, the preexposure drug and the subsequent drug (unconditioned stimulus) are never in the system simultaneously, such that there is no opportunity for them to interact pharmacologically. This paradigm can provide a unique opportunity for the assessment of the mechanisms underlying drug discrimination (11,34). That is, if preexposure to one drug can disrupt the acquisition of a CTA to another drug, then the effects of the preexposure drug could be said to have generalized to the conditioning drug. This would imply that two seemingly different drug stimuli must, in fact, share common properties for the preexposure drug to disrupt the novelty of the conditioning drug (34). Hence, the more the stimulus properties produced by the preexposure drug resemble the stimulus properties of the conditioning drug, the less likely it is that there will be a CTA to the conditioning drug. Conversely, the less a preexposure drug resembles the conditioning drug, the less likely it is that a CTA to the conditioning drug will be disrupted. The preexposure paradigm has been utilized in order to identify common stimulus properties shared by various drugs (1,9,31,34,35).

METHOD

Animals

Male Wistar rats (Charles River, Canada) weighing between 300–325 g at the start of the experiment were used. Rats were individually housed in stainless steel cages with standard lab chow and tap water freely available prior to the onset of each experiment. Throughout all experiments the animals were maintained in a room regulated for constant temperature and humidity on a 12-L:12-D cycle.

Drugs

(−)-Nicotine di-d-tartrate (Research Biochemical International) 1 mg /kg was dissolved in saline at a concentration of 1 mg/ml. Ethanol solution in concentration of 20% v/v was prepared by mixing 95% ethanol with saline. Ethanol was injected in a volume of 1.2 g/kg.

Procedure

Experiment I: Ethanol pretreatment on nicotine-induced CTA. Following 1 week of acclimatization to the laboratory housing conditions, 31 male Wistar rats were placed on a 23 h and 20-min water deprivation schedule. Tap water was presented to the animals in stoppered plastic tubes fitted with stainless steel ball bearing spouts for 40 min beginning at noon each day. The spouts were inserted through the wire mesh in front of the home cages. Rats were presented with water in this fashion for 6 consecutive days following the last acclimatization day. A one-bottle drinking procedure was used for all drinking sessions.

On day 7, animals were randomly assigned to one of four treatment groups. All injections were administered IP. Group vehicle–vehicle ($n = 8$) received a single injection of saline 60 min prior to presentation of a novel 0.1% (w/v) sodium saccharin solution given in place of normal drinking water. Immediately following this 20-min exposure to the saccharin solution, rats in this group were injected twice with saline spaced 30 min apart. Group vehicle–nicotine ($n = 8$) was administered a single injection of saline 60 min prior to presentation of saccharin and then injected with nicotine (1 mg/kg), twice, 30 min apart immediately following saccharin presenta-

tion. This regimen of nicotine was adapted from Etscorn and colleagues (14), who demonstrated that a single injection of nicotine 1 mg/kg failed to produce a CTA.

Extending the duration of nicotine through repeated injections of IP nicotine spaced 30 min apart has been shown to produce a CTA (14). Group ethanol—nicotine ($n = 8$) was administered a single injection of ethanol (1.2 g/kg) 60 min prior to saccharin presentation and was then administered nicotine (1 mg/kg) twice spaced 30 min immediately following saccharin presentation. Group ethanol–vehicle ($n = 7$) received a single injection of ethanol (1.2 g/kg) 60 min prior to presentation of saccharin and was then subsequently injected with saline twice spaced 30 min apart.

On the following days, animals were maintained on restricted water access. The conditioning procedure (pairing day) that took place on day 7, was also repeated on days 10 and 13. Days 16, 19, and 22 constituted drug-free test days. On these days, animals were presented with saccharin for 20 min without a corresponding drug treatment. On intervening days, between conditioning and test days, animals were presented with water for 40 min, beginning at noon.

Experiment II: Nicotine pretreatment on ethanol-induced CTA. Following 1 week of acclimatization to the laboratory housing conditions 32 male Wistar rats were placed on the same water deprivation schedule as in Experiment 1. On day 7, animals in group nicotine–ethanol ($n = 8$) received a single injection of nicotine (2 mg/kg), 60 min prior to the presentation of a novel saccharin solution (0.1% w/v) given instead of the drinking water. Immediately following this 20-min exposure to saccharin, animals in this group received a single injection of ethanol (1.2 g/kg). Animals in group nicotine–vehicle ($n = 8$) received a single injection of nicotine (2 mg/kg) 60 min prior to the saccharin presentation, and were then subsequently injected with saline. Animals in group vehicle–ethanol ($n = 8$) were administered a single injection of saline 60 min prior to saccharin administration, and then following saccharin exposure were injected with ethanol (1.2 g/kg). This dose of ethanol has been shown to produce a CTA (31). Animals in group vehicle–vehicle ($n = 8$) were administered a single injection of saline 60 min prior to saccharin treatment, and were then injected with saline immediately following saccharin exposure. As in Experiment 1, there were 3 drug-free test days. Water was presented for 40 min between conditioning and test days in a manner identical to Experiment 1.

Experiment III: Ethanol preexposure on nicotine-induced CTA. After 1 week of adaptation to the laboratory housing conditions 32 male Wistar rats were placed on a 23-h 20-min water-deprivation schedule with free access to lab chow in a manner similar to that of the previous experiments; however, after 3 days of adaptation to the water-deprivation schedule, animals were randomly assigned to one of four groups.

The preexposure injections were administered on days 4, 5, and 6, and 60 min following the 40-min water session. All injections were administered IP. Animals in groups ethanol–nicotine ($n = 8$) and ethanol–vehicle ($n = 8$) were preexposed to a single injection of ethanol (1.2 g/kg), while animals in groups vehicle–vehicle ($n = 8$) and vehicle–nicotine ($n = 8$) were preexposed to a single injection of saline. On day 7, 24 h after the last pre exposure injection, rats were presented with a novel 0.1% (w/v) saccharin solution for 20 min. Within 1 min after the completion of the saccharin intake period, animals in groups ethanol–nicotine and vehicle–nicotine were injected with nicotine twice at a dose of 1 mg/kg per injection spaced 30 min apart, while animals in groups ethanol–vehicle and vehicle–vehicle were injected with saline. This injection regimen of nicotine was identical to Experiments 1 and 2. A second and third pairing between the saccharin solution and drug or vehicle injections took place on days 10 and 13. On all intervening days animals were presented with water for 40 min beginning at noon. Days 16, 19, and 22 constituted drug-free test days whereby the animals were presented with saccharin solution for 20 min without any subsequent drug pairings.

Experiment IV: Nicotine preexposure on ethanol-induced CTA. After 1 week of adaptation to the laboratory housing conditions 32 male Wistar rats were placed on a 23-h 20-min water-deprivation schedule, with free access to lab chow in a manner similar to that of the previous experiments. After 3 days of adaptation to the water-deprivation schedule, animals were randomly assigned to one of four groups.

Animals in groups nicotine–ethanol ($n = 8$) and nicotine–vehicle ($n = 8$) were preexposed to a single injection of nicotine (2 mg/kg), while animals in groups vehicle–vehicle ($n = 8$) and vehicle–ethanol ($n = 8$) were preexposed to a single injection of saline. On day 7, 24 h after the last preexposure injection, the rats were presented with a novel 0.1% (w/v) saccharin solution for 20 min. Within 1 min after the completion of the saccharin intake period, animals in groups nicotine–ethanol and vehicle–ethanol were administered a single injection of ethanol (1.2 g/kg), while animals in groups nicotine–vehicle and vehicle–vehicle were administered a single injection of saline. A second and third pairing between the saccharin solution and drug or vehicle injections took place on days 10 and 13. On all intervening days animals were presented with water for 40 min, beginning at noon. Days 16, 19, and 22 constituted drug-free test days.

Data Analysis

In all experiments, a CTA was defined as a significant reduction in saccharin intake of a given experimental group relative to its own baseline saccharin intake (i.e., pairing day 1). A failure to observe an increase in saccharin intake by itself was not considered sufficient evidence to indicate a CTA induced by a conditioning agent (22). Because the failure to increase saccharin intake may not, by itself, reflect a taste aversion but rather a maintenance of taste neophobia, the more conservative definition of CTA that incorporates an observable avoidance response was applied to the present data.

In the present study, a symmetrical interaction between substances was defined as an identical magnitude of disruption of CTA by either drug pretreatment or drug preexposure (e.g., nicotine blocks CTA to ethanol and ethanol blocks CTA to nicotine). Conversely, an asymmetrical interaction between drugs was defined by unequal magnitude of CTA disruption by either drug pretreatment or drug preexposure (e.g., nicotine blocks CTA to ethanol but ethanol merely attenuates CTA to nicotine). Both a failure to decrease saccharin intake on an any day as well as a lack of difference between control groups on all days after pairing day 1, signified a blocked CTA. A failure to decrease saccharin intake on any day, but a difference between control groups on at least 1 day after pairing day 1 was indicative of an attenuated CTA.

RESULTS

Experiment I

A two-way (4×6) ANOVA with repeated measures on the days factor was conducted on the saccharin intake data. The analysis revealed significant group, $F(3, 27) = 7.366$, $p <$

0.001, days, $F(5, 135) = 8.086$, $p < 0.001$ and group × days interaction effects, $F(15, 135) = 5.211$, $p < 0.001$.

Test of simple main effects (24) revealed that the groups did not differ significantly at pairing day 1 (Fig. 1). However, the same analysis revealed that the groups differed significantly ($p < 0.05$) at every other day save for test day 3.

Within-subjects simple comparisons revealed that both groups v–v and e–v significantly ($p < 0.05$) increased their saccharin consumption across the days relative to their own baseline saccharin consumption's (pairing day 1). Group v–n significantly decreased its saccharin intake at test day 1 relative to its baseline saccharin consumption, which was indicative of a nicotine-induced CTA. Group e–n maintained its baseline saccharin intake across all days.

Between-subjects simple comparisons revealed that on test days 1 and 2, group v–n consumed significantly less saccharin relative to all other groups. In addition, group e–n differed significantly from groups e–v and v–v on pairing days 2, 3, and test day 1, which suggested that ethanol pretreatment attenuated a nicotine CTA.

Experiment II

A two-way ANOVA (4 × 6) with repeated measures across the days factor was conducted on the saccharin intake data to assess the effect of nicotine pretreatment on an ethanol CTA. The analysis yielded significant group, $F(3, 28) = 6.077$, $p < 0.01$, days, $F(5, 140) = 18.017$, $p < 0.001$, and group × days interaction effects, $F(15, 140) = 6.196$, $p < 0.0001$.

Test of simple main effects revealed that the groups did not differ at baseline saccharin intake (Fig. 2). The groups did, however, differ significantly on all other days except for test day 3.

Within-subjects simple comparisons revealed that both groups v–v and n–v significantly increased ($p < 0.05$) their saccharin consumption across all days relative to their own baseline saccharin consumptions. In contrast, saccharin consumption decreased significantly for group v–e on pairing days 2, 3, and test day 1 relative to its baseline saccharin consumption. This reduced departure from baseline saccharin consumption suggested an ethanol-induced CTA. Group n–e significantly increased their saccharin consumption across all days relative to their baseline.

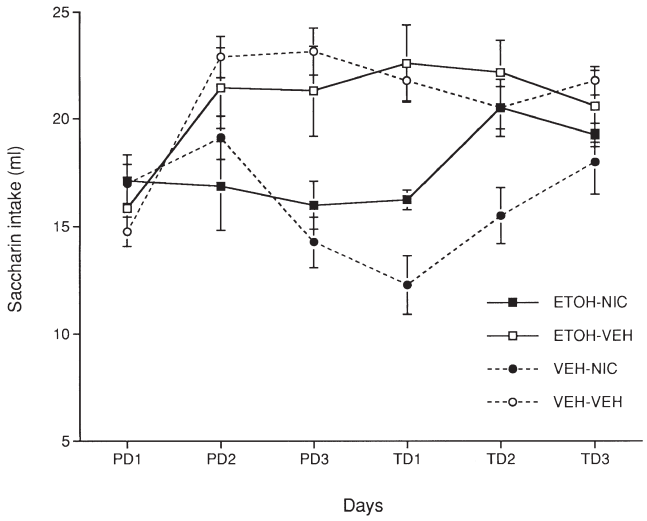

FIG. 1. Effects of pretreatment ethanol on a nicotine-induced conditioned taste aversion as reflected in mean consumption of saccharin solution for pairing days 1–3 (PD1, PD2, PD3) and test days 1–3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

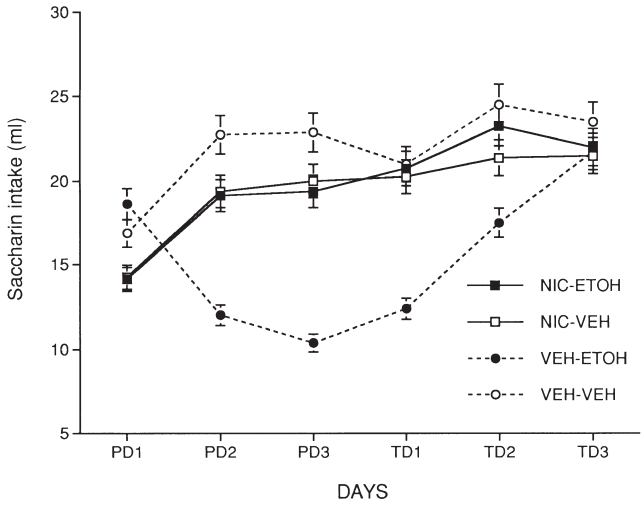

FIG. 2. Effects of pretreatment nicotine on an ethanol-induced conditioned taste aversion as reflected in mean consumption of saccharin solution for pairing days 1–3 (PD1, PD2, PD3) and test days 1–3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

Between-subjects analysis revealed that group v–e consumed significantly ($p < 0.05$) less saccharin compared to all other groups at pairing days 2 and 3, as well as test day 1. In addition, group n–e did not differ significantly from groups n–v or v–v on any day, suggesting that nicotine pretreatment completely blocked an ethanol CTA.

Experiment III

A two-way ANOVA (4 × 6) with repeated measures on the days factor was conducted on saccharin intake data to assess the effect of ethanol preexposure on a nicotine-induced CTA. This analysis yielded significant group, $F(3, 28) = 4.298$, $p < 0.05$, days, $F(5, 140) = 6.657$, $p < 0.0001$, and group × days interaction, $F(15, 140) = 3.001$, $p < 0.0.001$ effects.

Test of simple effects revealed that the groups did not differ in baseline saccharin consumption; however, they did differ significantly ($p < 0.05$) on pairing day 3, test days 1 and 2 (Fig. 3).

Within-subjects simple comparisons revealed that relative to their baseline saccharin consumptions, saccharin intake increased significantly for groups e–v and v–v across all days. Conversely, saccharin intake decreased significantly for group v–n on test day 1 compared to its baseline saccharin intake, which suggested a nicotine-induced CTA. Saccharin intake did not change for group e–n relative to its baseline saccharin intake.

Between-subjects simple comparisons revealed that group v–n differed significantly from all other groups at pairing day 3 and test day 1. Group e–n did not differ significantly from groups e–v and v–v on any day, which suggested that ethanol preexposure completely blocked the formation of a nicotine-induced CTA.

Experiment IV

A two-way ANOVA (4 × 6) with repeated measures on the days factor was conducted on the saccharin intake data to as-

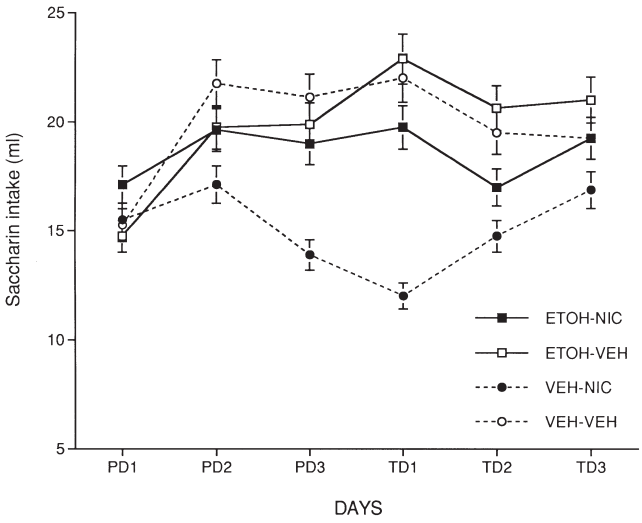

FIG. 3. Effects of pre exposure ethanol on a nicotine-induced conditioned taste aversion as reflected in mean consumption of saccharin solution for pairing days 1–3 (PD1, PD2, PD3) and test days 1–3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

sess the effect of nicotine preexposure on an ethanol-induced CTA. This analysis yielded significant days, $F(5, 140) = 12.788$, $p < 0.0001$ and group × days interaction, $F(15, 140) = 5.334$, $p < 0.0001$ effects. There was no significant group effect, $F(3, 28) = 2.449$, $p > 0.05$.

Test of simple effects revealed that the groups did not differ in their baseline saccharin consumption, but did differ significantly ($p < 0.05$) on pairing day 3, test days 1 and 2 (Fig. 4).

Within-subjects simple comparisons revealed that saccharin intake increased significantly for all groups except for group v–e on all days relative to their own baseline saccharin consumptions. Saccharin intake decreased significantly for group v–e on pairing day 3 and test day 1 compared to its baseline, suggesting an ethanol-induced CTA. Saccharin intake increased significantly for group n–e across all days relative to baseline.

Between-subjects simple comparisons revealed that group v-e differed significantly from all other groups at pairing day 3, test days 1 and 2. In addition, group n–e did not differ significantly from groups n–v and v–v on any day, which suggested that nicotine preexposure completely blocked the formation of an ethanol-induced CTA.

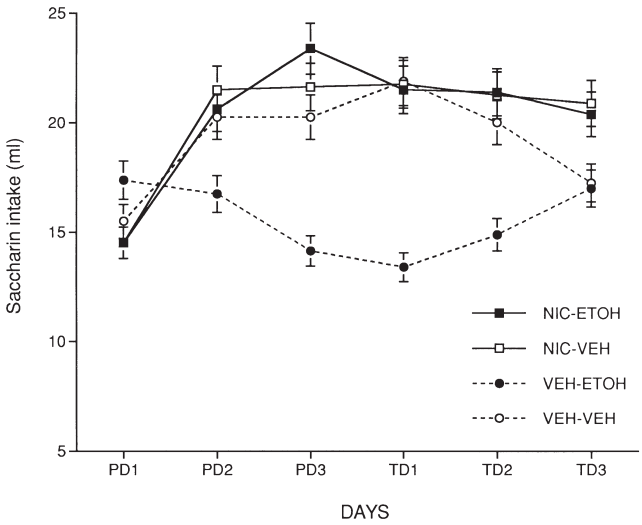

FIG. 4. Effects of preexposure nicotine on an ethanol-induced conditioned taste aversion as reflected in mean consumption of saccharin solution for pairing days 1–3 (PD1, PD2, PD3) and test days 1–3 (TD1, TD2, TD3). Vertical lines represent the S.E.M.

DISCUSSION

The results of the pretreatment study suggested that ethanol and nicotine interacted asymmetrically. By this we mean that nicotine pretreatment completely blocked the formation of an ethanol-induced CTA, while ethanol pretreatment merely attenuated the formation of a nicotine-induced CTA. These results suggested a unidirectional and pharmacologically specific interaction between ethanol and nicotine.

Traditionally, pretreatment effects have been explained in terms of general interference effects (13). Such a view holds that pretreatment with a given drug will disrupt the association that can be made between the taste experience and a subsequent conditioning drug treatment (13). By definition, such a notion would predict that pretreatment effects should be symmetrical. In other words, drug pretreatments should equally disrupt CTA to each other. The present pretreatment effects between ethanol and nicotine do not support this notion. In fact, ethanol and nicotine interacted asymmetrically in the pretreatment paradigm. The present results are not the first demonstration of asymmetrical pretreatment effects between self-administered drugs. It has previously been shown that morphine and diazepam interact asymmetrically in the pretreatment paradigm (6). More recently it has been demonstrated that cocaine and ethanol interact asymmetrically in the pretreatment paradigm (27). That some drugs may interact asymmetrically argues against the notion that all pretreatment effects are due merely to general interference effects. In fact, it supports the idea that there may be specific and unidirectional pharmacological interactions between drugs that can be reflected in the pretreatment CTA paradigm. In the context of the present experiment, the pretreatment asymmetry between ethanol and nicotine may shed light on clinical observations that there is a directional and unique interaction between ethanol and nicotine (15). It should be mentioned that in the present pretreatment experiments, nicotine produced a rather weak CTA in relation to ethanol. In light of this observation, it is possible that the relative strength of CTA produced by both drugs may have accounted for the present asymmetry. However, it should be mentioned that the use of higher nicotine doses has been shown to produce convulsions in rats, which may make the use of such doses in CTA studies problematic (14).

Unlike the results of the pretreatment study, which revealed a specific and unidirectional pharmacological interaction between nicotine and ethanol, the results of the preexposure study demonstrate that nicotine and ethanol may interact functionally as well. Preexposure with ethanol (with the last preexposure occurring 24 h prior to nicotine conditioning) blocked the formation of a nicotine-induced CTA and nicotine preexposure (with the last injection 24 h prior to ethanol conditioning) blocked an ethanol-induced CTA. These symmetrical results demonstrate that the effects of preexposure to ethanol and or nicotine have generalized to conditioning with

nicotine and ethanol, respectively. These results suggest that two seemingly different drugs such as ethanol and nicotine may, in fact, share some common stimulus properties, at least as it is reflected in the preexposure paradigm.

Preexposure effects have also been explained in terms of associative interference effects (4). Braveman proposed that preexposure to any CTA-inducing agent should at least attenuate the formation of a CTA normally induced by another agent. Regardless of which preexposure or conditioning drugs are used, attenuation of CTA should occur as long as both can induce aversions. Once again, such a notion subsumes that all preexposure effects should be symmetrical. Several studies that have demonstrated asymmetrical preexposure effects have challenged this associative explanation. For example, it was reported that amphetamine and amobarbital will interact asymmetrically in the preexposure paradigm (35), and morphine and amphetamine have been shown to interact asymmetrically as well (9).

Braveman (5) attempted to reconcile his position by arguing that preexposure to an agent that more readily induced a CTA would more readily block a CTA to a less potent conditioning agent, and that preexposure to a less potent CTA-inducing agent would less readily attenuate a CTA to a more potent conditioning agent. Such an explanation was ruled out by a study that demonstrated that equiaversive doses of diazepam, morphine and Δ-9-THC could interact asymmetrically in the preexposure paradigm (34). More recently, it was demonstrated that equiaversive doses of cocaine and ethanol could also interact asymmetrically in the preexposure paradigm (27). That not all drugs interact symmetrically precludes the argument that all preexposure effects are due merely to general interference effects. In fact, it suggests that rats can discriminate between drug properties in the preexposure paradigm, and that not all such discriminations are bidirectional (34).

Taken together, the present study demonstrates that ethanol and nicotine can interact differently in different variants of the CTA paradigm. In the preexposure paradigm, ethanol and nicotine appear functionally related, and share common stimulus properties accounting for a sufficiently large portion of the variance to cause the symmetrical generalization seen in this paradigm. However, in the pretreatment procedure, nicotine and ethanol appear to interact pharmacologically in a unidirectional fashion, suggesting some unique and unshared pharmacological properties of each agent. The present study demonstrates the utility of employing both the pretreatment and preexposure procedures within the same investigation as a means of examining drug interactions. The pretreatment CTA enables one to examine whether drugs can interact pharmacologically, presumably due to common pharmacological effects; the preexposure variant permits one to assess whether drugs can interact independent of their pharmacological interaction, presumably due to functional similarities. One possible limitation of the present study has to do with the fact that a single dose of each drug was compared. In light of this fact, we cannot definitively rule out the possibility that additional doses of each drug may have produced a different pattern of results. Further studies are being conducted to identify those common psychopharmacological factors shared by nicotine and ethanol.

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