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Preexposure Effects of Nicotine and Acetaldehyde on Conditioned Taste Aversion Induced by Both Drugs

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KUNIN, D., M. W. LATENDRESSE, S. GASKIN, B. R. SMITH AND Z. AMIT. *Preexposure effects of nicotine and acetaldehyde on conditioned taste aversion induced by both drugs.* PHARMACOL BIOCHEM BEHAV **66**(4) 695–699, 2000.—Previous assessments have demonstrated an interaction between ethanol and nicotine in the conditioned taste-aversion (CTA) paradigm. The present study assessed whether acetaldehyde, the primary reinforcing metabolite of ethanol, would interact with nicotine as well. In six experiments, water-deprived male Wistar rats were preexposed to either acetaldehyde (0.2 or 0.3 g/kg, IP) or nicotine (0.8, 1.2, or 2 mg/kg, SC) for 3 consecutive days and then subsequently conditioned, 24 h later, with either nicotine (0.8, 1.2, or 2 mg/kg, SC) or acetaldehyde (0.2 or 0.3 g/kg, IP), respectively. There were 4 conditioning days and 4 drug-free test days, each spaced 72 h apart. On test days, animals were offered a free choice between water and saccharin. The results of the following set of experiments demonstrated a dose-related interaction between nicotine and acetaldehyde, where lower doses of each drug failed to attenuate CTA induced by one another, but a higher nicotine dose (2 mg/kg) attenuated the formation of a CTA induced by acetaldehyde (0.3 g/kg). It was argued that the primary metabolite of ethanol may play a role in the interaction between nicotine and ethanol previously observed. © 2000 Elsevier Science Inc.

Acetaldehyde Conditioned taste aversion (CTA) Nicotine Rats

AN accumulated body of data has pointed to an interaction between nicotine and ethanol [e.g., (22)]. During the past decade, several studies have documented both behavioral as well as biochemical interactions between these two substances (3,4,7,9,10,17,21). There is also a growing body of evidence suggesting that the interaction between nicotine and ethanol is at the level of the nicotine–acetylcholine receptor (3,21).

Recently, we have reported that nicotine and ethanol interacted in the conditioned taste aversion paradigm (17). Specifically, we demonstrated that when acting as preexposure agents, nicotine and ethanol blocked the conditioned taste aversions (CTA) of one another. This symmetrical interaction suggested that nicotine and ethanol may share common stimulus properties. The following experiment was designed to examine whether acetaldehyde, the primary reinforcing metabolite of ethanol, would also interact with nicotine in the preexposure CTA paradigm. Over the past 2 decades, it has been repeatedly documented that acetaldehyde, the primary reinforcing metabolite of ethanol, may mediate many of ethanol's behavioral effects (20), including an ethanol induced CTA (2). In the present study, we hypothesized that if acetaldehyde in fact mediates many of the psychopharmacological effects of ethanol, including ethanol CTA, then acetaldehyde should also interact with nicotine in a manner similar to that previously observed between nicotine and ethanol (17).

EXPERIMENT 1A–C

We have previously demonstrated (17) that preexposure with nicotine will block the formation of an ethanol induced CTA. The present study was designed to determine whether nicotine and acetaldehyde would also interact in the preexposure CTA paradigm. Acetaldehyde has been reported to me-

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diate many of the behavioral effects of ethanol; therefore, we hypothesized that nicotine should block an acetaldehyde induced CTA. Experiments 1a–c assessed the effect of preexposure with nicotine (0.8, 1.2, or 2 mg/kg) on conditioned taste aversion induced by acetaldehyde (0.2 or 0.3 g/kg).

Method

Subjects. Subjects were 96 male Wistar rats (Charles River, Quebec), $n = 32$ per experiment, weighing between 225–250 g at the start of the experiment. The animals were individually housed in stainless steel cages and had free access to lab chow and water for a 7-day acclimatization period. The animals were maintained in a room regulated for constant temperature and humidity on a 12 L: 12 D cycle. All subjects used in the present set of experiments were treated in accordance with the guidelines of the Canadian Council for Animal Care.

Drugs. Nicotine ditartrate salt (Sigma Chemical Co.) was dissolved in 1 ml/kg of 0.9% saline solution, and was injected at doses of 0.8, 1.2, and 2 mg/kg. All doses of nicotine were calculated as the nicotine salt, and all nicotine injections were administered SC. Acetaldehyde 5% (v/v) was diluted with saline from a 99% stock solution (Aldrich Chemical Company). Acetaldehyde was injected at doses of 0.2 and 0.3 g/kg. All acetaldehyde injections were administered IP.

General procedure. Following 7 days of acclimatization to the colony room conditions, rats were placed on a 23-h and 40-min water-deprivation schedule. Tap water was presented to the animals in two stoppered plastic tubes fitted with stainless steel ball bearing spouts for 20 min, beginning at noon each day. The spouts were inserted through the fronts of the home cages, and were presented in this manner at the same time daily. Fluid was measured to the nearest milliliter. A two-bottle free choice procedure was used throughout the experiment, as such a procedure is thought to be more sensitive to the detection of weak CTAs (12,14).

After 3 days of adaptation to the water-deprivation schedule, animals were randomly assigned to one of the treatment conditions. The preexposure injections, which began on day 4, were repeated on days 5 and 6 following the 20-min water session (17). There were eight animals assigned to each group. Animals assigned to groups nicotine–acetaldehyde (N-A) and nicotine–vehicle (N-V) were preexposed to nicotine while, animals assigned to groups vehicle–acetaldehyde (V-A) and vehicle–vehicle (V-V) were preexposed to saline. On day 7, 24 h after the final preexposure injection, rats were presented with two bottles of a novel tasting 0.1% saccharin solution for 20 min at noon. Within 1 min after completion of the 20-min saccharin drinking session, animals in groups N-A and V-A were injected with acetaldehyde while, animals in groups V-V and N-V were injected with saline in the same manner. A second, third, and fourth pairing of the saccharin solution and the drug or vehicle injections was repeated on days 10, 13, and 16 of this experiment. Days 19, 22, 25, and 28 comprised drug-free test days. On these days, animals were presented with a choice of water and saccharin solution. The position of the tubes was rotated on every test day to control for the development of a side preference (13). On intervening days, between conditioning and test days, animals were presented with water for 20 min, beginning at noon.

Experiment 1a examined the effects of 0.8 mg/kg nicotine (measured as the salt) preexposure on a 0.2 g/kg acetaldehyde induced CTA. Experiment 1b examined the effects of preexposure to 1.2 mg/kg nicotine on a 0.2 g/kg acetaldehyde induced CTA. Experiment 1c examined the effects of preexposure to 2 mg/kg nicotine on a 0.3 g/kg acetaldehyde induced CTA. Both doses of acetaldehyde (0.2 and 0.3 g/kg) have previously been shown to produce CTA (2).

Data analysis. A saccharin preference ratio (total saccharin consumed/total fluid) was calculated for each group. Consistent with a two-bottle test (13), a CTA was defined as a significant decrease in saccharin preference relative to group V-V. Preference scores were obtained by collapsing the average of 2 successive test days (i.e., test days 1 and 2 and test days 3 and 4). Test days were collapsed because the position of the tubes was rotated on every test day to control for the development of a side preference (13). In addition, saccharin intake data obtained over four CS-US (saccharin-drug) pairings, for each experiment, was also subject to separate analysis. For all experiments, statistical significance was set at $p < 0.05$.

Results

Experiment 1a: Nicotine (0.8 mg/kg)–Acetaldehyde (0.2 g/kg). A two-way (4 × 4) analysis of variance (ANOVA) with repeated measures across four CS-US pairings was conducted on saccharin intake data. The analysis revealed a significant group effect, $F(3, 27) = 7.991$, $p < 0.05$, no significant day effect, $F(3, 81) = 1.828$, $p > 0.05$, and a significant group × day interaction effect, $F(9, 81) = 5.059$, $p < 0.05$. Test of simple effects ($\alpha = 0.05$) indicted that saccharin intake decreased significantly for groups V-A and N-A across the four CS-US pairings; however, these groups did not differ significantly from one anther on any of these days.

A two-way (4 × 2) analysis of variance (ANOVA) with repeated measures on the day factor was conducted on saccharin preference ratio data. The analysis revealed a significant group effect, $F(1, 30) = 7.535$, $p < 0.05$, no significant day effect, $F(1, 30) = 2.378$, $p > 0.05$, and no significant group × day interaction effect, $F(1, 30) = 2.034$, $p > 0.05$. Newman–Keuls post hoc analysis revealed that saccharin preference ratios for groups V-A and N-A were significantly lower than that observed for group V-V and N-V across the days. Furthermore, saccharin preference did not differ significantly between group V-A and N-A (Fig. 1a). That groups V-A and N-A differed significantly from V-V but not from each other suggested that while acetaldehyde produced a CTA, preexposure to nicotine had no effect on an acetaldehyde induced CTA.

Experiment 1b: Nicotine (1.2 mg/kg)–Acetaldehyde (0.2 g/kg). A two-way (4 × 4) analysis of variance (ANOVA) with repeated measures across four CS-US pairings conducted on saccharin intake data revealed a significant group, $F(3, 28) = 3.593$, $p < 0.05$, day, $F(3, 84) = 24.477$, $p < 0.05$, and group × day interaction effect, $F(9, 84) = 2.840$, $p < 0.05$. Test of simple effects indicted that all groups with the exception of V-A increased their saccharin intake across the four CS-US pairing days; however, groups V-A and N-A did not differ significantly from one another on any of these days.

A two-way (4 × 2) ANOVA with repeated measures on the day factor conducted on saccharin preference ratio data revealed a significant group effect, $F(3, 27) = 3.136$, $p < 0.05$, no significant day, $F(1, 27) = 0.584$, $p > 0.05$, or group × day interaction effect, $F(3, 27) = 1.429$, $p > 0.05$. Newman–Keuls post hoc analysis on the significant group main effect revealed that group V-A had a significantly lower saccharin preference ratio relative to group V-V, suggesting that acetaldehyde produced a CTA (Fig. 1b). However, no other group differences were observed; specifically, group V-A was not significantly different from group N-A, suggesting that nicotine had no effect upon a subsequent acetaldehyde-induced CTA.

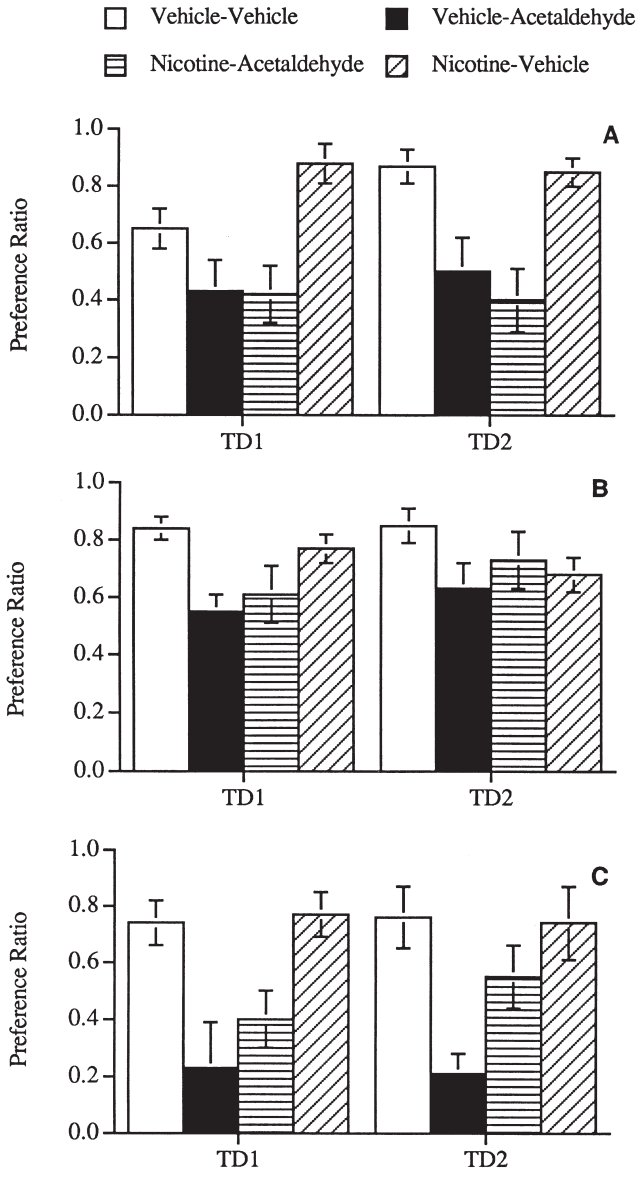

FIG. 1. Effect of preexposure with one of three doses of nicotine [0.8 mg/kg (A), 1.2 mg/kg (B), or 2 mg/kg (C)] on a conditioned taste aversion induced by acetaldehyde [0.2 (A, B) or 0.3 mg/kg (C)] as reflected in mean preference ratio. TD1 is collapsed across test days 1 and 2 and TD2 is collapsed across test days 3 and 4. Vertical lines represent the SEM.

Experiment 1c: Nicotine (2 mg/kg)–Acetaldehyde (0.3 g/kg). A two-way (4 × 4) analysis of variance (ANOVA) with repeated measures across four CS-US pairings conducted on saccharin intake data revealed a significant group, $F(3, 29) = 9.337$, $p < 0.05$, a nonsignificant day, $F(3, 87) = .008$, $p > 0.05$, and a significant group × day interaction effect, $F(9, 87) = 3.055$, $p < 0.05$. Test of simple effects indicted that group V-A significantly decreased its saccharin intake across the pairing days; however, groups V-A and N-A failed to differ significantly from each other.

A two-way (4 × 2) ANOVA with repeated measures on the day factor conducted on saccharin preference ratio data revealed a significant group effect, $F(3, 26) = 11.217$, $p < 0.01$, no significant day, $F(1, 26) = 0.169$, $p > 0.05$, or group × day interaction effect, $F(3, 26) = 0.325$, $p > 0.05$. Newman–Keuls post hoc analysis on the significant group main effect revealed that group V-A and N-A showed a lower saccharin preference relative to group V-V. In addition, group V-A showed a lower saccharin preference relative to group N-A (Fig. 1c). Together, these results suggested that while group V-A and N-A acquired a CTA, nicotine preexposure attenuated the acetaldehyde induced CTA.

EXPERIMENT 2A–C

Experiment 2 was designed to assess the effect of preexposure with acetaldehyde (0.2 or 0.3 g/kg) on CTA induced by nicotine (0.8, 1.2, or 2 mg/kg).

Method

Subjects. A total of 96 male ($n = 32$ per experiment) Wistar rats weighing between 225–250 g were used in the following three experiments, and were housed in conditions described in Experiment 1.

General procedure. The experimental procedures used in this experiment were identical to that used in the previous experiment with the following exceptions. The preexposure injections consisted of injections of acetaldehyde for groups A-N and A-V, and saline for groups V-N and V-V. On pairing days, animals assigned to group A-N and V-N were conditioned with nicotine, while animals assigned to group A-V and V-V were conditioned with saline.

Experiment 2a examined the effects of acetaldehyde (0.2 g/kg) preexposure on a nicotine (0.8 mg/kg) induced CTA. Experiment 2b examined the effects of preexposure to acetaldehyde (0.2 g/kg) on a nicotine (1.2 mg/kg)-induced CTA. Experiment 2c examined the effects of preexposure to 0.3 g/kg acetaldehyde on a nicotine (2 mg/kg)-induced CTA.

Results

Experiment 2a: Acetaldehyde (0.2 mg/kg)–Nicotine (0.8 mg/kg). A two-way (4 × 4) analysis of variance (ANOVA) with repeated measures across four CS-US pairings conducted on saccharin intake data revealed no significant group effect, $F(3, 28) = 1.883$, $p > 0.05$, a significant day effect, $F(3, 84) = 37.098$, $p < 0.05$, and a significant group × day interaction effect, $F(9, 84) = 2.672$, $p < 0.05$. Test of simple effects indicted that with the exception of group V-N, all groups significantly increased their saccharin intake across the four CS-US pairing days. Furthermore, saccharin consumption for group V-N was significantly less compared to all other groups on pairing day 4.

A two-way (4 × 2) ANOVA with repeated measures on the day factor conducted on saccharin preference ratio data revealed no significant group effect, $F(1, 30) = 1.462$, $p > 0.05$, a significant day effect, $F(1, 30) = 7.043$, $p < 0.05$, and a nonsignificant group × day interaction effect, $F(1, 30) = 1.944$, $p > 0.05$. Figure 2a displays the saccharin preference data for the groups across the test days. Nicotine (0.8 mg/kg) failed to produce a CTA.

Experiment 2b: Acetaldehyde (0.2 g/kg)–Nicotine (1.2 mg/kg). A two-way (4 × 4) analysis of variance (ANOVA) with repeated measures across four CS-US pairings conducted on saccharin intake data revealed no significant group effect, $F(3, 27) = 2.055$, $p > 0.05$, a significant day effect, $F(3, 81) =$

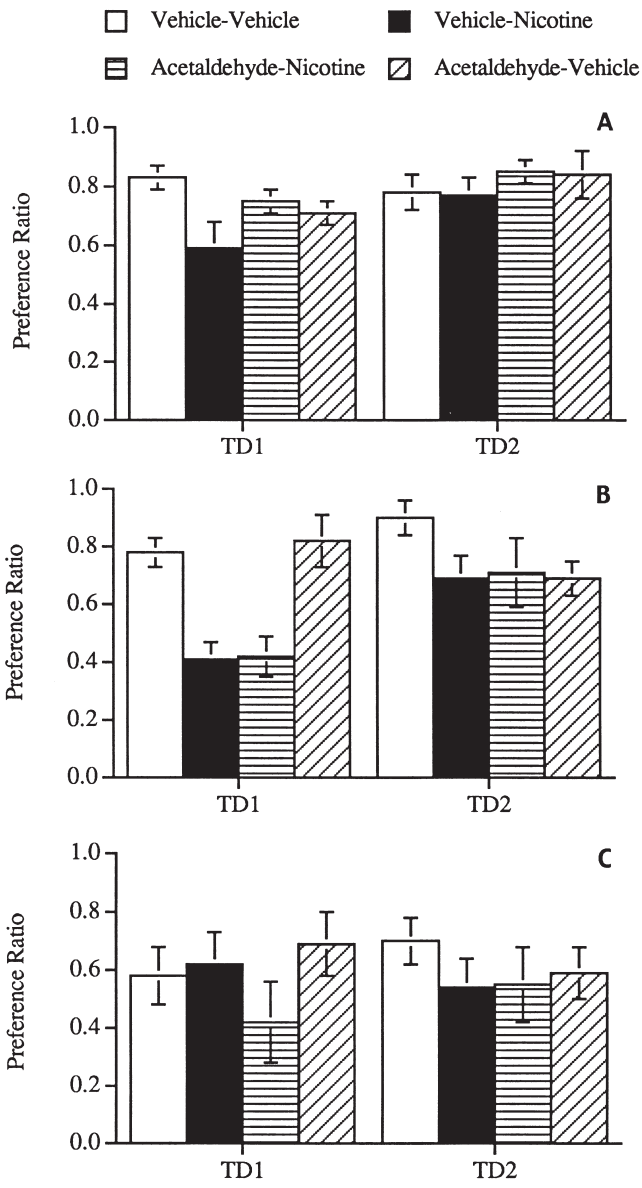

FIG. 2. Effect of preexposure with one of two doses of acetaldehyde [0.2 g/kg (A, B) or 0.3 g/kg (C)] on conditioned taste aversion induced by nicotine [0.8 mg/kg (A) 1.2 mg/kg (B) or 2 mg/kg (C)] as reflected in mean preference ratio. TD1 is collapsed across test days 1 and 2 and TD2 is collapsed across test days 3 and 4. Vertical lines represent the SEM.

16.199, $p < 0.05$, and a nonsignificant group × day interaction effect, $F(9, 81) = 0.865$, $p > 0.05$.

A two-way (4 × 2) ANOVA with repeated measures on the day factor conducted on saccharin preference ratio data revealed a significant group, $F(1, 30) = 6.235$, $p < 0.05$, day, $F(1, 30) = 8.418$, $p < 0.05$, and group × day interaction effect, $F(1, 30) = 4.317$, $p < 0.05$. Test of simple effects revealed that group V-N and A-N differed significantly from group V-V on TD1. However, between subjects simple comparisons revealed that group V-N and A-N did not differ from each other, suggesting that while nicotine produced a CTA, preexposure with acetaldehyde had no effect on a nicotine induced CTA (Fig. 2b).

Experiment 2c: Acetaldehyde (0.3 g/kg)–Nicotine (2 mg/kg). A two-way (4 × 4) analysis of variance (ANOVA) with repeated measures across four CS-US pairings conducted on saccharin intake data revealed a significant group, $F(3, 25) = 4.055$, $p < 0.05$, day, $F(3, 75) = 15.118$, $p < 0.05$, and group × day interaction effect, $F(9, 75) = 2.291$, $p < 0.05$. Test of simple effects indicted that all groups with the exception of group V-N significantly increased their saccharin consumption across the four pairing days; however, groups V-N and A-N did not differ significantly from one another on any of the pairing days.

A two-way (4 × 2) ANOVA with repeated measures on the day factor conducted on saccharin preference ratio data revealed no significant group, $F(3, 25) = .837$, $p > 0.05$, day, $F(1, 25) = 0.042$, $p > 0.05$, and group × day interaction effect, $F(3, 25) = 0.718$, $p > 0.05$. Figure 2c displays the saccharin preference data for the groups across the test days. Nicotine (2 mg/kg) failed to produce a CTA.

GENERAL DISCUSSION

The present series of experiments were designed to assess whether nicotine and acetaldehyde could interact in the preexposure conditioned taste aversion paradigm. Experiment 1a–c assessed the effect of preexposure with one of three nicotine doses (0.8, 1.2, or 2 mg/kg) on CTA to acetaldehyde (0.2 or 0.3 g/kg). These experiments demonstrated a dose-related interaction whereby the lower doses of nicotine (0.8 or 1.2 mg/kg) failed to interact with the lower acetaldehyde dose, but preexposure with the higher nicotine dose (2 mg/kg) attenuated a robust CTA induced by acetaldehyde (0.3 g/kg).

Experiments 2a–c were essentially a replication of the first series of experiments, but tested the effect of preexposure with one of two doses of acetaldehyde (0.2 or 0.3 g/kg) on CTA induced by nicotine (0.8, 1.2, or 2 mg/kg). The results of Experiments 2a and 2c precluded us from making any meaningful interpretations regarding the effects of acetaldehyde preexposure on a nicotine-induced CTA, as the doses of nicotine (0.8 and 2 mg/kg) tested in these experiments failed to produce a CTA. However, the results of Experiment 2b indicated no interaction between acetaldehyde and nicotine where preexposure with acetaldehyde (0.2 mg/kg) had no effect upon a CTA-induced by nicotine (1.2 mg/kg).

It is noteworthy that in the present study, preexposure with a dose of nicotine (2 mg/kg), which in itself was unable to produce a CTA, proved capable of attenuating a fairly robust CTA induced by acetaldehyde (0.3 g/kg). This latter finding is at odds with the notion implicit in an associative interference account where the strength of the disruptive effects of drug preexposure is thought to be directly related to the CTA inducing strength of a given drug (5,6). Instead, we argue that the ability of nicotine to attenuate a CTA induced by acetaldehyde is likely related to some similarity in the effects involved in the preexposure and conditioning drug treatments but unrelated to their ability to produce aversion as nicotine (2 mg/kg) failed to produce a CTA.

It has previously been shown that doses of morphine that are insufficient to produce a CTA are also nevertheless capable of attenuating a morphine-induced CTA (15). The authors argued that some properties of the morphine preexposure may be detectable by animals, even if these properties were not capable of inducing a CTA. The present study demonstrates that the same phenomenon may occur even with

seemingly unrelated drugs. It is our view that the present findings regarding the interaction of acetaldehyde and nicotine underscores the notion that the interaction between drugs in the CTA paradigm may be unrelated to their aversive properties. It follows that the signals that may give rise to CTAs to self-administered agents need not be aversive, a point argued elsewhere (16).

Data emanating from our laboratory has previously shown that nicotine and ethanol interacted in the preexposure CTA paradigm (17). It was demonstrated that preexposure to nicotine and ethanol blocked CTA induced by one another. From these results, we argued that both nicotine and ethanol shared common stimulus properties as reflected in the preexposure CTA paradigm. In the present study it was demonstrated that nicotine and acetaldehyde interacted in a dose-related fashion, whereby lower nicotine doses appeared unrelated to acetaldehyde while a higher nicotine (2 mg/kg) dose attenuated the formation of a CTA induced by a higher dose of acetaldehyde (0.3 g/kg). Taken together, we believe that the present results may provide some indication that the previous interaction observed between nicotine and ethanol in the CTA may, in part, occur via acetaldehyde, the putative reinforcing metabolite of ethanol (20).

With the range of doses of nicotine used in the present study, it was difficult to observe a CTA to nicotine. These results may have something to do with the fact that while other laboratories have reported CTAs to nicotine, they have done so using significantly higher doses (13,18). In the present study, the nicotine doses used were within the range that has been reported to possess positive reinforcing properties (1,8,11,19). The present findings demonstrating that nicotine, at a dose within the range of self-administration, can attenuate an acetaldehyde-induced CTA, lend support for the notion that CTA to this class of drugs may not be reflective of the aversive stimuli resulting from their administration (16).

In conclusion, we believe that the present results may provide some evidence for the notion that the putative reinforcing metabolite of ethanol may play a role in the interaction previously observed between nicotine and ethanol. Continued investigation of the interaction between nicotine and ethanol is merited, as it may contribute to a better understanding of the complex motivational properties that underlie the interaction between these substances so widely abused in conjunction with one another.

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