



# The Effects of Nicotine on Ethanol-Induced Conditioned Taste Aversions

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## Rationale and Objectives

- Drug acceptability is a function of the balance between its rewarding and aversive effects and can be affected by polydrug use.
- Nicotine and alcohol are two of the most commonly co-used drugs, and reportedly, the heaviest drinkers are also the heaviest consumers of nicotine.
- Thus, examining how the interaction of these drugs impacts their affective properties may help determine the mechanism mediating their co-use.
- Recent reports show that, in adult men, nicotine delivered prior to ingesting alcohol increased the desire to drink more, and that smoking cigarettes increased responding for alcohol.
- Animal self-administration models have shown that nicotine increases the rate of acquisition and responding for ethanol, suggesting that chronic nicotine may increase the rewarding effects of alcohol.
- While examining reward gives insight into some of the motivational characteristics of nicotine and alcohol combined, both can produce conditioned taste aversions (CTA) independently, and interestingly it has been shown that drug combinations can result in both weakened or potentiated aversions.
- Thus, the present experiments used the CTA design to examine the effects of nicotine on ethanol-induced CTA to assess the possibility that increases in acceptability of the combination are due to an attenuation in ethanol's aversive effects and to explore potential mechanisms by which nicotine may be altering ethanol-induced CTAs.

## Procedures & Results

### Subjects

- 125 female Long Evans rats ( $n = 41-42$  per experiment), approximately 90 days old

### Experiment 1: Nicotine-induced CTA

- 20-min access to novel saccharin solution, followed by one of four doses of nicotine (0, 0.4, 0.8 or 1.2 mg/kg)
- Conditioned for four trials, followed by a one-bottle test
- Nicotine induced aversions at all three doses (Fig. 1).

### Experiment 2: Ethanol-induced CTA

- 20-min access to novel saccharin solution, followed by one of four doses of ethanol (0, 0.5, 1.0, 1.5 g/kg)
- Conditioned for four trials, followed by a one-bottle test
- Ethanol induced aversions at all three doses in a dose-dependent manner (Fig. 2).

### Experiment 3: Nicotine/Ethanol CTA

- 20 min access to novel saccharin solution, followed by saline, nicotine (0.8mg/kg) alone, ethanol (1g/kg) alone or nicotine (0.8mg/kg) immediately followed by ethanol (1g/kg)
- Conditioned for five trials, followed by a two-bottle test
- The nicotine/ethanol combination induced aversions across conditioning trials (Fig. 3) and significantly reduced saccharin preference in the two-bottle test more so than any other group (Fig. 4).

### Hypothermia and Blood Alcohol Concentration

- Animals from Exp. 3 were given injections based on previously assigned groups.
- Core body temperatures were assessed immediately prior to injection and 15, 60 and 180 min post-injection.
- Tail blood samples were collected immediately after temperatures at 15, 60 and 180 min post-injection.
- BAC was analyzed by gas chromatography (NIAAA).
- The nicotine/ethanol combination reduced core body temperature more so than any other group at 15 min post-injection (Fig. 5), but nicotine had no effect on BAC (Fig. 6)

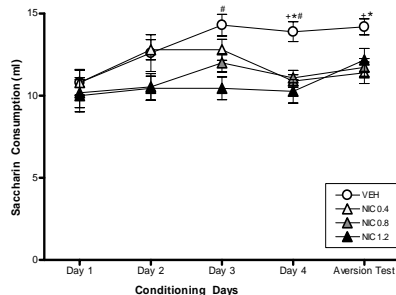


Figure 1. Experiment 1 - Nicotine induced taste aversions (at all doses) compared to controls: \*NIC 0.4 < VEH, \*NIC 0.8 < VEH, \*NIC 1.2 < VEH.

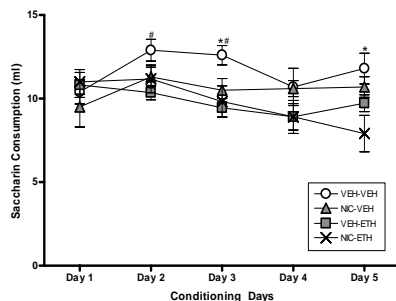


Figure 3. Experiment 3 - The nicotine(0.8mg/kg)/ethanol (1 g/kg) combination induced a taste aversion compared to controls: \*NIC-ETH < VEH-VEH, \*VEH-ETH < VEH-VEH.

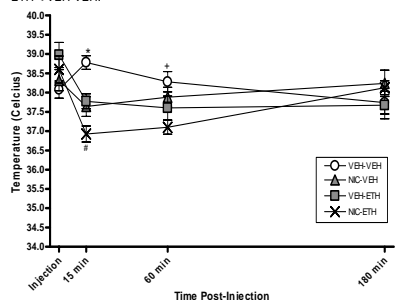


Figure 5. Experiment 3 - The nicotine(0.8mg/kg)/ethanol(1 g/kg) combination produced a greater hypothermic effect than any other group: \*NIC-ETH < all other groups, \*NIC-ETH < VEH-VEH, \*NIC-VEH & VEH-ETH < VEH-VEH.

## Figures

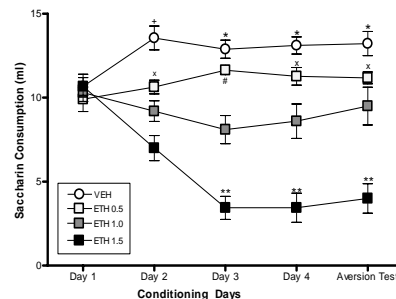


Figure 2. Experiment 2 - Ethanol induced dose-dependent taste aversions: \*All drug groups < VEH, \*ETH 1.5 < ETH 0.5, \*ETH 1.0 & ETH 1.5 < VEH, \*ETH 1.0 & ETH 1.5 < ETH 0.5, \*\*ETH 1.5 < ETH 1.0.

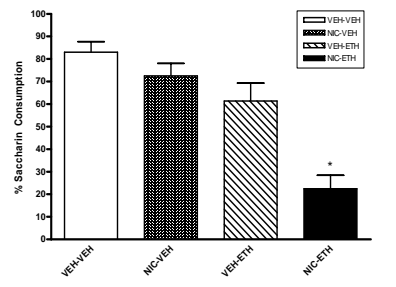


Figure 4. Experiment 3 - The nicotine(0.8mg/kg)/ethanol(1 g/kg) combination induced a significantly lower saccharin preference than any other group in the two-bottle test: \*NIC-ETH < VEH-VEH, NIC-VEH & VEH-ETH.

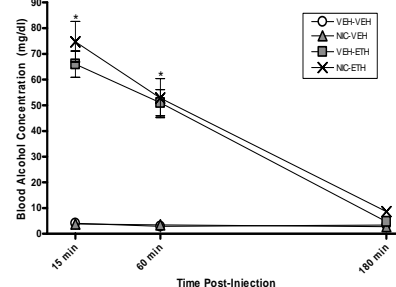


Figure 6. Experiment 3 - Nicotine(0.8mg/kg) had no effect on BAC produced by ethanol(1 g/kg): \*NIC-ETH & VEH-ETH > NIC-VEH & VEH-VEH.

## Conclusions

- Concurrent administration of nicotine and ethanol:
  - induces taste aversions greater than either drug alone, as well as the sum of the aversions produced by the individual drugs, suggesting that nicotine may be impacting the aversive properties of ethanol.
  - produces effects on BAC not significantly different than ethanol alone. Therefore, changes in BACs are not likely mediating the potentiated aversions in the combination group.
  - produces greater hypothermic effect than ethanol alone. However, this effect was simply additive and did not parallel the much more pronounced CTAs induced by the combination. While it may contribute somewhat, drug-induced hypothermia is not solely responsible for increased aversions.
- Because of the dissociation between reward and aversion, changes in the aversive properties do not necessitate changes in reward. That is, nicotine may impact the aversive properties of ethanol while also potentiating the rewarding properties, perhaps to a greater extent than the aversive effects.
- Concurrent assessments of changes in the rewarding effects of the drug combination need to be made under conditions comparable to those presently used to yield further insights on the biobehavioral bases of polydrug abuse.

## Selected References

- Clark A, Lindgren S, Brooks SP, Watson WP, Little HJ. (2001). Chronic infusion of nicotine can increase operant self-administration of alcohol.
- Etkind SA, Fantegrossi WE, Riley AL. (1998). Cocaine and alcohol synergism in taste aversion learning. *Pharmacol Biochem Behav* 59: 649-55.
- Hunt T, Amil Z. (1987). Conditioned taste aversion induced by self-administered drugs: paradox revisited. *Neurosci Biobehav Rev* 11: 107-30.
- Kouri EM, McCarthy EM, Faust AH, Lukas SE. (2004). Pretreatment with transdermal nicotine enhances some of ethanol's acute effects in men. *Drug Alcohol Depend* 75: 55-65.
- LeBlanc AE, Cappell H. (1975). Antagonism of morphine-induced aversive conditioning by naloxone. *Pharmacol Biochem Behav* 3: 185-8.
- National Institute on Alcohol Abuse and Alcoholism (1998). *Alcohol Alert No. 39: Alcohol and Tobacco*. Accessed October, 2006. Available from: <http://pubs.niaaa.nih.gov/publications/aa39.htm>.
- Perkins KA, Fonte C, Grobe JE (2000) Sex differences in the acute effects of cigarette smoking on the reinforcing value of alcohol. *Behav Pharmacol* 11: 63-70
- van der Kooy D, O'Shaughnessy M, Mucha RF, Kalant H. (1983). Motivational properties of ethanol in naive rats as studied by place conditioning. *Pharmacol Biochem Behav* 19: 441-5.

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