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Nicotine affects ethanol-conditioned taste, but not place, aversion in a simultaneous conditioning procedure

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ABSTRACT

The conditioned taste aversion (CTA) induced by ethanol is a key factor limiting ethanol intake. Nicotine, a drug co-consumed with ethanol, may decrease this aversion by modulating the unconditioned effects of ethanol or by disrupting the association between ethanol and its associated cues. This study analyzed ethanol-induced CTA and conditioned place aversion (CPA) in Long-Evans rats with subchronic exposure to nicotine. The rats were treated with nicotine (0.0 or 0.4 mg/kg) three times before conditioning (on lickometer training sessions 3, 4, and 5) and across conditioning days. During the conditioning the rats were given ethanol (1.3 g/kg) preceded and followed by presentation of a taste (NaCl) and tactile (rod or hole floors) conditioned stimulus (CS+), respectively. On CS– conditioning days, the rats were given vehicle and exposed to alternative stimuli. Three CTA and CPA testing sessions were then conducted. It was found that nicotine reduced ethanol-induced CTA and enhanced locomotor activity, but did not significantly modify the magnitude of ethanol-induced CPA. The effects of nicotine on CTA were observed during both conditioning and testing sessions, and were specific to the NaCl CS+, having no effect on reactivity to water. The dissociation between the effect of nicotine on ethanol-induced CTA and CPA suggests that nicotine does not alter ethanol's motivational properties by generally increasing its positive rewarding effects, nor does it blunt all aversive-like responses to this drug. Instead, nicotine may impede ethanol-induced CTA induced by ethanol by disrupting the neural underpinnings of this specific form of associative learning.

Introduction

Alcohol (ethanol) has reinforcing properties, but these can be mitigated by its aversive motivational effects (e.g., dysphoria, gastrointestinal distress). In preclinical models, these aversive properties are often measured via conditioned taste or place aversion paradigms (CTA and CPA, respectively), during which avoidance of a taste or chamber paired with the effects of ethanol is considered an index of the aversive effects of the drug (Acevedo, Nizhnikov, Spear, Molina, & Pautassi, 2013). These studies also suggest that reduction in the sensitivity to the aversive effects of ethanol modulates the transition to escalated alcohol intake. Adolescent rats, for instance, drink significantly greater amounts of ethanol than adult rats (Doremus, Brunell, Rajendran, & Spear, 2005), a response which is correlated with a significantly reduced CTA induced by ethanol. Further, an exacerbated response to the aversive effects of ethanol is associated with very low levels of ethanol drinking – as shown by rats and humans with deficient breakdown of acetaldehyde (a metabolite of ethanol) (Peana et al., 2017). It is thus important to analyze which factors affect ethanol-induced aversion.

Nicotine, a psychoactive agent widely co-consumed with ethanol (Anthony & Echeagaray-Wagner, 2000; Falk, Yi, & Hiller-Sturmhöfel, 2006), likely diminishes the aversive properties of ethanol. For example, Zarrindast, Meshkani, Rezayof, Beigzadeh, and Rostami (2010) found conditioned place preference after the central co-administration of nicotine and ethanol, but not after the administration of either drug alone. Nicotine administration attenuated (Bienkowski, Piasecki, Koros, Stefanski, & Kostowski,

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1998) or blocked (Kunin, Smith, & Amit, 1999) the acquisition of CTA by ethanol while also reducing the hypothermic effects of ethanol (Rinker et al., 2011), an aversive property necessary for the establishment of ethanol-induced CPA (Dickinson & Cunningham, 1998). In other studies, nicotine heightened the locomotor stimulant effect of ethanol in mice with a genetic propensity for ethanol-induced stimulation (Gubner, McKinnon, Reed, & Phillips, 2013). Additionally, the development, albeit not the expression, of ethanol-induced behavioral sensitization was significantly greater when the drug was co-administered with nicotine (Gubner & Phillips, 2015). These studies (Gubner et al., 2013; Gubner & Phillips, 2015) suggest that nicotine and ethanol act synergistically on common neurobehavioral mechanisms that promote the transition from drinking to AUD (Camarini & Pautassi, 2016).

Nicotine may also affect ethanol-induced aversion by disrupting normal neurotransmission patterns at the basal forebrain, hippocampus, and prefrontal cortex (Placzek & Dani, 2009; Placzek, Zhang, & Dani, 2009). For instance, acquisition of CTA depends on the ability for novel tastes to trigger acetylcholine (ACh) release from the nucleus basalis of Meynert to several neocortical areas critical for acquisition of taste learning integration (particularly the insular cortex; Rodriguez-Garcia & Miranda, 2016), and nicotine significantly modulates these pathways (Arnold, Nelson, Sarter, & Bruno, 2003; Sato, Kawano, Yin, Kato, & Toyoda, 2017). Thus, it is possible that nicotine administration disrupts the acquisition of an association between taste stimuli and their post-ingestive consequences, regardless of any effect on the overall aversive properties of ethanol, and therefore results in the observed attenuation of ethanol-induced CTA (Bienkowski et al., 1998; Kunin et al., 1999; Rinker et al., 2011).

The present study analyzed the effects of subchronic exposure and pre-treatment with nicotine on simultaneously induced ethanol-induced CTA and CPA, in which the conditioned stimulus (CS+) was sodium chloride solution or a tactile floor cue, respectively, and the unconditioned stimulus (US) was the same injection of ethanol (1.3 g/kg). The rats were given nicotine (0.4 mg/kg) three times before commencement of conditioning, and every day – including CS– sessions – during conditioning. We expected this procedure to yield ethanol-induced CTA and CPA. We hypothesized that if nicotine affects ethanol reinforcement by increasing its rewarding properties, then nicotine would reduce CPA. Conversely, if nicotine specifically affects the neural mechanisms responsible for the association of tastes and ethanol aversion, we expected CTA by ethanol to be selectively affected.

Material and methods

Experimental design

A 2 (nicotine treatment: 0.0 or 0.4 mg/kg nicotine) × 2 (ethanol treatment: 0.0 g/kg or 1.3 g/kg on CS+ trials) factorial design was used. The conditioned stimulus (CS+) was sodium chloride solution or a tactile floor cue for CTA and CPA, respectively, and the unconditioned stimulus (US) was the same injection of ethanol (1.3 g/kg) for both CTA and CPA. All rats received vehicle (i.e., 0.0 g/kg ethanol) on CS– trials. The groups that received alternating ethanol/vehicle injections on CS+ and CS– trials will be referred to as *experimental* CTA/CPA groups, whereas those that received vehicle on both trials will be described as *control* CTA/CPA groups. Note that nicotine was given on CS+ *and* CS– days in an attempt to ameliorate the formation of nicotine-CS or nicotine-ethanol associations and to more closely match the experimental procedures employed in similar studies demonstrating nicotine-induced reduction in the strength of CTA conditioned by ethanol (Kunin et al., 1999). Sample sizes were 12–13 rats per group.

Subjects and housing

Forty-nine adult male Long-Evans rats (Envigo, Haslett, Michigan) weighing approximately 350 g upon arrival were individually housed in polycarbonate cages in a temperature- and humidity-controlled environment on a reverse 12:12-h light cycle. Following acclimatization, the rats were weighed and handled daily for three consecutive days prior to commencement of pre-training procedures. All rats were maintained on ~23-h water deprivation schedule throughout training and testing in order to facilitate stimulus consumption. Food was provided *ad libitum* (standard rodent chow, Envigo 2018). Throughout the experiment, the rats were identified through tail marks made by permanent marker. Experimental procedures were approved by the University at Buffalo Institutional Animal Care and Use Committee and complied with the regulations of the Guide for Care and Use of Laboratory Animals (NIH Publications No. 80–23; revised 1996). The authors further attest that all efforts were made to minimize the number of animals used and their suffering.

Drugs

(-)-Nicotine hydrogen tartrate (Sigma Aldrich, St. Louis, Missouri) was dissolved in saline at a final concentration of 0.4 mg/mL (expressed as the free base), and the pH was adjusted to 7.2–7.4 with sodium hydroxide and was injected subcutaneously at a dose of 0.4 mg/kg. Ethanol was the unconditioned stimulus (US) in the CTA and CPA procedures. Two hundred proof ethanol was diluted with saline to a final concentration of 16% v/v and was administered intraperitoneally, at a volume of 10 mL/kg, yielding a dose of 1.3 g/kg. The intraperitoneal injections were performed in less than 10 s and were targeted between the diaphragm and the genitalia. Controls were administered isovolumetric injections of the vehicle solution (0.9% v/v saline). Sodium chloride (NaCl, Sigma Aldrich, St. Louis, Missouri) served as the CS in the CTA procedure, and was dissolved in tap water. A 0.1 M NaCl solution was used during the acquisition of CTA, whereas a range of concentrations (0.01, 0.1, 0.2, 0.3, 0.6, and 1.0 M) was employed during CTA expression sessions.

Conditioned taste and conditioned place aversion procedures

The procedure, depicted in Table 1, included five lickometer training sessions that served to train the rats to drink from a lickometer, a CPA pre-test session, eight simultaneous CTA/CPA conditioning sessions (i.e., four alternating days of CS+ and CS– [conditioning days 2, 4, 6, and 8] presentations for eight total days of conditioning), and three expression sessions. There was no counterbalancing or randomization of the sequence of CS+ and CS– days. All *experimental* rats received pairings of NaCl and a texture with ethanol's effects on conditioning days 1, 3, 5, and 7 (CS+ days) and were given access to just water and exposed to an alternative texture on conditioning days 2, 4, 6, and 8 (CS– days). *Control* rats were administered vehicle across all days.

A Davis rig (Davis MS-160, DiLog Instruments, Tallahassee, Florida) served as the lickometer used to deliver the taste stimuli during the CTA procedures. This apparatus consists of a polycarbonate cage coupled to a motorized table that contains several fluid reservoirs; access to each fluid reservoir is occluded by a computer-controlled shutter. Licks to the various taste stimuli were recorded via a contact lickometer and were compiled using the Davis rig software.

Sixteen conditioned place apparatus (previously described in Cunningham, Tull, Rindal, & Meyer, 2002) were used during CPA conditioning. Two tactile cues were stainless-steel “rod” or perforated metal “hole” interchangeable floor halves that could be