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Acute nicotine delays extinction of contextual fear in mice

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Abstract

Smoking is linked to Post-Traumatic Stress Disorder (PTSD) which suggests smoking is either a risk factor or an attempt at self-medication. The ability to reduce or extinguish fear-related memories may be altered in patients with PTSD and it is possible that nicotine modulates this. Although there are numerous studies examining the effects of nicotine on acquisition of fear learning, the effects of nicotine on extinction of contextual fear are not well understood. In the present study, we examined the effects of acute nicotine (0.18 mg/kg) on extinction of contextual fear in C57BL/6J mice. Animals were first trained in a background contextual fear conditioning paradigm using a white noise as a conditioned stimulus (CS), which co-terminated with a 2 s 0.57 mA unconditioned foot-shock stimulus (US). Animals were then administered either nicotine or saline and exposed to either the training context or a novel context in order to measure freezing to the context during extinction. Our results demonstrate that nicotine administration during extinction delays extinction of contextual freezing while nicotine did not affect cued freezing or freezing to the novel context.

Keywords

Nicotine; Extinction; Context; Fear Conditioning; PTSD; Anxiety

1. Introduction

Although traumatic events in the course of a person's life are fairly common (Breslau, Kessler et al., 1998), the negative emotional response associated with the traumatic event (e.g. re-experiencing, avoidance, and hyperarousal) usually extinguishes with time. However, for individuals who suffer from Post-Traumatic Stress Disorder (PTSD) the negative emotional responses do not diminish but become more persistent and generalized to contexts other than the trauma context (Rothbaum & Davis, 2003). Hence, in order to ameliorate PTSD symptoms, during exposure therapy, the patient is given exposure to the

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cues that are associated with the trauma to extinguish the negative emotional responses to these cues (Rothbaum & Schwarz, 2002)

There are numerous studies indicating a relationship between smoking and PTSD (see Feldner, Babson, & Zvolensky, 2007 for a review). For example, Lasser, Boyd et al. (2000) reported that 63% of the individuals diagnosed with PTSD had a history of smoking, a percentage significantly higher than the non-clinical population. Also, studies suggest that in humans, the severity of nicotine dependence is positively correlated with total PTSD symptoms such as hyperarousal and avoidance (Thorndike, Wernicke, Pearlman, & Haaga, 2006). Furthermore, while smoking prior to trauma increases the chances of the person developing PTSD (Koenen, Hitsman et al., 2005), daily rate of smoking and the rate of smoking initiation also increase after development of PTSD (Breslau, Davis, & Schultz, 2003; Breslau, Novak, & Kessler, 2004). The question remains whether smoking is a risk factor for developing PTSD or patient with PTSD smokes in an attempt to reduce symptoms.

Animal studies have utilized fear conditioning, a model of PTSD, to examine the effects of nicotine on learning and memory (Gould & Wehner, 1999; Gould & Higgins, 2003; Gould & Lommock, 2003; Davis & Gould, 2006; Davis, Porter, & Gould, 2006, see Gould & Leach, 2014 for a review). These studies suggest that an acute dose of nicotine enhances hippocampus-dependent contextual and trace fear conditioning but it does not have any effect on hippocampusin-dependent delay fear conditioning (Gould & Wehner, 1999; Gould, Feiro, & Moore, 2004). The enhancing effect of an acute dose of nicotine on contextual learning can be blocked by nicotinic acetylcholine receptor (nAChR) antagonists mecamylamine, a nonselective/noncompetitive nAChR antagonist (Feiro & Gould, 2005); and dihydro-betaerythroidine (Dh β E), a competitive $\alpha 4\beta 2^*$ nAChR antagonist (* denotes potential unknown subunit; Davis, Kenney, & Gould, 2007), which suggests that high affinity nAChRs in the hippocampus (e.g. $\alpha 4\beta 2^*$ nAChR) are responsible for the enhancing effect of nicotine on contextual learning. Conversely, studies from our laboratory found that while chronic nicotine had no effect on contextual fear conditioning, 24h withdrawal from chronic nicotine impaired this type of learning (Davis, James, Siegel, & Gould, 2005; Portugal, Wilkinson, Turner, Blendy, & Gould, 2012).

In contrast to the extensive research on the effects of nicotine on fear acquisition, only a few studies have examined the effects of chronic and acute administration of nicotine on extinction. For example, Tian, Gao, et al. (2008) found that prior chronic nicotine exposure for 14 days did not affect within-session extinction but impaired between-session extinction of the cued fear response. Furthermore, the same study reported that chronic nicotine affected neither acquisition nor extinction of contextual fear but enhanced the retention of contextual fear conditioning. Similarly, Smith, McDonald et al. (2006) demonstrated that chronic administration of a relatively low dose of nicotine (1 mg/kg/day) for 15 days during adolescence in rats enhanced acquisition and impaired extinction of cued fear; however, no effect was seen when nicotine was given during adulthood. Recently, Barrett and Bevins (in press) investigated the effects of acute nicotine (0.40 mg/kg) on extinction of operant response for sucrose or a visual stimulation reward and found that animals responded more during the extinction session when nicotine was administered prior to both training and extinction. Finally, Elias, Gulick, Wilkinson, and Gould (2010) investigated the effects of

acute nicotine administrations (0.09 mg/kg) on extinction and renewal of cued fear conditioning in both AAA (acquisition, extinction, and retesting in the same context) and ABA (Extinction in a novel context) designs. The results of the study showed that while in the AAA design, acute nicotine injections only during extinction enhanced extinction of cued fear, whereas injections during both training and extinction impaired extinction of cued fear conditioning. In contrast, Elias et al. (2010) found no effect of acute nicotine injections on extinction of contextual fear conditioning, however, the study was not explicitly designed to examine extinction of contextual fear as the cue was always presented with the context during extinction. The study also found that in the ABA design, nicotine administration before extinction enhanced extinction but blocked renewal of cued fear as a result of context switch, while nicotine administration during both training and extinction did not affect extinction but enhanced renewal. These results suggest that nicotine increases the processing contextual information (acquisition, consolidation, and retrieval of the contextual information; Kenney & Gould, 2008) and strong contextual associations may interfere with cued fear extinction. Taken together, nicotine enhances hippocampal-independent cued extinction but this effect may also be influenced by changes in hippocampal-dependent contextual memories. In contrast to the previous studies investigating the effects of nicotine on cued extinction, in the present study, we aimed to isolate and examine the effects of acute nicotine on extinction of contextual freezing. Experiment 1 tested the effects of acute nicotine on contextual extinction and Experiment 2 investigated context specificity of the nicotine effects across days.

2. Methods

2.1 Subjects

Subjects were 7-week old male C57BL/6 mice (Jackson Laboratory, Bar Harbor, ME) with an average weight of 24.4g. All subjects were group-housed in a colony room maintained on a 12 hour light/dark cycle and had access to food and water *ad libitum*. All training and testing occurred between 9:00 am and 6:00 pm. Behavioral procedures used in this study were approved by the Temple University Institutional Animal Care and Use Committee.

2.2 Apparatus

Contextual conditioning training and testing took place in 2 identical conditioning chambers (18.8 × 20 × 18.3 cm) placed in sound-attenuating boxes (MED Associates, St. Albans, VT). Ventilations fans were located at the back of the boxes providing a background noise (65 dB). A white noise conditioned stimulus (CS, 85 dB) was produced by a speaker located on the right wall of the conditioning chambers. The front wall and ceiling of the chambers were composed of Plexiglas and the floors were metal grids (0.20 cm and 1.0 cm apart) connected to a shock generator which produces a 2-sec long, 0.57 mA foot-shock unconditioned stimulus (US). The stimuli were controlled by an IBM-PC compatible computer running MED-PC software.

The cued testing in Experiment 1 took place in 2 novel testing chambers (23.5 × 22 × 25.3 cm), distinguished by different floors and walls and an added vanilla olfactory scent. Ventilation fans were located at the back of the boxes and a speaker was mounted on the left

wall and generated an 85 dB white noise CS. The same chambers were used as novel contexts in Experiment 2. All chambers were cleaned with 70% ethanol between each subject.

2.3 Drugs and administration

Nicotine hydrogen tartrate salt (0.18 mg/kg freebase, Sigma, St. Louis, MO) dissolved in saline or saline alone was injected intraperitoneally (i.p.) 2–4 mins prior to behavioral testing. The 0.18 mg/kg dose was selected because our pilot work and other studies from our lab showed that this dose enhances contextual fear conditioning (Portugal et al., 2012; Portugal, Wilkinson, Kenney, Sullivan, & Gould, 2012b). Similarly, the time course of the injections was chosen because the half-life of nicotine is approximately 10 mins in mice and nicotine concentration reaches its peak in 2–4 mins (Petersen, Norris, & Thompson, 1984). Both saline and nicotine injection volumes were 10 ml/kg.

2.4 Behavioral procedures

For both experiments, freezing was used as the dependent variable. A time sampling procedure was used to score freezing behavior where each subject was observed every 10 sec for a duration of 1 sec and scored as either freezing or active. During scoring, experimenters were blinded to the drug conditions. As in previous studies (Davis et al., 2006), freezing was defined as the absence of voluntary movement except respiration. Finally, freezing scores were converted to percent freezing.

Training of background contextual fear conditioning was identical to previous studies (e.g. Gould & Wehner, 1999). During training, mice were placed in the conditioning chambers and baseline freezing was assessed for 120 s. Subjects then received two CS-US pairings in which a 30 s CS co-terminated with a 2 s 0.57 mA foot-shock. After the first CS-US pairing, freezing was assessed for 120 s as a measure of immediate freezing to the US. Animals remained in the chamber for 30 sec after the second CS-US pairing and were then removed. The next day, animals were returned to the conditioning chambers to assess contextual freezing. For contextual testing, the animals were placed back in the same context as they were exposed to during training, and freezing was measured for 5 mins in the absence of both the CS and US. In Experiment 1, animals were tested for cued freezing in the altered testing chambers (Novel Context). During cued testing, freezing to the novel context was assessed for 3 min (pre-CS) and then freezing to the CS was assessed for the last 3 min. Both contextual and cued freezing tests were repeated 24 hours later but this time animals were injected with either saline or nicotine as described above (Figure 1).

As shown in Figure 1, for Experiment 2, animals were only tested for contextual freezing in the training context but not given cued testing. Subsequently, the subjects were divided into 4 groups, Saline-Same Context, Nicotine-Same Context, Saline-Novel Context, and Nicotine- Novel Context. Animals in the Same Context condition were given 5 contextual extinction sessions in the training context while animals in the Novel Context condition were given the same number of extinction sessions in a novel context. As described above, Nicotine group animals were given nicotine injections 4 mins prior to the extinction sessions and Saline group animals were given saline vehicle injections.

2.4 Statistical Analysis

Contextual and cued freezing levels during testing and extinction sessions were examined using a repeated-measure ANOVA. Cued and contextual freezing were analyzed separately in Experiment 1. Planned comparison t-tests were used for post-hoc analysis at $\alpha = 0.05$ level. A total of 3 mice were removed from the analysis as their freezing levels were 2 standard deviations above the mean. Group sizes were indicated in figure captions. All statistical analyses were run using SPSS 16.0.

3. Results

3.1 Experiment 1

Separate repeated measures ANOVAs found that the Test Day (Test and Retest) $\times$ Drug (Saline and Nicotine) interaction was significant for Contextual testing, $F(1,13) = 8.885$, $p = 0.011$, and for Pre-CS freezing, $F(1,13) = 4.877$, $p = 0.046$, but not for Cued testing, $F(1,13) = 1.968$, $p = 0.184$. Planned comparison t-tests showed that the difference between the freezing levels of Saline and Nicotine groups for context retesting was significant ($t(13) = 3.416$, $p = 0.005$). The difference between Saline and Nicotine groups during retesting was not significant for the pre-CS period but approached significance, ($t(13) = 2.007$, $p = 0.066$). These results showed that while contextual freezing extinguished in the Saline group, extinction was impaired in the Nicotine group (Figure 2). Furthermore, the nicotine treatment had no effect on extinction of cued freezing. Figure 3 shows averaged percent freezing over 100-sec bins within the test and retest sessions (1st 100 s, 2nd 100 s, & 3rd 100 s). A repeated measures ANOVA yielded a significant main-effect of Drug (Nicotine vs. Saline) within the retest session ($F(1,13) = 12.372$, $p = 0.004$). In addition, planned comparison t-tests showed that the difference between Saline and Nicotine groups freezing levels during the retest session was significant for the 1st 100 s ($t(13) = 2.640$, $p = 0.020$) and the 2nd 100 s bins ($t(13) = 2.512$, $p = 0.026$) but not for the 3rd 100 s bin ($t(13) = 1.099$, $p = 0.292$). These results suggest that the impaired extinction is likely a result of enhanced recall of contextual fear memory in the nicotine group.

3.2 Experiment 2

A one-way ANOVA yielded no difference in freezing levels between the 4 groups (Saline-Same Context, Nicotine-Same Context, Saline-Novel Context, and Nicotine-Novel Context) in the initial test session ($F(3,30) = 0.461$, $p = 0.712$). Therefore, all four groups had similar freezing levels prior to injections and retest sessions. A repeated measures ANOVA yielded no significant interaction between Trial (Retest1, Retest2, Retest3, Retest4, and Retest5) $\times$ Drug (Saline and Nicotine) $\times$ Context (Same and Novel) $F(4,104) = 1.426$, $p = 0.231$. However, both Trial $\times$ Context and Trial $\times$ Drug interactions were significant ($F(4,104) = 6.921$, $p = 0.013$ and $F(4,104) = 3.342$, $p < 0.001$, respectively) indicating a differential effect in freezing between both context and drug conditions. Furthermore, the same test yielded a significant 2-way interaction between Drug $\times$ Context across extinction trials ($F(1,26) = 9.993$, $p = 0.004$) suggesting that nicotine had a differential effect on the levels of freezing between different context conditions.

Planned comparison t-tests showed that the difference between Same-Saline and Same-Nicotine groups freezing levels was significant during Retest-2 ($t(13)=2.854$, $p=0.014$) and Retest-3 ($t(13)=3.516$, $p=0.004$) and approached significance during Retest-4 ($t(13)=2.117$, $p=0.054$). However not significant, on Retest1 the trend of the difference between Same-Saline and Same-Nicotine groups' freezing levels replicates Experiment 1. The lack of significant difference between groups may be attributed to the methodological differences between Experiment 1 and 2. Importantly, in the experimental design of Experiment 2 the cued testing in a novel context was omitted.

Overall, as shown in Figure 4, results suggest that acute nicotine administrations delayed extinction of contextual freezing when tested in the same context but it did not affect contextual freezing to a novel context.

4. Discussion

Our results demonstrate that acute nicotine administration during extinction impairs extinction of contextual fear conditioning while not affecting cued extinction (Experiment 1) or freezing in a novel context (Experiment 2). Additionally, our results suggest that nicotine impaired extinction is a result of enhanced recall of the contextual fear memory (Figure 3). This result supports the findings of Kenney and Gould (2008), which demonstrate that acute nicotine does not affect the Context-US association as our results also suggested that acute nicotine does not enhance Context-NoUS learning during extinction but instead enhances the retrieval of the contextual memory, which may prevent extinction

In contrast to our results, Elias et al. (2010) did not report any effect of acute nicotine on contextual fear extinction. However, there are number of differences between the experimental design used in the present study and the design used by Elias et al. (2010). First, even though the training was identical in both studies, in the Elias et al. (2010) study the CS was presented six times during each extinction session while in the present study no CS presentations were given during the context tests. Also, due to CS presentations, extinction sessions used in the Elias et al. (2010) study was substantially longer than the extinction sessions used in our study (19 mins and 5.5 mins, respectively). Thus, it is possible that CS presentations during extinction in the Elias et al. (2010) study accelerated extinction of contextual fear. In addition, as explained above, subjects received extinction sessions which were longer than the retest sessions used in the present study. Therefore, it is possible that at the end of the first extinction session contextual freezing was already extinguished. To test this hypothesis we analyzed the contextual freezing data from the first extinction session of the Elias et al. (2010) study. In line with our results, further analysis indicates that an acute dose of nicotine partially impaired contextual extinction in the AAA but not in the ABA design (Figure 5). Furthermore, unlike Elias et al. (2010) study, the results of Experiment 1 in our study did not show any effect of nicotine on extinction of the cue (Figure 2). The reason for this result might be that in the present study the length and pattern of cue exposure was not enough to detect the effect of nicotine on extinction of cued fear conditioning. Overall, Elias et al. (2010) results and the results from the present study appear to be in agreement regarding the effects of acute nicotine on extinction of contextual fear.

The results of the present study have several implications in the clinical domain. For example, together with Elias et al. (2010) study, our results suggest that initiation of smoking after a traumatic event may interfere with the extinction of fear response to a trauma-associated context by enhancing the recall of the contextual fear memory. Therefore, it is possible that even after successful exposure therapy in a neutral context, re-occurrence of fear may be triggered by a nicotine-enhanced contextual memory. Our results also show that the effect of nicotine is specific to the trauma associated context and does not enhance generalization of contextual fear to other neutral contexts (e.g. the therapy context). Interestingly, Breslau et al. (2003, 2004) found that both initiation of smoking and smoking rates increased after the development of PTSD. While smoking may be an attempt to cope with the stress of PTSD; increased initiation of smoking rates following the development of PTSD might be a contributing factor to the relapse to symptoms of PTSD, a common problem in the treatment of PTSD and other anxiety disorders (Craske, 1999).

In sum, we found that an acute dose of nicotine delays extinction of contextual fear conditioning but it does not affect cued freezing or freezing to a novel context. Our results also suggest that this effect might be a result of enhanced retrieval of the contextual memory. As noted above, extinction is a crucial process for the treatments of anxiety disorders such as PTSD. A better understanding of the molecular and pharmacological bases of extinction is needed to help develop more effective treatment methods for these disorders.

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Research Highlights

We tested the effects of acute nicotine on extinction of contextual fear.

Our results showed that acute nicotine impaired extinction of contextual fear.

Our results also indicated that this effect was not based on generalized freezing.

Figure 1.

The schematic experimental designs of Experiment 1 and 2. While each box represents a phase of the experiment, the syringes represent nicotine or saline injections and the thunder bolt symbol indicates the presentations of the foot-shocks (FC = Fear Conditioning).

Experiment 1

Figure 2.

The effects of acute nicotine injections prior to the retest phase. Extinction of contextual fear conditioning was impaired in the nicotine group ($n=8$) comparing to the saline group ($n=7$) while pre-CS freezing and cued extinction was unaffected (CX: context). Error bars indicate Standard Error of the Mean (SEM) and asterisks represent differences at the $p < 0.05$ level.

Experiment 1 - Within Session

Figure 3.

The effects of acute nicotine injections on contextual freezing prior to the retest phase within the test and retest sessions. Each point represents an averaged freezing level over a 100 sec bin. Error bars indicate Standard Error of the Mean (SEM) and asterisks represent differences at the $p < 0.05$ level.

Experiment 2

Figure 4.

The effects of acute nicotine administration prior to 5 retest sessions. Extinction of contextual fear conditioning was delayed in the nicotine group ($n=8$) comparing to the saline group ($n=7$) whereas nicotine did not have any effect on the freezing response to a novel context (CX: context). Error bars indicate Standard Error of the Mean (SEM) and asterisks represent differences at the $p < 0.05$ level.

Figure 5.

Data from Elias et al. (2010) within the first extinction session in Context A (AAA) or in Context B (ABA). Extinction of contextual freezing was delayed in the AAA design but not in the ABA design. A t-test showed that freezing to the context during the 3rd 120 s bin was significant ($t(16)=2.136, p=0.048$). Error bars indicate Standard Error of the Mean (SEM) and asterisks represent differences at the $p < 0.05$ level.