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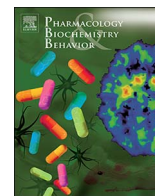
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Nicotine pretreatment reduced cocaine-induced CPP and its reinstatement in a sex- and dose-related manner in adult C57BL/6J mice



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ABSTRACT

Previous preclinical studies have shown that nicotine pretreatment during adolescence increases the reinforcing actions of cocaine. However, little is known about the effect of prior nicotine administration on cocaine-induced conditioned place preference (CPP) and its reinstatement in adult mice. Besides, little information is available regarding the role of sex in this cross-talk between nicotine and cocaine. Thus, we examined if nicotine administration during adulthood would differentially alter cocaine-induced CPP, its extinction and reinstatement in male versus female mice and if the dose of nicotine was important in this regard. To this end, mice were pretreated with saline or nicotine (0.25 or 1 mg/kg; twice daily for seven days) and then tested for place preference before and after single and repeated conditioning with cocaine (15 mg/kg). Mice were then exposed to extinction training and tested for reinstatement of CPP. Our results showed that male and female mice pretreated with saline and conditioned with cocaine each exhibited a robust CPP after a single cocaine conditioning. However, this response was blunted in mice pretreated with the lower but not higher dose of nicotine. Female mice pretreated with the lower dose nicotine also failed to show CPP after repeated conditioning. Reinstatement of cocaine-induced CPP was also blunted in these mice compared to their respective controls. Together, these results suggest that nicotine administration during adulthood exerts differential effects on cocaine-induced CPP and its reinstatement in male and female mice and the dose of nicotine is important in this regard.

1. Introduction

The initial use of some drugs during adolescent period primes the brain to bolster consumption of illicit substances later in life, leading to polydrug use in some individuals (McCabe et al., 2006). For example, previous studies have shown that nicotine exposure during adolescence can pave the way to the use and abuse of cocaine, alcohol, and other addictive substances (Levine et al., 2011; McQuown et al., 2007; Orsini et al., 2008). Interestingly, an epidemiological study has shown that, just alone in the United States, 90.4% of adults (between the ages of 18–34), who had used cocaine at least once had also smoked cigarettes before (Levine et al., 2011). Many preclinical studies have also demonstrated the effect of early nicotine use on the reinforcing and rewarding effects of cocaine. For instance, pretreatment with nicotine has been shown to facilitate cocaine self-administration (McQuown et al., 2007), cocaine-induced reward (Li et al., 2014) and locomotor sensitization (Kandel and Kandel, 2014). Additionally, pretreatment with nicotine (0.32 mg/kg) produced a leftward shift in the cocaine's dose-response curve in Rhesus monkeys (Mello and Newman, 2011). Together, these findings suggest that nicotine may serve as a gateway drug to facilitate the rewarding and reinforcing actions of cocaine [but see, (Kelley and Middaugh, 1999; Kelley and Rowan, 2004)].

Age has been shown to play a critical role in the initiation and maintenance of addiction to nicotine and other drugs of abuse. Research in the past has shown that nicotine use is initiated during adolescent period and proceeds to the use and abuse of other drugs (Best et al., 2000; Businelle et al., 2013; Carmody et al., 1985; DiFranza and Guerrero, 1990; Lisha et al., 2014; McKee et al., 2011; Rimm et al., 1995; Romberger and Grant, 2004; Torabi et al., 1993; York and Hirsch, 1995). This period of life is a very sensitive age in which the negative affective state associated with nicotine withdrawal is reduced while the rewarding action of nicotine is enhanced compared to adults (Carcoba et al., 2014; Dickson et al., 2014; Dickson et al., 2011; Hutchison and Riley, 2008; Lee et al., 2015; McQuown et al., 2009; Natividad et al., 2012; Natividad et al., 2010; Natividad et al., 2013; O'Dell et al., 2004; O'Dell et al., 2006; O'Dell et al., 2007; Shram et al., 2008; Torres et al., 2008; Wilmoth and Spear, 2004), making adolescents a vulnerable target to nicotine use and abuse as well as for use of other addictive drugs during adulthood. Consistent with this notion, previous studies have shown that nicotine exposure during adolescence can prime the use and abuse of cocaine, alcohol, and other addictive substances (Bechtholt and Mark, 2002; DiFranza and Guerrero, 1990; Horger et al., 1992; Hutchison and Riley, 2008; Kandel and Kandel, 2015; Kandel and Kandel, 2014; Kelley and Rowan, 2004; Kouri et al., 2001; Levine et al., 2011; Li

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et al., 2014; McQuown et al., 2007; McQuown et al., 2009; Meliska et al., 1995; Natividad et al., 2010; Rinker et al., 2011; Rosenberg, 2014; Schindler et al., 2012; Schneider et al., 2012). There is also evidence showing that about 90% of regular smokers start using tobacco at an early age, and that early onset smoking carries a major risk for the development of addiction to other drugs of abuse (Rimm et al., 1995). Indeed, previous studies have shown that nicotine exposure during adolescence period alter the aversive (Hutchison and Riley, 2008) and rewarding (Kelley and Rowan, 2004; Schochet et al., 2004) effects of cocaine. Although an earlier study reported that prior nicotine treatment only enhanced the rewarding action of cocaine in adolescents but not adult rats (McQuown et al., 2009; Mojica et al., 2014), limited information is available on the impact of nicotine exposure during adulthood on cocaine reward, extinction and reinstatement in mice.

There is accumulating clinical and preclinical evidence suggesting that there are sex-related differences in the neurobiology of addiction [for reviews, (Andersen et al., 2012; Anker and Carroll, 2011; Becker and Hu, 2008; Quinones-Jenab and Jenab, 2012)]. Previous reports have shown that female rats acquire cocaine-induced conditioned place preference (CPP) after lower doses and fewer conditioning sessions compared to male rats, suggesting that females may be more sensitive to the rewarding action of cocaine (Russo et al., 2003). Likewise, adolescent (PND34) and adult (PND 66) female rats were more sensitive and acquire cocaine CPP at lower doses than male rats (Zakharova et al., 2009). In general, females have a greater propensity to self-administer cocaine or to exhibit greater sensitivity to the rewarding action of cocaine in the CPP paradigm. Furthermore, accumulating clinical and preclinical evidence suggests that there are sex-related differences in the neurobiology of addiction to nicotine (O'Dell and Torres, 2014; Torres et al., 2009; Vastola et al., 2002). However, there is a limited number of studies regarding the role of sex in the gateway action of nicotine. Importantly, there are no prior studies on the role of sex regarding the effect of prior nicotine treatment on extinction and reinstatement of cocaine-induced CPP. Therefore, we determined whether prior nicotine treatment during adulthood would alter cocaine-induced CPP, its extinction and reinstatement and if there was an effect of nicotine dose and/or sex of animals in these responses.

2. Material and methods

2.1. Subjects

Male and female C57BL/6J mice bred in house were used between the ages of 4–6 months for all experiments. The original breeding pairs were obtained from the Jackson Laboratories (Bar Harbor, ME, USA). Subjects were maintained under a 12-hour light/dark cycle (6 am–6 pm) in a temperature-controlled environment and had free access to food and water in their home cages except at the time of testing. All experiments were conducted during the light cycle between 9 am–5 pm, and were according to the NIH guidelines for the care and use of animals in research and approved by the Institutional Animal Care and Use Committee at Western University of Health Sciences (Pomona, California, USA).

2.2. Drugs

Nicotine bi-tartrate obtained from MP biomedical (Solon, Ohio) was dissolved in saline and administered subcutaneously (s.c.). Cocaine hydrochloride obtained from Sigma/Aldrich (St. Louis, Missouri) was dissolved in saline and administered intraperitoneally (i.p.). Control mice were injected with saline (s.c. and/or i.p.). The dose of nicotine is as the bi-tartrate salt.

2.3. Effects of low dose nicotine pretreatment on cocaine-induced conditioned place preference (CPP), its extinction and reinstatement in male and female mice

We used an unbiased conditioned place preference (CPP) paradigm to determine the effect of prior nicotine treatment on cocaine-induced CPP, its

extinction and reinstatement. To this end, male and female mice were first randomly assigned and received nicotine (0.25 mg/kg, s.c.) or saline (10 ml/kg, s.c.) twice a day (9 am and 5 pm) for seven consecutive days. We then tested the effect of this seven-day nicotine treatment on cocaine-induced CPP, its extinction and reinstatement. The CPP paradigm was conducted 24 h after the last saline/nicotine injection over an 11-day period and consisted of five phases: (1) preconditioning test, (2) single as well as repeated conditionings, (3) postconditioning test, (4) extinction training and (5) reinstatement test. Each experiment was repeated at least twice with a cohort of 3 mice per treatment (saline vs. lower or higher dose of nicotine) and sex (male vs. female). Different groups of naive animals were used for each experiment. On day 1 (D1), mice were tested for baseline place preference, in which mice were placed in the neutral central chamber of the CPP apparatus and allowed them to freely explore the CPP chambers for 15 min. The amount of time that mice spent in each chamber was recorded and used as baseline place preference. Mice were then conditioned with either cocaine (15 mg/kg, i.p.) in one chamber, i.e., the drug-paired chamber (DPCh) or saline in the opposite chamber, assigned as the vehicle-paired chamber (VPCh). To assess whether pretreatment with nicotine had any effect on the rewarding actions of acute cocaine, mice were tested for place preference after this single conditioning the next day (day 3; D3), as described for day 1. Shortly thereafter, mice received their respective twice-daily conditioning on this day and also on day 4 and tested for CPP after repeated conditioning on day 5 (D5), as described for day 1. On day 9, the animals received extinction training, in which saline administration was associated with both conditioning chambers and tested for extinction the following day (Ext). Lastly, mice were tested for reinstatement (Reinstatement) of cocaine CPP following a challenge dose of cocaine (7.5 mg/kg) on day 11. On each test day, mice were placed in the neutral central chamber of the CPP apparatus, allowed to freely roam all the CPP chambers, and the amount of time that mice spent in each conditioning chamber was recorded, as described above for day 1.

2.4. Effects of high dose nicotine pretreatment on cocaine-induced conditioned place preference (CPP), its extinction and reinstatement in male and female mice

The experimental protocol was identical to the above procedure except male and female mice were pretreated with saline or a higher dose of nicotine (1 mg/kg, s.c.) twice daily for seven days prior to the initiation of the CPP protocol.

2.5. Data analysis

The data are presented as means (\pm S.E.M.) of the amount of time that animals spent in the drug-paired chamber (DPCh) versus vehicle-paired chamber (VPCh). A three-way repeated measure analysis of variance (ANOVA) was performed followed by Fisher LSD *post-hoc* test for multiple comparisons. The between factors were drug pretreatment (saline vs. nicotine) and the conditioning side. The test day (time) was used as the within factor. A $P < 0.05$ was considered statistically significant.

3. Results

3.1. Pretreatment with the lower dose of nicotine (0.25 mg/kg) blunted the acute rewarding action of cocaine in male mice with no alterations in the CPP response induced by repeated conditioning and no change in reinstatement

Fig. 1 depicts the amount of time that male mice treated with saline (left panel) or the lower dose nicotine (right panel) spent in the vehicle-paired chamber (VPCh) and drug-paired chamber (DPCh) on days 1 (D1), 3 (D3), 5 (D5) as well as on test days for extinction (EXT) and reinstatement of cocaine CPP (Reinstatement). A three-way repeated-measure ANOVA revealed a significant effect of conditioning side ($F_{1,4} = 32.16$; $P < 0.001$), a significant interaction between the conditioning side and test days ($F_{4,4} = 5.78$; $P < 0.0003$) and a significant interaction between

Male mice sal vs low dose nic

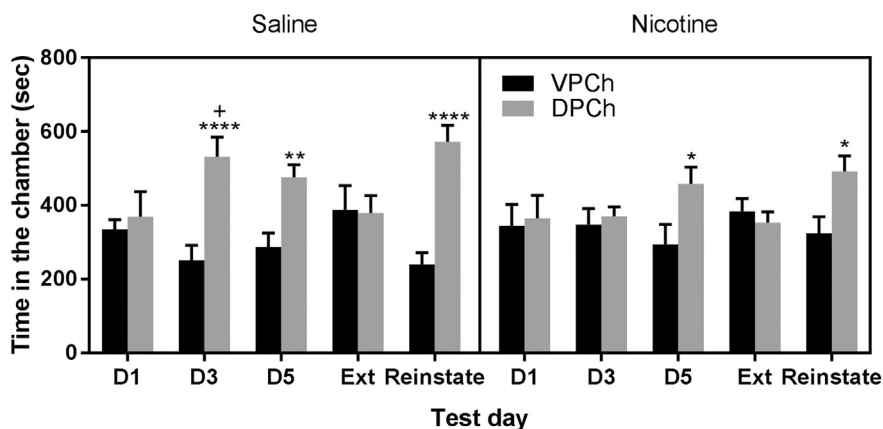


Fig. 1. CPP induced by single (D3) or repeated (D5) cocaine conditioning as well as its extinction and reinstatement in male mice pretreated with saline (left panel) or the lower dose of nicotine (right panel). Data are means (\pm S.E.M.) of the amount of time that animals spent in the drug-paired (DPCh) and vehicle-paired (VPCh) chambers before (D1) and after single (D3) and repeated (D5) conditioning with cocaine as well as on the extinction (EXT) and reinstatement (Reinst) test days ($n = 6$ mice per treatment; $*P < 0.05$; $**P < 0.01$; $****P < 0.0001$ (significant difference in the amount of time that mice spent in the DPCh vs. its respective VPCh, respectively; $^+ P < 0.05$ significant difference in the amount of time that control mice spent in the DPCh vs. nicotine-pretreated mice)).

pretreatment and the conditioning side ($F_{1,4} = 5.55$; $P < 0.03$). The Fisher LSD test revealed that male mice pretreated with saline and exposed to a single cocaine conditioning trial spent a significantly greater amount of time in the DPCh compared to VPCh ($P < 0.0001$), showing that cocaine induced a significant CPP in these mice. When these mice exposed to additional conditioning and tested on day 5 (D5), they still exhibited a significant CPP ($P < 0.01$) and this response was extinguished and reinstated following a challenge dose of cocaine ($P < 0.0001$). On the other hand, the same dose of cocaine failed to induce CPP in male mice pretreated with the lower dose of nicotine, as there was no significant difference in the amount of time that these mice spent in the DPCh vs. VPCh following single cocaine conditioning ($P > 0.05$). However, male mice pretreated with this dose of nicotine exhibited a significant ($P < 0.05$) CPP after repeated conditioning with cocaine (D5; DPCh vs. VPCh) but weaker (although not significantly different than controls) reinstatement. These findings suggest that prior low dose nicotine treatment reduced the rewarding action of acute cocaine in male mice.

3.2. Prior treatment with the lower dose of nicotine (0.25 mg/kg) blunted the CPP response induced by single or repeated conditioning with cocaine as well as its reinstatement in female mice

The amount of time that female mice pretreated with saline (left panel) or the lower dose nicotine (right panel) spent in the VPCh and DPCh on different test days is shown in Fig. 2. A three-way repeated-measure ANOVA indicated a significant effect of the conditioning side ($F_{1,4} = 8.04$; $P < 0.006$), a significant interaction between the conditioning side and test days ($F_{4,4} = 2.64$; $P < 0.05$), and a significant interaction between

pretreatment and conditioning side ($F_{1,4} = 22.92$; $P < 0.0001$). The post-hoc test showed that control mice, i.e., pretreated with saline, and conditioned with cocaine exhibited a significant CPP following single or repeated conditioning ($P < 0.001$) and this response was extinguished and reinstated following a challenge dose of cocaine ($P < 0.0001$). In contrast, the same dose of cocaine failed to induce CPP in female mice pretreated with the lower dose of nicotine, as there was no significant difference in the amount of time that these mice spent in the DPCh vs. VPCh following single or repeated cocaine conditioning ($P > 0.05$). Likewise, reinstatement of cocaine CPP was blunted in these mice. These results show that pretreatment with the lower dose of nicotine attenuated the rewarding action of acute and repeated cocaine as well as its reinstatement in female mice.

3.3. Pretreatment with the higher dose of nicotine (1 mg/kg) did not alter CPP induced by single and repeated conditioning with cocaine or its reinstatement in male mice

Fig. 3 illustrated the amount of time that mice spent in the VPCh and DPCh on different test days in male mice. Three-way ANOVA revealed a significant effect of the conditioning side ($F_{1,4} = 98.59$; $P < 0.0001$), a significant interaction between the conditioning side and test days ($F_{4,4} = 11.26$; $P < 0.0001$) but no significant interaction between pretreatment and conditioning side ($F_{1,4} = 1.27$; $P > 0.05$). The Fisher LSD test showed that saline-pretreated controls exhibited a robust CPP response after single or repeated conditioning with cocaine ($P < 0.0001$; left panel). Likewise, they exhibited extinction and reinstatement ($P < 0.0001$). Moreover, cocaine was able to induce a robust CPP after single or repeated conditioning in male mice pretreated with the higher dose of nicotine

Female mice sal vs low dose nic

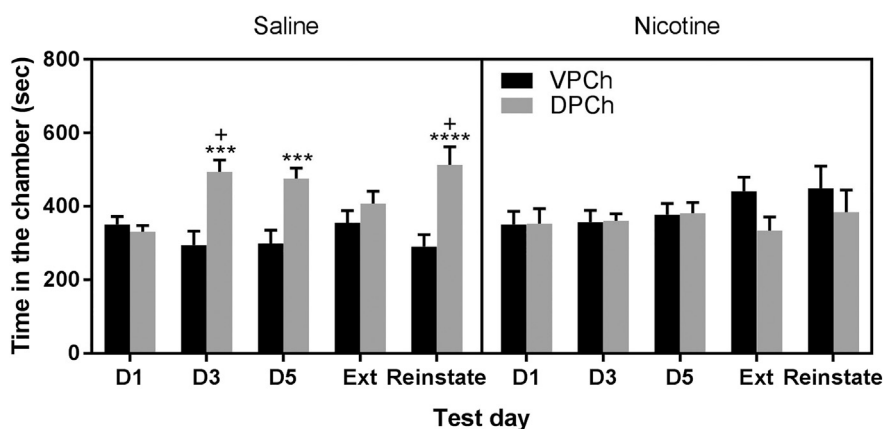


Fig. 2. CPP induced by single (D3) or repeated (D5) cocaine conditioning as well as its extinction and reinstatement in female mice pretreated with saline (left panel) or the lower dose of nicotine (right panel). Data are means (\pm S.E.M.) of the amount of time that animals spent in the drug-paired (DPCh) and vehicle-paired (VPCh) chambers before (D1) and after single (D3) as well as repeated (D5) conditioning with cocaine and during the extinction (EXT) and reinstatement (Reinst) test days ($n = 8$ mice per treatment; $****P < 0.0001$; $***P < 0.001$; $^+ P < 0.05$ significant difference in the amount of time that mice spent in the DPCh vs. its respective VPCh, respectively; $^+ P < 0.05$ significant difference in the amount of time that control mice spent in the DPCh compared to nicotine-pretreated mice)).

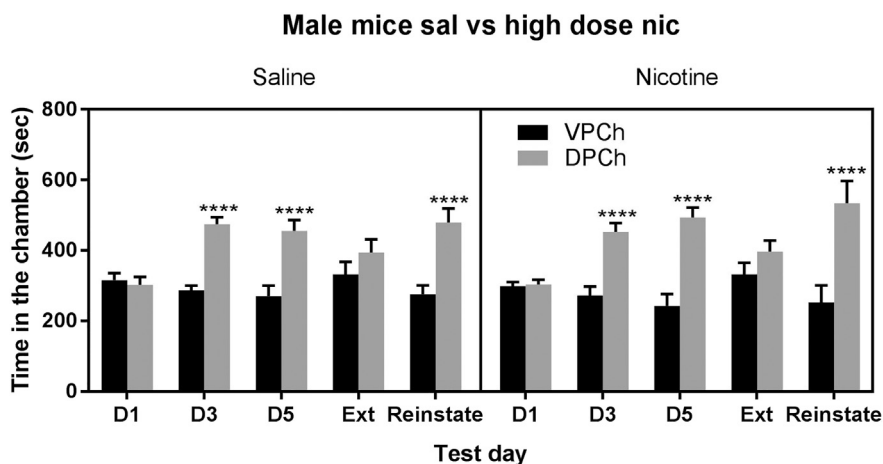


Fig. 3. CPP induced by single (D3) or repeated (D5) cocaine conditioning as well as its extinction and reinstatement in male mice pretreated with saline (left panel) or the higher dose of nicotine (right panel). Data are means (± S.E.M.) of the amount of time that animals spent in the drug-paired (DPCh) and vehicle-paired chamber (VPCh) before (D1) and after single (D3) and repeated (D5) conditioning with cocaine as well as on the extinction (EXT) and reinstatement (Reinstatement) test days (n = 9 mice per treatment; ****P < 0.0001 (significant increase in the amount of time that mice spent in the DPCh vs. its respective VPCh)).

(Fig. 3, right panel). Similarly, these mice exhibited a robust reinstatement, suggesting that pretreatment with the higher dose nicotine did not alter CPP or its reinstatement in male mice (Fig. 4).

3.4. Prior treatment with high dose nicotine (1 mg/kg) failed to alter cocaine-induced CPP or its reinstatement in female mice

Fig. 4 depicts the amount of time that mice spent in the VPCh and DPCh on various test days in female mice. Analysis of the data showed a significant effect of the conditioning side (F1,4 = 139.4; P < 0.0001), a significant interaction between the conditioning side and test days (F4,4 = 22.86; P < 0.0001) but no significant interaction between pretreatment and conditioning side (F1,4 = 1.10; P > 0.05). The post-hoc test revealed that control mice exhibited a robust CPP response after single or repeated conditioning with cocaine (P < 0.001; left panel). Additionally, female control mice exhibited extinction (although there appeared to be some residual CPP response) and reinstatement following the challenge dose of cocaine (P < 0.001). Unlike the low dose nicotine, pretreatment with the high dose nicotine failed to alter cocaine-induced CPP or its reinstatement in female mice (Fig. 4, right panel). These results suggest pretreatment with the higher dose of nicotine did not alter CPP induced by single or repeated conditioning with cocaine in female mice. Similarly, the magnitude of the CPP response was not altered on the reinstatement test day in these mice.

4. Discussion

The main findings of the present study are that single as well as repeated cocaine conditioning induced a robust CPP in saline-pretreated male and female mice. The CPP response was extinguished following saline conditioning and reinstated when mice were challenged with cocaine, showing that cocaine induced CPP in mice of both sexes and this response was extinguished and reinstated. In contrast, single conditioning with cocaine failed to induce CPP in both male and female mice pretreated with the lower (0.25 mg/kg) but not higher (1 mg/kg) dose of nicotine. Furthermore, repeated cocaine conditioning did not induce CPP in female mice pretreated with the lower dose of nicotine. Similarly, reinstatement of cocaine-induced CPP was blunted in female but not male mice pretreated with the lower dose of nicotine. Together, these results suggest that nicotine pretreatment during adulthood in mice may even reduce cocaine-induced CPP and its reinstatement in a dose- and sex-related manner.

Many studies have reported that nicotine may serve as a gateway drug for cocaine and other illicit drugs (Dickson et al., 2014; Dickson et al., 2011; Levine et al., 2011; Li et al., 2014; McQuown et al., 2007; Orsini et al., 2008). However, there is limited information on the effect of nicotine treatment on the rewarding action of cocaine if nicotine is administered during adulthood. In particular, there is a dearth of information regarding the effect of nicotine pretreatment on extinction and reinstatement processes. Therefore, we assessed the effect of prior nicotine treatment on the acquisition, extinction and reinstatement of cocaine CPP, and tested if there was any sex-related difference in this

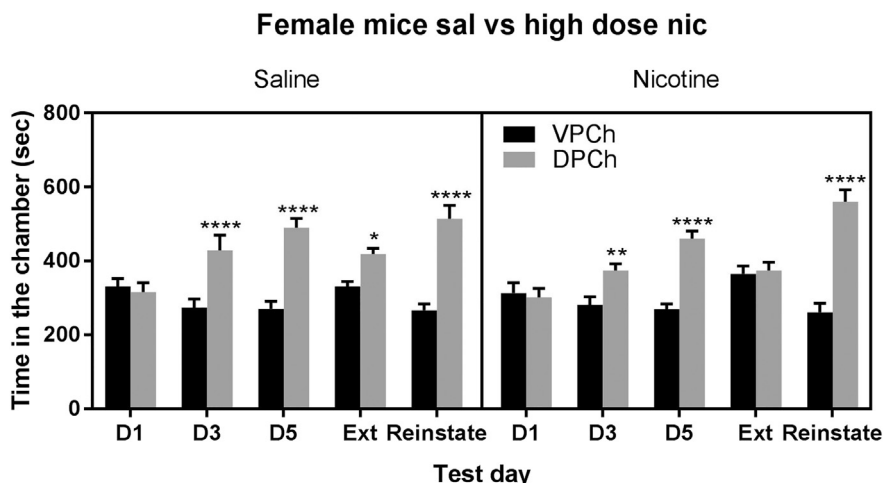


Fig. 4. CPP induced by single (D3) or repeated (D5) cocaine conditioning as well as its extinction and reinstatement in female mice pretreated with saline (left panel) or the higher dose of nicotine (right panel). Data are means (± S.E.M.) of the amount of time that animals spent in the drug-paired (DPCh) and vehicle-paired chamber (VPCh) before (D1) and after single (D3) and repeated (D5) conditioning with cocaine as well as on the extinction (EXT) and reinstatement (Reinstatement) test days (n = 7 mice per treatment; **P < 0.01; ****P < 0.0001 (significant increase in the amount of time that mice spent in the DPCh vs. its respective VPCh, respectively)).

regard. Our results showed that pretreatment with the lower nicotine dose (0.25 mg/kg, s.c.) reduced the rewarding actions of acute cocaine in both male and female mice. Pretreatment with this dose of nicotine also blunted the CPP response induced by repeated cocaine conditioning and its reinstatement in female but not male mice, showing sex-differences in the inhibitory effect of nicotine pretreatment on cocaine reward. On the other hand, male and female mice pretreated with the higher nicotine dose (1 mg/kg) exhibited a CPP response that was comparable to their respective saline-pretreated controls. Likewise, reinstatement of CPP was not altered in mice pretreated with the higher dose of nicotine. Our results are consistent with previous studies in rats showing that nicotine pretreatment increased cocaine-induced reinforcement (McQuown et al., 2007) as well as locomotor sensitization (McQuown et al., 2009) in adolescent but not adult rats. Interestingly, nicotine withdrawal has been shown to differentially regulate extracellular levels of accumbal dopamine in adolescent versus adult rats (Natividad et al., 2010). Likewise, the rewarding actions of nicotine are more pronounced in adolescence compared to adult rats (Natividad et al., 2013). Thus, age of animals may play a major role in the gateway effect of nicotine.

A novel finding of the present study is that pretreatment with the lower dose of nicotine blunted the rewarding action of acute cocaine in both male and female mice. Although the underlying mechanism of blunted cocaine-induced CPP with the lower dose of nicotine is not clear, it is possible that nicotine may have caused desensitization of certain nicotinic acetylcholine receptors, which are shown to be important in mediating the rewarding action of cocaine (Sanjakdar et al., 2015). Indeed, differences in the affinity of nicotine for different subtype ($\alpha 7$, $\alpha 4\beta 2$) of nicotinic acetylcholine receptors as well as differences in the rate of desensitization of different subtypes by nicotine (Buccafusco et al., 2009; Giniatullin et al., 2005; Lewis and Picciotto, 2013; Papke et al., 2009) have been reported in the literature, which may explain the results of the current study. However, further studies using a subtype selective agonist that does not cause strong desensitization or mice lacking different subtypes of nicotinic acetylcholine receptors (Marubio et al., 2003) are needed to define the underlying mechanism of these differential effects of low and high dose nicotine on cocaine reward.

One caveat of the present study is that we have used a single dose of cocaine. Therefore, one may argue that pretreatment with nicotine may have shifted the dose-response curve of cocaine to the left, as shown previously (Mello and Newman, 2011), and therefore we observed no CPP in male and female mice pretreated with the low dose nicotine. We propose that the two doses of nicotine target different subtypes of nicotinic acetylcholine receptors, as discussed above, or may affect other neurotransmitter system(s) that may shift the dose-response curve in female mice pretreated with the low but not high dose nicotine. In line with this, nicotine has been shown to cause the release of beta-endorphin (Olive et al., 2001). Notably, nicotine-induced CPP was blunted in mice lacking beta-endorphin (Trigo et al., 2009), showing that beta-endorphin is involved in the rewarding action of nicotine. Interestingly, we have previously shown that the rewarding action of cocaine is also reduced in mice lacking beta-endorphin (Marquez et al., 2008). Thus, it is possible that nicotine may have caused a sensitized response via the beta-endorphin system. However, whether the two doses of nicotine used in the present study would differentially regulate the release of beta-endorphin and whether that response is different between male and female mice require further research. The other caveat of the present study is that we did not measure basal locomotor activity as well as the motor stimulatory action of cocaine in these mice during the conditioning sessions. It is possible that basal locomotor activity or cocaine-induced hyperlocomotion may be different between males and females or in mice pretreated with the low vs. high nicotine dose, and potentially impacted the CPP data.

In summary, we found that cocaine induced a robust CPP response in both male and female mice. The CPP response was extinguished and

reinstated in mice of both sexes. Pretreatment with nicotine (0.25 mg/kg twice daily for seven days) blunted cocaine-induced CPP and its reinstatement in female mice as well as CPP induced by single cocaine conditioning in male mice. However, the higher dose of nicotine (1 mg/kg) had no inhibitory effect on cocaine-induced CPP and its reinstatement in female or male mice, showing that cocaine-induced CPP and its reinstatement were altered by nicotine pretreatment in a dose- and sex-related manner.

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List of author contribution

KL contributed to the design of the experiments, analysis and interpretation of the data, and writing and revising of the manuscript. PKS conducted the experiments, analyzed and interpret the data and wrote the first draft of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

References

- Andersen, M.L., Sawyer, E.K., Howell, L.L., 2012. Contributions of neuroimaging to understanding sex differences in cocaine abuse. *Exp. Clin. Psychopharmacol.* 20 (1), 2–15.
- Anker, J.J., Carroll, M.E., 2011. Females are more vulnerable to drug abuse than males: evidence from preclinical studies and the role of ovarian hormones. *Curr. Top. Behav. Neurosci.* 8, 73–96.
- Bechtolt, A.J., Mark, G.P., 2002. Enhancement of cocaine-seeking behavior by repeated nicotine exposure in rats. *Psychopharmacology* 162 (2), 178–185.
- Becker, J.B., Hu, M., 2008. Sex differences in drug abuse. *Front. Neuroendocrinol.* 29 (1), 36–47.
- Best, D., Rawaf, S., Rowley, J., Floyd, K., Manning, V., Strang, J., 2000. Drinking and smoking as concurrent predictors of illicit drug use and positive drug attitudes in adolescents. *Drug Alcohol Depend.* 60 (3), 319–321.
- Buccafusco, J.J., Beach, J.W., Terry Jr., A.V., 2009. Desensitization of nicotinic acetylcholine receptors as a strategy for drug development. *J. Pharmacol. Exp. Ther.* 328 (2), 364–370.
- Businelle, M.S., Lam, C.Y., Kendzor, D.E., Cofta-Woerpel, L., McClure, J.B., Cinciripini, P.M., Wetter, D.W., 2013. Alcohol consumption and urges to smoke among women during a smoking cessation attempt. *Exp. Clin. Psychopharmacol.* 21 (1), 29–37.
- Carcoba, L.M., Orfila, J.E., Natividad, L.A., Torres, O.V., Pipkin, J.A., Ferree, P.L., Castaneda, E., Moss, D.E., O'Dell, L.E., 2014. Cholinergic transmission during nicotine withdrawal is influenced by age and pre-exposure to nicotine: implications for teenage smoking. *Dev. Neurosci.* 36 (3–4), 347–355.
- Carmody, T.P., Brischetto, C.S., Matarazzo, J.D., O'Donnell, R.P., Connor, W.E., 1985. Co-occurrence use of cigarettes, alcohol, and coffee in healthy, community-living men and women. *Health Psychol.* 4 (4), 323–335.
- Dickson, P.E., Rogers, T.D., Lester, D.B., Miller, M.M., Matta, S.G., Chesler, E.J., Goldowitz, D., Blaha, C.D., Mittleman, G., 2011. Genotype-dependent effects of adolescent nicotine exposure on dopamine functional dynamics in the nucleus accumbens shell in male and female mice: a potential mechanism underlying the gateway effect of nicotine. *Psychopharmacology* 215 (4), 631–642.
- Dickson, P.E., Miller, M.M., Rogers, T.D., Blaha, C.D., Mittleman, G., 2014. Effects of adolescent nicotine exposure and withdrawal on intravenous cocaine self-administration during adulthood in male C57BL/6J mice. *Addict. Biol.* 19 (1), 37–48.
- DiFranza, J.R., Guerrera, M.P., 1990. Alcoholism and smoking. *J. Stud. Alcohol* 51 (2), 130–135.
- Giniatullin, R., Nistri, A., Yakel, J.L., 2005. Desensitization of nicotinic ACh receptors: shaping cholinergic signaling. *Trends Neurosci.* 28 (7), 371–378.
- Horger, B.A., Giles, M.K., Schenk, S., 1992. Preexposure to amphetamine and nicotine predisposes rats to self-administer a low dose of cocaine. *Psychopharmacology* 107 (2–3), 271–276.
- Hutchison, M.A., Riley, A.L., 2008. Adolescent exposure to nicotine alters the aversive effects of cocaine in adult rats. *Neurotoxicol. Teratol.* 30 (5), 404–411.
- Kandel, D.B., Kandel, E.R., 2014. A molecular basis for nicotine as a gateway drug. *N. Engl. J. Med.* 371 (21), 2038–2039.

- Kandel, D., Kandel, E., 2015. The Gateway Hypothesis of substance abuse: developmental, biological and societal perspectives. *Acta Paediatr.* 104 (2), 130–137.
- Kelley, B.M., Middaugh, L.D., 1999. Periadolescent nicotine exposure reduces cocaine reward in adult mice. *J. Addict. Dis.* 18 (3), 27–39.
- Kelley, B.M., Rowan, J.D., 2004. Long-term, low-level adolescent nicotine exposure produces dose-dependent changes in cocaine sensitivity and reward in adult mice. *Int. J. Dev. Neurosci.* 22 (5–6), 339–348.
- Kouri, E.M., Stull, M., Lukas, S.E., 2001. Nicotine alters some of cocaine's subjective effects in the absence of physiological or pharmacokinetic changes. *Pharmacol. Biochem. Behav.* 69 (1–2), 209–217.
- Lee, H., Kang, M.S., Chung, J.M., Noh, J., 2015. Repeated nicotine exposure in adolescent rats: reduction of medial habenular activity and augmentation of nicotine preference. *Physiol. Behav.* 138, 345–350.
- Levine, A., Huang, Y., Drisaldi, B., Griffin Jr., E.A., Pollak, D.D., Xu, S., Yin, D., Schaffran, C., Kandel, D.B., Kandel, E.R., 2011. Molecular mechanism for a gateway drug: epigenetic changes initiated by nicotine prime gene expression by cocaine. *Sci. Transl. Med.* 3 (107), 107–109.
- Lewis, A.S., Picciotto, M.R., 2013. High-affinity nicotinic acetylcholine receptor expression and trafficking abnormalities in psychiatric illness. *Psychopharmacology* 229 (3), 477–485.
- Li, H., Bu, Q., Chen, B., Shao, X., Hu, Z., Deng, P., Lv, L., Deng, Y., Zhu, R., Li, Y., Zhang, B., Hou, J., Du, C., Zhao, Q., Fu, D., Zhao, Y., Cen, X., 2014. Mechanisms of metabonomic for a gateway drug: nicotine priming enhances behavioral response to cocaine with modification in energy metabolism and neurotransmitter level. *PLoS One* 9 (1), e87040.
- Lisha, N.E., Carmody, T.P., Humfleet, G.L., Delucchi, K.L., 2014. Reciprocal effects of alcohol and nicotine in smoking cessation treatment studies. *Addict. Behav.* 39 (3), 637–643.
- Marquez, P., Baliram, R., Dabaja, I., Gajawada, N., Lutfy, K., 2008. The role of beta-endorphin in the acute motor stimulatory and rewarding actions of cocaine in mice. *Psychopharmacology* 197 (3), 443–448.
- Marubio, L.M., Gardier, A.M., Durier, S., David, D., Klink, R., Arroyo-Jimenez, M.M., McIntosh, J.M., Rossi, F., Champtiaux, N., Zoli, M., Changeux, J.P., 2003. Effects of nicotine in the dopaminergic system of mice lacking the alpha4 subunit of neuronal nicotinic acetylcholine receptors. *Eur. J. Neurosci.* 17 (7), 1329–1337.
- McCabe, S.E., Cranford, J.A., Morales, M., Young, A., 2006. Simultaneous and concurrent polydrug use of alcohol and prescription drugs: prevalence, correlates, and consequences. *J. Stud. Alcohol* 67 (4), 529–537.
- McKee, S.A., Sinha, R., Weinberger, A.H., Sofuoglu, M., Harrison, E.L., Lavery, M., Wanzler, J., 2011. Stress decreases the ability to resist smoking and potentiates smoking intensity and reward. *J. Psychopharmacol.* 25 (4), 490–502.
- McQuown, S.C., Belluzzi, J.D., Leslie, F.M., 2007. Low dose nicotine treatment during early adolescence increases subsequent cocaine reward. *Neurotoxicol. Teratol.* 29 (1), 66–73.
- McQuown, S.C., Dao, J.M., Belluzzi, J.D., Leslie, F.M., 2009. Age-dependent effects of low-dose nicotine treatment on cocaine-induced behavioral plasticity in rats. *Psychopharmacology* 207 (1), 143–152.
- Meliska, C.J., Bartke, A., Vandergriff, J.L., Jensen, R.A., 1995. Ethanol and nicotine consumption and preference in transgenic mice overexpressing the bovine growth hormone gene. *Pharmacol. Biochem. Behav.* 50 (4), 563–570.
- Mello, N.K., Newman, J.L., 2011. Discriminative and reinforcing stimulus effects of nicotine, cocaine, and cocaine + nicotine combinations in rhesus monkeys. *Exp. Clin. Psychopharmacol.* 19 (3), 203–214.
- Mojica, C.Y., Belluzzi, J.D., Leslie, F.M., 2014. Age-dependent alterations in reward-seeking behavior after brief nicotine exposure. *Psychopharmacology* 231 (8), 1763–1773.
- Natividad, L.A., Tejada, H.A., Torres, O.V., O'Dell, L.E., 2010. Nicotine withdrawal produces a decrease in extracellular levels of dopamine in the nucleus accumbens that is lower in adolescent versus adult male rats. *Synapse* 64 (2), 136–145.
- Natividad, L.A., Buczynski, M.W., Parsons, L.H., Torres, O.V., O'Dell, L.E., 2012. Adolescent rats are resistant to adaptations in excitatory and inhibitory mechanisms that modulate mesolimbic dopamine during nicotine withdrawal. *J. Neurochem.* 123 (4), 578–588.
- Natividad, L.A., Torres, O.V., Friedman, T.C., O'Dell, L.E., 2013. Adolescence is a period of development characterized by short- and long-term vulnerability to the rewarding effects of nicotine and reduced sensitivity to the anorectic effects of this drug. *Behav. Brain Res.* 257, 275–285.
- O'Dell, L.E., Torres, O.V., 2014. A mechanistic hypothesis of the factors that enhance vulnerability to nicotine use in females. *Neuropharmacology* 76 (Pt B), 566–580.
- O'Dell, L.E., Bruijnzeel, A.W., Ghozland, S., Markou, A., Koob, G.F., 2004. Nicotine withdrawal in adolescent and adult rats. *Ann. N. Y. Acad. Sci.* 1021, 167–174.
- O'Dell, L.E., Bruijnzeel, A.W., Smith, R.T., Parsons, L.H., Merves, M.L., Goldberger, B.A., Richardson, H.N., Koob, G.F., Markou, A., 2006. Diminished nicotine withdrawal in adolescent rats: implications for vulnerability to addiction. *Psychopharmacology* 186 (4), 612–619.
- O'Dell, L.E., Torres, O.V., Natividad, L.A., Tejada, H.A., 2007. Adolescent nicotine exposure produces less affective measures of withdrawal relative to adult nicotine exposure in male rats. *Neurotoxicol. Teratol.* 29 (1), 17–22.
- Olive, M.F., Koenig, H.N., Nannini, M.A., Hodge, C.W., 2001. Stimulation of endorphin neurotransmission in the nucleus accumbens by ethanol, cocaine, and amphetamine. *J. Neurosci.* 21 (23), RC184.
- Orsini, C., Bonito-Oliva, A., Conversi, D., Cabib, S., 2008. Genetic liability increases propensity to prime-induced reinstatement of conditioned place preference in mice exposed to low cocaine. *Psychopharmacology* 198 (2), 287–296.
- Papke, R.L., Kem, W.R., Soti, F., Lopez-Hernandez, G.Y., Horenstein, N.A., 2009. Activation and desensitization of nicotinic alpha7-type acetylcholine receptors by benzylidene anabasines and nicotine. *J. Pharmacol. Exp. Ther.* 329 (2), 791–807.
- Quinones-Jenab, V., Jenab, S., 2012. Influence of sex differences and gonadal hormones on cocaine addiction. *ILAR J.* 53 (1), 14–22.
- Rimm, E.B., Chan, J., Stampfer, M.J., Colditz, G.A., Willett, W.C., 1995. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *BMJ* 310 (6979), 555–559.
- Rinker, J.A., Hutchison, M.A., Chen, S.A., Thorsell, A., Heilig, M., Riley, A.L., 2011. Exposure to nicotine during periadolescence or early adulthood alters aversive and physiological effects induced by ethanol. *Pharmacol. Biochem. Behav.* 99 (1), 7–16.
- Romberger, D.J., Grant, K., 2004. Alcohol consumption and smoking status: the role of smoking cessation. *Biomed Pharmacother* 58 (2), 77–83.
- Rosenberg, J.M., 2014. A molecular basis for nicotine as a gateway drug. *N. Engl. J. Med.* 371 (21), 2038.
- Russo, S.J., Jenab, S., Fabian, S.J., Festa, E.D., Kemen, L.M., Quinones-Jenab, V., 2003. Sex differences in the conditioned rewarding effects of cocaine. *Brain Res.* 970 (1–2), 214–220.
- Sanjekar, S.S., Maldoon, P.P., Marks, M.J., Brunzell, D.H., Maskos, U., McIntosh, J.M., Bowers, M.S., Damaj, M.I., 2015. Differential roles of alpha6beta2* and alpha4beta2* neuronal nicotinic receptors in nicotine- and cocaine-conditioned reward in mice. *Neuropsychopharmacology* 40 (2), 350–360.
- Schindler, A.G., Messinger, D.L., Smith, J.S., Shankar, H., Gustin, R.M., Schattauer, S.S., Lemos, J.C., Chavkin, N.W., Hagan, C.E., Neumaier, J.F., Chavkin, C., 2012. Stress produces aversion and potentiates cocaine reward by releasing endogenous dynorphins in the ventral striatum to locally stimulate serotonin reuptake. *J. Neurosci.* 32 (49), 17582–17596.
- Schneider, T., Bizarro, L., Asherson, P.J., Stolerman, I.P., 2012. Hyperactivity, increased nicotine consumption and impaired performance in the five-choice serial reaction time task in adolescent rats prenatally exposed to nicotine. *Psychopharmacology* 223 (4), 401–415.
- Schochet, T.L., Kelley, A.E., Landry, C.F., 2004. Differential behavioral effects of nicotine exposure in adolescent and adult rats. *Psychopharmacology* 175 (3), 265–273.
- Shram, M.J., Siu, E.C., Li, Z., Tyndale, R.F., Le, A.D., 2008. Interactions between age and the aversive effects of nicotine withdrawal under mecamylamine-precipitated and spontaneous conditions in male Wistar rats. *Psychopharmacology* 198 (2), 181–190.
- Torabi, M.R., Bailey, W.J., Majd-Jabbari, M., 1993. Cigarette smoking as a predictor of alcohol and other drug use by children and adolescents: evidence of the “gateway drug effect”. *J. Sch. Health* 63 (7), 302–306.
- Torres, O.V., Tejada, H.A., Natividad, L.A., O'Dell, L.E., 2008. Enhanced vulnerability to the rewarding effects of nicotine during the adolescent period of development. *Pharmacol. Biochem. Behav.* 90 (4), 658–663.
- Torres, O.V., Natividad, L.A., Tejada, H.A., Van Weelden, S.A., O'Dell, L.E., 2009. Female rats display dose-dependent differences to the rewarding and aversive effects of nicotine in an age-, hormone-, and sex-dependent manner. *Psychopharmacology* 206 (2), 303–312.
- Trigo, J.M., Zimmer, A., Maldonado, R., 2009. Nicotine anxiogenic and rewarding effects are decreased in mice lacking beta-endorphin. *Neuropharmacology* 56 (8), 1147–1153.
- Vastola, B.J., Douglas, L.A., Varlinskaya, E.I., Spear, L.P., 2002. Nicotine-induced conditioned place preference in adolescent and adult rats. *Physiol. Behav.* 77 (1), 107–114.
- Wilmouth, C.E., Spear, L.P., 2004. Adolescent and adult rats' aversion to flavors previously paired with nicotine. *Ann. N. Y. Acad. Sci.* 1021, 462–464.
- York, J.L., Hirsch, J.A., 1995. Drinking patterns and health status in smoking and non-smoking alcoholics. *Alcohol. Clin. Exp. Res.* 19 (3), 666–673.
- Zakharova, E., Wade, D., Izenwasser, S., 2009. Sensitivity to cocaine conditioned reward depends on sex and age. *Pharmacol. Biochem. Behav.* 92 (1), 131–134.