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Early Adolescent Sub-Chronic Low Dose Nicotine Exposure Increases Subsequent Cocaine and Fentanyl Self-Administration in Sprague Dawley Rats

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Abstract

An exponential rise in nicotine-containing electronic-cigarette use has been observed during the period of adolescence. Preclinical studies have shown that nicotine exposure during early adolescence, but not adulthood, increases subsequent drug intake and reward. Although growing clinical trends highlight that stimulant use disorders are associated with the opioid epidemic, very few studies have assessed the effects of adolescent nicotine exposure on opioid intake. The objective of our current study is to develop a new animal model to assess the causal relationship of adolescent nicotine exposure on subsequent opioid intake. In this effort, we first replicate previous studies using a well-established 4-day nicotine paradigm. Rats are pretreated with a low dose of nicotine (2x, 30 μg/kg/0.1 mL, i.v.) or saline during early adolescence (PN 28–31) or adulthood (PN 86–89). Following nicotine pretreatment on PN 32 or PN 90, animals underwent operant intravenous self-administration for the psychostimulant, cocaine (500 μg/kg/infusion (inf)) or the opioid, fentanyl (2.5 μg/kg/inf). We successfully show that adolescent, but not adult, nicotine exposure enhances cocaine self-administration in male rats. Furthermore, we illustrate early adolescent, but not adult nicotine exposure enhances fentanyl self-administration, independent of sex. Overall, our findings highlight that adolescence is a unique period of development that is vulnerable to nicotine-induced enhancement for cocaine and fentanyl self-administration in rats.

Keywords

Drug Addiction; Opioids; E-cigarettes; Vaping; Substance Use

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Conflict of Interest: None declared

Introduction

Nicotine use is primarily initiated and established during the transitional period of adolescence (U.S.D.o.H.a.H.S. 2014). While tobacco use has decreased in recent years (CDC 2017a; Farrelly et al. 2014), electronic-cigarettes (e-cigarettes) are currently on the rise and the most commonly used form of nicotine among teens in the United States (Camenga et al. 2014; CDC 2017a; NIDA 2018). Data illustrates that nearly 5.4 million adolescents use e-cigarettes, with an increase of 1.5 million adolescents using nicotine-containing products from 2017–2018 (CDC 2019; Johnston 2019). During adolescence, brain circuitry involved in reward and motivation is vulnerable to nicotine, with long-lasting behavioral and neurochemical alterations in cholinergic, dopaminergic, serotonergic, GABAergic, opioidergic, and endorphin systems (Alajaji et al. 2016; Azam et al. 2007; Dwyer et al. 2009; Mojica et al. 2014a; Mojica et al. 2014b; Ren and Lotfipour 2019; Spear 2016; Thomas et al. 2018; Yuan et al. 2015).

The rapid increase in adolescent nicotine use highlights the pressing need to better understand the consequences of developmental exposure. This is particularly important as epidemiological studies have observed a progression from nicotine to illicit drug use (Kandel 1975). Preclinical studies highlight that early adolescent nicotine exposure increases cocaine, methamphetamine, and ethanol intake in rats (Dao et al. 2011; McQuown et al. 2007), as well as cocaine, amphetamine, and morphine reward in adult mice (Alajaji et al. 2016; Kota et al. 2018; Vihavainen et al. 2008). In regards to opioids, growing clinical data highlights that co-use with stimulants is driving the 4th wave of the overdose crisis (Ahmad 2020).

Approximately 130 Americans die each day due to an opioid overdose (CDC 2017b). Fentanyl, a μ opioid receptor (MOR) agonist that is 100–200 times more potent than morphine, is responsible for approximately half of opioid-related overdose deaths in the nation (Jones et al. 2018). Opioids are currently the most effective medications for pain management (Stanley 2014). Clinical and preclinical evidence suggest a bidirectional relationship between nicotine use and opioid reward implicating nicotine as a potential contributor to high rates of opioid misuse (Alajaji et al. 2016; Kohut 2017; Kota et al. 2018; Le Merrer et al. 2009; Zale et al. 2015). However, nicotine-induced effects on opioid self-administration have not been extensively studied, especially during adolescence.

This study is the first to evaluate the effects of nicotine exposure on fentanyl intravenous self-administration (IVSA) in both adult and adolescent Sprague Dawley rats. We hypothesize that adolescent, but not adult, nicotine exposure will enhance intravenous fentanyl self-administration in male and female rats. An absence of a sex dependent effect is proposed, given prior work highlighting that developmental nicotine's effects on subsequent drug intake are sex-independent (Linker et al. 2020; McQuown et al. 2007). To test our hypothesis, we used a well-established 4-day, low dose early adolescent nicotine pretreatment paradigm that produces age-specific increases in cocaine, methamphetamine, and ethanol IVSA (Dao et al. 2011; Linker et al. 2020; McQuown et al. 2007). This low dose nicotine exposure (60 μg/kg/day) yields nicotine blood levels similar to a few cigarettes per day in humans and produces nicotine blood levels that reflect smoking pharmacokinetics

(Benowitz and Jacob 1990; Matta et al. 2007). Thus, our chosen paradigm models adolescent initiation of nicotine smoking behavior. One day after nicotine pretreatment, animals underwent operant self-administration for cocaine or fentanyl.

Methods

Animals

For cocaine IVSA, only male Sprague-Dawley rats (Charles Rivers) were used given prior studies illustrating sex-independent effects using this paradigm (Linker et al. 2020; McQuown et al. 2007). For fentanyl IVSA, male and female Sprague-Dawley rats (Charles Rivers) were used. All animals arrived at postnatal day (PN) 17 or PN 74. Juveniles were weaned and separated based on sex (when applicable) on PN 21. Animals were group-housed in a controlled 12-hour light-dark cycle (lights on 0700–1900) in an AAALAC-accredited vivarium. Food and water were provided *ad libitum* except the day before intravenous self-administration. Animals were weighed daily to ensure maintenance of normal growth. To avoid potential litter effects, one pup per litter per experimental group was used for data collection. Animals were allocated to experimental groups using a random sequence generator. All experiments were carried out in accordance with the Institutional Animal Care and Use Committee at the University of California, Irvine.

Drugs and Reagents

Nicotine tartrate (Glentham), cocaine HCl (Sigma Aldrich), and fentanyl citrate (Patterson Veterinary) were dissolved in saline to prepare a stock solution (pH 7.2–7.4). Nicotine was calculated as a base.

Surgical Procedure

Three days prior to catheter implantation, all animals were handled daily for 2 minutes to minimize stress. On PN 24 or PN 82, catheters were surgically implanted into the right jugular vein as previously described (Belluzzi et al. 2005). Animals were injected with Equithesin (0.35 mL/100 g, i.p.) a general anesthesia. Cannulas were flushed daily with sterile heparinized saline solution (0.6 mL of 1000 units/mL heparin in 30 mL saline) to maintain patency. All animals were given 3 days to recover from surgery.

Nicotine Pretreatment

Two intravenous (i.v.) injections of nicotine (0.03 mg/kg/0.1 mL) or saline, spaced one minute apart, were administered daily across 4 days (PN 28–31 or PN 86–89). The dose of nicotine delivered was divided into two injections to reduce nicotine receptor desensitization and toxic effects (McQuown et al. 2007).

Fentanyl and Cocaine Self-Administration

One day after nicotine pretreatment, on PN 32 or PN 90, animals were tested in self administration chambers that measured at 28×25×30 cm high with two nose pokes holes. The animals underwent a 2 hour nose poke session on a Fixed Ratio 1 (FR1) schedule to administer either cocaine (500 μg/kg/infusion(inf)) (McQuown et al. 2007) or fentanyl (2.5

μg/kg/inf) (van Ree et al. 1978) with a time out period of 20 seconds. During this time period, animals were restricted from receiving another reinforced response. Following IVSA, the animals were administered propofol, a rapid anesthetic (5–10 sec), to determine catheter patency (0.05 mL for adolescents, 0.1 mL for adults, i.v.).

Statistical Analysis

Data were analyzed with JMP (SAS Institute). Animals that did not display immediate anesthesia from propofol were excluded from analysis. Predefined exclusion criteria for cocaine and fentanyl IVSA were applied after separating by all groups, e.g. outliers of box and whisker plot separated by age (adolescent/adult) x pretreatment (saline/nicotine) or age x sex (male/female) x pretreatment. Cocaine self-administration mean response data over time was analyzed by a repeated measure four-way ANOVA for pretreatment x age x reinforced/non-reinforced x time, with a repeated measure on reinforced/non-reinforced and time. Cocaine self-administration total response data was analyzed by a repeated measure three-way ANOVA for pretreatment x age x reinforced/non-reinforced responses, with a repeated measure on reinforced/non-reinforced responses. Fentanyl self-administration mean response data over time was analyzed by a repeated measure five-way ANOVA for pretreatment x age x sex x reinforced/non-reinforced x time, with a repeated measure on reinforced/non-reinforced and time. Fentanyl self-administration total response data was analyzed by a four-way ANOVA for age x sex x pretreatment x reinforced/non-reinforced responses, with a repeated measure on reinforced/non-reinforced responses. Bonferroni corrected post-hoc analysis was applied for significant main or interactive effects with 1- or 2-tailed t-tests, as appropriate.

Results

Adolescent Acquisition of Cocaine Self-Administration

When evaluating cocaine self-administration mean response data over time, our results illustrate that adolescent nicotine exposure potentiated cocaine intake (pretreatment x age x reinforced/non-reinforced x time, $F_{7,266}=4.51$, $p=0.0001$). Post hoc analysis illustrates that adolescent nicotine, but not saline treated animals exhibit enhanced cocaine intake at all time points ($p<0.05$, Figure 1A) and preference for reinforced over non-reinforced responding after 105 minutes (*$p<0.05$, data not shown). When evaluating total mean response during cocaine self-administration, our results illustrate that adolescent, but not adult, nicotine exposure enhances cocaine self-administration (reinforced/non-reinforced responding x age x pretreatment, $F_{1,39}=9.35$, $p=0.004$, Figure 1). Post hoc analysis illustrates that nicotine versus saline pretreated adolescents have higher cocaine reinforcement ($p<0.05$, Figure 1B). Further, nicotine pretreated adolescents exhibit discrimination for reinforced versus non-reinforced responding, highlighting a preference for cocaine intake ($p<0.05$, Figure 1B). Taken together, our findings replicate age-dependent nicotine-induced enhancement of cocaine IVSA using an established 4-day nicotine pretreatment paradigm.

Adolescent Acquisition of Fentanyl Self-Administration

When evaluating fentanyl self-administration mean response data over time, our results illustrate that adolescent nicotine exposure potentiates fentanyl intake (age x reinforced/non-

reinforced x time, $F_{7,770}$=9.36, p=0.0001; pretreatment x reinforced/non-reinforced x time, $F_{7,770}$=3.20, p=0.002). Post hoc analysis illustrates that adolescent nicotine versus saline treated animals exhibit enhanced fentanyl intake after 105 min (p<0.05, Figure 2A) and preference for reinforced versus non-reinforced responding after 30 minutes (*p<0.05, data not shown). Total mean responses in the second hour of fentanyl self-administration illustrate that adolescent, but not adult, nicotine exposure enhances fentanyl self-administration (reinforced/non-reinforced responding x age x pretreatment, $F_{1,111}$=4.02, p=0.047, Figure 2B). Post-hoc analysis illustrates that nicotine versus saline pretreated adolescents have higher fentanyl reinforcement (p<0.01, Figure 2B). Overall, our studies illustrate that adolescent nicotine exposure enhances susceptibility to fentanyl self-administration in male and female rats.

Discussion

In our current study, we successfully replicate early adolescent nicotine-induced enhancement of cocaine self-administration. We add to this work by showing for the first time that sub-chronic, low dose nicotine exposure during adolescence enhances fentanyl self-administration. Our data fits with a growing body of preclinical and clinical literature highlighting the consequences of adolescent nicotine exposure (Alajaji et al. 2016; Dao et al. 2011; Kandel 1975; Kota et al. 2018; Linker et al. 2020; McQuown et al. 2007; Vihavainen et al. 2008). Taken together, this work provides evidence for a new animal model assessing the impacts of adolescent nicotine exposure on subsequent opioid self-administration.

Investigators have used adapted paradigms to illustrate cross-species effects of adolescent nicotine exposure on the long-term consequences of alcohol, cocaine and morphine reward in mice, which persists to adulthood (Alajaji et al. 2016; Kota et al. 2018; Vihavainen et al. 2008). Using the 4-day nicotine paradigm in rats, prior research has illustrated the long-term consequences of adolescent nicotine exposure on subsequent cocaine intake 10 days post-exposure (Dao et al., 2011). Observed effects are unique to early (PN 28–31), but not late, adolescent (PN 38–41) nicotine exposure, highlighting a brief developmental window for nicotine's effects on brain and drug self-administration behavior (Dao et al., 2011). In contrast, saline treated adolescent rats respond less for cocaine self-administration compared to adults (Belluzzi et al. 2005; Dao et al. 2011; Linker 2017), which is consistent with data from our current studies. Adolescents are hyposensitive to cocaine and exhibit lower rates of dependence than adults (Chen and Kandel 2002; Spear 2000). These effects are suggested to be mediated by immature function of the prefrontal cortex in the adolescent brain (Chambers and Self 2002; Leslie et al. 2004).

In our study, we use a low dose sub-chronic nicotine exposure paradigm because it closely models nicotine initiation observed in human adolescents (McQuown et al. 2007; Yuan et al. 2015). Adolescents are more sensitive to the rewarding effects of nicotine, developing dependence with minimal exposure (Kandel and Chen 2000). We use a sub-chronic exposure timeline to prevent the development of nicotine tolerance (Kota et al. 2007). Furthermore, intermittent exposure over 4 days best represents how adolescent smokers would be exposed to nicotine (ie. at school or with peers) versus chronic exposure via osmotic minipump (24 hr exposure). The low dose sub-chronic nicotine exposure paradigm uses a very low dose

that is administered in two injections spaced one minute apart to minimize desensitization (McQuown et al. 2007). Further, age-dependent effects of nicotine-induced enhancement of cocaine reinforcement have previously been shown to be mediated by increased D2 receptor activity (Cao et al. 2010), microglia activation (Linker et al. 2020), and altered limbic function via 5-HT1A receptors (Dao et al. 2011). During adolescence, nicotine uniquely impacts the mesolimbic dopamine system through functionally immature nicotinic receptors and enhanced neuronal activity (Counotte et al. 2009; Placzek et al. 2009; Dao et al. 2011; Yuan et al. 2015). Identification of the exact mechanisms mediating these effects are important as it could lead to therapeutic prevention and intervention strategies.

We are the first group to use the well-established 4-day nicotine pretreatment paradigm in rats to illustrate nicotine effects on potentiated intravenous fentanyl self-administration in adolescents. Other groups have assessed the effect of adolescent nicotine exposure on fentanyl consumption (Klein 2001), by assessing oral intake during adulthood. As oral intake has potential confounds based on taste preference, our studies are unique as we illustrate that intravenous administration of sub-chronic low dose nicotine exposure (equivalent to a 1–2 cigarettes per day) (Matta et al., 2007), is able to enhance intravenous fentanyl self-administration. Interestingly, we observe nicotine-induced enhancement of adolescent fentanyl self-administration occurs late in the two hour session. This effect is driven by maintained response rates of nicotine exposed adolescents at later time points (Figure 2A–B). In contrast, we observe nicotine-induced enhancement of cocaine reinforcement in adolescents early in the self-administration paradigm and this effect persists throughout the two hour session (Figure 1A–B). Psychostimulants and opiates result in distinct behaviors, which may expain why we observe different self-administration patterns. We speculate that these effects are mediated by different neural systems regulating opiate versus psychostimulant self-administration (Badiani et al. 2011). Thus, our cocaine and fentanyl data suggest nicotine pretreatment may further alter psychostimulant and opioid potentiation of self-administration through different mechanisms that are age-dependent, and needs to be further explored. This is relevant, as the underlying mechanisms mediating the nicotine-induced age-dependent enhancement of fentanyl intake are unknown. Given that the age-dependent nicotine-induced effects for fentanyl self-administration are present only in the second hour versus the full two-hour session for cocaine, it would be important to follow-up our studies with, for example, the assessment of the persistence of the nicotine effects on fentanyl self-administration across several days, different schedules of reinforcement, and/or extended access schedules. If confirmed, such studies would be helpful in identifying whether our age- and nicotine-dependent effects on fentanyl self-administration are spurious or consistent, thus enhancing the translational significance of our findings and its relevance to the human population (Chambers et al. 2003; Crews et al. 2007; Yuan et al. 2015).

Conclusion

Adolescent rats are a valid translational model for drug studies because they undergo a developmental transition with similar physiological and behavioral changes to adolescent humans (Spear 2007; 2013). Our study is the first to illustrate early adolescent nicotine exposure enhances acquisition of fentanyl self-administration. Our studies support prior

work that have demonstrated that nicotine effects on opioid reward are long-lasting in mice (Alajaji et al. 2016; Klein 2001; Kota et al. 2018; Torabi et al. 2019; Vihavainen et al. 2008). We provide evidence that even a short, low dose exposure to nicotine increases adolescent, but not adult susceptibility to subsequent opioid intake. Follow-up studies are needed to determine the long-term consequences of brief nicotine exposure on opioid intake in rodents. Such studies may inform clinicians on whether to consider the history of adolescent recreational nicotine use when prescribing opioids for young patients. Without knowing the effects of these products used together or alone, effective regulatory interventions cannot be developed.

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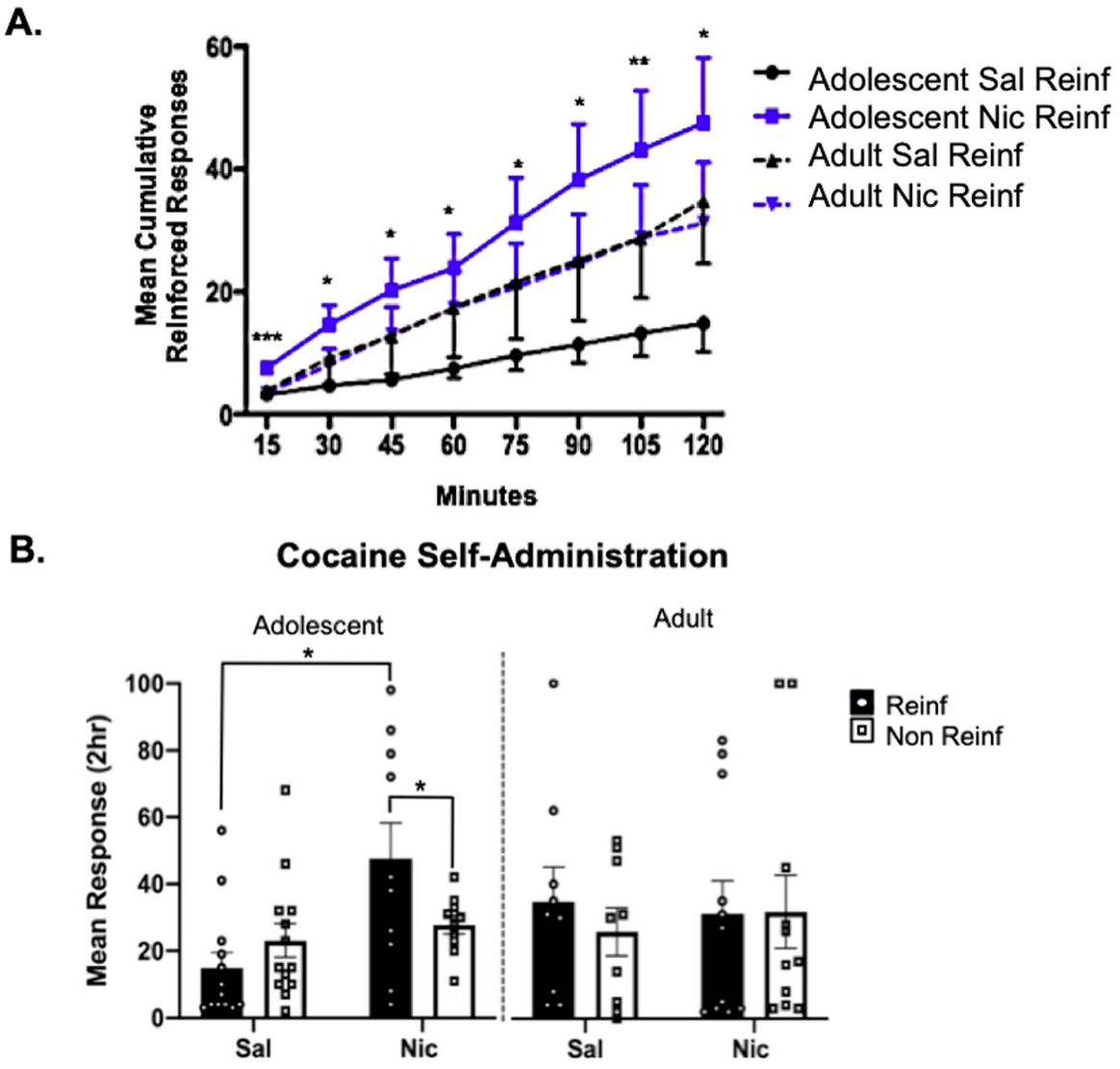

Figure 1.

Adolescent, but not adult, nicotine exposure enhances cocaine (500 μg/kg/infusion) self-administration in male Sprague Dawley rats. A.) Cumulative mean cocaine response over time ± SEM, *p<0.05, **p<0.01, ***p<0.001 Adolescent nicotine (Nic) vs. adolescent saline (Sal) reinforced (Reinf) responses B.) Mean 2hr response ± SEM. *p<0.05 Adolescent Nic vs. Adolescent Sal Reinf responses; Reinf vs. Non Reinforced (NR) responses. n=9–13/group. Open and closed circles or squares represent individual animals.

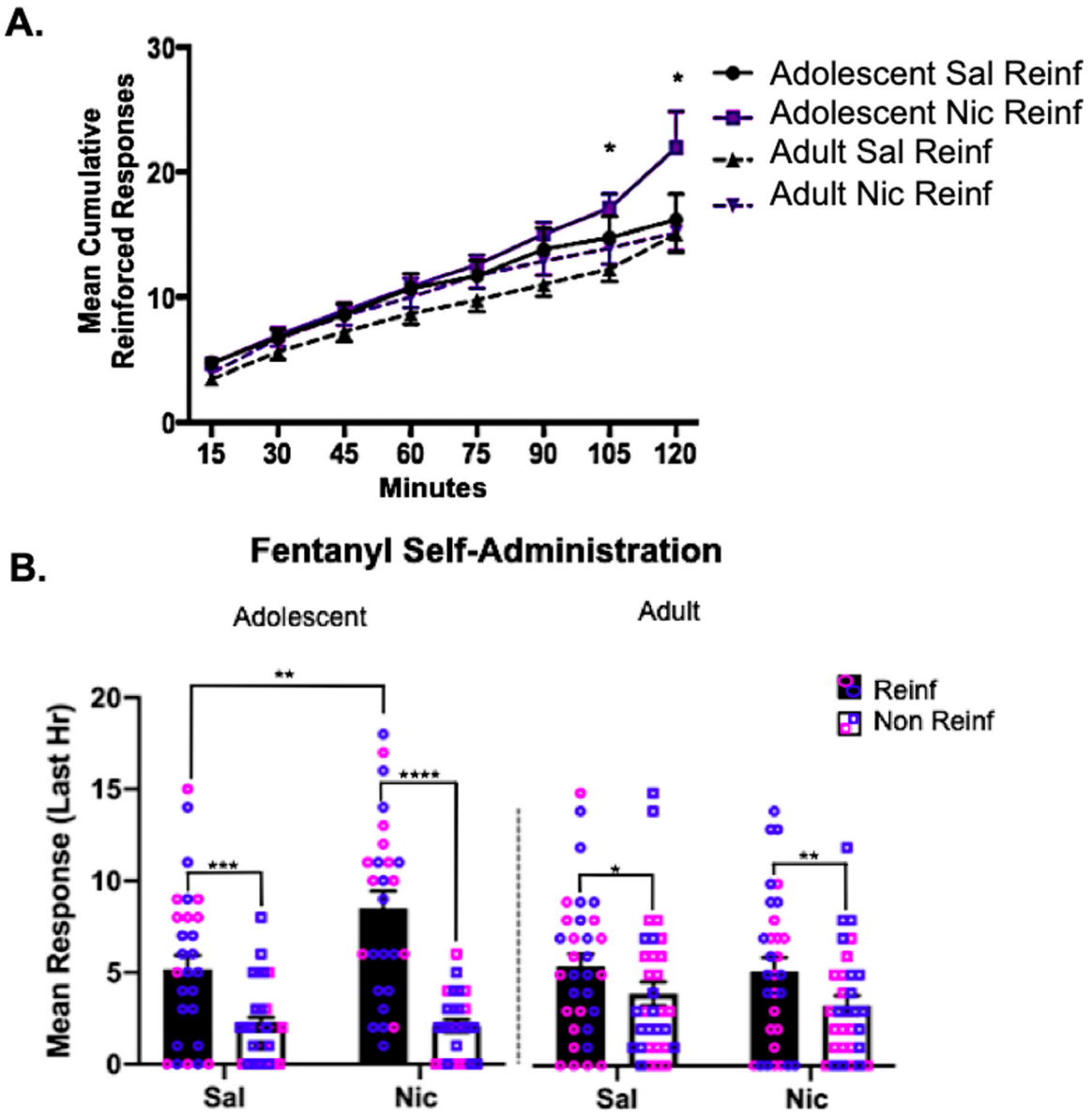

Figure 2.

Adolescent, but not adult, nicotine exposure enhances fentanyl (2.5 μg/kg/inf) self-administration in male and female Sprague Dawley rats. A.) Cumulative mean fentanyl response over time ± SEM. *p<0.05 Adolescent Nic vs. Adolescent Sal Reinf responses. B.) Mean response in second hour of self-administration ± SEM, **p<0.05 Adolescent Nic Reinf response vs. Adolescent Sal Reinf response; ****p<0.0001, ***p<0.01, **p<0.01, *p<0.05 Reinf vs. NR responses. n=25–34/group. Open and closed pink circles and squares represent individual female animals. The open and closed blue circles and squares represent individual male animals.