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Adolescent nicotine exposure fails to impact cocaine reward, aversion and self-administration in adult male rats

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ABSTRACT

The present experiments examined the effects of adolescent nicotine pre-exposure on the rewarding and aversive effects of cocaine and on cocaine self-administration in adult male rats. In Experiment 1, adolescent Sprague–Dawley rats (postnatal days 28–43) were given once daily injections of nicotine (0.6 mg/kg) or vehicle and then tested for the aversive and rewarding effects of cocaine in a combined conditioned taste avoidance (CTA)/conditioned place preference (CPP) procedure in adulthood. In Experiment 2, adolescent Sprague–Dawley rats were pre-exposed to nicotine then tested for cocaine self-administration (0.25 or 0.75 mg/kg), progressive ratio (PR) responding, extinction and cue-induced reinstatement in adulthood. In Experiment 1, rats showed significant dose-dependent cocaine-induced taste avoidance with cocaine-injected subjects consuming less saccharin over trials, but no effect of nicotine pre-exposure. For place preferences, cocaine induced significant place preferences with cocaine injected subjects spending significantly more time on the cocaine-paired side, but again there was no effect of nicotine history. All rats in Experiment 2 showed clear, dose-dependent responding during cocaine acquisition, PR testing, extinction and reinstatement with no effect of nicotine pre-exposure. These studies demonstrate that adolescent nicotine pre-exposure does not have an impact on cocaine's affective properties or its self-administration at least with the specific parametric conditions under which these effects were tested.

1. Experiment 1 introduction

In 2011, approximately 8,400 adolescents a day tried an illicit drug for the first time (NIDA, 2012) with many of these new users continuing to use drugs daily. Given that adolescents are using drugs, it is essential to understand how and to what extent adolescent use impacts the long-term vulnerability to future drug abuse. In addressing this latter question, much of the clinical literature has focused on the impact of adolescent alcohol consumption, finding that early initiation of alcohol use correlates with chronic adult use (Guttmannova et al., 2011) and predicts not only adult alcohol dependence (Grant et al., 2006) but also the use of other illicit drugs (Hicks et al., 2010). However, such vulnerability changes are not limited to experience with alcohol. In fact, Degenhardt et al. (2011) suggested that early onset use of *any* illicit substance is related to the risk for later drug abuse, depending on the extent of prior usage and the age of initiation. Since adolescent abuse patterns correlate with future use, adolescent drug history may be an important factor related to subsequent drug vulnerability (Toumbourou et al., 2007).

Although it is clear that an adolescent history with certain drugs of abuse is related to adult use, surprisingly little is known about similar relationships with one of the most commonly used drugs in adolescence, i.e., nicotine (Johnston et al., 2012). What is known suggests that adult nicotine use is significantly impacted by adolescent nicotine use, even at low doses (DiFranza et al., 2007). Buchmann et al. (2011) reported that adolescents who found the experience of the first cigarette pleasurable were more likely to become regular smokers as adults. Age and experience of the first cigarette, combined with adolescent use patterns, clearly appear to impact future nicotine abuse.

These potential changes in vulnerability have been supported by preclinical studies reporting that adolescent drug history impacts subsequent self-administration of many drugs, including cocaine (Zhang and Kosten, 2007), alcohol (O'Dell et al., 2004) and nicotine (Levin et al., 2003). Prior drug history alters the self-administration not only of the same drug, but also of varying drug combinations such as methamphetamine to cocaine (Crawford et al., 2011) and MDMA to cocaine (Fletcher et al., 2001). Recently, two studies have examined adolescent nicotine pretreatment on adult self-administration of another drug, namely cocaine (Anker and Carroll, 2011; Dickson et al., 2012). In both studies, nicotine history impacted cocaine self-administration, e.g., rats exposed to nicotine during adolescence showed evidence of higher rates of responding for cocaine (Dickson et al., 2012) or greater reinstated responding by cocaine and cocaine-associated cues (Anker and Carroll, 2011). Given the fact that both nicotine and cocaine interact with the dopaminergic systems of the brain, it might be expected that

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nicotine would impact the rewarding effects of cocaine through common neural substrates (Pich et al., 1997), thus impacting the behavioral response to the drug. This interaction may explain these reported effects of nicotine on cocaine self-administration.

Although adolescent nicotine exposure appears to impact adult cocaine self-administration, it does not indicate the processes mediating such an effect. An understanding of these processes may be important in modifying future drug taking behavior. It has been argued that overall drug intake is a function of a drug's rewarding effects that support self-administration and its aversive effects that limit it (Mariathasan and Stolerman, 1994; Riley, 2011). Further, limited preclinical research suggests that adolescent drug exposure can impact these affective properties in adults (Vastola et al., 2002), which may in turn alter subsequent self-administration. These changes in reward and aversion can also be seen when the pre-exposure and conditioning drugs are different (for reward see: Andersen, et al., 2002; Achat-Mendes et al., 2003; for aversion see: Grahan and Diaz-Granados, 2006; Hutchison and Riley, 2008). It is of interest to note that adolescent pre-exposure does not always produce changes in adults, suggesting that pre-exposure effects may be dependent on the drug and pre-exposure regimens used (Cunningham et al., 2002; Schramm-Sapyta et al., 2004; Wetzell and Riley, 2012).

In relation to adolescent nicotine exposure, Kelley and Middaugh (1999) reported that adult cocaine-induced place preference conditioning (CPP, a common measure of drug reward, see Tzschentke, 1998; 2007; see also Kelley and Rowan, 2004) was reduced. On the other hand, McMillen et al. (2005) reported that such a history increased cocaine-induced CPP in adulthood. With aversions, Hutchison and Riley (2008) found no effect of nicotine pre-exposure on adult cocaine-induced taste avoidance (CTA, a common measure of the aversive effects of drugs, see Riley and Tuck, 1985; Riley, 2011). These results may be due to procedural differences in adolescent nicotine exposure, nicotine and/or cocaine dose, conditioning duration and species, making it unlikely that the results from these studies can be directly compared. Importantly, for each of these studies, assessments of reward and aversion were done in separate groups of animals. If it is the balance of reward and aversion that determines drug intake, it is impossible to assess the relative contribution of changes in each of these two factors or the potential impact on self-administration when they are examined in two different groups.

Given the position that overall drug intake is a function of the balance between a drug's rewarding and aversive effects (see Riley, 2011) and the reported effects of adolescent nicotine history on cocaine self-administration (Anker and Carroll, 2011 and Dickson et al., 2012), it might be predicted that a history of adolescent nicotine would impact cocaine reward and aversion. Accordingly, Experiment 1 examined the effects of adolescent exposure to nicotine on the rewarding (CPP) and aversive (CTA) effects of cocaine in adult subjects. These changes were assessed in the same animals using a combined CTA/CPP procedure (Simpson and Riley, 2005; Verendeev and Riley, 2011), which may allow for a determination of any potential alterations in cocaine's affective properties following an adolescent history with nicotine and, in turn, may provide insight into potential treatment and prevention strategies for drug use and abuse in adulthood.

2. Materials and methods

2.1. Method

2.1.1. Subjects and housing

Sixty four experimentally naive male Sprague–Dawley rats arrived at the on-site animal colony on postnatal day 21 (PND 21). Animals were randomly assigned to nicotine or saline pre-exposure groups and housed in groups of three or four in OptiRat Plus housing bins (38.9 × 56.9 × 26 cm; 1181 sq cm) until procedures began. Animals were then housed two per OptiRat Plus bin, separated by a Plexiglas divider, for the remainder of the experiments. They were given ad libitum access to food and water and maintained at an ambient temperature of 23 °C and on a 12:12 h light/dark cycle (lights on at 0800 h). All experimental manipulations occurred in the light phase of the cycle between 1000 and 1500 h. All procedures were conducted under the guidelines established by the Institutional Animal Care and Use Committee at American University and the Guidelines for the Care and Use of Laboratory Animals (National Research Council, 2011).

2.1.2. Drugs

Nicotine hydrogen tartrate salt (Sigma Aldrich Co., St. Louis, MO) was dissolved in 0.9% saline to a concentration of 1 mg/5 ml. Saccharin (0.1% sodium saccharin, Sigma Chemical Co) was prepared as a 1 g/l solution in tap water. Cocaine hydrochloride salt (NIDA) was prepared as a 10 mg/ml solution in 0.9% saline. Vehicle injections were saline and were matched in volume to the corresponding drug.

2.1.3. Apparatus

CPP: The apparatus (San Diego Instruments Place Preference System, San Diego, CA) was made up of two main chambers (28 × 21 × 34.5 cm) connected by a smaller middle chamber (14 × 21 × 34.5 cm). One main chamber consisted of white walls and a white aluminum, diamond patterned floor. The other chamber was made up of black walls and a black plastic, haircell-textured floor. The middle, connecting chamber had gray walls and a steel rod floor. Each chamber featured a 16 × 4 photo beam array for recording seconds spent in each chamber. The room in which place preferences were assessed was lit with a 25-watt red light mounted in the ceiling, and a white noise generator was used to mask background noise. Eight identical chambers were used for testing. Data were recorded using the San Diego Instruments Place Preference System.

2.1.4. Procedure

2.1.4.1. Pre-exposure. Beginning on PND 28, rats were weighed and subcutaneously (SC) injected once daily with 0.6 mg/kg nicotine (calculated as freebase) or 0.9% saline. Dosage and route of administration were based on previous studies of adolescent nicotine exposure (Horger et al., 1992; Vastola et al., 2002; Adriani et al., 2006). Injections were repeated daily until PND 42–43, which is commonly regarded as the early through late adolescence period in rats (Spear, 2000). Following nicotine or vehicle injections, all rats were allowed to age undisturbed to early adulthood, approximately PND 66. Ad libitum food and water were available throughout this entire period.

2.1.4.2. Water habituation and CPP pretest. On PND 66, water was removed from the animals 24 h prior to the initial water-adaptation session. On the following day, the rats were placed in wire-mesh testing cages (24.9 × 19 × 18 cm) and given 20-min access to water. Immediately after this period, they were returned to their home cages with no access to water until the following day during which they were again given 20-min water access in the test cages. After water consumption was stable (i.e., all rats drank within 2 s of bottle presentation and average consumption did not vary by more than 2 ml with no consistent increase or decrease), all rats were placed in the CPP apparatus for 15 min and allowed access to the entire chamber. Location in the chamber was recorded to assess any pre-existing side preferences.

2.1.4.3. CTA/CPP conditioning and testing. On PND 67, animals were given 20-min access to a novel saccharin solution in the test cages, immediately injected intraperitoneally (IP) with vehicle or cocaine (5.6, 10 or 18 mg/kg) and placed in their non-preferred CPP chamber (DPS; drug-paired side) for 30 min. This resulted in eight experimental groups (N-0, N-5.6, N-10, N-18, S-0, S-5.6, S-10, S-18) with the letter referring to the pre-exposure condition (nicotine or saline) and the number referring to the cocaine dose given during testing. After conditioning,