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Short communication

Periadolescent nicotine exposure causes heterologous sensitization to cocaine reinforcement

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Abstract

There is increasing concern that abuse of tobacco during periadolescence increases the potential for later abuse of other drugs. To test this hypothesis, Sprague–Dawley rats received once-daily injections of either water or 0.4 mg/kg nicotine from postnatal day 35 through 44. Beginning on postnatal day 80, animals were tested in a 12-day cocaine-induced conditioned place preference (CPP) paradigm. Prior nicotine treatment enhanced the dose–response to cocaine. CPP training with 3.0 mg/kg i.p. cocaine increased time in drug-paired chambers by 50% in control rats and 94% in nicotine-exposed animals. Thus, periadolescent nicotine exposure produced long-term sensitization to an indirect-acting dopamine agonist.

Keywords: Nicotine; Cocaine; Behavioral conditioning; Development; Substance abuse; Rat

1. Introduction

Initiation of tobacco use is an example of a pattern that begins for the vast majority of adult tobacco users before the age of 18 years (Chen and Millar, 1998; Choi et al., 2001). One concern is that this early experimentation may make subsequent abuse of other drugs more likely, potentially due to persistent changes in brain neurochemistry. Liability for these types of persistent changes to permanently alter brain function may be greatest during sensitive periods of juvenile development (e.g. Soderstrom and Johnson, 2003; Soderstrom and Tian, 2004; Spear, 2000).

Nicotine from tobacco induces release of dopamine from the ventral tegmental mesolimbic dopaminergic neurons that may be involved in the reinforcing properties of the drug (Pidoplichko et al., 1997; Pich et al., 1997). Even brief exposure to this drug has the ability to induce long-term changes in both cholinergic and dopaminergic systems (Li et al., 1995; Serova and Sabban, 2002). These properties are likely related to the variable structure of neuronal nicotinic cholinergic receptors which are composed of five subunits assembled from a pool of at least 16 different gene products (Lukas et al., 1999). For example, in mid-brain slices obtained from juvenile rats, postnatal days 15–25, exposure to nicotine results in a rapid desensitization of the β2* nicotinic cholinergic receptors with little change in the α7* receptors (Wooltorton et al., 2003). Changes in nicotinic cholinergic receptor expression may have behavioral correlates: Collins and Izenwasser (2004) reported that once-daily nicotine treatment for seven days increases motor activity induced by nicotine and increases the locomotor activity induced by cocaine one day later in adult, but not adolescent male, rats. This result provides evidence that nicotine can produce heterologous sensitization to other classes of drugs.

Lasting effects of nicotine exposure during juvenile development have only recently begun to be investigated. Trauth and colleagues used young rats to demonstrate that early nicotine exposure persistently: (1) increased nicotinic cholinergic receptor expression; (2) increased expression of the high-affinity choline transporter; (3) reduced choline acetyltransferase activity; and (4) reduced midbrain norepi-

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nepherine turnover in male rats upon acute nicotine challenge at adulthood (Trauth et al., 1999, 2000, 2001). Ten days of i.p. injections of 0.4 mg/kg nicotine beginning on postnatal day 35 resulted in enhanced levels of the α5, α6, and β7 nicotinic receptor subunits in the brains of the rats at postnatal day 80 (Adriani et al., 2003). These nicotinic cholinergic receptor expression changes were only associated with periadolescent treatment and did not occur in postadolescent animals treated for the same period. Importantly, the same report described that peri- but not postadolescent nicotine exposure increases nicotine self-administration at adulthood.

Adriani et al. (2003) results demonstrated that exposure to modest doses of nicotine at the beginning of puberty and adolescence results in persistent alterations of receptors and behavior that last at least into young adulthood. We used the same periadolescent nicotine exposure protocol to investigate persistent effects on cocaine-induced reward. Results support the hypothesis that periadolescent nicotine exposure persistently alters responsiveness to reinforcing properties of other classes of abused drugs.

2. Methods and materials

2.1. Rats and treatment

A group of 24 and a group of 18 male 30-day old Sprague–Dawley rats were purchased from Harlan Sprague–Dawley (Frederick, MD). All procedures were in accordance with the *NIH Guide to the Care and Use of Laboratory Animals*. Rats were divided into two pre-treatment groups, water and 0.4 mg/kg nicotine, and then subdivided into three conditioning groups, vehicle, 1.0 and 3.0 mg/kg cocaine. These doses of cocaine were based on previous experiments that suggested 1.0 mg/kg i.p. would be near threshold for a response (Nomikos and Spyraki, 1987; Jones and McMillen, 1995). The rats were housed in pairs with free access to food and water. On postnatal day 35, each rat was weighed and nicotine or water injected i.p. in a volume of 1.0 ml/kg bodyweight and repeated daily for 10 days. No further treatment was given for 35 days.

2.2. Cocaine-induced conditioned place preference

Each rat was handled for 5 min once daily for 3 days before cocaine-induced conditioned place preference (CPP) training began on postnatal day 80. The CPP apparatus consisted of a three-chamber gray wooden box with distinct visual and tactile cues. Two large end chambers (34×25 cm) were separated by guillotine doors from a small central chamber (11×25 cm) that served as a choice point (Jones and McMillen, 1995).

On days 1, 2 and 3, each rat was placed in the neutral chamber and the doors removed to allow exploration of the entire apparatus for 15 min. On the third day, the movements were recorded with the aid of a program, BEHAVIOR, by Prof. L. W. Means. On days 4, 6, 8 and 10 each rat received an injection of either: 0.01 M Na-citrate buffer vehicle (pH6.5), 1.0 or 3.0 mg/kg i.p. cocaine immediately before confinement for 15 min in the least preferred chamber. On days 5, 7, 9 and 11 vehicle was administered before confinement in the preferred chamber. On day 12, each rat was placed in the neutral chamber, the doors removed, and the movements recorded for 15 min. The time spent in the least preferred chamber was analyzed (GB-STAT, Dynamic Microsystems, Silver Spring, MD) by 3-way repeated measures analysis of variance and the Tukey/Kramer procedure (Zar, 1984). The total number of chamber entries during the pre-conditioning observation period was used as a measure of spontaneous locomotion and analyzed by a 2-way analysis of variance.

2.3. Drugs and sources

(−)-Nicotine hydrogen tartrate salt was purchased from Sigma-Aldrich Co., St. Louis, MO and cocaine–HCl was obtained from Research Triangle Institute, Inc., Research Triangle Park, NC through the National Institute on Drug Abuse. Doses were calculated as the free base.

3. Results

The data from the two groups of animals were combined to yield 7 animals in each of six cells. Table 1 presents the activity data and demonstrates that through randomization the baseline locomotor activity of the rats was the same across all groups. The administration of nicotine during the periadolescent period did not affect the spontaneous exploratory activity during the third exposure to the CPP apparatus ($F2,36=0.771$, ns). In addition, Fig. 1 shows that there were no differences between groups in the time spent in the least preferred chamber before CPP training.

Table 1
Effect of periadolescent nicotine exposure on motor activity before CPP training

Group[a]	Number of entries
Water	
Vehicle	35.6±6.1
1.0 Cocaine	43.7±3.8
3.0 Cocaine	49.6±5.3
Nicotine	
Vehicle	35.4±6.8
1.0 Cocaine	46.1±4.8
3.0 Cocaine	44.3±5.3

Either water or 0.4 mg/kg nicotine was injected i.p. daily for 10 days beginning on postnatal day 35. The number of chamber entries made during 15 min on the day before start of injections for CPP training is shown above (mean±S.E.M.).

[a] $N=7$ per cell.

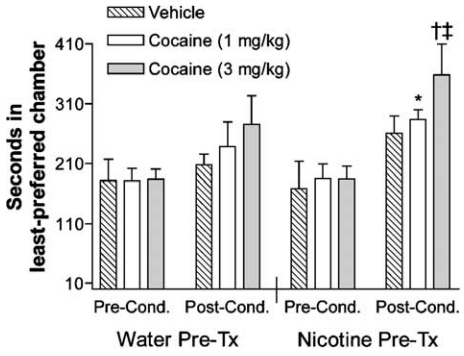

Fig. 1. Effect of periadolescent nicotine exposure on cocaine-induced CPP. Either water or 0.4 mg/kg nicotine was injected once daily for 10 days beginning on postnatal day 35 and then cocaine conditioning began on postnatal day 80. Bars represent the time spent on the least preferred side of the CPP apparatus ±S.E.M. *P<0.05, $^{\dagger}p$<0.01 different from pre-conditioning; $^{\ddagger}p$<0.05 different from same dose after water pre-treatment (N=7 per cell).

Fig. 1 presents the data for the time spent on the least preferred side in the CPP apparatus during the pre-conditioning phase and post-conditioning. As expected, there was a dose-related increase in time spent in the cocaine-paired chamber (Factor C, pre/post, F1,36=37.822, P<0.001). In addition, there was a significant interaction between the administration of nicotine and the repeated measure (Factor A×C, F1,42=4.724, P<0.05). The analysis of individual groups revealed that only in the nicotine-treated animals did cocaine produce a significant increase in time spent in the least preferred chamber. Injection of 3.0 mg/kg cocaine resulted in more time spent in the least preferred chamber by the nicotine-exposed rats than did the water-exposed control rats conditioned with this same dose.

4. Discussion

Periadolescent nicotine exposure is associated with neurochemical changes that (1) persist into adulthood (Adriani et al., 2003; Trauth et al., 2000) and; (2) include altered striatal dopaminergic signaling likely relevant to reinforcement produced across classes of abused drugs (Trauth et al., 2001). This evidence led us to hypothesize that persistent effects of periadolescent nicotine exposure may generalize to altered responsiveness to reward across classes of abused drugs. The experiments described above demonstrate that these effects extend to include heterologous sensitization to drug reinforcement with cocaine. These findings may be significant in the context of the proposed role of nicotine as a "gateway" drug that leads to increased likelihood of dependence on other drugs (Yu and Williford, 1992).

Selective effects on processes related to reinforcement are suggested by lack of efficacy on baseline exploratory activity (Table 1 and Fig. 1). Thus, differences in cocaine-conditioned CPP are not attributable to general activity differences. As expected, both early nicotine-treated and control group rats exhibited dose-related increases in time spent in cocaine-paired chambers (Fig. 1). In response to 3.0 mg/kg i.p. cocaine, time spent in paired chambers increased by 50% in controls and by 94% in animals treated with nicotine as periadolescents. This latter group clearly had the most robust response to cocaine in the CPP paradigm.

The five-week period without treatment that followed postnatal days 35–44 nicotine injections is relatively long for developing rats. During this time the rat progresses from adolescence to early adulthood. In humans, the analogous period of development is associated with greatest risk to begin the use and abuse of not only tobacco, but also many other substances (Chen and Millar, 1998; Choi et al., 2001). These data demonstrate that exposure of one substance can result in heterologous sensitization to a substance in a different class. The implication is to put further emphasis on prevention of the initiation of use during the periadolescent period, with the goal of reducing future use and abuse of many different substances.

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