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Differential behavioral and neuroendocrine effects of repeated nicotine in adolescent and adult rats

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Abstract

Despite the high prevalence of tobacco abuse among adolescents, the neurobiology of nicotine addiction has been studied mainly in adult animals. Repeated administration of this drug to adult rats induces behavioral sensitization. Nicotine activates the HPA axis in adult rats as measured by drug-induced increases in ACTH and corticosterone. Both behavioral sensitization and corticosterone are implicated in drug addiction. We examined the expression of behavioral sensitization induced by nicotine as well as the changes in corticosterone levels after repeated injections of nicotine in adolescent and adult animals. Adolescent and adult rats received subcutaneous (s.c.) injections of saline or 0.4 mg/kg of nicotine once daily for 7 days. Three days after the last injection animals were challenged with saline or nicotine (0.4 mg/kg; s.c.). Nicotine-induced locomotion was recorded in an activity cage. Trunk blood samples were collected in a subset of adolescent and adult rats and plasma corticosterone levels were determined by radioimmunoassay. Adult, but not adolescent, rats expressed behavioral sensitization. Pretreatment with nicotine abolished corticosterone-activating effect of this drug only in adult animals, indicating the development of tolerance at this age. Our results provide evidence that adolescent rats exposed to repeated nicotine display behavioral and neuroendocrine adaptations distinct from that observed in adult animals.

Keywords: Nicotine; Behavioral sensitization; Corticosterone; Locomotor activity; Adult; Adolescent; Rat

1. Introduction

Drug abuse among humans often begins during adolescence, a period of ontogeny in which individuals exhibit age-specific behavioral characteristics, such as risk taking and novelty seeking, which could predispose them to initiate drug use (Spear, 2000). Despite prevention efforts, rates of cigarette smoking among adolescents have been resistant to change (Gilpin et al., 1999). In 2000, approximately 13% of youths aged 12–17 reported use of cigarettes, and more than 4% reported smoking daily (NHSDA, 2000). Initiation of smoking during adolescence is associated with higher daily consumption and a lower probability of quitting (Chen and Milliar, 1998). Moreover, studies in rats have shown that nicotine is a neuroteratogen and that the adolescent brain is particularly vulnerable to the toxic effects of nicotine (Slotkin, 2002).

Evidence suggests that nicotine, which acts at neuronal nicotinic acetylcholine receptors, is one of the active components in tobacco smoke responsible for tobacco addiction (Stolerman and Jarvis, 1995). The acute effects of nicotine vary depending on nicotine dosage, subject sex, age, and possibly subject strain (Elliot et al., 2004; Cheeta et al., 2001; Faraday et al., 1999). Despite the variability observed in the acute effects of nicotine on locomotor activity, repeated administration of this drug to

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adult rats, like other drugs of abuse, induces behavioral sensitization, as evidenced by an enhanced locomotor response to a subsequent injection of the drug (Clarke and Kumar, 1983; Domino, 2001; Kita et al., 1999; Shim et al., 2001). Behavioral sensitization has been suggested as an animal model of neuroplasticity associated mainly with repeated administration of psychostimulant drugs. Behavioral sensitization has been implicated in the development of drug addiction (Robinson and Berridge, 1993; Covington and Miczek, 2001) and drug-induced psychosis (Robinson and Becker, 1986). Psychostimulant-induced behavioral sensitization has been related to both pre and postsynaptic drug-induced increase in dopamine activity (Nestler and Aghajanian, 1997; Paulson and Robinson, 1995).

Although the relationship between behavioral sensitization and nicotine addiction has not been clearly established, it has been shown that nicotine-induced changes in dopamine mesolimbic system might be similar to those produced by psychostimulant drugs. For example, it has been shown that repeated nicotine enhances accumbal dopamine output (Benwell and Balfour, 1992; Shim et al., 2001). In addition, long-term administration of nicotine enhanced locomotor response to the dopamine D1/D2 receptor agonist apomorphine (Suemaru et al., 1993).

Despite the high prevalence of tobacco abuse among adolescents, the neurobiology of nicotine addiction has been studied mainly in adult animals. Although few studies in animal models have been carried out to examine the effects of nicotine in adolescents, there is evidence that they respond to nicotine differently than adults. For example, adolescent rats, as compared to adult, were more sensitive to the initial effect of nicotine on locomotor activity (Collins and Izenwasser, 2004; Faraday et al., 2001) but did not develop behavioral sensitization during 7 days of treatment with the drug (Collins and Izenwasser, 2004). Adolescent rats also seem to be more sensitive to the reinforcing effect of nicotine as evidenced by conditioning place preference (Vastola et al., 2002). Adriani et al. (2002) also provide relevant evidence that nicotine effects depend on the age of the animal. They showed that nicotine oral self-administration during early adolescence (postnatal day (P) 24–35) increased the preference for the nicotine solution when the concentration was reduced as well as the locomotor response to the drug. These effects were not observed when nicotine was self-administrated by either middle (P37–P48) or late (P50–P61) adolescent mice.

Nicotine activates the HPA axis in adult rats as measured by nicotine-induced increases in ACTH (Andersson et al., 1983) and corticosterone (Balfour et al., 1975). Systemically administered nicotine stimulates the hypothalamus–pituitary–adrenal (HPA) axis through a centrally-mediated corticotropin-releasing-hormone (CRH)-dependent mechanism (Cam and Basset, 1984; Calogero et al., 1989).

Recently, a great interest has been devoted to the interaction between addiction and the hypothalamic–pituitary–adrenal (HPA) axis (Goeders, 2003; Piazza and Le Moal, 1996; Sarnyai, 1998; Marinelli and Piazza, 2002; De Jong and De Kloet, 2004). These studies mostly concern psychostimulant drugs like cocaine and amphetamine. However, the role of glucocorticoids in regulating nicotine addiction is unclear.

Corticosterone modulation of behavioral responses to nicotine is quite complex (Caggiula et al., 1998). For example, adrenalectomy increased nicotine responsiveness as measured by nicotine-induced Y maze crossings, heart rate and body temperature, and increases in the startle response. The effects of adrenalectomy were prevented by corticosterone replacement (Pauly et al., 1988). There is also evidence that corticosterone participate in neuroadaptive changes underlying conditioned tolerance to nicotine (Caggiula et al., 1998). Concerning locomotor activity, it has been reported that the depressant effects of nicotine were potentiated while the activating effects were attenuated by adrenalectomy (Shoaib and Shippenberg, 1996). On the other hand, Domino (2001) showed that daily treatment with dexametasone produced only slight changes in both depressant and activating effects of nicotine on locomotor activity.

It has been shown that the elevation in corticosterone levels after administration of drugs of abuse, such as cocaine, amphetamine and morphine, is attenuated in younger animals relative to their more mature counterparts (Laviola et al., 1995, 1999; Adriani and Laviola, 2000). This fact can have implications on the development of addiction. Indeed, it has been demonstrated that corticosterone release may contribute to the reinforcing effects of drugs of abuse as well as drug or stress-induced behavioral sensitization (Piazza et al., 1993; Deroche et al., 1992).

Few studies investigated the involvement of glucocorticoids on repeated nicotine effect on locomotor activity and sensitization. Shoaib and Shippenberg (1996) have shown that adrenalectomy did not affect the depressant effect of repeated nicotine but blocked the stimulation induced by this drug. In addition, Johnson et al. (1995) showed that adrenalectomy disrupted the development, but not the expression of nicotine-induced locomotor sensitization.

Despite the relevance of the interaction between drugs and the HPA axis, the effect of acute or chronic nicotine on the activation of HPA axis in adolescent animals has not been investigated.

Understanding the differences in nicotine effects between adolescents and adults may lead to different strategies of prevention and treatment, specific for each age. Thus, the aim of our experiments was to examine the expression of behavioral sensitization induced by nicotine as well as the changes in corticosterone levels after repeated injections of this drug in adolescent and adult animals.

2. Materials and methods

2.1. Subjects

Male Wistar adolescent (postnatal day (P) 28–P35 as defined by Spear and Brake, 1983) and adult (P90–P99) rats from the animal breeding facility of the University Estadual Paulista were used. Groups of 3–4 animals were housed in plastic cages 32 (width)×40 (length)×16 (height) cm in a room maintained at 21–23 °C. Rats were kept in a 12:12 h light/dark cycle (lights on at 07:00) and were allowed free access to food and water. All experiments were performed during the light phase. Each animal was used only in one experimental procedure.

Mean body weights at the beginning of the experiments were: adolescents (150–170 g) and adults (300–350 g).

The experimental protocol was approved by Ethical Committee for use of Human or Animal Subjects of the School of Pharmaceutical Science-UNESP (CEP-24/2003) and were conducted according to ethics principles of the Brazilian College of Animals' Experimentation (COBEA).

2.2. Apparatus

Behavioral testing was conducted in commercially available (Columbus Instruments, CA) activity monitoring chambers, consisting of Plexiglas cages. The chambers included 10 pairs of photocells beams, which were used to measure the horizontal locomotor activity. The consecutive interruption of two beams was recorded as one locomotion unit.

2.3. Radioimmunoassay

The radioimmunoassay for corticosterone was conducted using antibody obtained from Sigma (St. Louis, MO) and (^{3}H)-corticosterone from New England Nuclear (Boston, MA). The method was adapted from that described by Sarnyai et al. (1992). Briefly, 20 μl of plasma was diluted 50 times with 0.01 M PBS and placed in a water bath at 75 °C for 1 h for heat inactivation of corticosterone plasma globulin. One hundred microliters of a solution of antibody and (^{3}H)-corticosterone (10,000–20,000 cpm/ml) was added to each sample, mixed and incubated overnight at 4 °C. Dextran-coated charcoal was used to adsorb free steroid after incubation. Tubes were centrifuged at 2000×*g* for 15 min at 4 °C, the supernatant from each tube was transferred to scintillation vials and the radioactivity was quantified by liquid scintillation spectrometry. Standard curves were constructed using 25, 50, 100, 250, 500, 750, 1000 and 2000 pg/100 ul of corticosterone (Sigma, St. Louis). After dilution all concentrations of corticosterone samples were within the linear range of the standard curve. Inter- and intra-assays variation was, respectively, 4.0 and 7.2%.

2.4. Experimental design

The whole sensitization protocol took 10 days. On days 1 to 7, the rats were weighed and given a subcutaneous (s.c.) injection of nicotine (Sigma) (0.4 mg/kg) (n=10) or saline (1 ml/kg) (n=10) once a day. Immediately after the injections, the animals were returned to their home cages. On days 8 and 9 the animals did not receive any treatment.

Adolescent and adult rats were respectively on P28 and P90 when nicotine treatment started.

On day 10 (test) both saline (SAL) and nicotine (NIC) pretreated groups received a challenge dose of nicotine (0.4 mg/kg; s.c.), respectively SAL+NIC and NIC+NIC groups. Immediately after the injections their locomotor activity was recorded. Photocell counts accumulated during a thirty-minute interval were recorded. The animals were allowed a 20-min adaptation period in the photocell apparatus prior to injections. A third group of animals (n=11) received s.c. injections of saline for a 7-day period and was challenged with saline (SAL+SAL) on the 10th day.

Adolescent and adult rats were, respectively, on postnatal day 37 and 99 when the tests were performed.

A subset of SAL+SAL, SAL+NIC or NIC+NIC groups of adult or adolescent animals were monitored for corticosterone plasma levels on experimental day 10. Fifteen minutes after a challenge s.c. injection of saline or nicotine (0.4 mg/kg), the animals were rapidly transported a short distance to an isolated room, where they were decapitated. Trunk blood was collected in heparinized tubes. Blood samples were centrifuged at 2000×*g* for 15 min at 4 °C. Plasma was stored at −20 °C, until the radioimmunoassay. Previous experiments showed that nicotine-induced corticosterone elevation peaks 15 min after injections (data not shown).

The experiment was carried out between 8:00 and 12:00 h. Blood samples were centrifuged and the plasma corticosterone levels were determined by radioimmunoassay as described above.

Each adolescent group had 7 animals and adult groups had 9 animals.

Nicotine dosages are expressed as nicotine base.

2.5. Statistical analysis

All data are expressed as means±SEM. Levene tests for homogeneity of variance were performed to behavioral and biochemical data. When Levene was statistically significant data were converted to the respective square root. Nicotine's effects on locomotion and corticosterone levels were analyzed by one-way ANOVA. When a significant (p<0.05) main effect was observed, F-tests for contrast analysis were applied.

3. Results

Levene test revealed the non-homogeneity of variance for locomotor activity in both adult [$F(2,28)=5.8$, $p<0.01$] and adolescent [$F(2,28)=3.7$, $p<0.01$] animals. Behavioral data were then converted to the respective square root. Levene test to the square root values did not reveal significant differences indicating the homogeneity of variances, which allowed the performance of ANOVA.

As indicated in Fig. 1, ANOVA showed significant differences in locomotor activity across groups in adult [$F(2,28)=11.8$, $p<0.001$] and adolescent rats [$F(2,28)=19.5$, $p<0.001$]. In adult animals pairwise comparisons indicated that the behavioral response to nicotine challenge in nicotine-pretreated (NIC+NIC) group was significantly higher when compared to the SAL+NIC [$F(1,28)=13.5$, $p<0.001$] and SAL+SAL groups [$F(1,28)=21.5$, $p<0.001$].

In adolescent animals pairwise comparisons indicated that the behavioral response to nicotine was higher in saline (SAL+NIC) [$F(1,28)=15.4$, $p<0.001$] and nicotine (NIC+NIC) [$F(1,28)=37.7$, $p<0.001$] pretreated groups compared to the SAL+SAL group. The behavioral response to nicotine challenge in nicotine pretreated rats was not significantly different than in saline pretreated group [$F(1.28)=3.6$, $p=0.06$].

Levene did not show statistically significant difference for corticosterone plasma levels in both adult and adolescent rats. ANOVA indicated that nicotine altered corticosterone plasma levels in adult [$F(2,24)=25.8$, $p<0.001$] and adolescent rats [$F(2,16)=18.36$, $p<0.001$]. In adult animals pairwise comparisons performed across groups revealed that nicotine significantly increased corticosterone levels in saline pretreated rats when compared to the SAL+SAL group [$F(1,24)=46.82$, $p<0.001$] and nicotine [$F(1,24)=28.8$, $p<0.001$] pretreated rats (Fig. 2).

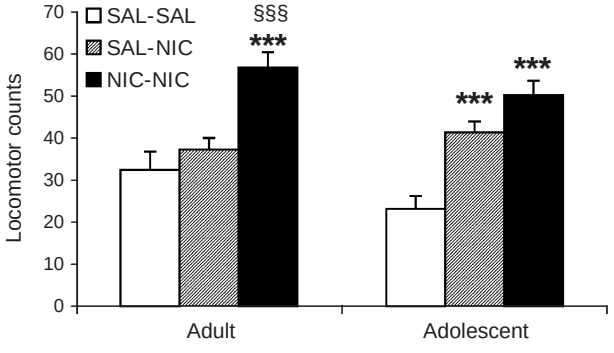

Fig. 1. Nicotine-induced locomotion in adolescent and adult rats. Animals were treated with saline or nicotine (0.4 mg/kg, s.c.) during 7 days. Seventy-two hours after the last injection the animals were habituated during 20 min in the activity chamber; then received s.c. injections of saline or nicotine 0.4 mg/kg and locomotion. Bars represent mean±SEM of square root of cumulative locomotion counts during 30 min after injections of 10–11 animals per group. ***$p<0.001$ compared to the SAL+SAL group. $^{§§§}p<0.001$ compared to the SAL-NIC group.

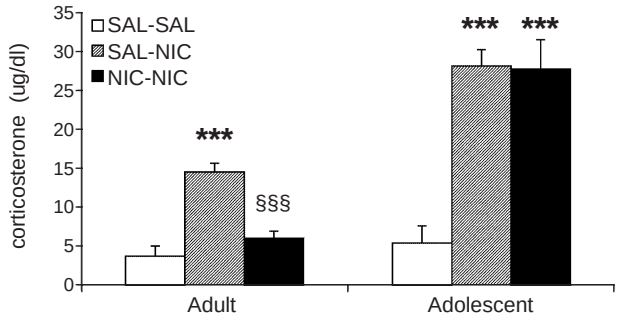

Fig. 2. Corticosterone plasma levels of adolescent and adult rats. Animals were treated with saline or nicotine (0.4 mg/kg, s.c.) during 7 days. Seventy-two hours after the last injection the animals were administrated saline or nicotine (0.4 mg/kg, s.c.). Blood samples were collected 15 min after injections. Bars represent mean±SEM of 7–9 animals per group. ***$p<0.001$ compared to the SAL+SAL group. $^{§§§}p<0.001$ compared to the SAL-NIC group.

In adolescent rats pairwise comparisons performed across groups revealed that nicotine significantly increased corticosterone levels in saline [$F(1.16)=27.35$, $p<0.001$] and nicotine [$F(1.16)=28.44$, $p<0.001$] pretreated groups when compared to the SAL+SAL group. Moreover, no difference was found for corticosterone levels when comparing the SAL+NIC and NIC+NIC groups [$F(1,16)=0.008$, $p<0.92$] (Fig. 2).

4. Discussion

We investigated the effects of repeated nicotine on locomotor activity and corticosterone plasma levels in adolescent and adult rats. Our results provide relevant evidence that nicotine induces distinct behavioral and neuroendocrine adaptations in adolescents as compared to adult rats.

The results of the present study demonstrate that acute injection of 0.4 mg/kg of nicotine in saline pretreated animals (SAL+NIC) significantly increased the locomotor activity in adolescent but not in adult rats as compared to the SAL+SAL group. These findings are in line with reports showing that adolescent animals are more sensitive to nicotine-induced locomotor activation (Adriani et al., 2002; Collins and Izenwasser, 2004; Schochet et al., 2004).

The increased sensitivity to nicotine associated to a significant preference for nicotine solutions in early adolescence as described by Adriani et al. (2002), correlates with epidemiological data suggesting a higher vulnerability of human adolescents to tobacco (Breslau and Peterson, 1996).

This pattern, in which adolescents are more sensitive than adults, to nicotine's stimulant actions on locomotion, contrasts with reports that adolescent rodents are less sensitive to the acute effects of other drugs such as cocaine and amphetamine (Laviola et al., 1999; Bolanos et al., 1998). The lack of behavioral sensitization to nicotine

in adolescent rats also contradicts reports showing increased locomotor response to cocaine and amphetamine in adolescent rats repeatedly exposed to these stimulant drugs (Adriani and Laviola, 2000; Planeta and Marin, 2002). It is interesting to note that in the Collins and Izenwasser (2004) study periadolescent rats pretreated with nicotine, cross-sensitized to the locomotor effects of cocaine, even though they did not sensitize to the effects of nicotine. This result indicates that nicotine may induce changes in dopamine transmission related to behavioral sensitization to psychostimulant drugs. Indeed, administration of nicotine to adolescent rats via continuous infusion for two weeks induced an increase in adenilyl cyclase activity in the striatum (Abreu-Villaça et al., 2003) an alteration that has been suggested to be involved in psychostimulant-induced sensitization (Nestler and Aghajanian, 1997). However, repeated nicotine appears to induce other neuroadaptations that specifically blocks or delays the expression of sensitization to its own effects in the adolescent rat.

The present results also demonstrated that repeated daily injections of nicotine markedly increased the locomotor response to a subsequent systemic challenge with nicotine in adult but not in adolescent rats. Thus, after repeated exposure to nicotine, only adult animals expressed behavioral sensitization. These results agree with observations by Schochet et al. (2004) who showed that although adolescent rats displayed an increased sensitivity to the first injection of nicotine, their response to the drug after repeated administration appeared blunted in comparison with adult animals. Sensitization to repeated nicotine has been also investigated by Collins and Izenwasser (2004). They also reported that adolescent rats, as compared to adult, were more sensitive to the initial effect of nicotine on locomotor activity and that sensitization did not develop within seven days of treatment. However, there are also conflicting data with reports of sensitization (Faraday et al., 2003), and no sensitization (Faraday et al., 2001) reported in adult rats. Moreover, in contrast to the present results, Faraday et al. (2003) showed that sensitization developed over a 12-day injection period in adolescent rats. The differences between Faraday results and the present study might be related at least to two factors. First, Faraday study was conducted using implanted micropumps to deliver nicotine, while our study utilized repeated injections. Second, the present study was confined to the periadolescent period, while Faraday study begins in the periadolecence and extended to late adolescence.

Since in our study the animals were challenged only one time-point (i.e. 3 days following the last injection of nicotine) we cannot rule out the possibility that adolescents and adults rats could require different withdrawal times to express sensitization.

In adult rats, our results showed that acute injection of 0.4 mg/kg of nicotine significantly increased corticosterone levels in saline pretreated groups. Pretreatment with nicotine abolished this effect. This finding agrees with previous observations that the corticosterone-activating effect of nicotine is blunted in adult animals repeatedly exposed to the drug (Benwell and Balfour, 1979; Bugajski et al., 2001), indicating to the development of tolerance. Tolerance, as defined by a decrease in the effects of a drug after repeated administration, was also observed to ACTH activating effect of nicotine in adult animals (Bugajski et al., 2001). In this regard it has been shown that the sequential administration of nicotine rapidly desensitize the ACTH release (Sharp and Beyer, 1986; Matta et al., 1998). Tolerance to nicotine-induced increase in ACTH and corticosterone appears to be the result of changes in cholinergic nicotinic receptors, rather than an alteration in nicotine metabolism (Marks et al., 1983). In fact, Marks et al. (1992) showed that although the number of ^{3}H-nicotine binding sites in the brain increases with repeated exposure to nicotine, functional desensitization occurs.

The effects of cortiscoterone on nicotine-induced locomotion and sensitization are contradictory. It has been reported that adrenalectomy potentiates and attenuates, respectively, the depressant and activating effects of nicotine (Shoaib and Shippenberg, 1996). On the other hand, Domino (2001) showed that daily treatment with dexametasone produced only slight changes in both depressant and activating effects of nicotine on locomotor activity. Concerning repeated administration of nicotine Shoaib and Shippenberg (1996) have shown that adrenalectomy did not affect the depressant effect to repeated nicotine, while it blocked the stimulant response.

Johnson et al. (1995) showed that adrenalectomy disrupted the development, but not the expression of sensitization, since it had no effect if performed in rats already sensitized. Based on this observation they concluded that the induction, but not the expression, of nicotine sensitization is dependent on glucocorticoids. Thus, our result corroborates the findings of Johnson et al. (1995), since in adult animals we observed that the expression of behavioral sensitization occurred in the presence of low levels of corticosterone.

In adolescent rats nicotine significantly increased corticosterone levels in saline and nicotine pretreated groups when compared to the SAL+SAL group. To our knowledge this is the first description of nicotine effects on corticosterone secretion in adolescent rats. Our results showed that, differently from adult, corticosterone-activating effect of nicotine did not develop tolerance in adolescent rats.

The lack of tolerance to the corticosterone-activating effect of nicotine in adolescent rats could be related to the absence of behavioral sensitization, since in these animals the high levels of corticosterone following repeated nicotine could maintain the nicotine chlolinergic receptors in the desensitized state. Indeed, Ke and Lukas (1996) have

suggested that steroid hormones, including corticosterone, can act as noncompetitive allosteric inhibitors of nicotinic chlolinergic receptors. The desensitization of nicotine receptors could then impair the action of nicotine on the mesolimbic dopaminergic system that is known to mediate behavioral sensitization (Quick and Lester, 2002). One can argue that desensitization of nicotinic receptors should also lead to a decreased response of the HPA axis to nicotine and consequently to the tolerance to corticosterone-activating effect of this drug. However, the effect of corticosterone on nicotine's actions are very complex, thus the actions of the glucocorticoids may vary for different nicotinic receptors subtypes and/or brain regions, as it has been suggested for nicotine's actions on its own receptors (Collins and Marks, 1996; Trauth et al., 1999).

Since corticosterone seems to have reinforcing properties (Deroche et al., 1993), the lack of tolerance to the corticosterone-activating effect of nicotine in adolescent rats may increase the reinforcing effect of nicotine and the vulnerability to tobacco's addiction during adolescence.

During late childhood and adolescence, neurobiological systems are still undergoing important developmental rearrangements. Thus, several mechanisms could account for age differences in nicotine's behavioral and neuroendocrine actions. For example, the pharmacokinetics of nicotine may be different in adolescent and adult rats (Trauth et al., 2000). Adolescent and adult rats may differ in distribution, density or affinity of central nicotine cholinergic receptors. The rate of nicotine receptors up-regulation or desensitization in response to repeated nicotine administration might also be different. In addition, some unique changes were observed in catecholaminergic transmission in the midbrain and hippocampus of adolescent rats exposed to nicotine (Slotkin, 2002; Badanich and Kirsteina, 2004). Thus it will be interesting in future studies to determine which neurochemical and molecular mechanisms may contribute to the differential effects of nicotine in adult and adolescent animals.

The findings of the present study point to the relevance of the research towards the effects of nicotine in animal's models of adolescence. The different responses to nicotine at this age should be taken into account when examining potential treatments for nicotine addiction. Moreover, further investigation on the role of glucocorticoids on the effects of nicotine may provide relevant knowledge to the development of therapeutic agents for the treatment of nicotine addiction.

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References

Abreu-Villaça Y, Seidler FJ, Slotkin TA. Impact of adolescent nicotine exposure on adenylyl cyclase-mediated cell signaling: enzyme induction, neurotransmitter-specific effects, regional selectivities, and the role of withdrawal. Brain Res 2003;988:164–72.

Adriani W, Laviola G. Unique hormonal and behavioral hyporesponsivity to both forced novelty and d-amphetamine in periadolescent mice. Neuropharmacology 2000;39:334–46.

Adriani W, Macri S, Pacifici R, Laviola G. Peculiar vulnerability to nicotine oral self-administration in mice during early adolescence. Neuropsychopharmacology 2002;27:212–4.

Andersson K, Siegel R, Fuxe K, Eneroth P. Intravenous injections of nicotine induced very rapid and discrete reductions of hypothalamic catecholamine levels associated with increases of ACTH, vasopressin and prolactin secretion. Acta Physiol Scand 1983;118:35–40.

Badanich KA, Kirsteina CL. Nicotine administration significantly alters accumbal dopamine in adult but not in the adolescent rat. Ann NY Acad Sci 2004;1021:410–7.

Balfour DJK, Khullar AK, Longden A. Effects of nicotine on plasma corticosterone and brain amines in stressed and unstressed rats. Pharmacol Biochem Behav 1975;3:179–84.

Benwell MEM, Balfour DJK. Effects of nicotine administration and its withdrawal on plasma corticosterone and brain 5-hidroxyindoles. Psychopharmacology (Berl) 1979;63:7–11.

Benwell MEM, Balfour DJK. The effects of acute and repeated nicotine treatment on nucleus accumbens dopamine and locomotor activity. Br J Pharmacol 1992;105:849–56.

Bolanos CA, Glatt SJ, Jackson D. Subsensitivity to dopaminergic drugs in periadolescent rats: a behavioral and neurochemical analysis. Brain Res Dev Brain Res 1998;111:25–33.

Breslau N, Peterson EL. Smoking cessation initiation and nicotine dependence in a cohort of young adults. Drug Alcohol Depend 1996;33:129–37.

Bugajski J, Gadek-Michalska A, Bugajski AJ. A single corticosterone pretreatment inhibits the hypothalamic-pituitary-adrenal response to adrenergic and cholinergic stimulation. J Physiol Pharmacol 2001;52:313–24.

Caggiula RA, Donny EC, Epstein LH, Sved FA, Knopf S, Rose C, et al. The role of corticosteroids in nicotine's physiological and behevioral effects. Psychoneuroendocrinology 1998;23:143–59.

Calogero AE, Kamilaris TC, Gómez MT, Johnson EO, Tartaglia ME, Gold PW, et al. The muscarinic cholinergic agonist arecoline stimulates the rat hypothalamic-pituitary-adrenal axis through a centrally mediated corticotropin-releasing hormone-dependent mechanism. Endocrinology 1989;125:2445–53.

Cam G, Basset J. Effects of prolonged exposure to nicotine and stress on the pituitary-adrenocortical response: the possibility of cross-adaptation. Pharmacol Biochem Behav 1984;20:221–6.

Cheeta S, Irvine EE, Tucci S, Sandhu J, File SE. In adolescence, female rats are more sensitive to the anxiolytic effect of nicotine than are male rats. Neuropsychopharmacology 2001;25:601–7.

Chen J, Milliar WJ. Age of smoking initiation: implications for quitting. Health Rep 1998;9:39–46.

Clarke PBS, Kumar R. The effects of nicotine on locomotor activity in nontolerant and tolerant rats. Br J Pharmacol 1983;78:587–94.

Collins SL, Izenwasser S. Chronic nicotine differentially alters cocaine-induced locomotor activity in adolescent vs adult male and female rats. Neuropharmacology 2004;46:349–62.

Collins AC, Marks MJ. Are nicotinic receptors activated or inhibited following chronic nicotine treatment? Drug Dev Res 1996;38:231–42.

Covington III HE, Miczek KA. Repeated social-defeat stress, cocaine or morphine: effects on behavioral sensitization and intravenous cocaine self-administration "binges". Psychopharmacology 2001;158:388–99.
De Jong IE, De Kloet ER. Glucocorticoids and vulnerability to psychostimulant drugs: toward substrate and mechanism. Ann NY Acad Sci 2004;1018:192–8.
Deroche V, Piazza PV, Casolini P, Maccari S, Le Moal M, Simon H. Stress-induced sensitization to amphetamine and morphine psychomotor effects depend on stress-induced corticosterone secretion. Brain Res 1992;598:343–8.
Deroche V, Piazza PV, Deminiere JM, Le Moal M, Simon H. Rats orally self-administer corticosterone. Brain Res 1993;622:315–20.
Domino F. Nicotine induced behavioral locomotor sensitization. Prog Neuro-psychopharmacol Biol Psychiatry 2001;25:59–71.
Elliot BM, Faraday MM, Phillips JM, Grunberg NE. Effects of nicotine on elevated plus maze and locomotor activity in male and female adolescent and adult rats. Pharmacol Biochem Behav 2004;77:21–8.
Faraday MM, Scheufele PM, Rahman MA, Grunberg NE. Effects of chronic nicotine administration on locomotion depend on rat sex and housing condition. Nicotine Tob Res 1999;1:143–51.
Faraday MM, Elliot BM, Grunberg NE. Adult vs Adolescent rats differ in biobehavioral response to chronic nicotine administration. Pharmacol Biochem Behav 2001;70:475–89.
Faraday MM, Elliott BM, Phillips JM, Grunberg NE. Adolescent and adult male rats differ in sensitivity to nicotine's activity effects. Pharmacol Biochem Behav 2003;74:917–31.
Gilpin EA, Choi WS, Berry C, Pierce JP. How many adolescents start smoking each year in the United States? J Adolesc Health 1999;25:248–55.
Goeders NE. The impact of stress on addiction. Eur Neuropsychopharmacol 2003;13:435–41.
Johnson DH, Svensson AI, Engel JA, Soderplam B. Induction but not expression of behavioral sensitization to nicotine in rats dependent on glucocorticoid. Eur J Pharmacol 1995;276:155–64.
Ke L, Lukas RJ. Effects of steroid on ligand binding and functional activities of diverse nicotinic acetylcholine receptor subtypes. J Neurochem 1996;67:1100–12.
Kita T, Okamoto M, Kubo K, Tanaka T, Nakashima T. Enhancement of sensitization to nicotine-induced ambulatory stimulation by psychological stress in rats. Prog Neuro-psychopharmacol Biol Psychiatry 1999;23:893–903.
Laviola G, Wood RD, Kuhn C, Francis R, Spear LP. Cocaine sensitization in periadolescent and adult rats. J Pharmacol Exp Ther 1995;275:345–57.
Laviola G, Adriane W, Terranova ML, Gerra G. Psychobiological risk factors for vulnerability to psychostimulants in human adolescents and animal models. Neurosci Biobehav Rev 1999;23:993–1010.
Marinelli M, Piazza PV. Interaction between glucocorticoid hormones, stress and psychoestimulant drugs. Eur J Neurosci 2002;16:387–94.
Marks MJ, Stitzel JA, Collins AC. Effects of chronic nicotine infusion on tolerance development and cholinergic receptors. J Pharmacol Exp Ther 1983;236:806–16.
Marks MJ, Pauly JR, Gross SD, Deneris ES, Hermans-Borgmeyer I, Heineman SF, et al. Nicotine binding and nicotinic receptor subunit mRNA after chronic nicotine treatment. J Neurosci 1992;12:2765–84.
Matta SG, Fu Y, Valentine JD, Sharp BM. Response of the hypothalamus–pituitary–adrenal axis to nicotine. Psychoneuroendocrinology 1998;23:103–13.
Nestler EJ, Aghajanian GK. Molecular and cellular basis of addiction. Science 1997;278:58–63.
NHSDA, Summary of findings from the 2000 national household survey on drug abuse. Substance Abuse and Mental Health Services Administration. Office of Applied Studies, Rockville, MD.
Paulson PE, Robinson TE. Amphetamine-induced time-dependent sensitization of dopamine neutransmission in the dorsal and ventral striatum: a microdialysis study in behaving rats. Synapse 1995;19:56–65.
Pauly JR, Ullman EA, Collins AC. Adrenocortical hormone regulation of nicotine sensitivity in mice. Physiol Behav 1988;44:109–16.
Piazza PV, Le Moal MI. Pathophysiological basis of vulnerability to drug abuse: role of an interaction between stress, glucocorticoids, and dopaminergic neurons. Annu Rev Pharmacol Toxicol 1996;36:359–78.
Piazza PV, Deroche V, Deminiere JM, Maccari S, Le Moal M, Simon H. Corticosterone in the range of stress induced levels possesses reinforcing properties: implications for sensation seeking behaviors. Proc Natl Acad Sci 1993;90:11738–42.
Planeta CS, Marin MT. Effect of cocaine on periadolescent rats with or without early maternal separation. Braz J Med Biol Res 2002;35:1367–71.
Quick MW, Lester RA. Desensitization of neuronal nicotinic receptors. J Neurobiol 2002;53:457–78.
Robinson TE, Becker TB. Enduring changes in brain and behavior produced by amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res Rev 1986;11:157–98.
Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Rev 1993;18:247–91.
Sarnyai Z. Neurobiology of stress and cocaine addiction. Studies on corticotropin-releasing factor in rats, monkeys, and humans. Ann NY Acad Sci 1998;851:371–87.
Sarnyai Z, Biro E, Penke B, Telegdy G. The cocaine-induced elevation of plasma corticosterone is mediated by endogenous corticotropin-releasing factor (CRF) in rats. Brain Res 1992;589:154–6.
Schochet TL, Kelley AE, Landry CF. Differential behavioral effects of nicotine exposure in adolescent and adult rats. Psychopharmacology (Berl) 2004;175:265–73.
Sharp BM, Beyer HS. Rapid desensitization of acute stimulatory effects of nicotine on rat plasma adrenocorticotropin and prolactin. J Pharmacol Exp Ther 1986;238:486–91.
Shim I, Javaid JI, Wirtshafter D, Jang SY, Shin KH, Lee HJ, et al. Nicotine-induced behavioral sensitization is associated with extracellular dopamine release and expression of c-FOS in the striatum and nucleus accumbens of the rat. Behav Brain Res 2001;121:137–47.
Shoaib M, Shippenberg TS. Adrenalectomy attenuates nicotine-induced dopamine release and locomotor activity in rats. Psychopharmacology (Berl) 1996;128:343–50.
Slotkin TA. Nicotine and the adolescent brain: insights from an animal model. Neurotoxicol Teratol 2002;24:369–84.
Spear LP. The adolescent brain and age-related behavioral manifestations. Neurosci Biobehav Rev 2000;24:417–63.
Spear LP, Brake SC. Periadolescent: age-dependent behavior and psychopharmacological responsivity in rats. Dev Psychobiol 1983;16:83–109.
Stolerman IP, Jarvis MJ. The scientific case that nicotine is addictive. Psychopharmacology 1995;117:2–10.
Suemaru K, Gomita Y, Furuno K, Araki Y. Chronic nicotine treatment potentiates behavioral responses to dopaminergic drugs in rats. Pharmacol Biochem Behav 1993;46:135–9.
Trauth JA, Seidler FJ, McCook EC, Slotkin TA. Adolescent nicotine exposure causes persistent upregulation of nicotinic cholinergic receptors in rat brain regions. Brain Res 1999;851:9–19.
Trauth JA, Seidler FJ, Slotkin TA. An animal model of adolescent nicotine exposure: effects on gene expression and macromolecular brain constituents in rat brain regions. Brain Res 2000;867:29–39.
Vastola BJ, Douglas LA, Varlinskaya EI, Spear LP. Nicotine-induced conditioned place preference in adolescent and adult rats. Physol Behav 2002;77:107–14.