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Review

A psychobiological framework of the substrates that mediate nicotine use during adolescence

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ABSTRACT

Adolescents are especially likely to initiate tobacco use and are more vulnerable to long-term nicotine dependence. A unifying hypothesis is proposed based largely on animal studies that adolescents, as compared to adults, experience enhanced short-term positive and reduced aversive effects of nicotine, as well as less negative effects during nicotine withdrawal. Thus, during adolescence the strong positive effects of nicotine are inadequately balanced by negative effects that contribute to nicotine dependence in adults. This review provides a neural framework to explain developmental differences within the mesolimbic pathway based on the established role of dopamine in addiction. This pathway originates in the ventral tegmental area (VTA) and terminates in the nucleus accumbens (NAcc) where dopamine is increased by nicotine but decreased during withdrawal. During adolescence, excitatory glutamatergic systems that facilitate dopamine are overdeveloped, whereas inhibitory GABAergic systems are underdeveloped. Thus, it is hypothesized that adolescents display enhanced nicotine reward and reduced withdrawal via enhanced excitation and reduced inhibition of VTA cell bodies that release dopamine in the NAcc. Although this framework focuses on adolescents and adults, it may also apply to the understanding of enhanced vulnerability to nicotine in adults that were previously exposed to nicotine during adolescence. The hypothesis presented in this review suggests that the clinical diagnostic criteria developed for nicotine dependence in adults, based primarily on withdrawal, may be inappropriate during adolescence when nicotine withdrawal does not appear to play a major role in nicotine use. Furthermore, treatment strategies involving nicotine replacement may be harmful for adolescents because it may cause enhanced vulnerability to nicotine dependence later in adulthood.

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1. Introduction

There is a plethora of epidemiological evidence demonstrating that adolescents are more likely to use nicotine and that nicotine exposure during adolescence causes a greater risk of long-term tobacco addiction (Adelman, 2006; DiFranza and Wellman, 2005, 2007; Ginzler et al., 2007; Nelson et al., 2008). Furthermore, both behavioral and neurochemical pre-clinical studies suggest that there are fundamental differences in the mechanisms that drive nicotine use in adolescents and adults (see Adriani and Laviola, 2004; Barron et al., 2005).

There are several potential factors that influence developmental differences to nicotine use, including sex differences, environmental conditions, genetic background, social factors, and constituents of tobacco other than nicotine that may contribute to enhanced nicotine use during adolescence. The working hypothesis proposed in this review is that nicotine use during adolescence is

driven by two factors: (1) the positive effects of nicotine during adolescence are greater than in adults and (2) the negative effects associated with nicotine and withdrawal from this drug are substantially lower than those experienced by adults. The overall result is that adolescents seek nicotine because the enhanced positive effects they experience are inadequately balanced against minimal negative effects. Behavioral evidence from animal studies is used to compare the positive and negative effects of nicotine in adolescent and adult rodents. A theoretical framework is also proposed to explain why adolescents are different from adults with regard to neurochemical mechanisms involving enhanced excitatory and underdeveloped inhibitory influences on dopamine transmission in the mesolimbic reward system.

The motivation to use nicotine is a complex balance between seeking the positive effects of nicotine and avoiding the negative effects of withdrawal. One problem encountered in reviewing developmental differences in nicotine effects is that most of the earlier studies focused on the positive effects of nicotine that were shown to be enhanced in adult rats that were pre-exposed to nicotine during adolescence (for a review see Slotkin, 2002). These studies provided valuable information suggesting that adolescence

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is a period of enhanced vulnerability to nicotine and that enhanced nicotine reward likely contributes to increased tobacco use during adolescence. However, it must be recognized that a comprehensive understanding of why adolescents are particularly vulnerable to nicotine cannot be developed without concurrent consideration of possible developmental differences in the negative effects associated with nicotine use.

Until recently, there had not been adequate consideration of developmental differences in the initial or long-term negative consequences of nicotine exposure. The few studies that have been conducted on the negative effects of nicotine suggest that the direct aversive effects of nicotine are lower in adolescent versus adult rats (Adriani et al., 2004; Cao et al., 2007; Shram et al., 2006; Wilmouth and Spear, 2004). Also, the physical and negative affective states produced by nicotine withdrawal are lower in adolescent versus adult rats (O'Dell et al., 2006, 2007; Shram et al., 2008c) and mice (Kota et al., 2007).

This review evaluates developmental differences in the direct effects of nicotine (both positive and negative) as well as long-term effects (primarily differences in withdrawal). In addition to reviewing developmental differences between adolescents and adults in response to nicotine in rodent models, a comprehensive hypothesis is developed based on the idea that nicotine use is driven by a dynamic and changing balance between positive and negative effects. Furthermore, this review proposes a neurochemical hypothesis for the physiological substrates that mediate developmental differences in the positive and negative effects of nicotine. Specifically, it is hypothesized that the enhanced drive to use nicotine in adolescence is mediated, at least in part, by enhanced excitation and reduced inhibition of dopamine cell bodies in the ventral tegmental area (VTA) that release dopamine in the nucleus accumbens (NAcc), a brain region that plays an important role in mediating drug-seeking behavior (Balfour, 2002; Corrigall et al., 1992; Koob and Kreek, 2007). Lastly, this review discusses the proposed comprehensive behavioral and neurochemical hypotheses as a framework for future pre-clinical studies of developmental differences in nicotine effects. It is especially important to note that the clinical implications of this comprehensive hypothesis suggest that the current diagnostic criteria for nicotine dependence that was developed for adults may be inappropriate for adolescents. Also, our hypothesis may shed light on why tobacco cessation treatments that focus on reducing withdrawal may be less effective in adolescent versus adult tobacco users.

2. Pre-clinical research

2.1. Modeling the adolescent period of development in rodents

When assessing the boundaries of the adolescent period in rodents, most researchers agree that the prototypic age range for adolescence conservatively ranges from postnatal day (PND) 28 to 45 (for a review see Spear, 2000). Historically, it has been difficult to define an exact time frame of adolescence since this phase of development is a period of transition that encompasses a series of events with no single discrete event that signals its onset or termination, such as puberty that signals sexual maturation. Adolescence reflects a period of “soft” events during which age-specific behavioral discontinuities from younger and older animals are most evident (Pickles et al., 1998). Some of the behavioral characteristics that have established adolescence as being defined between PND 28 and 45 include, accelerated growth rates, emergence from the protected nest (Galef, 1981), and enhanced social interaction (Primus and Kellogg, 1989) risk-taking and novelty-seeking (Spear et al., 1980; Spear and Brake, 1983) behavior. These innate developmental differences are important to consider when

evaluating the behavioral effects of drugs of abuse in rats from different stages of development.

Much research has shown that the behavioral effects of nicotine are different in rats that are tested during the adolescent period of development (see below). Further, there is a growing body of literature demonstrating that within adolescence the behavioral effects of nicotine vary during the earlier versus later parts of this developmental period. For example, Belluzzi et al. (2004) demonstrated that early adolescent (PND 28) animals displayed a preference for an environment paired with a single injection of nicotine, whereas late adolescent (PND 38) and adult animals did not display this effect. Leslie et al. (2004) also demonstrated that the pattern of c-fos induction produced by nicotine was distinct in sensory and limbic cortex collected from adolescent rats from young (i.e., PND 14, 21, 30, 38) versus more mature rats (PND 60). Interestingly, the latter study also demonstrated that the ability of nicotine to enhance performance on a cognitive task was enhanced in young rats tested in the early versus late phases of the adolescent period. These studies suggest that there are important differences to consider when evaluating the behavioral and neurochemical effects of nicotine in young rats that are tested during different stages of the adolescent period.

2.2. Short-term direct effects of nicotine

When considering the abuse liability of a particular substance, one must consider that a drug produces initial short-term effects that likely influence whether or not the drug is used in the future. This is particularly important to consider with nicotine because it produces both positive and negative effects following initial use.

2.2.1. Enhanced rewarding effects of nicotine during adolescence

The intravenous self-administration (IVSA) paradigm has been widely used to study the rewarding effects of drugs of abuse, including nicotine (for a review see Corrigall, 1991). In this model, rats perform an operant response to receive infusions of nicotine. Developmental studies comparing nicotine IVSA in adolescents versus adults have demonstrated that adolescent rats generally display enhanced rewarding effects of nicotine relative to adult animals. For example, both male and female adolescent rats acquire nicotine IVSA more readily and display higher levels of nicotine intake relative to their adult counterparts under both limited (Levin et al., 2003, 2007) and extended (Chen et al., 2007) access conditions. Belluzzi et al. (2005) also demonstrated that acetaldehyde, a major component of tobacco smoke enhanced nicotine IVSA in adolescent but not adult rats. These findings suggest that adolescent rats are more sensitive to the reward enhancing effects of acetaldehyde on nicotine intake relative to their adult counterparts. The majority of IVSA studies demonstrate that nicotine is more reinforcing in adolescent versus adult rodents. However, we also acknowledge that Shram et al. (2008a,b) recently reported that adolescent rats displayed reduced nicotine IVSA under progressive and fixed ratio schedules of reinforcement. The authors of the latter report acknowledge that their findings are inconsistent with previous IVSA and conditioning studies (including their own) demonstrating enhanced rewarding effects of nicotine during adolescence, and they suggest that this discrepancy may be due to methodological issues including nicotine doses and strain differences.

Studies using oral self-administration procedures have demonstrated that adolescent rats display enhanced nicotine intake relative to adults. For example, adolescent mice during the early adolescent period (PND 24–35) exhibited a stronger preference for drinking a nicotine solution versus water relative to middle (37–48) and late adolescent (50–61) mice (Adriani et al., 2002). The latter study also demonstrated that early adolescent mice displayed

a compensatory increase in nicotine intake when the dose of nicotine was reduced, and this effect was not observed in middle or late adolescent mice. Subsequent studies also demonstrated that adolescent mice that were initially more responsive to novel stimuli displayed enhanced preference for an oral nicotine solution (Abreu-Villaça et al., 2006). Based on these findings, the authors suggested that enhanced motivation to seek out new experiences contributes to adolescent nicotine use.

The rewarding effects of nicotine have also been studied using place-conditioning procedures (see Tzschentke, 2007). These studies involve repeated administration of drug on one side of a conditioning apparatus and saline on an adjacent side. Following conditioning, animals are allowed free access to both compartments simultaneously in the absence of drug. The nature of the affective properties of the drug is evident on this test day when the environmental cues elicit either conditioned place preference (i.e., CPP) or aversion (CPA) to the drug-paired side relative to the neutral side. The IVSA and oral nicotine intake procedures described above measure the direct reinforcing effects of drugs, whereas CPP procedures measure conditioned rewarding effects.

Several place-conditioning studies have demonstrated that adolescent rats display enhanced rewarding effects of nicotine relative to adults. Recent work in our laboratory demonstrated that across various doses of nicotine, adolescents displayed enhanced CPP relative to adult rats (see Fig. 1). Our findings are consistent with other laboratories demonstrating that adolescents display CPP at doses of nicotine that do not produce this effect in adult rats (Shram et al., 2006; Vastola et al., 2002). In addition, Belluzzi et al. (2004) demonstrated that a single injection of nicotine produced CPP in early adolescent (PND 28) but not late adolescent (PND 38) or adult (PND 90) rats, even in procedures involving 4 additional conditioning trials for adult rats. Recent work using mice also demonstrated that both male (Kota et al., 2007) and female (Kota et al., 2008) adolescents displayed CPP at low doses that did not produce this effect in adult mice.

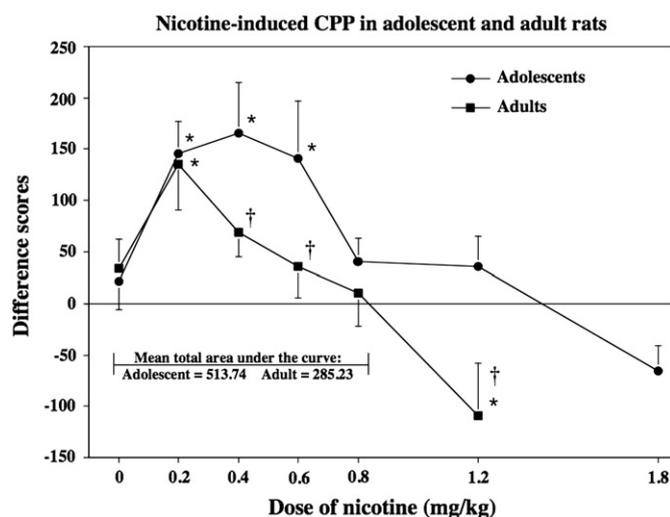


Fig. 1. Enhanced rewarding and reduced aversive effects of nicotine during adolescence. Adolescent and adult rats ($n = 8-14$) were conditioned with various nicotine doses (0, 0.2, 0.4, 0.6, 0.8 or 1.2 mg/kg, base, sc). An additional group of adolescent rats received 1.8 mg/kg of nicotine during conditioning in order to address higher metabolic rates of nicotine in adolescent versus adult rats. Difference scores (\pm SEM) reflect time spent in the initially non-preferred side after conditioning minus before conditioning such that values above "0" reflect a positive shift in preference (i.e., CPP) and values below "0" reflect an aversion (i.e., CPA). The mean total area under the curve reflects the sum of the averages for each age group from 0 to 0.8 mg/kg dose of nicotine. Adolescents display CPP across a wider range of doses relative to controls ($*p \leq 0.05$), and this effect was enhanced relative to adult rats ($†p \leq 0.05$). These data are published in Torres et al. (2008).

In conclusion, the majority of the literature comparing developmental differences to nicotine demonstrates that adolescent rats display enhanced rewarding effects of nicotine relative to adults. Thus, adolescent rats display enhanced rewarding effects of nicotine in self-administration and place-conditioning procedures under a variety of experimental conditions relative to their adult counterparts. These studies provide converging lines of evidence that enhanced tobacco use during adolescence is driven in large part by strong rewarding effects of nicotine that are experienced during this young period of development.

2.2.2. Reduced aversive effects of nicotine during adolescence

Emerging lines of evidence suggest that the aversive effects of nicotine are lower during adolescence. Recent studies in our laboratory observed that adult rats display CPA for an environment that was previously paired with a high nicotine dose. However, this effect was absent in adolescent rats (see Fig. 1). The aversive effects of nicotine have also been studied using conditioned taste aversion (CTA) procedures which measure conditioned aversive effects. This procedure pairs flavored solutions with drug administration, such that the aversive effects of the drug are evident on the test day where the animals avoid (i.e., CTA) the flavor previously paired with the drug. Previous studies have demonstrated that adult rats display an aversion to a flavor that was previously paired with a high dose of nicotine, and this effect is lower in adolescents (Shram et al., 2006; Wilmouth and Spear, 2004). These findings suggest that the aversive effects of nicotine are reduced during the adolescent period of development.

2.2.3. Reduced anxiogenic effects of nicotine during adolescence

There is substantial evidence showing that nicotine induces behavioral and neurochemical anxiogenic-like effects that play an important role in tobacco use (see Balfour, 1991; Buijnzeel and Gold 2005; Loughlin et al., 2006). For example, nicotine IVSA and withdrawal from this treatment regimen produced an increase in anxiogenic behavior in rats, suggesting that nicotine is self-administered despite its anxiogenic effects (Irvine et al., 2001). Thus, stress is an important aspect to consider when evaluating developmental differences to nicotine since the behavioral effects of nicotine are likely different depending on the response of the organism to stress induced by nicotine exposure.

Recent studies comparing the effects of nicotine on stress demonstrate that the anxiogenic effects of nicotine are different in adolescent versus adult rats. For example, nicotine stimulates the hypothalamic-pituitary-adrenal (HPA) axis in the brain, and this produces an increase in plasma corticosteroid levels in adult rats (Cao et al., 2007). However, the latter report demonstrated that nicotine produced an increase in corticosterone levels and c-fos mRNA expression in the paraventricular nucleus of the hypothalamus of adult but not adolescent rats. This developmental difference appears to be specific to nicotine, since corticosterone release in response to other stressors reaches adult levels by adolescence (Choi and Kellogg, 1996; Vázquez, 1998). Consistent with a reduced response to stress following nicotine exposure, Adriani et al. (2004) found that after 12 days of oral nicotine consumption, mid-adolescent (PND 36–48) mice displayed a reduction in anxiety-like behavior in the elevated plus maze (EPM) relative to pre-adolescent (PND 23–35) and post-adolescent (PND 49–61) mice. However, it should be noted that the later study also reported that an acute injection of nicotine reduced anxiety-like behavior in adult but not adolescent mice. Also, Torrella et al. (2004) demonstrated nicotine produced an increase in time spent in an initially non-preferred compartment, and the authors interpreted this finding as nicotine enhancing anxiolytic effects in adolescent but not adult rats. Overall, these studies suggest that nicotine produces less anxiety-like behavior during adolescence; however, this effect may be

different across nicotine regimens and during different phases of the adolescent period.

Overall, pre-clinical studies examining the short-term effects of nicotine have demonstrated that the rewarding effects of nicotine are enhanced whereas the aversive effects of nicotine (and possibly anxiety-like behaviors produced by nicotine) are lower during adolescence.

2.3. Long-term effects of nicotine

When considering the long-term effects of nicotine two relevant issues arise. First, in adults that received chronic exposure to nicotine, removal of the drug produces a withdrawal syndrome that involves both physical and negative affective components. Second, adolescents that are exposed to nicotine display behavioral and neurochemical consequences that are manifested later during adulthood. Both of these long-term effects of nicotine are relevant to our discussion regarding tobacco use during adolescence and the long-term consequences of adolescent nicotine exposure.

2.3.1. Reduced nicotine withdrawal during adolescence

Nicotine withdrawal has been widely studied in rats using chronic nicotine administration via subcutaneous osmotic mini-pumps (Kenny and Markou, 2001; Malin, 2001; O'Dell et al., 2004, 2007). Most studies examining nicotine withdrawal use a protocol whereby rats are first prepared with pumps that deliver nicotine for 5–7 days. Withdrawal is then assessed following the cessation of nicotine via pump removal (i.e., spontaneous withdrawal) or administration of a nicotinic receptor antagonist (i.e., precipitated withdrawal). Several studies have demonstrated that the nicotine withdrawal syndrome is comprised of both physical and affective components.

The physical signs of nicotine withdrawal in rats include abdominal constrictions, facial fasciculation, writhes, gasps, eye blinks, and ptosis (Malin, 2001; O'Dell et al., 2004; Shram et al., 2008c; Watkins et al., 2000). Initial studies examining developmental differences to nicotine withdrawal demonstrated that administration of the nicotinic receptor antagonist mecamylamine precipitated fewer physical signs of withdrawal in adolescents versus adult rats that received the same nicotine dose in their pumps (O'Dell et al., 2004). Subsequent work adjusting for metabolic differences to nicotine verified that adolescents still display fewer withdrawal signs compared to adults displaying similar levels of blood nicotine (see Fig. 2). This is consistent with a recent report demonstrating that adolescent rats display fewer signs of nicotine withdrawal following mecamylamine administration relative to adult rats that received equivalent nicotine doses to produced dependence (Shram et al., 2008c). The latter study demonstrated that although precipitated withdrawal produced robust developmental differences, adolescent and adult rats displayed similar physical signs of nicotine withdrawal following pump removal. Thus, it appears that precipitated withdrawal produces more robust age differences relative to spontaneous withdrawal that produces mild effects. In mice, however, male adolescents display fewer physical signs withdrawal relative to their adult counterparts under conditions of both spontaneous and precipitated nicotine withdrawal (Kota et al., 2007). A recent report from the same laboratory demonstrated that female adolescent mice display enhanced physical signs of withdrawal relative to adult mice (Kota et al., 2008). These reports suggest that there may be important sex differences to consider when evaluating the hypothesis presented in this review, since male mice appear to display more robust developmental differences to nicotine relative to females.

The affective properties of nicotine withdrawal have been assessed using intracranial self-stimulation (ICSS) procedures. In

Nicotine and cotinine levels and withdrawal signs seven days after mini-pump implantation

Dose of nic. (mg/kg/day)	Plasma levels (ng/ml)		Withdrawal signs
	Nicotine	Cotinine	
Adolescent:			
0 (n=4)	-----	-----	13.5±3.3
1.6 (n=8)	26.6±5.2	150.4±18.8	11.5±1.9
3.2 (n=6)	40.5±2.0	265.6±50.1	14.3±2.1
4.7 (n=8)	76.2±7.6	460.5±74.2	14.8±2.6
Adult:			
0 (n=4)	-----	-----	9.2±1.5
1.0 (n=8)	22.9±3.2	143.0±42.2	15.2±2.7
2.1 (n=8)	33.8±6.4	179.3±38.1	21.7±2.6*
3.2 (n=7)	65.4±9.5	297.8±53.6	27.1±3.3*

Fig. 2. Reduced physical signs of nicotine withdrawal during adolescence. Adolescent and adult rats ($n = 8–15$) received nicotine via osmotic pump for 7 days. Withdrawal was then precipitated using mecamylamine (1.5 mg/kg, sc) and total overt signs of withdrawal were measured (\pm SEM). Eight hours later, plasma nicotine and its metabolite cotinine were measured (\pm SEM). Given equivalent plasma nicotine levels, adolescents display fewer signs of withdrawal relative to adults. Asterisks (*) denote a significant difference from controls ($p \leq 0.05$). These data illustrate that adolescent rats require approximately 1.5 fold higher nicotine doses to achieve equivalent nicotine plasma levels as adults, consistent with other laboratories (Trauth et al., 2000). These data are published in O'Dell et al. (2006).

ICSS studies, rats are allowed to self-administer small amounts of electrical current to the brain via an electrode placed in a brain region (i.e., medial forebrain bundle) consisting of efferent projections to several reward-related structures of the mesolimbic pathway. The stimulation is highly reinforcing, and can be easily used to generate a threshold measure of the activity of brain reinforcement circuitry. Previous research has demonstrated that nicotine-dependent adult rats display an increase in current intensity thresholds during nicotine withdrawal (see Kenny and Markou, 2001; Panagis et al., 2000). Recent reports have illustrated that nicotine-dependent mice also display an increase in current intensity thresholds during withdrawal similar to rats experiencing nicotine withdrawal (Johnson et al., 2008; Stoker et al., 2008). The need for higher current levels is believed to reflect a decrease in brain reward function because the animal has a difficulty experiencing pleasure during withdrawal. Using ICSS procedures, we compared the changes in current intensity thresholds in adolescent and adult rats experiencing nicotine withdrawal (see Fig. 3). Changes in ICSS behavior were compared following mecamylamine administration and 6, 12, and 24 h after pump removal. The results revealed that adult rats displayed a decrease in brain reward function (i.e., an elevation of ICSS thresholds) following precipitated and spontaneous withdrawal conditions relative to controls. However, this effect was absent in adolescent rats. These data support our hypothesis that adolescents experience less negative affect during nicotine withdrawal relative to adults. Furthermore, the negative affective properties of nicotine withdrawal are lower in adolescents under the drug-free conditions of spontaneous withdrawal, suggesting that the behavioral effects produced by mecamylamine are not due to differences in sensitivity to this drug. Collectively, these findings suggest that there is a basic distinction in reward functions mediated by the medial forebrain bundle in adolescents and adults, probably related to developmental differences in dopamine neurotransmission.

The affective properties of nicotine withdrawal have also been studied using CPA procedures. In these studies, animals receive chronic nicotine via osmotic pumps for 5–7 days. During conditioning, the animal receives a nicotinic receptor antagonist to precipitate withdrawal and is confined to one side of the apparatus, and on alternating days they receive saline in the other compartment. Following conditioning, nicotine-dependent adult rats reliably display a CPA for the compartment where they experienced

Lowered negative affect during adolescence following precipitated and spontaneous withdrawal

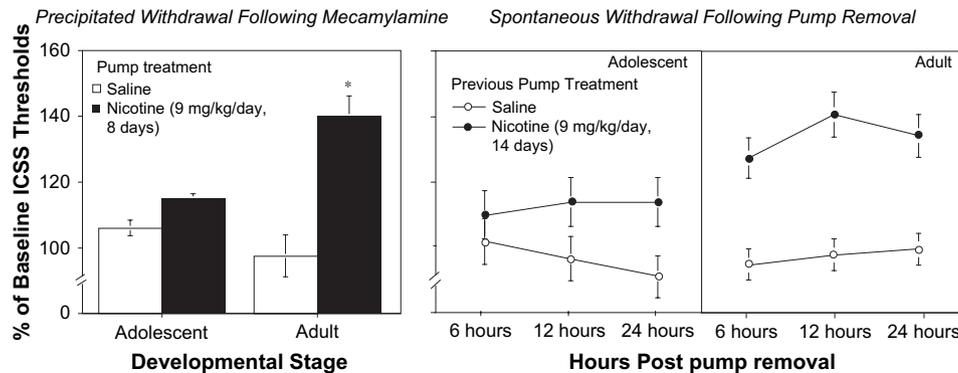


Fig. 3. Reduced affective properties of nicotine withdrawal during adolescence. Rats ($n = 5-12$) received ICSS training and saline or nicotine pumps. Changes in ICSS thresholds were examined following mecamylamine and then again 7 days later after pump removal. Data reflect % baseline (\pm SEM) such that values of 100 reflect no change from baseline. Adults displayed a significant decrease in brain reward function during precipitated and spontaneous withdrawal relative to control rats ($*p \leq 0.05$), and this effect was absent in adolescents. The data in the left panel are published in O'Dell et al. (2006).

withdrawal (Ise et al., 2000; Suzuki et al., 1996, 1999; Watkins et al., 2000). However, recent work in our laboratory demonstrated that the ability of nicotine withdrawal to produce CPA was lower in adolescent versus adult rats (see Fig. 4). This suggests that the negative affective properties of nicotine withdrawal are lower during adolescence.

Recent pre-clinical studies have compared developmental differences to anxiety-like behavior produced by nicotine withdrawal using EPM procedures. This procedure assesses how rats respond to an approach-avoidance situation involving open elevated spaces that are avoided versus enclosed safe areas that are preferred. Adult rats experiencing nicotine withdrawal display an increase in anxiety-like behavior, as measured by a decrease in open-arm time relative to controls. However, the latter effect has been demonstrated to be lower in male adolescent rats (Wilmouth and Spear, 2006) and mice (Kota et al., 2007) relative to their adult counterparts. Contrary to the findings in male mice, however, female adolescent mice displayed a decrease in anxiety-like behavior during nicotine withdrawal that was not observed in their adult counterparts (Kota et al., 2008). The discrepancy in female mice highlights the importance of considering sex differences when comparing nicotine withdrawal in male and female rats from different stages of development.

These findings described above suggest that adolescents are less sensitive to the anxiety-inducing effects of nicotine withdrawal. However, it should be noted that ontogenic differences in withdrawal-induced behavioral effects might be dependent on the behavior being measured. Also, nicotine withdrawal may be qualitatively different in adolescent as compared with adults, such that physical and affective effects may be stronger in adults but cognitive effects may be more pronounced in adolescents. Consistent with this, Wilmouth and Spear (2006) demonstrated that during nicotine withdrawal the affective and physical effects of withdrawal were stronger in adults whereas cognitive deficits were more pronounced in adolescent rats.

In summary, several lines of evidence support the hypothesis that rewarding effects of nicotine are enhanced whereas the negative effects of nicotine are reduced during the adolescent period of development. Following chronic nicotine exposure; however, the behavioral effects of withdrawal from this drug are lower in adolescent versus adult rats. The studies reviewed above have informed our hypothesis that the rewarding effects of nicotine are enhanced whereas the negative effects of nicotine and withdrawal from this drug are lower during adolescence. Our hypothesis regarding adolescent tobacco use relies heavily on the contribution

of positive effects of nicotine, since a lack of withdrawal is not expected to mediate smoking behavior on its own. Also, our hypothesis regarding the negative effects of nicotine is meant to incorporate all negative aspects of nicotine, including both the aversive effects of nicotine and withdrawal from this drug. Lastly, one of the most problematic long-term effects of smoking is relapse. To our knowledge, developmental differences to reinstatement of nicotine-seeking behavior have not been compared in adolescent and adult rats. However, we suggest that this effect would be enhanced in adolescent versus adult rats based on our hypothesis that the rewarding effects of nicotine are enhanced during the adolescent period of development.

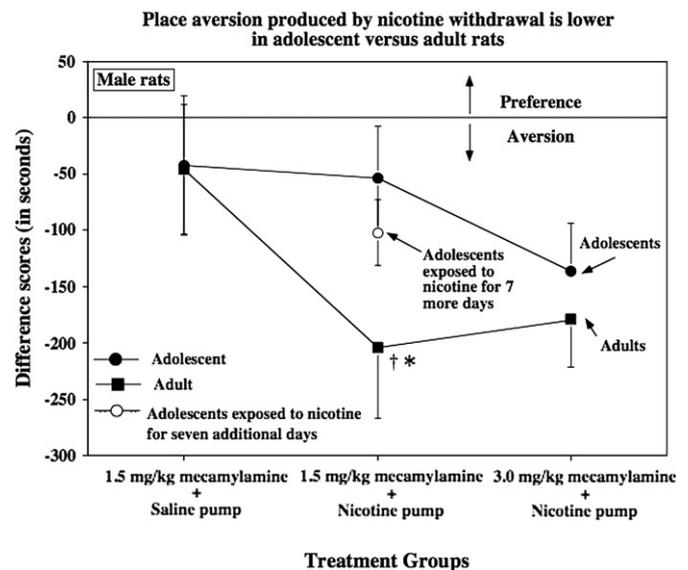


Fig. 4. Reduced affective properties of nicotine withdrawal during adolescence. Adolescent and adult rats ($n = 7-14$) were tested for initial preference and were then prepared with saline or nicotine pumps. After 7 days, rats received mecamylamine in their initially preferred side and on alternate days received saline in the non-preferred side. An additional group of adolescents were conditioned after 14 days of nicotine exposure (open circle). The data reflect difference scores (\pm SEM) that were calculated as time spent in the initially preferred side after minus before conditioning, such that negative values reflect a CPA. Adult rats displayed a significant decrease in time spent in their withdrawal side on the test day relative to controls ($*p \leq 0.05$) and relative to adolescents receiving the same dose of mecamylamine ($\dagger p \leq 0.05$). Adolescents did not display CPA, even after 7 additional days of nicotine exposure. These data are published in O'Dell et al. (2007).

2.3.2. Long-term effects of adolescent nicotine exposure expressed later in adulthood

Several pre-clinical studies support the hypothesis that pre-exposure to nicotine during adolescence enhances the rewarding effects of nicotine during adulthood. For example, adult rats that initiated nicotine IVSA during adolescence self-administered more nicotine as compared to adults that initiated IVSA during adulthood (Levin et al., 2003). Nicotine IVSA is also increased in rats that received non-contingent nicotine injections during adolescence relative to rats that received nicotine as adults (Adriani et al., 2003). A related study demonstrated that gestational exposure to both nicotine and ethanol enhanced nicotine IVSA in young adult rats (Matta and Elberger, 2007). Consistent with IVSA studies, nicotine CPP is facilitated in adult rats that were exposed to nicotine during adolescence (Adriani et al., 2006). These studies suggest that nicotine exposure during adolescence alters long-term vulnerability to nicotine use.

Few studies have compared the long-term consequences of adolescent nicotine exposure on the aversive effects of nicotine or withdrawal from this drug. Recent work in our laboratory demonstrated that a high dose of nicotine produced CPA in naïve adult rats; however, this effect was absent in adults that were pre-exposed to nicotine during adolescence (see Fig. 5). With regard to the long-term consequences of nicotine, adult rats that were pre-exposed to nicotine during adolescence also displayed an increase in anxiety-like behavior in an open-field test conducted later in adulthood (Smith et al., 2006). Consistent with this report, adolescent nicotine exposure produced an increase in anxiety-like behavior in the open-field test that persisted beyond acute nicotine withdrawal (Slawecki et al., 2003). However, a subsequent study from this laboratory demonstrated that adolescent nicotine exposure produced a decrease in the ability of corticotropin releasing factor to induce EEG changes in brain later during adult development (Slawecki and Ehlers, 2003). Based on these findings, these authors suggested that adolescent nicotine exposure produces long-term decreases in neurophysiological responses to stress.

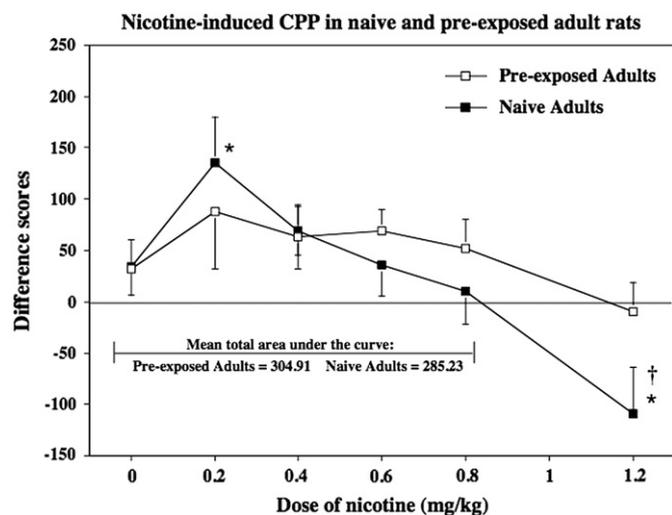


Fig. 5. Reduced negative effects of nicotine in adult animals that were pre-exposed to nicotine during adolescence. The naïve adults in this figure also appear in Fig. 1. Naïve adult rats and adults that were pre-exposed to nicotine during adolescence ($n = 9-14$) were conditioned using various nicotine doses (0, 0.2, 0.4, 0.6, 0.8 or 1.2 mg/kg, base, sc). The data are presented as difference scores (\pm SEM), which reflect time spent in the initially non-preferred side after conditioning minus before conditioning such that values above "0" reflect a positive shift in preference (i.e., CPP) and values below "0" reflect an aversion (i.e., CPA). The mean total area under the curve reflects the sum of the averages for each age group from 0 to 0.8 mg/kg dose of nicotine. Naïve adults displayed CPP at the lowest and highest dose of nicotine relative to controls ($*p \leq 0.05$). However, the CPA produced by a high dose was not observed in adults that were pre-exposed to nicotine during adolescence ($*p \leq 0.05$). These data are published in Torres et al. (in press).

In summary, these studies suggest that the long-term consequences of adolescent nicotine exposure may involve a reduction in the aversive effects of nicotine and an enhancement in anxiety produced by withdrawal later in adulthood. These findings are discrepant with those observed in adolescent rats that display reduced aversive effects of nicotine and withdrawal from this drug. However, there are likely distinct mechanisms that mediate tobacco use in adolescents versus adults that were pre-exposed to nicotine during adolescence, a suggestion that is supported by several pre-clinical studies (for a review see Slotkin, 2002). Also, a recent report comparing acetylcholine pre-synaptic activity during nicotine withdrawal in adolescent, adult, and adult animals that were pre-exposed to nicotine during adolescence reported a different pattern of changes across these groups that were sex- and brain-region dependent (Slotkin et al., 2008).

Below we provide biochemical evidence to support our behavioral hypothesis regarding enhanced reward and reduced negative effects of nicotine in adolescent versus adult rats. Although this framework is derived mainly from rodent models, it is intended to provide a possible explanation for why adolescents are different from adults with regard to neurochemical mechanisms involving enhanced excitatory and underdeveloped inhibitory influences on dopamine transmission in the mesolimbic reward system.

3. Neurochemical research

Nicotine binds to a family of cholinergic receptors consisting of pentameric membrane proteins of homomeric or heteromeric complexes of α or β subunits. To date, 12 subunits have been identified ($\alpha 2-10$ and $\beta 2-4$), and the various combinations of these subunits lead to differences in channel activation and desensitization in the presence of nicotine. It is well established that the emergence of the various nicotine acetylcholine receptors (nAChRs) is developmentally different, and the expression and/or functional properties of these subunits are likely to contribute to behavioral differences to nicotine in adolescent and adults (see Slotkin, 2002). Furthermore, there are several reported long-term effects of adolescent nicotine exposure on cholinergic regulation of transmitter release, neurite outgrowth, cell survival, and synaptogenesis (see Dwyer et al., 2008). Although there are likely several important changes within the cholinergic or possibly serotonergic (Collins and Izenwasser, 2004; Shearman et al., 2008; Slotkin et al., 2007) systems to explain developmental differences to nicotine, the framework provided below focuses on those changes within the mesolimbic dopamine system.

3.1. The mesolimbic dopamine pathway

The behavioral effects of nicotine are mediated in part by dopamine transmission in the mesolimbic pathway (see Balfour, 2002; Corrigan et al., 1992; Di Chiara, 2000; Mansvelder and McGehee, 2002). This pathway originates in the VTA and terminates in several forebrain structures including the NAcc, which has been shown to play an important role in mediating drug addiction (see Koob and Kreek, 2007). The link between nicotine reward and NAcc dopamine transmission has motivated a great deal of research examining factors that influence the excitability of VTA dopamine neurons. Overall, this large body of work has shown that NAcc dopamine release from VTA projections is regulated by a balance between excitatory and inhibitory inputs on VTA dopamine neurons.

The excitatory glutamatergic inputs to the VTA arise primarily from the prefrontal cortex, which provides the major excitatory control of VTA neuron activity and ultimately dopamine release in the NAcc (Johnson et al., 1992; Kalivas et al., 1989; Mansvelder et al., 2003; Sesack and Pickel, 1992; Saud-Chagny et al., 1992; Taber and

Fibiger, 1995). With respect to the neurochemical effects of nicotine, blockade of glutamate receptors in the VTA inhibits nicotine-induced increases in NAcc dopamine release (Schilström et al., 1998). This finding implies that there is nicotinic modulation of glutamate transmission that regulates VTA dopamine output. Consistent with this, electrophysiological procedures have shown that systemic nicotine administration produces an increase in dopamine firing in the VTA that is inhibited by blockade of glutamate receptors in this region (Erhardt et al., 2002).

The principal inhibitory inputs to the VTA are GABAergic, and they include local interneurons as well as projections from the NAcc and ventral pallidum (Kalivas et al., 1993). Local inhibition of VTA dopamine plays an important role in mesolimbic dopamine neuronal excitability. For example, Erhardt et al. (2002) demonstrated that the nicotine-induced increases in dopamine firing were facilitated by blockade of VTA GABA receptors. These findings suggest that the mesolimbic pathway is under inhibitory regulation via local GABA transmission in the VTA.

The specific manner in which nicotine alters dopamine transmission in the mesolimbic pathway has also been a topic of much research (for a review see Mansvelder et al., 2003). Nicotine receptors are anatomically positioned to alter dopamine transmission in this pathway since cholinergic projections to the VTA synapse directly onto mesoaccumbens dopamine neurons (see Omelchenko and Sesack, 2006). Three cell types in the VTA have been shown to express nAChRs: dopamine neurons, gamma-aminobutyric acid (GABA) interneurons, and glutamate pre-synaptic terminals (Xu et al., 2006; Mansvelder and McGehee, 2002). Dopamine neurons express $\alpha 2$ –10 and $\beta 2$ –4 subunits (Mansvelder et al., 2003). Glutamate terminals in the VTA contain $\alpha 7$ nAChRs that regulate glutamate release, whereas GABA cell bodies contain $\alpha 4\beta 2$ sites that regulate GABA release in this region (see Marchi et al., 2002; Nomikos et al., 2000). As an example, an $\alpha 7$ preferring agonist produced an increase in dopamine release from striatal synaptosomes that was blocked by a glutamate receptor antagonist (Kaiser and Wonnacott, 2000). Also, blockade of $\alpha 7$ receptors in the VTA have been demonstrated to reduce nicotine-induced increases in NAcc dopamine levels (Fu et al., 2000; Schilström et al., 1998).

Cholinergic drive to VTA GABA neurons can be inhibited via blockade of nACh receptors or via desensitization due to nicotine exposure. When nicotine is administered, $\alpha 4\beta 2$ nAChRs desensitize within minutes and these receptors on GABA neurons recover very slowly from desensitization (see Gentry et al., 2003; Mansvelder and McGehee, 2002; Pidoplichko et al., 2004; Wang and Sun, 2005). In fact, in the first 15 min after nicotine exposure GABA neurons do not respond to nicotine application, and they take approximately 1 h to reach normal levels of sensitivity (Mansvelder et al., 2002). Therefore, as a result of nicotine exposure, the VTA dopamine neurons receive less inhibition from GABA than before nicotine and this decrease in inhibitory tone results in enhanced action potential firing in dopaminergic neurons. In contrast, $\alpha 7$ nAChRs controlling glutamate excitation are much less susceptible to desensitization following nicotine exposure than GABA neurons (Wooltorton et al., 2003). The latter study was conducted at low concentrations of nicotine (20–80 nM) to model low levels of nicotine used by chronic smokers. However, it should be noted that the desensitization of $\alpha 7$ receptors is dose-dependent, as desensitization of this receptor has been reported at higher concentrations (i.e., above 500 nM; for a review see Picciotto et al., 2008). A comparison study of cholinergic regulation of mesolimbic dopamine transmission following nicotine exposure revealed that although the $\beta 2$ heteromeric nAChRs become rapidly desensitized, $\alpha 7$ sites remain functional and actively enhance glutamate excitation of dopamine neurons in the VTA (Dani et al., 2001). Nicotine, therefore, causes a shift from tonic inhibition towards excitation of VTA dopamine neurons that result in enhanced dopamine transmission in the reward circuits of the

NAcc. Consistent with this, Yin and French (2000) demonstrated that VTA GABAergic neurons had a lower electrophysiological response to nicotine (relative to dopamine neurons) that displayed a pronounced and rapid desensitization. This rapid desensitization was purported to lead to a disinhibition of dopamine neurons thereby facilitating a more sustained increase in mesolimbic dopamine neurotransmission following nicotine administration.

3.2. Hypothesized substrates mediating nicotine use during adolescence

The hypothesized substrates in this review focus on neurochemical changes in the mesolimbic pathway. This is based on reports demonstrating a reduction of dopamine neuronal activity and glutamate neurotransmission at the level of the VTA that persist even after the physical signs of withdrawal have vanished (for a review see Pulvirenti and Diana, 2001). This suggests that the VTA undergoes long-lasting changes in neural plasticity that endures following chronic drug intake. Furthermore, intra-VTA infusions of nicotine produce long-lasting increases in NAcc dopamine release that were not observed following intra-NAcc infusions (Nisell et al., 1994). Based on these findings the authors suggest that nAChRs in the VTA are of greater significance than those located in the NAcc for mediating the behavioral effects of nicotine. Our focus on neural mechanisms in the VTA is also supported by a recent report showing that intra-VTA infusions of nicotine produce preference or aversion depending on the dose that was administered during conditioning (Laviolette and van der Kooy, 2003b). Specifically, intra-VTA administration of low doses of nicotine produced a CPA that was due to activation of $\alpha 4\beta 2$ sites that presumably increase GABA transmission in the VTA, whereas high doses produced CPP that was due to activation of $\alpha 7$ sites that facilitate glutamate transmission in this region. Laviolette and van der Kooy (2003a) have also emphasized the importance of dopamine in the aversive effects of nicotine based on their finding that blockade of mesolimbic dopamine reduces the aversive effects of nicotine. Thus, the VTA is a site where the positive and negative effects of nicotine are mediated via excitatory and inhibitory systems that regulate dopamine transmission.

It is hypothesized that enhanced nicotine reward in adolescents is due to greater increases in NAcc dopamine and fewer changes dopamine levels during withdrawal relative to adults (see diagram in Fig. 6). In adult rats, nicotine produces an increase in NAcc dopamine levels; however, dopamine transmission in this region is reduced during withdrawal from this drug (Carboni et al., 2000; Hildebrand et al., 1998; Rada et al., 2001; Rahman et al., 2004; Shoab et al., 2004). Furthermore, blockade of nAChRs in the VTA induces somatic signs of withdrawal and reduces dopamine output in the ipsilateral NAcc of nicotine-dependent adult rats (Hildebrand et al., 1999).

Few studies have compared nicotine-induced dopamine release in the NAcc of adolescent and adult rats. A recent report demonstrated that nicotine produced an increase in NAcc dopamine and the dopamine metabolite, 3,4-dihydroxyphenylacetic acid (DOPAC) levels that were higher in adolescent versus adult rats (Shearman et al., 2008). The most profound developmental difference in monoamines levels in the NAcc was a large increase in serotonin levels in adolescent versus adult rats, suggesting that serotonin systems also play an important role in mediating developmental differences to nicotine. Also, this report demonstrated that across several brain regions there were fewer changes in monoamines in adolescent versus adult rats, suggesting that changes in NAcc dopamine do not entirely explain developmental differences to nicotine. However, consistent with the pattern of developmental differences in NAcc dopamine levels, Azam et al. (2007) demonstrated that nicotine-stimulated ^3H dopamine release was enhanced in synaptosomes collected from the NAcc of adolescent

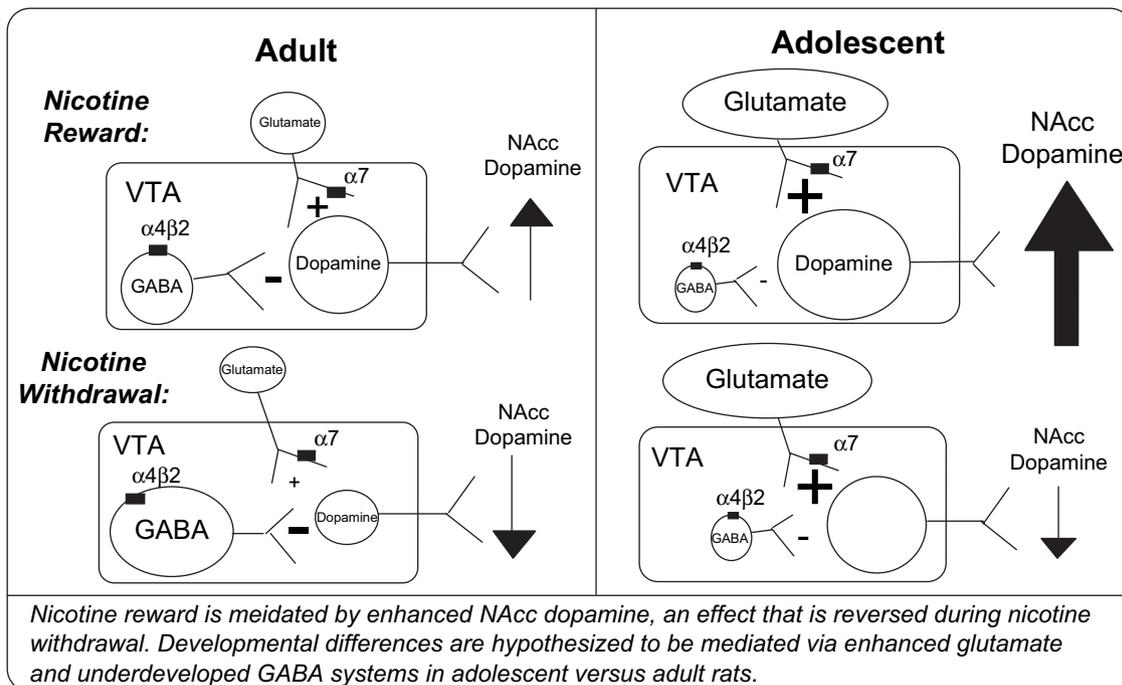
Hypothesized substrates mediating developmental differences to nicotine

Fig. 6. Hypothesized mechanisms mediating nicotine use during adolescence. The rewarding effects of nicotine are mediated via enhanced dopamine transmission in the mesolimbic pathway. The cell body region of this pathway is under inhibitory control via GABA and excitatory regulation via glutamate release in VTA that contains the cell bodies that release dopamine in the NAcc. During nicotine withdrawal, dopamine levels in the NAcc are decreased, an effect that is hypothesized to be related to enhanced GABA and reduced glutamate in the VTA. We hypothesize that adolescent rats will display higher increases in NAcc dopamine following nicotine and fewer changes in this measure during withdrawal. We also hypothesize that these developmental differences are related to overdeveloped glutamate and underdeveloped GABA systems that modulate dopamine cell bodies in the VTA that project to the NAcc.

relative to adult rats. This effect was larger in adolescent males that were in the younger (PND 30) versus later (PND 40) stages of adolescence. The latter report also demonstrated that this developmental difference to nicotine was not observed in female rats in the NAcc or across any age group in tissue collected from the dorsal striatum. These findings suggest that the ability of nicotine to increase NAcc dopamine is facilitated during the adolescent period of development, and this effect may be more pronounced in male versus female rats. This is consistent with unpublished behavioral studies in our laboratory showing that developmental differences to the rewarding effects of nicotine are more pronounced in adolescent male versus female rats (unpublished observations). It should be noted that another report found that nicotine produced an increase in NAcc dopamine levels that were higher in adult versus adolescent rats (Badanich and Kirstein, 2004). However, this report collapsed their data across male and female rats, they only reported values that were above basal levels, and they only used one dose of nicotine. Thus, these factors may have contributed to a lack of developmental differences in the latter report.

Much work has demonstrated that nicotine-dependent adult rats display a significant decrease in dopamine levels in the NAcc during nicotine withdrawal (Carboni et al., 2000; Hildebrand et al., 1998; Rada et al., 2001). To our knowledge, no one has compared developmental differences to the decreases in NAcc dopamine levels during withdrawal. However, recent unpublished observations in our laboratory demonstrate that adult rats display a 45% decrease in NAcc dopamine levels, whereas adolescent rats only display a 20% decrease in this measure. Collectively, these studies suggest that during adolescence the dopaminergic mechanisms mediating the nicotine reward are enhanced, whereas changes in this system during withdrawal are reduced relative to adult rats. However, more research is needed to provide a more thorough

assessment of the hypothesized neurochemical changes that mediate developmental differences to nicotine proposed in this review.

It is hypothesized that these developmental differences to nicotine are mediated via compensatory changes in excitatory glutamate and inhibitory GABA systems in the VTA that regulate dopamine transmission in the NAcc (see Fig. 6). Specifically, enhanced reward (increased dopamine) and reduced withdrawal (decreased dopamine) in adolescents may be related to overdeveloped glutamate and underdeveloped GABA systems that modulate dopamine cell bodies in the VTA that project to the NAcc.

3.2.1. Enhanced glutamatergic regulation of dopamine during adolescence

Glutamate is a ubiquitous excitatory amino acid in the brain and glutamate neurons predominate in cortical regions where the control of subcortical areas is regulated. It has been suggested that enhanced cortical glutamate regulation provides over stimulation of striatal dopamine pathways, and this may contribute to enhanced nicotine reward during adolescence (Spear, 2000). This is largely based on the finding that excitatory amino acid pathways undergo transient overshoots and overproduction of glutamate terminals during adolescence (de Graaf-Peters and Hadders-Algra, 2006; McDonald and Johnston, 1990). For example, excitatory amino acid pathways in the frontal cortex are overproduced in the early postnatal periods of rats (7–14 days) and humans (1–2 years; see Herlenius and Lagercrantz, 2004). Although pruning of excitatory projections occurs during adolescence, enhanced levels of glutamate receptors (NMDA) and enhanced generation of synapses support the hypothesis that adolescence reflects a period of enhanced glutamate cortical innervation (Dunah et al., 1996; Herlenius and Lagercrantz, 2004).

Glutamate acts on several different receptor subtypes, including metabotropic and fast-acting ionotropic sites. The NMDA receptor subtype dominates in the immature brain when synaptic transmission is weak and extremely plastic (Luján et al., 2005). In fact, the NR2B NMDA receptor subunit is highly expressed during early development, and is suggested to allow for enhanced activation of the channel and increased capacity of glutamate to strengthen synapses. The high expression of this receptor in combination with enhanced calcium influx during adolescence also produces enhanced sensitivity to excitotoxicity via excessive release of glutamate that leads to neural apoptosis in developing neurons. As an example, ethanol is an NMDA antagonist and excessive inhibition of these receptors causes apoptosis that has been suggested to play a role in fetal alcohol syndrome (see Olney et al., 2002). Furthermore, the ontogeny of enhanced glutamate receptor expression during early periods of development has been demonstrated to be consistent in human and rodent tissues (see Ritter et al., 2001).

The developmental differences in glutamate that modulate sensitivity to nicotine have not been widely studied in adolescent and adult rats. However, chronic nicotine produces an up-regulation of $\alpha 7$ receptors in adolescent but not adult rats (Slotkin et al., 2004). Furthermore, adolescent rats display higher basal levels of $\alpha 7$ receptors that may enhance nicotine-induced dopamine release (see Dwyer et al., 2008). Consistent with this suggestion, adolescent rats display a higher expression of $\alpha 7$ receptors in the VTA relative to adult rats (Azam et al., 2007). Another report demonstrated that in cortical slices, the ability of nicotine to enhance excitatory postsynaptic potentials (EPSPs) was higher in tissue collected from juvenile (PND 8–16) versus adult rats (Aramakis and Metherate, 1998). Interestingly, this report also demonstrated that nicotine enhanced NMDA receptor-mediated EPSPs via $\alpha 7$ receptors in an age-dependent manner, since this effect was blocked by $\alpha 7$ receptor antagonists in young but not older rats. Although this report was conducted in cortical tissue, it supports our hypothesis that the ability of $\alpha 7$ receptors to modulate glutamate transmission is enhanced during adolescence. Thus, during adolescence enhanced dopamine release produced by nicotine as well as fewer decreases in dopamine during withdrawal may be due to enhanced excitatory glutamate transmission via up-regulation of $\alpha 7$ receptors in the VTA.

3.2.2. Reduced GABAergic regulation of dopamine during adolescence

Before taking on its role as an inhibitory neurotransmitter GABA serves as a trophic factor during early development of neural organization (see Kellogg, 1998). Although GABA is considered to be the main inhibitory transmitter in the mature brain, it is the principal inhibitory neurotransmitter in adults, paradoxically, it is an excitatory neurotransmitter in early postnatal life (Ben-Ari et al., 1997; Cherubini et al., 1991; Luján et al., 2005; Rivera et al., 1999). The paradoxical effect of GABA is due to an inverted chloride gradient (Herlenius and Lagercrantz, 2004). In young nerve cells, the chloride concentration is high such that when GABA opens a chloride channel, an excitatory depolarization occurs. However, during maturation, the chloride concentration decreases and this results in an opposite effect of GABA which transports chloride ions out of the cell and produces an inhibitory hyperpolarization of the cell. In this way, GABA switches from being an excitatory to inhibitory neurotransmitter in the developing brain. Electrophysiological studies have demonstrated that during adolescence, inhibitory postsynaptic potentials (IPSPs) in GABA neurons are slower, less frequent, and weaker in response to GABA agonists relative to neurons from more mature animals (see Cohen et al., 2000). The latter report demonstrated that by PND 21 GABA agonist-induced IPSPs are still weak, reflecting continued immaturity in synaptic structure and function persisting through adolescence. Also, GABA-mediated inhibition by postsynaptic

GABA_B receptors is not functional early in life and GABA currents in neonatal rat neurons are insensitive to benzodiazepine activation of GABA_A receptors, suggesting that there is immaturity in synaptic function during early development (Cherubini et al., 1991). The differential role of GABA neurotransmission across development has been verified across a number of mammalian species in the central nervous system (see Simeone et al., 2003). The excitatory role of GABA switches to inhibition around 1 week after birth in the hippocampus and about PND 7–14 in the frontal cortex of rat brain (Miles, 1999; Rivera et al., 2005). Although this precedes the time frame of adolescence as described here, we suggest that GABA may not fully inhibit VTA dopamine neurons during adolescence and this might explain enhanced rewarding effects of nicotine during adolescence. Consistent with this suggestion, the rewarding effects of ethanol are enhanced during adolescence and the ability of ethanol to enhance IPSPs in GABA neurons is reduced in adolescent relative to adult rats (Li et al., 2006). Thus, reduced inhibition of the mesolimbic pathway might explain increased NAcc dopamine following nicotine and a lack of (or fewer) changes in NAcc dopamine during nicotine withdrawal in adolescent versus adult rats.

3.2.3. Are the hypothesized mechanisms sufficient to understand developmental differences to nicotine?

The proposed framework is intended to provide a testable hypothesis regarding developmental differences to the behavioral effects of nicotine. This mechanism involves dopamine transmission in the mesolimbic pathway and its regulation via excitatory and inhibitory mechanism in the cell body region of this pathway. This hypothesis is based on existing work which emphasizes the importance of the mesolimbic pathway and it builds upon this literature by suggesting that there are important regulatory mechanisms in the VTA that may mediate developmental differences to nicotine. Although this framework focuses on one particular neural system, it is also recognized that the proposed mechanisms are not likely sufficient to explain the complex developmental differences to the behavioral effects of nicotine. For example, emerging data suggest that stress systems play an important role in mediating nicotine dependence (see Koob and Kreek, 2007). We reviewed several studies showing that adolescent animals display lower anxiety-like responses to nicotine and withdrawal from this drug, suggesting that differences to stress may modulate developmental differences to nicotine. Also, opiate antagonists precipitate withdrawal (Biala et al., 2005; Malin et al., 1993) and produce CPA in nicotine-dependent adult rats (Ise et al., 2000; Watkins et al., 2000). Recent unpublished observations from our laboratory have demonstrated that kappa-opioid receptor agonists elicit nicotine withdrawal in adult but not adolescent animals. These findings suggest that developmental differences to kappa-opioid receptors may also contribute to developmental differences to nicotine. Lastly, recent work has demonstrated lasting effects of adolescent nicotine exposure on serotonergic systems (Slotkin et al., 2007). Furthermore, Shearman et al. (2008) also showed that the most profound developmental difference produced by nicotine administration was a robust increase in serotonin in the NAcc of adolescent versus adult rats. These studies suggest that there are likely other neural systems (outside of the mesolimbic dopamine pathway) that also play an important role in mediating developmental differences to nicotine.

4. A psychobiological framework of the substrates that mediate nicotine use during adolescence

4.1. Opponent process theory of addiction

Organisms are equipped with homeostatic mechanisms that regulate internal parameters within limits that promote survival.

This internal stability is maintained by negative feedback systems involving opponent processes that correct for deviations outside of ordinary parameters. Following chronic drug use, Koob and Le Moal (2001) suggest that the counteradaptive opponent processes that limit reward function fail to return to a normal homeostatic range. This forms an allostatic state that represents a chronic deviation of reward set point that causes an enhanced state of vulnerability that results in a loss of control over drug use.

The opponent process theory of addiction also describes addiction as a cycle that involves changes in neural systems that modulate positive rewarding effects (a-process) and negative states (b-process) produced by drug use. With chronic drug use, the organism has to vary all of the parameters to maintain stability in order to defend the altered set point that confers vulnerability to addiction. This allostatic state reflects a dysregulation in the mechanisms that mediate the relationship between positive drug states (a-process) that decrease over time, and negative states (b-process) that become larger over time and mask the initial hedonic effects of the drug (see Fig. 7). These counteradaptive changes are hypothesized to be a driving force that emerges with the development of drug dependence in adults. Thus, this theory relies heavily on the emergence of negative affective states that grow with chronic drug use and lead to relapse during abstinence. It is unclear whether the mechanisms that confer drug dependence are similar across various stages of development.

The opponent process theory of addiction has provided a useful framework for studying individual differences that mediate whether or not an individual is able to maintain periodic drug use in the absence of drug dependence. It is suggested that adolescence represents a window of development whereby the opponent processes mediating drug addiction differ from those described for dependence in adult addicts. Below the opponent process theory of addiction is extended to include our hypotheses regarding nicotine use in adolescents.

4.2. Opponent processes mediating the short-term effects of nicotine during adolescence

During initial drug use, it is hypothesized that greater positive (a-process) and reduced negative (b-process) effects of nicotine

contribute to enhanced tobacco use during adolescence (see top panel in Fig. 7). A lack of counteradaptive opponent processes (b-process) that do not balance the activational process (a-process) implies that tobacco use is largely driven by the ability of nicotine to produce a strong a-process during adolescence. Thus, an adolescent that experiences a strong positive hedonic mood state retains the a-process in the absence of b-processes that oppose positive effects and limit drug use.

It is presently unclear whether the positive rewarding effects of nicotine change with repeated exposure during adolescence. However, adolescent male rats that initiate nicotine IVSA during adolescence display a decrease in nicotine intake as they approach adulthood (Levin et al., 2007). Interestingly, the latter report also noted that female adolescent rats maintain high levels of nicotine intake as they progress into adulthood. Future studies are needed to determine whether the discrepancy between male and female rats is due to sex-dependent differences in drug tolerance or in the neural mechanisms that mediate drug intake over the course of development. Despite this, we denote the change in the a-process during adolescence as a gradual decrease over time based on the decrease in the rewarding effects of drugs of abuse that is generally observed in adult drug users.

4.3. Opponent processes mediating nicotine withdrawal during adolescence

With continued nicotine use during adolescence, it is hypothesized that the strong positive mood states are unopposed by negative effects (see bottom panel in Fig. 7). Since the a-process remains largely unopposed, the counteradaptive opponent b-processes do not develop and are not expressed during withdrawal. It is important to note; however, that with sufficient nicotine exposure, adolescents may develop counteradaptive processes that are expressed during withdrawal. This is denoted as an eventual drop in the b-process following repeated drug exposure during adolescence. This is based on clinical studies that document withdrawal signs in abstinent adolescent smokers (DiFranza et al., 2000; Eisenberg and Balster, 2000). Also, adolescent rats that receive extended exposure to nicotine (14 days via pump) will display

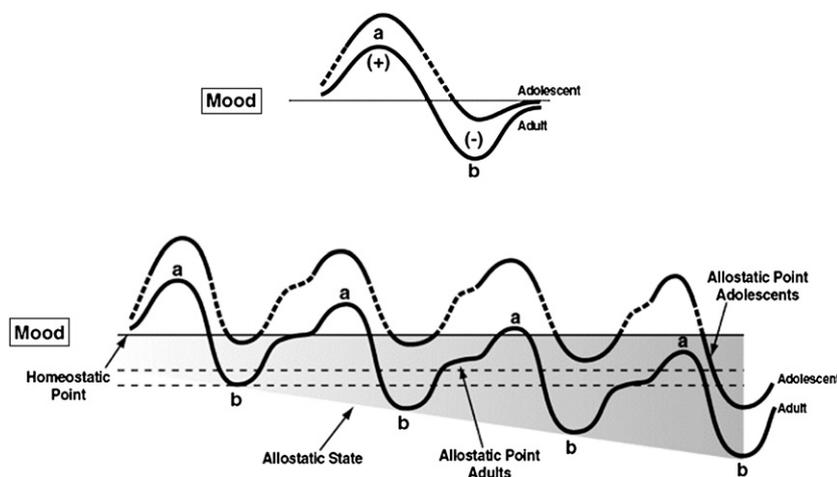


Fig. 7. Hypothesized role of opponent processes in mediating adolescent nicotine use. The diagram has superimposed our hypothesis regarding adolescent nicotine use (dotted line) onto Koob and Le Moal's opponent process theory in adults (solid line). The top panel depicts the initial drug experience that involves both positive (a-process) and negative (b-process) states. The bottom panel is meant to depict changes in the relationship between these states that confer the transition to dependence. The opponent process theory posits that there are counteradaptive opponent processes (b-process) that balance the activational process (a-process). In a drug dependent adult, the b-process does not balance the a-process that never returns to the original homeostatic level. This creates a greater allostatic state in brain reward systems. This theory also posits that an adult that experiences a positive mood state from a drug of abuse with sufficient time between re-administering the drug is hypothesized to retain a normal a-process. In other words, an appropriate counteradaptive opponent b-process that balances the activational process a-process does not lead to the allostatic state. It is hypothesized that during adolescence, a strong a-process is unbalanced by a relatively reduced b-process. With continued exposure to nicotine the b-processes eventually can emerge during adolescence, albeit still lower than the withdrawal states observed in adults. Since it is unclear whether the relationship between a- and b-processes is established during adolescence, we denote the connection between these processes with a dotted line. This diagram was modified from Koob and Le Moal (2001).

withdrawal signs, albeit still lower than their adult counterparts (O'Dell et al., 2006).

4.4. Opponent processes mediating the long-term effects of adolescent nicotine exposure

Data from our laboratory suggest that adolescent nicotine exposure reduces the aversive effects of high doses later in adult development (see Fig. 5). Thus, it is suggested that (similar to the effects produced during adolescence), an adult that was pre-exposed to nicotine during adolescence experiences enhanced positive effects of nicotine following initial drug use that are unopposed by negative effects that might limit nicotine intake (see top panel of Fig. 8).

It is hypothesized that adolescent nicotine exposure produces a strengthening of the relationship between the a- and b-processes as the organism develops into adulthood. The strength of this relationship is suggested to lead to stronger opponent b-processes that drive drug dependence. This is denoted in the earlier emergence of dependence in pre-exposed adults relative to naïve adults (see bottom panel of Fig. 8). In short, it is suggested that dysregulation mediating drug dependence in naïve adults is exacerbated in an adult that was exposed to nicotine during adolescence. To our knowledge, no one has examined the long-term effects of adolescent nicotine exposure on withdrawal in adult rats. However, it is possible that stress associated with nicotine withdrawal may be enhanced in adult rats that were pre-exposed to nicotine during adolescence. This is supported by the finding that adolescent nicotine exposure produced an increase in anxiety-like behavior in the open-field test that persisted beyond acute nicotine withdrawal (Slawecki et al., 2003). Although this study does provide support for this hypothesis, future studies are needed to fully examine the long-term effects of adolescent pre-exposure on nicotine withdrawal.

4.5. Opponent process theory with drugs of abuse other than nicotine

There is evidence from other drugs of abuse to support the hypothesis that rewarding effects are enhanced and aversive effects

are reduced during the adolescent period of development. For example, it has been suggested that adolescent rats appear to be protected from the aversive effects of amphetamine and more vulnerable to the rewarding effects of this drug relative to adult rats (Laviola et al., 1999). Consistent with this finding, adolescent rats display 2–3 times higher levels of ethanol intake relative to adult rats (Brunell and Spear, 2005). Also, young animals are less sensitive to the acute intoxicating, sedative, and dysphoric effects of high doses of ethanol that adult rats find aversive (Molina et al., 2007; Silveri and Spear, 1998; York and Chan, 1993). Lastly, previous work has demonstrated that adolescent nicotine exposure enhances opiate consumption and stress responsiveness later in adult development (Klein, 2001), suggesting that adolescent nicotine exposure also enhances the rewarding effects of other drugs of abuse later in adulthood.

4.6. Neural substrates mediating nicotine use during adolescence

Koob and Le Moal (2001) postulate that the allostatic state is fueled by a dysregulation in the brain circuits that mediate drug reward. Nicotine produces an increase in dopamine in the NAcc that is reversed during withdrawal from this drug. It is suggested that these changes in dopamine are mediated via counteradaptive processes in excitatory a-processes that map onto glutamate systems and inhibitory b-processes that map onto GABAergic systems in the VTA that regulate dopamine release in the NAcc. Specifically, enhanced reward (increased dopamine) and reduced withdrawal (decreased dopamine) in the NAcc of adolescents is due to overdeveloped glutamate and underdeveloped GABA systems that modulate dopamine cell bodies in the VTA that project to the NAcc.

There is evidence to support the convergence of a-processes with glutamatergic functioning. First, pre-clinical studies suggest that the rewarding effects of nicotine are mediated in large part via enhanced glutamate release, an effect that is decreased during nicotine withdrawal (see Markou, 2007). The decrease in the strength of the a-process is believed to reflect compensatory changes in glutamate transmission over time. A withdrawal mechanism involving decreased glutamate in the VTA is supported

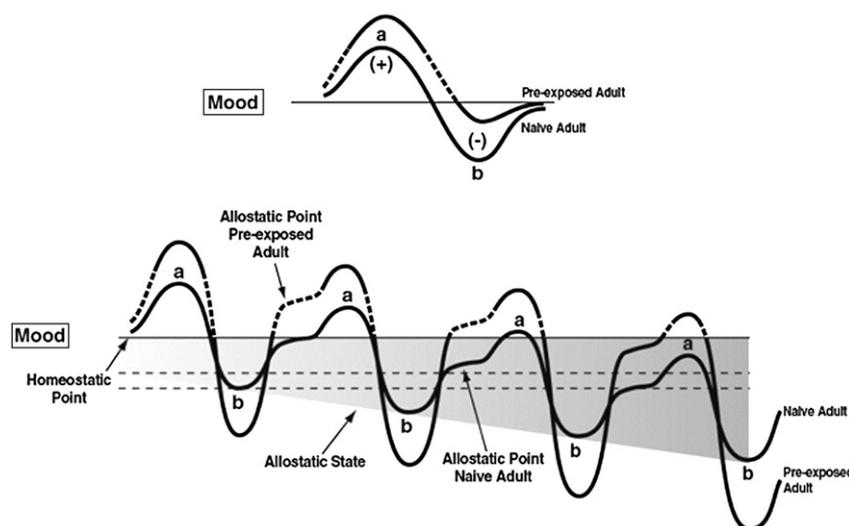


Fig. 8. Hypothesized role of opponent processes in mediating long-term effects produced by adolescent nicotine exposure. The diagram has superimposed our hypothesis regarding adolescent nicotine exposure (dotted line) onto Koob and Le Moal's opponent process theory in naïve adults (solid line). It is hypothesized that an adolescent that continues to use tobacco into adulthood sets into motion a pattern in the mechanisms that establish the relationship between the activational a-processes and opponent b-processes that become stronger with repeated nicotine exposure. Thus, an adult that was exposed to nicotine as an adolescent may be more vulnerable to nicotine dependence compared to a naïve adult who has not begun to establish the relationship between these processes. This is denoted as an earlier onset of allostatic states in adults that were pre-exposed to nicotine relative to naïve adults. The fact that the mechanisms that confer dependence in adulthood may be separate relative to adults that were pre-exposed to nicotine during adolescence is denoted by a dotted line between the a- and b-processes of pre-exposed adults. This diagram was modified from Koob and Le Moal (2001).

by the finding that blockade of glutamate receptors in the VTA elicits morphine withdrawal (Wang et al., 2004). Also, VTA glutamate levels are reduced during morphine withdrawal (Manzoni and Williams, 1999). Lastly, adolescent nicotine exposure produces a long-term up-regulation of $\alpha 7$ receptors on glutamate terminals (Barik and Wonnacott, 2006). Thus, during withdrawal decreased excitatory input from the VTA would be expected to contribute to the decreases in NAcc dopamine that are observed in adult rats experiencing withdrawal. However, adolescent rats that display enhanced glutamatergic regulation of VTA dopamine transmission would be expected to display fewer changes in NAcc dopamine levels during withdrawal.

It is also suggested that excitatory a-processes are opposed by inhibitory GABAergic b-processes. Specifically, GABAergic mechanisms that inhibit dopamine release might increase over time such that compensatory changes in this system would be evident as an increase in VTA GABA in adult rats experiencing nicotine withdrawal. However, adolescent rats that display underdeveloped GABA systems are hypothesized to display less inhibitory regulation of VTA dopamine transmission and as a result fewer changes in NAcc dopamine levels during withdrawal. One report using *in vivo* microdialysis procedures found that withdrawal from chronic amphetamine produced an increase in the inhibitory GABAergic regulation of dopamine levels in the VTA (Giorgetti et al., 2002). This report supports the hypothesis that GABA transmission is enhanced during withdrawal from stimulant drugs, such as amphetamine. Future studies are needed to fully understand how inhibitory processes play a role in nicotine use and withdrawal across the various stages of development.

5. Clinical research

5.1. Clinical reports that parallel our hypothesis

To our knowledge the initial subjective effects of nicotine have not been directly compared in adolescent and adult tobacco users. However, adult smokers that initiated smoking during adolescence report more pleasant effects and fewer unpleasant effects (dizziness and sickness) following their first smoking episode, whereas adults that initiated smoking as adults report that they experienced more aversive effects following their first smoking episode (see Eissenberg and Balster, 2000; Pomerleau et al., 1993). These studies imply that the strong initial positive subjective effects of nicotine may contribute to adolescent tobacco use. Clinical reports have also shown that heightened sensitivity to the initial effects of nicotine (nausea, dizziness, and lightheadedness) is an important predictor of smoking (DiFranza et al., 2000). Based on these findings it may be suggested that adolescents are more susceptible to continued tobacco use because they are more sensitive to the effects of nicotine (albeit positive and/or negative) relative to their adult counterparts.

To our knowledge, the intensity of nicotine withdrawal symptoms has not been directly compared in adult and adolescent smokers. However, it has been suggested that adolescents might have a higher propensity to develop nicotine dependence relative to adults because young smokers show signs of dependence despite low cigarette use (Kassel et al., 2007; O'Loughlin et al., 2003). Adolescent smokers also display acute impairments in memory after smoking cessation that are more severe with earlier age of smoking onset (Jacobsen et al., 2005). Taken together, these studies challenge the notion that nicotine dependence takes years to develop. However, a recent study directly comparing adolescent smokers to non-smokers found that young smokers only exhibit mild symptoms during withdrawal (anger and craving) that do not appear to be associated with self-reports of dependence or biological markers of cigarette use (Smith et al., 2008a,b). Another

report from this laboratory found that withdrawal symptoms on the quit day were not related to relapse behavior in adolescent smokers (Smith et al., 2008a,b). These studies suggest that abstinence from chronic tobacco use only produces mild withdrawal symptoms that are not related to continued use or relapse behavior during adolescence.

There are likely factors other than nicotine reward and withdrawal that also contribute to enhanced tobacco use during adolescence. These might include social and environmental factors, since adolescent humans engage more readily in risky choices and they display a heightened responsiveness to incentives and emotional contexts—all of which are believed to contribute to adolescent drug use (Laviola et al., 1999; Silveri et al., 2004). Also, adolescents may initiate smoking on the basis of biological factors including self-medication of depression and/or attention deficit hyperactivity disorder. Brain imaging studies examining biological factors have demonstrated adolescent humans display reduced prefrontal cortical control of impulse behaviors (Casey et al., 2005; Giedd, 2004) and enhanced subcortical activation of the NAcc and amygdala, which are regions associated with evaluation of incentives and affective information (Ernst et al., 2005; Galvan et al., 2006). Based on these studies, Casey et al. (2008) proposed a neurobiological model whereby heightened responsiveness to rewards in the NAcc and amygdala in combination with immaturity in behavioral control areas of the prefrontal cortex bias adolescents to seek immediate gains and engage in risky behaviors such as drug use. Their model also proposes that the NAcc matures faster than the prefrontal cortex such that a more rapid maturation of the NAcc and an exaggerated response to reward presentations likely contributes to enhanced drug use during adolescence. Their hypothesis is based on animal studies showing that throughout adolescence there is more prolonged pruning of axons and synapses in the prefrontal cortex versus the NAcc (Andersen et al., 2000; Teicher et al., 1995). Furthermore, a more developed NAcc during adolescence is consistent with the finding that dopamine receptor expression is highest in this brain region during adolescence (Tarazi et al., 1998). This is also consistent with the current hypothesis suggesting that enhanced dopamine transmission in the NAcc likely contributes to enhanced nicotine use during the adolescent period of development.

5.2. Concluding statements regarding the clinical implications of our hypothesis

There are several clinical implications of our hypothesis regarding the short-term effects of nicotine. First, nicotine produces strong rewarding effects that drive tobacco use during adolescence. Also, it is likely that tobacco use enhances the positive effects of other substances, such as alcohol that is commonly abused in adolescents (Schmid et al., 2007). Enhanced positive effects of nicotine may also facilitate affective states produced by social interaction and risk-taking behavior that elicit positive affective states in adolescents. Thus, the most effective avenue for reducing smoking behavior may involve avoidance strategies that prevent tobacco use during adolescence. Lastly, the short-term positive effects of nicotine are unopposed by negative effects that limit nicotine intake. As a result of reduced punishing effects with initial use, adolescents may be more likely to experiment with tobacco products in the future.

There are also several clinical implications of our hypothesis regarding nicotine withdrawal. First, the current diagnostic criteria for nicotine dependence are steeped in terms that are used to diagnose negative affective states during nicotine withdrawal in adults that are long-term smokers. However, these diagnostic criteria may need to be reconsidered for adolescent tobacco users that experience less nicotine withdrawal compared to adults.

Second, adolescents may be less likely to consider quitting because they are less aware of their dependence upon nicotine due to a lack of withdrawal symptoms. However, it should be noted that adolescents may also be less likely to consider quitting if they experience high levels of withdrawal that maintain continued use. Lastly, the current treatment strategies for smoking cessation focus on alleviating withdrawal via pharmacological approaches or nicotine replacement therapies. However, a lack of withdrawal during adolescence implies that these treatments may be less effective in adolescent nicotine users. Consistent with this suggestion, clinical studies in adolescents have found that long-term abstinence rates are not closely associated with nicotine replacement therapies (Hanson et al., 2003; Hurt et al., 2000; Moolchan et al., 2005). Furthermore, there is some evidence to suggest that the nicotine patch does not prevent the expression of nicotine withdrawal symptoms in adolescent smokers (Killen et al., 2001; however, Smith et al., 1996).

With regard to the long-term consequences of nicotine, it is also suggested that adolescent nicotine exposure promotes the dysregulation of allostatic processes that confer drug dependence. This includes enhancing the rewarding effects of nicotine and possibly the aversive effects associated with nicotine withdrawal. Thus, putting a nicotine patch on an adolescent may be harmful because it might facilitate the development of dependence in young tobacco users who do not normally experience nicotine withdrawal. This concern has been previously raised in a review of pre-clinical studies emphasizing the long-term neurotoxic consequences of adolescent nicotine exposure (Slotkin, 2008).

6. Future directions

The hypotheses presented in this review are meant to provide a working framework to study the psychobiological substrates mediating adolescent nicotine use. Although our neurochemical hypothesis focused on adolescents and adults, it may also present an avenue for understanding the mechanisms that confer enhanced vulnerability to nicotine in an adult that was exposed to nicotine during adolescence. Future studies might also consider the role of sex differences, environmental conditions, and prior drug history in developmental differences to nicotine use.

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