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Research report

Nicotine administration in adolescence reprograms the subsequent response to nicotine treatment and withdrawal in adulthood: Sex-selective effects on cerebrocortical serotonergic function

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ABSTRACT

Nicotine exposure in adolescence produces lasting changes in subsequent behavioral responses to addictive agents. We gave nicotine to adolescent rats (postnatal days PN30–47), simulating plasma levels in smokers, and then examined the subsequent effects of nicotine given again in adulthood (PN90–107), focusing on cerebrocortical serotonin levels and utilization (turnover) as an index of presynaptic activity of circuits involved in emotional state. Our evaluations encompassed responses during the period of adult nicotine treatment (PN105) and withdrawal (PN110, PN120, PN130), as well as long-term changes (PN180). In males, prior exposure to nicotine in adolescence greatly augmented the increase in serotonin turnover evoked by nicotine given in adulthood, an interaction that was further exacerbated during withdrawal. The effect was sufficiently large that it led to significant depletion of serotonin stores, an effect that was not seen with nicotine given alone in either adolescence or adulthood. In females, adolescent nicotine exposure blunted or delayed the spike in serotonin turnover evoked by withdrawal from adult nicotine treatment, a totally different effect from the interaction seen in males. Combined with earlier work showing persistent dysregulation of serotonin receptor expression and receptor coupling, the present results indicate that adolescent nicotine exposure reprograms future responses of 5HT systems to nicotine, changes that may contribute to life-long vulnerability to relapse and re-addiction.

1. Introduction

The standard view of developmental neurotoxicity is that the immature brain is more susceptible to damage by neuroactive drugs and chemicals because it is in the process of forming structures and circuits (Barone et al., 2000; Cuomo, 1987; Grandjean and Landrigan, 2006). Yet, at the same time, the heightened plasticity of the developing brain allows it to offset damage more readily than in the mature brain, in part because of the ability to generate new neurons. This explains why, in some circumstances, normal function can be maintained even after extreme damage early in life (Lorber, 1981; Priestley and Lorber, 1981). Likewise, it clarifies why adverse neurodevelopmental effects of maternal cigarette smoking tend to be greater than those from cocaine; cocaine is used in discrete episodes, allowing for recovery and neuroregeneration in between exposures, whereas fetal nicotine exposure from cigarette use is sustained throughout pregnancy (Coles, 1993; Slotkin, 1998). Neural plasticity in the immature brain is highly influenced by patterns of synaptic activity because neurotransmitters act as morphogens, controlling neuronal cell replication, differentiation and circuit formation (Dreyfus, 1998; Lauder, 1985; Whitaker-Azmitia, 1991). For normal development to proceed, synaptic stimulation has to follow discrete spatial and temporal patterns, with a specified level of signal intensity (Slotkin, 2004, 2008). Yet, it is this aspect that leaves the brain vulnerable to neuroactive drugs and chemicals that disrupt brain development, not by causing outright damage, but rather by disrupting the spatiotemporal organization of neurotransmitter signals, leading to abnormalities at the functional, rather than the gross structural level, essentially "plasticity gone awry."

It is now evident that the development and programming of synaptic circuits continues into adolescence, well past the completion of gross brain structure (Rakic et al., 1994; Slotkin, 2002, 2008; Spear, 2000; Walker et al., 1999). This is especially important in light of the fact that adolescence is the likely point for initiation of cigarette smoking. Studies over the past few years show that the adolescent brain is much more responsive to nicotine than the adult with regard to both synaptic and behavioral responses (Adriani et al., 2003, 2004; Faraday et al., 2001, 2003; Klein, 2001; Levin, 1999; Slawecki and Ehlers, 2002; Slawecki et al., 2003; Slotkin,

Abbreviations: 5HIAA, 5-hydroxyindoleacetic acid; 5HT, 5-hydroxytryptamine serotonin; ANOVA, analysis of variance; PN, postnatal day.

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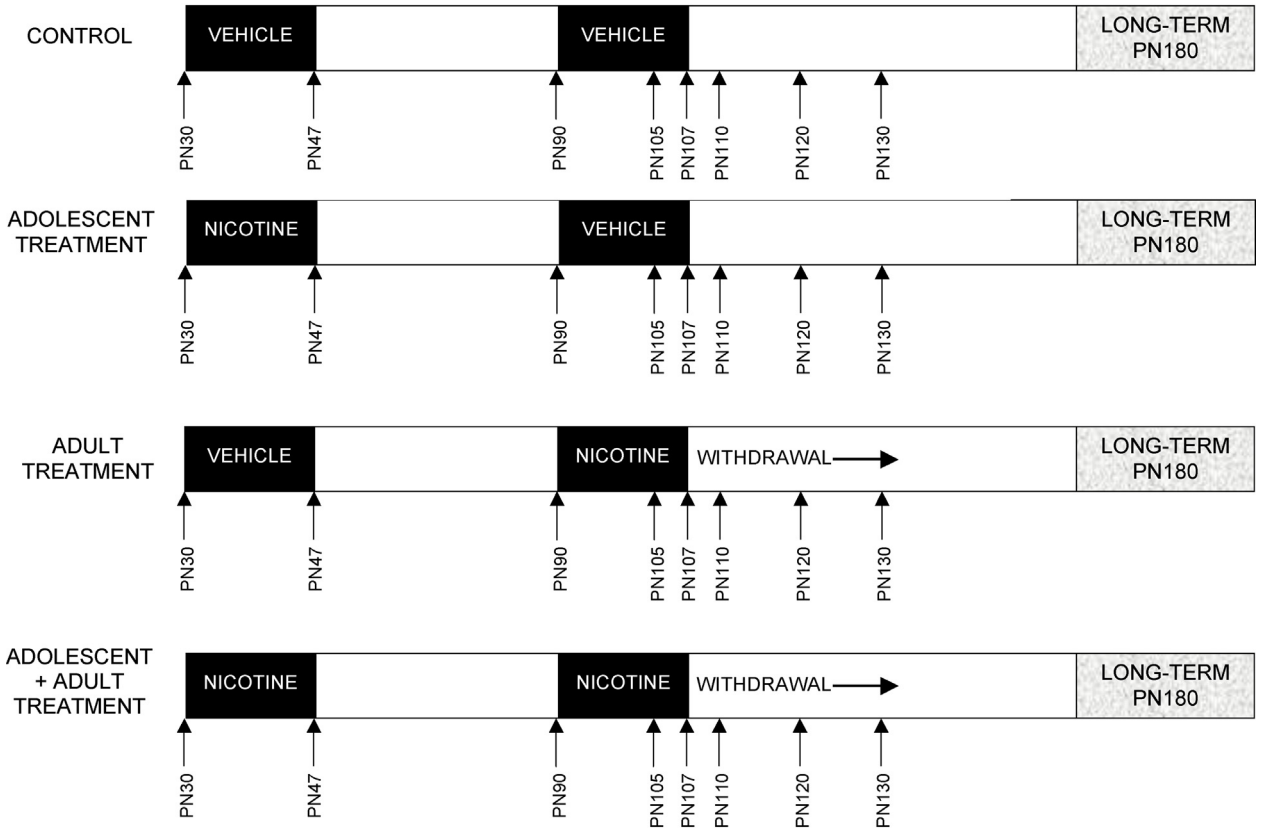

Fig. 1. Schematic of nicotine treatment regimens and sampling times.

2002, 2008; Trauth et al., 2000b). More importantly, in smokers, adolescent nicotine exposure promotes future addiction liability and reduces the likelihood of being able to quit (Chen and Millar, 1998). In fact, nicotine exposure in adolescence affects the subsequent adult responses to a wide variety of other addictive drugs (Adriani et al., 2006; Bracken et al., 2011; Hutchison and Riley, 2008; Imad Damaj et al., 2009; Kelley and Middaugh, 1999; Klein, 2001; Marco et al., 2006; Rinker et al., 2011; Santos et al., 2009). In our earlier work, we explored some of the mechanisms underlying this reprogramming and found major contributions from effects on cerebrocortical serotonergic (5HT) pathways involved in emotional behaviors (Slotkin, 2002; Slotkin et al., 2006, 2007a; Slotkin and Seidler, 2007, 2009; Xu et al., 2001, 2002). This is particularly important in light of the close connection between tobacco addiction and depressive disorders: adolescent tobacco use is highly correlated with depression (Goodman and Capitman, 2000; Patten et al., 2000; Wu and Anthony, 1999), and depressive symptoms exacerbated by nicotine withdrawal contribute to the failure of therapies for smoking cessation (Colby et al., 2000; Salin-Pascual et al., 1995; Tsoh et al., 2000), especially in adolescent smokers (Colby et al., 2000; Hurt et al., 2000). Our findings identified essentially permanent changes in the expression of 5HT receptors associated with depression, as well as the 5HT transporter, which is the major target for antidepressant therapy (Slotkin et al., 2006, 2007a; Slotkin and Seidler, 2009; Xu et al., 2001, 2002); further, we showed that adolescent nicotine exposure altered the responses of these synaptic proteins to nicotine given subsequently in adulthood (Slotkin and Seidler, 2009).

The changes in receptor or transporter expression evoked by adolescent nicotine treatment can represent primary reprogramming of synaptic function, or alternatively could be adaptive responses to underlying defects in presynaptic activity; for example, receptor upregulation could be compensatory for a reduction in presynaptic input, essentially restoring synaptic function to normal. In the current study, we resolved this issue by monitoring 5HT levels and utilization (turnover) so as to assess presynaptic activity. We contrasted the effects of adolescent nicotine treatment with those obtained for nicotine in adulthood, and then evaluated how adolescent exposure reprograms the response to subsequent adult nicotine treatment.

2. Materials and methods

2.1. Animals and nicotine treatments

All procedures utilized tissues that were archived from earlier studies and maintained frozen at −45° C, so that no additional animals were actually used for this study. Details of animal husbandry, institutional approvals, maternal and litter characteristics, and growth curves, have all been presented in earlier work from the original animal cohorts (Slotkin et al., 2008a, b; Slotkin and Seidler, 2009). Sprague-Dawley rats (Charles River Laboratories, Raleigh, NC) were housed individually and allowed free access to food and water. There were four treatment groups (shown schematically in Fig. 1): controls (adolescent vehicle + adult vehicle), adolescent nicotine treatment (adolescent nicotine + adult vehicle), adult nicotine administration (adolescent vehicle + adult nicotine), and those receiving the combined treatment (adolescent nicotine + adult nicotine). On postnatal day (PN) 30, each rat was quickly anesthetized with ether, a 2 cm × 2 cm area on the back was shaved, and an incision was made to permit subcutaneous insertion of a type 1002 Alzet osmotic minipump (Durect Corp., Cupertino, CA). Pumps were prepared with nicotine bitartrate (Sigma Chemical Co., St. Louis, MO) dissolved in bacteriostatic