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Review article

If nicotine is a developmental neurotoxicant in animal studies, dare we recommend nicotine replacement therapy in pregnant women and adolescents? ☆

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Abstract

Tobacco use in pregnancy is a leading cause of perinatal morbidity and contributes in major ways to attention deficit hyperactivity disorder, conduct disorders and learning disabilities that emerge in childhood and adolescence. Over the past two decades, animal models of prenatal nicotine exposure have demonstrated that nicotine is a neurobehavioral teratogen that disrupts brain development by preempting the natural, neurotrophic roles of acetylcholine. Through its actions on nicotinic cholinergic receptors, nicotine elicits abnormalities of neural cell proliferation and differentiation, promotes apoptosis and produces deficits in the number of neural cells and in synaptic function. The effects eventually compromise multiple neurotransmitter systems because of the widespread regulatory role of cholinergic neurotransmission. Importantly, the long-term alterations include effects on reward systems that reinforce the subsequent susceptibility to nicotine addiction in later life. These considerations strongly question the appropriateness of nicotine replacement therapy (NRT) for smoking cessation in pregnant women, especially as the pharmacokinetics of the transdermal patch may actually enhance fetal nicotine exposure. Further, because brain maturation continues into adolescence, the period when smoking typically commences, adolescence is also a vulnerable period in which nicotine can change the trajectory of neurodevelopment. There are also serious questions as to whether NRT is actually effective as an aid to smoking cessation in pregnant women and adolescents. This review considers the ramifications of the basic science findings of nicotine's effects on brain development for NRT in these populations.

Keywords: Adolescence; Brain development; Nicotine; Nicotine replacement therapy; Pregnancy; Smoking; Tobacco

Contents

Abbreviations: ETS, environmental tobacco smoke; nAChR, nicotinic acetylcholine receptor; NRT, nicotine replacement therapy.

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1. Introduction

The prevalence of neurodevelopmental disorders appears to be increasing and emerging evidence points to significant contributions of fetal exposures to neurotoxicant chemicals as a likely contributor [219,220]. Maternal cigarette smoking during pregnancy, which involves up to one-fourth of all pregnancies in the U.S. [11,43], represents one of the major factors influencing development. Although recent surveys indicate a drop in maternal smoking rates to 11–13% [28,34,159], these conclusions are based primarily on self-reported consumption which may grossly underestimate the incidence [175]; in addition, the higher rates of maternal smoking in many other countries, combined with aggressive marketing and increased consumption in Asia and Africa, ensures that the impact of smoking during pregnancy is increasing worldwide [34,85,243]. Superimposed on active maternal smoking, fetal exposures occur via environmental tobacco smoke (ETS), which involves approximately 35% of all pregnancies [93] and contributes significantly to adverse outcomes [7,48,64,157,163,195]. The cost of tobacco-related developmental damage includes immediate perinatal events, such as spontaneous abortions, intrauterine growth retardation and perinatal deaths, and Sudden Infant Death Syndrome, but the consequences extend much further, encompassing subsequent learning disabilities, cognitive dysfunction, behavioral problems, attention deficit hyperactivity disorder, psychiatric disorders, conduct disorders, criminal behaviors and school and career failure [18,25,40,42,43,49,78,97,129–131,152,162,167,238,239].

It is obvious that a successful approach to smoking cessation for pregnant women would have a major impact on public health. Prominent among recent proposals is the expansion of the use of nicotine replacement therapy (NRT) to pregnant women and for children as young as 12 years old, in the belief that the current warnings and restrictions on these products discourage stopping smoking [6,19] and that "clean nicotine" [65] provides a safe and effective way to achieve cessation in this population. In contrast, the U.S. Surgeon General's Report on Women and Smoking [233] expressed concerns about the safety of NRT products in pregnancy, reinforcing their assignment to Pregnancy Categories C for nicotine gum ("risk cannot be ruled out") and D ("positive evidence of risk") for transdermal patches; a recent review detailed many of the reservations about both the safety and efficacy of NRT in pregnancy and in achieving smoking cessation in children and adolescents [59]. Thus, this review will focus on what is known about the developmental neurotoxicity of nicotine per se, covering exposures at stages ranging from the fetus to the adolescent, and to relate that information to the potential use or misuse of NRT in these populations. This review will draw upon information from a series of previous periodic analyses of the field that have appeared over the past two decades [99,189–191,193–195], but in addition to presenting that information, we will also draw on newer studies that detail the relationship of fetal nicotine exposure to subsequent addiction liability in adolescence and on the unique attributes of the adolescent brain that influence the response and lasting effects of nicotine.

2. Animal models of nicotine exposure

Designing an appropriate animal model for prenatal nicotine exposure is not a straightforward proposition, as there are considerations of appropriate dose, route and frequency of administration, achieving and maintaining appropriate maternal plasma nicotine levels, pharmacologic effects in the mother and fetus as well as potential withdrawal problems [99,190,191,194,195]. In particular, rodents metabolize nicotine much more rapidly than humans or other primates, so that much lower plasma levels are achieved at doses comparable to those corresponding to nicotine intake in smokers or NRT users. A possible choice is to increase the dose of nicotine but if this is delivered by injections, each bolus of drug produces acute episodes of hypoxia and ischemia, secondary effects that most certainly produce adverse effects on brain development and behavior [112,113,133,197,198,199]. This is hardly an appropriate way in which to model the effects of nicotine, especially as the transdermal nicotine patch is concerned, where continuous delivery achieves a steady-state plasma concentration; indeed, because of the longer half-life of nicotine in humans, smokers also tend to maintain a fairly constant plasma level rather than displaying extinction of nicotine levels in between cigarettes [20]. Beginning in the 1980s, we and other researchers developed models utilizing implantable osmotic minipumps to deliver nicotine by continuous infusion, a technique that avoids the peak plasma levels and resultant hypoxic episodes, as well as preventing withdrawal that would otherwise occur from the rapid disappearance of nicotine in between doses [106,125,135–137,190,199,200]. This delivers a fixed dose of drug simulating the steady-state plasma levels seen in smokers or users of transdermal NRT patches [106,125]. The minipump model has since become the most common way of delivering nicotine to pregnant animals, with recent studies extending the technique to subhuman primates [166,210].

The next issue is how to deliver an appropriate dose that mimics as closely as possible the corresponding actions of nicotine in humans. Certainly, higher overall doses need to be delivered to rodents because of the shorter half-life of nicotine, but there are two other key elements: the matching of plasma concentrations (not total dose) to those seen in typical smokers, but perhaps more importantly, consideration of the pharmacodynamic differences between species [12,106]. In rats, a dose rate of 6mg/kg/day produces plasma levels in the range of 25–75ng/ml, with younger animals showing distinctly lower levels for the same daily dose [106,125,228]. Although the higher value is at the upper limit for nicotine levels in heavy smokers [20], this actually provides a close match in terms of the pharmacologic effects of nicotine in the developing brain. Maternal cigarette smoking produces fetal

nicotinic acetylcholine receptor (nAChR) upregulation of approximately 20–50% depending on the brain region [126], a value quite comparable (30% upregulation) to that in the rat model at a dose of 6mg/kg/day [199]. Indeed, this dose in the rat may even be conservative, given that nAChRs are approximately doubled in the maternal rat brain [203], whereas they are increased up to 4-fold in human smokers [158]. The same approach has been used in minipump nicotine delivery in other species: administration of 0.7 mg/kg/day of nicotine to monkeys produces maternal plasma nicotine levels of approximately 30ng/ml and nAChR upregulation of 20–100% depending upon brain region [209]; this daily dose, which is lower than in the rat but higher than in typical smokers or NRT users, nevertheless reproduces the appropriate pharmacologic conditions to mimic the effects of nicotine in human pregnancy. As a reinforcement for the validity of the model, a number of studies have been conducted at substantially lower daily doses in pregnant rats, doses that produce no discernible growth retardation or other secondary effects, but that nevertheless produce upregulation of nAChRs in the fetal brain comparable to those in human fetuses [136] and that still elicit permanent neurobehavioral deficits [53], just as seen at higher doses. The latter point cannot be emphasized enough: the presence or absence of growth retardation per se is *not* an adequate indicator of nicotine safety, as adverse effects on brain development occur at exposures below the threshold for growth impairment [99,189–191,193,195]. Indeed, this was recognized over 20 years ago [145]. Nevertheless, as we will discuss later, growth impairment is still the most commonly-used measure proposed for evaluation of the safety of NRT in pregnancy, and it is a distinctly inappropriate endpoint.

There are certainly other models of nicotine delivery in use for animal models of developmental neurotoxicity, although none of these is readily suitable for large cohort studies as required for detection of subtle neurochemical or behavioral effects. Rodents do not readily self-administer nicotine and the only successful models for self-administration require implantation of intravenous catheters and an extended period of behavioral training; even then, reliable self-administration typically involves a brief daily period of access to nicotine rather than continuous administration as required to maintain steady-state plasma levels as found in smokers [103,104,186] and the technique works primarily in adolescent rodents, who will self-administer far more than adults [102–104]. Some mouse strains will drink nicotine-laced solutions, but only when they are primed by a period of water restriction and with flavorants to obscure the taste of nicotine (so they are not really self-administering nicotine for "addictive" reasons) [8,9]; where this approach has been used, results have been generally comparable to those achieved with the minipump paradigm [156]. However, the drinking technique does not work as well in rats, who will reduce their water intake to the bare minimum rather than consume nicotine-laced solutions [125,132]. Nevertheless, the issue of infusion vs. divided doses of nicotine may actually be a moot point from the view of fetal actions. The placenta slows the entry and exit of nicotine from the fetal compartment so that fetal nicotine clearance is substantially slower than in the mother [60] and further, the amniotic fluid maintains a large nicotine reservoir, so that nicotine levels in the fetal compartment actually do not decay overnight when the mother is not smoking; the proof of that relationship is that, at delivery, nicotine and cotinine levels in amniotic fluid, meconium and fetal blood still reflect the maternal levels that were established during smoking, despite hours or days of discontinuing smoking by the mother [107,109,153]. Accordingly, there may be less of a pharmacokinetic and pharmacodynamic difference among smoking, NRT, and animal models utilizing minipump delivery than it might first appear. Nevertheless, as will be discussed in the final section of this review, if anything, continuous administration paradigms such as the transdermal nicotine patch, tend to maximize entry into the fetal compartment relative to episodic administration, an important consideration in comparing NRT strategies.

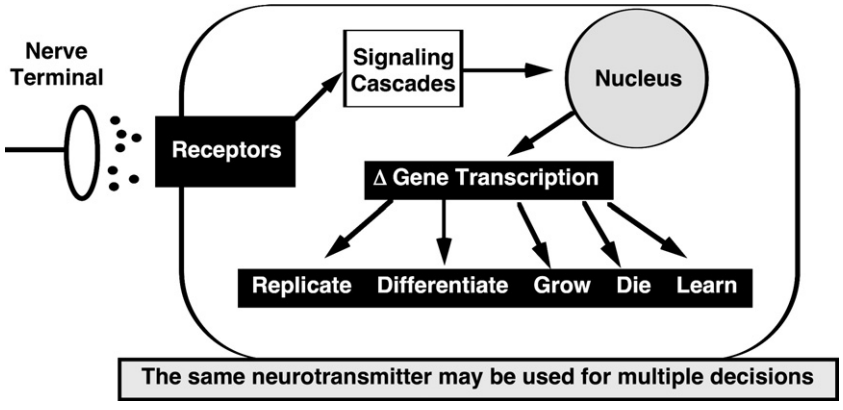
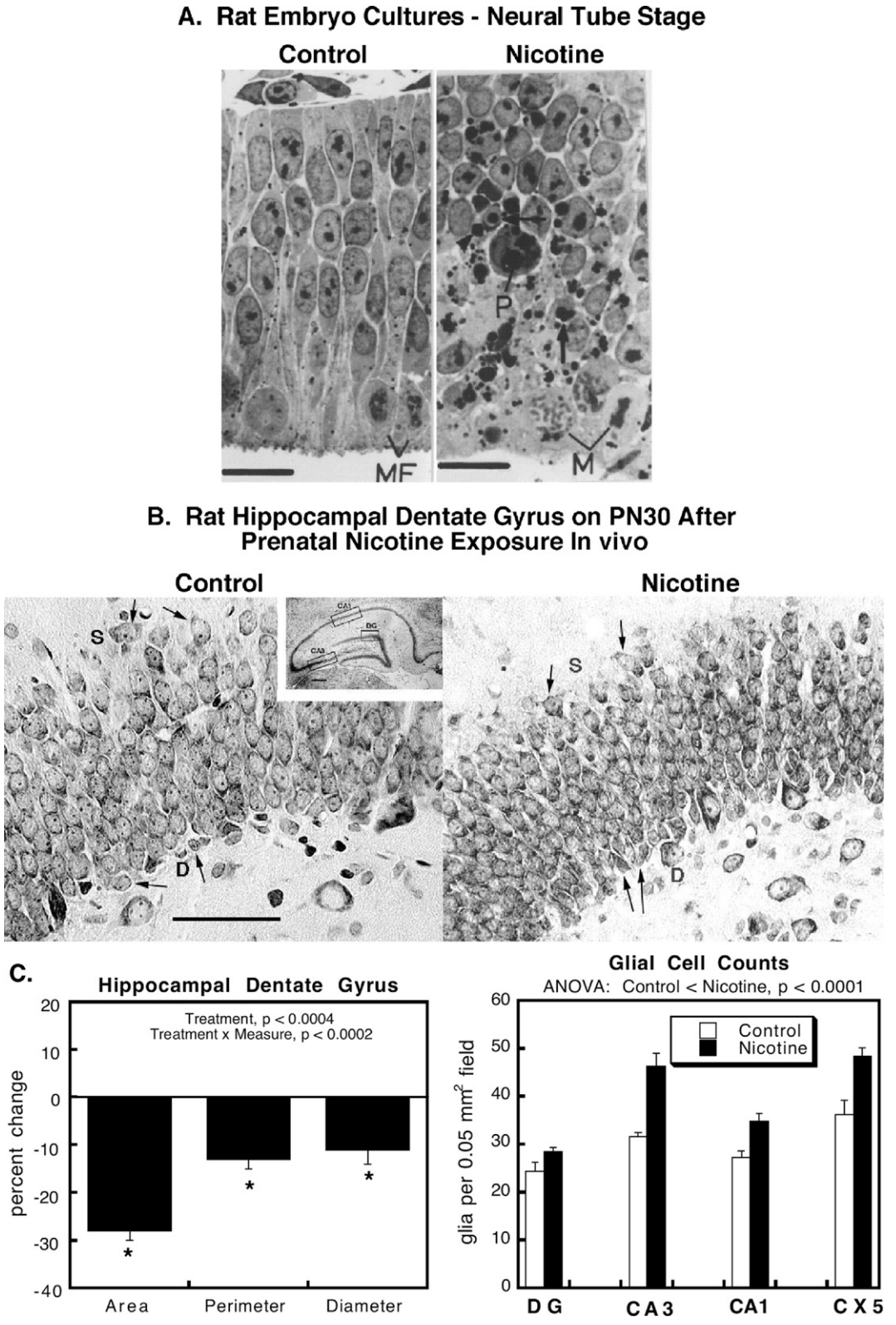


Fig. 1. Schematic representation of how neurotransmitter signals control neuronal cell development during specified critical periods. Depending on the context in which stimulation occurs, the same neurotransmitter, operating through the same receptors and signaling pathways, can promote cell replication, can elicit a switch from replication to differentiation, can promote or arrest cell growth, can evoke apoptosis, or can program the genes that determine the future responsiveness of the cell to external stimulation (cell learning).

3. Effects of prenatal nicotine exposure

The exquisite sensitivity of the developing brain to nicotine is a reflection of the fact that nicotine acts on nAChRs to mimic the effects of acetylcholine. During development, neurotransmitters control and coordinate the cellular and architectural assembly of the central nervous system [95,240] (Fig. 1). Within the appropriate developmental context, stimulation of neurotransmitter receptors has sequentially different effects on cellular development: (1) promoting neural cell replication, (2) initiating the switch from neural cell replication to differentiation, (3) initiating and then terminating axonogenesis and synaptogenesis, (4) evoking or retarding apoptosis, or (5) enabling the appropriate migration and localization of specific



cell populations within each brain region. Under normal circumstances, each pathway and neurotransmitter produces a coordinated set of signals at the proper time and with the proper intensity; obviously, though, delivery of exogenous, neuroactive substances can "hijack" the developmental process by blocking the proper signals or by activating the processes at the inappropriate time or with inappropriate intensity. Thus, the multiple developmental roles of neurotransmitters control the normal development of the brain and mediate the plasticity necessary for learning during development, but at the same time, render the developing brain vulnerable to neuroactive chemicals such as nicotine, with sensitivity extending through all phases of brain assembly, from the early embryonic stage through adolescence [249].

Given the specific action of nicotine on nAChRs, one critical issue is the point in development at which these receptors first arise and exert control of neurodevelopment. At first, it was thought that nAChRs were not expressed in sufficient numbers to elicit cellular responses until the second trimester, so that presumably, the developing brain would not be sensitive to disruption by nicotine until that point [128,190,191]. However, more recent work shows that receptors are present and biologically active much earlier, previous to the formation of synapses, at the neural tube stage [10,182], and that excessive stimulation of nAChRs by nicotine produces profound disruption at both cellular and architectural levels [171] (Fig. 2A). Similarly, it is now apparent that the human fetal brain expresses nAChRs in the first trimester, and activation of these from maternal smoking participates in the neurodevelopmental sequelae [69]. Although the initial morphological changes elicited by nicotine exposure during early neurodevelopment are striking [171], structural features are actually relatively normal by gross examination in early adulthood [174]; however, quantitative morphology confirms that there are long-lasting alterations caused by gestational nicotine exposure, particularly in the hippocampus and somatosensory cortex [172–174] (Fig. 2B, C). Thus, prenatal nicotine exposure evokes long-term alterations in structure but the effects are not qualitatively obvious — from a morphological standpoint, nicotine is a subtle neuroteratogen, not a classical "neurotoxin".

Notwithstanding the morphological consequences of prenatal nicotine exposure, neurochemical evidence has provided far more information about the mechanisms underlying the initial damage and later-emerging functional deficits. With the nicotine infusion model in developing rats, standard biomarkers of cell injury indicate that prenatal nicotine exposure damages the developing brain, triggering apoptosis, reductions in the numbers of neuronal cells, truncation of axonogenesis and deficient synaptogenesis [99,135,136,189–191,195,199,200,205,226]. Importantly, damage and cell loss actually intensify in the postnatal period despite the discontinuation of nicotine exposure [191,193], involving the constitutive activation of genes associated with apoptosis [191,205]. There are two notable features of this delayed-onset cell loss. First, nicotine-induced apoptosis in the developing brain stands in opposition to its neuroprotective effect in the mature brain [84,88,154,248], emphasizing that the developmental context is critical for evoking damage. This has been confirmed with hippocampal progenitor cells, which likewise display apoptosis in response to nicotine only in early differentiation [21]. The second issue is the fact that the delayed-onset changes occur when nicotine is no longer present in the system, indicating that nicotine does not simply produce direct neurodevelopmental injury but rather changes the *trajectory* of brain development, that is, it alters the program for the establishment and functioning of circuits and connections. In turn, this means that many of the adverse effects emerge later in life after a period of apparent normality. This is particularly important for patterns of synaptic activity, which display initial deficits in the early postnatal period but tend to recover by juvenile stages, only to show a reemergence of hypoactivity in adolescence [99,190,191,195] (Fig. 3). At that point, there is a ubiquitous deficit in the ability of nAChRs to elicit responses, whether to nicotine itself or to the endogenous neurotransmitter, acetylcholine [5,23,105,184]. As will be discussed later, the alterations that first appear in adolescence play an important role in dictating the addiction liability upon reexposure to nicotine. Notably, though, the late-emerging defects in synaptic function differ distinctly from the initial, direct actions of nicotine on the fetal brain; the sensitivity to the direct effects corresponds to the concentration of nAChRs in each fetal brain region, whereas the long-term alterations in developmental trajectories compromise synaptic function even in regions that are very sparse in nAChRs or cholinergic projections, such as the cerebellum. Furthermore, the deficits emerge in parallel for a wide variety of neurotransmitters other than acetylcholine, including the monoamines such as serotonin, which plays a key role in the control of mood [99,190,191,195,213,214,216,245]. These cumulative changes in other neurotransmitter systems reflect both the altered trajectory of neurodevelopment caused by prenatal nicotine exposure, as well as the fact that nAChRs are present on presynaptic nerve terminals for monoamines, amino acids and neuropeptides;

Fig. 2. Effects of prenatal nicotine exposure on brain morphology during exposure and in adolescence. Results were excerpted from primary studies that contain the experimental details [171,174]. (A) Effects of nicotine on brain development in cultured rat embryos. Exposure occurred for a 48 h period beginning at 9. 5 days of gestation. On the left, neuroepithelium from a control embryo, showing closely apposed pseudostratified cells at different phases of mitosis, and their processes. The mitotic figures (MF) are localized to the lumenal surface. On the right, a nicotine-exposed embryo, exhibiting dying cells and debris, in the form of intra- and extracellular bodies, often engulfed by healthy cells, including those undergoing mitosis (M). A large nucleated phagosome (P) contains multiple dark bodies. Scale bar=20 μm. (B) Morphological changes evident in the ectal limb of the hippocampal dentate gyrus on PN30. Pregnant rats received continuous nicotine infusions throughout gestation. The left panel shows a control tissue whereas the right is from a nicotine-exposed animal. Note the smaller cell size and increased packing density in the nicotine group. For both groups, the early-born large neurons are in the superficial part (S) whereas late-born neurons are in the deep part (D) of the layer; compare cell sizes shown with arrows. Scale bar=50 μm. Inset shows a photomicrograph of the hippocampus at PN30, showing segments sampled for the pyramidal cell layers of CA1 and CA3, and the granule cell layer of the ectal limb of the dentate gyrus (DG). Scale bar=300 μm. (C) Quantitative morphometry of the dentate gyrus (left) and glial cell counts (right) in hippocampal dentate gyrus (DG), CA3, and CA1, and in layer 5 of the somatosensory cortex (CX5), from the same study shown in (B). Data are shown as means and standard errors. Note the decreases in parameters of cell size and the global increase in glial cells, characteristic of reactive gliosis consequent to cell damage.

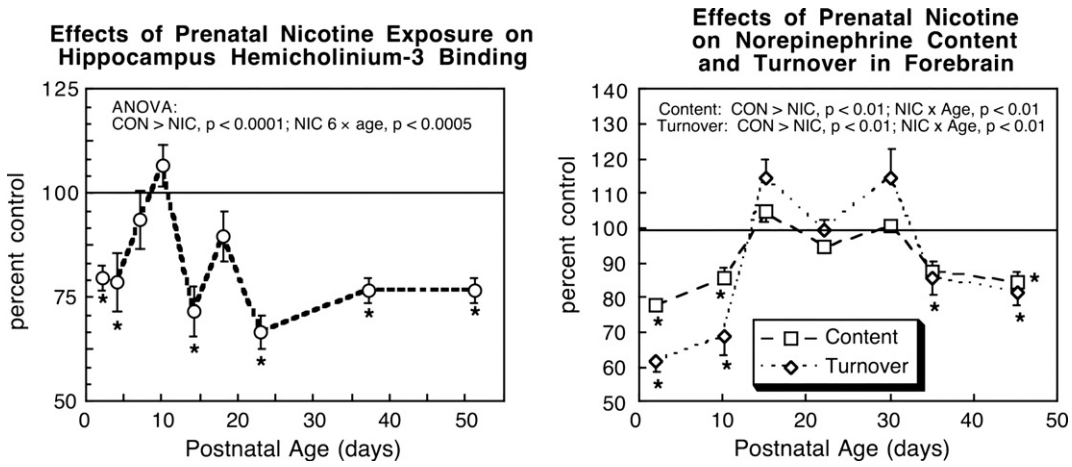


Fig. 3. Prenatal nicotine exposure impairs the development of synaptic activity in multiple neurotransmitter pathways. Data were taken from papers that contain the experimental details [135,191,205,253]. Rats were exposed to nicotine via maternal infusions throughout gestation and all values are presented as means and standard errors. The left panel shows the effects on hippocampal cholinergic activity, as delineated with hemicholinium-3 binding to the high affinity choline transporter. Note the biphasic effect: initial deficits are corrected for a brief period, only to reappear later in development. The right panel shows impairment of noradrenergic activity, as delineated with norepinephrine levels and utilization rate (turnover). Again, note the biphasic effect.

accordingly, nicotine in the fetal brain produces inappropriate release of all these transmitters during the same critical developmental stages, producing a cascade of neuroteratogenic events spreading beyond cholinergic systems. Indeed, a number of studies have elucidated the cellular mechanisms underlying the ability of nicotine to change the developmental programming of synaptic function in a global sense. Prenatal nicotine exposure alters the expression and function of cell signaling proteins shared by numerous neurotransmitter receptors, thus eliciting heterologous changes in a wide variety of signals [201,202,207,252]. As part of these effects, there is a shortfall in the functional capacity of G-protein coupled receptors [138,254], likely involving changes in the expression of receptor proteins [138,139,199,201,254] as well as in the downstream signaling molecules themselves. Developmental disruption by nicotine thus compromises synaptic function at numerous loci, ranging from outright cell loss to specific alterations of neural activity, to misprogramming of receptor signaling mechanisms.

Accordingly, it is evident that the change in neurodevelopmental trajectory after prenatal nicotine exposure leads to the continual emergence of functional deficits throughout the life span. As will be discussed in the section on NRT in pregnancy, one critical issue is whether the reduction in intrauterine growth associated with maternal smoking provides an adequate index for predicting the eventual neurodevelopmental deficits, since this marker has been proposed as a surrogate for establishing the safety of NRT [13,19,37,76,89,183]. Here again, evaluations with animal models of prenatal nicotine exposure provide essential information. Lowering the dose of nicotine in rats to the point where growth impairment vanishes still produces all the signs of fetal brain damage and subsequent alterations in synaptic function [99,136,184,191,193]. Indeed, greater sensitivity of brain development relative to growth is entirely commensurate with the targeting of nAChRs, which respond to nicotine at nanomolar concentrations [26,68,115,199]. The receptors are present even in the earliest stages of brain formation, before the neural tube stage [10,182] and nicotine has the ability to produce tonic stimulation of the receptors, as evidenced by receptor upregulation [136,199]. Thus, for both the initial effects of nicotine on the fetal brain, and the subsequent emergence of functional anomalies as part and parcel of the alteration of the trajectory of neurodevelopment, the dose threshold lies far below that of growth impairment [41,99,100,101,136,169,184].

In recent work, we conducted an extensive series of studies detailing the underlying mechanisms and consequences of the altered trajectory of brain development after prenatal nicotine exposure, at stages extending from adolescence to adulthood [5,213–216,245]. Turning first to acetylcholine systems, the deficits in synaptic activity that reemerge in adolescence remain present throughout the life span [5,214,215,253]. However, a major change occurs during the transition from adolescence to adulthood (Fig. 4): although the deficits are initially present in both males and females, males show more long-lasting effects, especially in the cerebral cortex [5,214,253], results in keeping with the greater recovery capacity of the female brain, in turn reflecting the important role of estrogen in neural plasticity [119,221]. Females are not totally spared but rather show deficits in a different region, the striatum [214], again with the effects emerging in early adulthood [215]. The transition from the pattern of effects in adolescence to that seen in adulthood likely represents long-term plasticity, especially in regions where there is ongoing neurogenesis throughout the life span [22,79,118], but in no case does the plasticity restore completely normal function of acetylcholine systems [173,174,250,251]. Similar conclusions have been reached for the long-term impact of prenatal nicotine on serotonergic synaptic function. Although the initial damage to developing serotonin projections occurs in both males and females [245], the eventual effects are selectively greater in males [213,214,216]. Here, too, the actual synaptic mechanisms underlying deficient serotonergic function undergo a transition between adolescence and adulthood; for example, whereas $5HT_{1A}$ receptor expression is elevated in

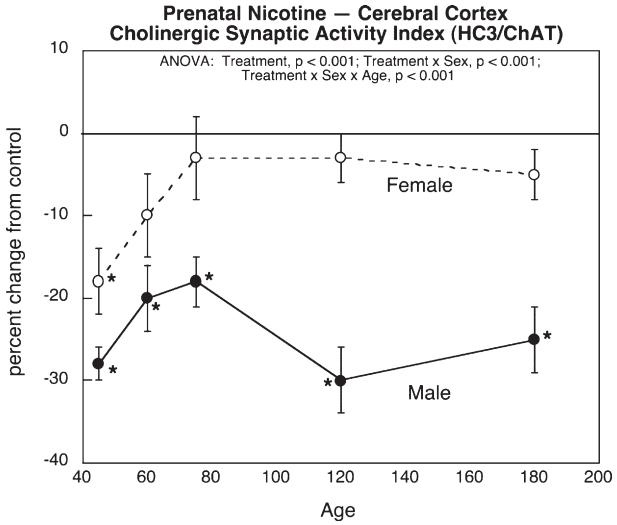


Fig. 4. Deficits in cholinergic synaptic activity in cerebrocortical projections after prenatal nicotine exposure of rats throughout gestation: the transition from adolescence to adulthood. Data were taken from papers that contain the experimental details [5,214,215,253] and are presented as means and standard errors. Abbreviations: HC3 = [^{3}H]hemicholinium-3 binding to the presynaptic choline transporter; ChAT = choline acetyltransferase activity. Expression of the transporter is regulated by presynaptic stimulation, whereas ChAT is expressed constitutively and is not activity-regulated, so that the HC3/ChAT ratio supplies a measure of cholinergic presynaptic activity relative to the number of presynaptic terminals. Although both males and females show deficits in adolescence, females recover in adulthood whereas males do not.

adolescence in animals given prenatal nicotine exposure, it is decreased when assessed at six months of age [213,214], with a distinct transition in young adulthood [216]. A similar, late-occurring transition also appears to take place for the long-term effects of prenatal nicotine on cell signaling intermediates, notably those involved in the formation of the second messenger, cyclic AMP [216]. Given the large family of G-protein-coupled receptors that signal through cyclic AMP, the delayed-onset changes are probably shared by many other neurotransmitter systems.

There are three important conclusions from the findings of a late transition in the lasting effects of prenatal nicotine on synaptic function. First, this reinforces the important concept that fetal nicotine exposure alters the trajectory of neurodevelopment, so that defects continue to emerge over the life span; it would be interesting to evaluate, for example, whether this hastens the onset of neurodegenerative disorders or other deficits in senescence. Second, the longitudinal effects do not represent simply a continuation of early damage but rather reflect a complex interplay among the altered trajectory of development, the sex-selective ability to repair or compensate for the damage, and alterations that may be adaptive to the initial effects but perhaps maladaptive in the long run. As will be discussed later, part of the maladaptive changes include enhanced susceptibility to nicotine dependence and addiction in adolescence, an important factor to consider for the consequences of NRT in pregnancy. Third, even where some synaptic parameters return nearly to control values, as seen more readily in females, this does not necessarily represent the restoration of completely normal function but rather can reflect adaptations to the initial damage and/or the subsequent change in the developmental trajectory of the affected circuits. In adults, that concept has been stated as the "sensitization-homeostasis" model of nicotine dependence, wherein a single episode of nicotine dependence reprograms the functioning of key pathways that then remain permanently susceptible to readdiction [44]. Here, in a developmental context, this sets the stage for the important realization that prenatal nicotine alters the subsequent response to nicotine in adolescence [4,5,83,103,213–216], as discussed later.

4. Nicotine in adolescence

It is increasingly clear that brain development extends into adolescence, encompassing all of the same processes that characterize earlier events of neuroproliferation, apoptosis and synaptic rearrangement, albeit at a lower level of activity than in the fetus or neonate [16,17,77]. In particular, central cholinergic systems that are involved in cognitive performance and reward reach their mature state in periadolescence [116,127,255]. Of course, adolescence is the period in which most drug experimentation commences, including cigarette smoking. In the U.S., approximately 3000 teenagers begin smoking each day [29,30,134], with the majority becoming daily smokers [134,142]. For those who begin in early adolescence, smoking rapidly becomes a long-term addiction, characterized by high consumption and low quit rates [33,160]. A number of studies indicate that adolescents are more susceptible to nicotine dependence, with rapid loss of autonomy over tobacco consumption [45–47].

Nevertheless, until the last decade, there was little or no information to characterize the neurochemistry or behavioral response to nicotine in the adolescent brain. We first developed a rodent model of adolescent nicotine administration based on the minipump infusion paradigm, designing regimens to reproduce the plasma nicotine levels seen in regular smokers (25ng/ml) [194] as well as the lower levels seen in occasional smokers or even trace levels characteristic of ETS exposure [2,3]. As presented in an earlier review [194], there are a number of key characteristics that indicate unique features of the response of the adolescent brain to nicotine (Fig. 5): more profound and persistent upregulation of nAChRs as compared to adults, especially in the midbrain areas mediating reward, and prolonged suppression of cholinergic synaptic activity upon withdrawal [3,194,227,229,230,245,246]. Many of the lasting alterations represent a continuation of the pattern of developmental neurotoxicity noted for fetal nicotine exposure, albeit to a lesser extent [2,194,225,228,246], and this turns out to be a critical feature in both the consequences of adolescent nicotine addiction and the implications for NRT: nicotine remains neurotoxic in the adolescent brain, producing persistent damage with permanent consequences [2,194,214,228]. As a consequence of the enhanced addiction liability during this developmental phase, adolescent rats will typically self-administer far more nicotine than do adults [102–104], and the biological substrates that govern nicotine intake show corresponding age-related differences centering around nAChR subtypes in brain regions that mediate reward responses [104]. The effects of

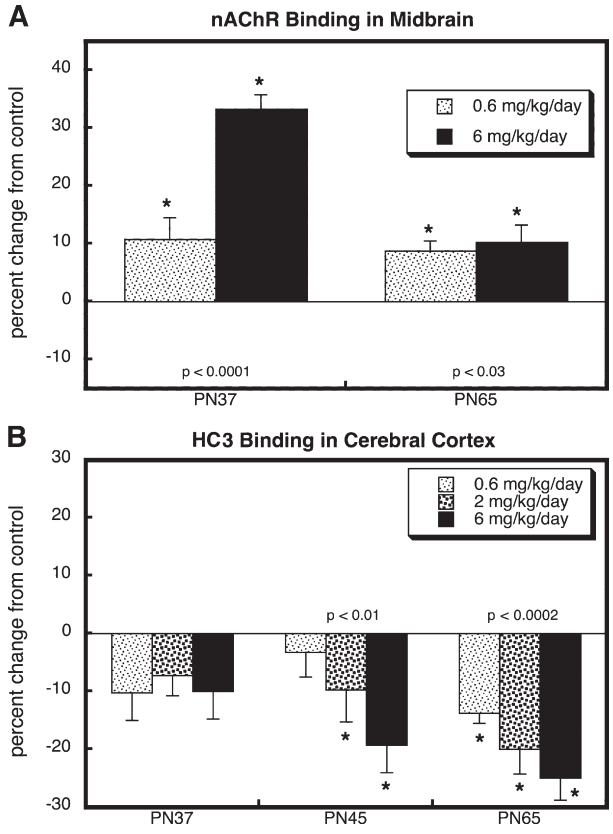


Fig. 5. Persistent changes in cholinergic systems after adolescent nicotine exposure. Rats were given nicotine infusions from postnatal (PN) days 30 through 37; for experimental details, see the original publication [3]. Data are presented as means and standard errors. (A) For α4β2 nicotinic acetylcholine receptors (nAChR), upregulation remains detectable in the midbrain even one month after discontinuing nicotine exposure, even at a low dose (0. 6 mg/kg/day) that produces nicotine plasma levels of 2.5 ng/ml, in the range of those seen with consumption of only a few cigarettes a day. In adults, even higher and more prolonged exposures show complete regression of upregulation by two weeks post-treatment [215,227]. (B) [^{3}H]Hemicholinium-3 (HC3) binding to the presynaptic choline transporter, an index of cholinergic neuronal activity, shows progressive deficits during the withdrawal period [3], with the greatest effect seen in the cerebral cortex. Again, the effects are prominent even at extremely low exposures.

adolescent nicotine in the rat model also reproduce sex-selective effects noted for adolescent tobacco smoking. Female rats show greater degrees of neural cell damage [2,225,228,247], greater initial impairment of synaptic activity of monoaminergic systems [230,245–247] and greater behavioral deficits [229]. Again, this directly parallels the human situation, as female adolescent smokers show more rapid onset of nicotine dependence, with loss of autonomy and signs of withdrawal after only a few cigarettes [47].

Recent findings point to the important differences in nicotine withdrawal as a factor that contributes to the enhanced susceptibility of the adolescent brain to nicotine addiction. At the behavioral level, adolescent rats undergoing withdrawal precipitated by nAChR antagonists are less likely to experience some of the negative aspects seen in adults [146–148]; on the other hand, with abstinence-induced withdrawal, they tend to show greater cognitive impairment [241]. However, examination of synaptic function reveals the most conclusive differences from the adult withdrawal pattern. In the adolescent, withdrawal produces lasting desensitization of cholinergic inputs to monoamine systems involved in reward and emotionality [1,196,213,214,230,245,246], likely contributing to the persistent loss of responsiveness to psychostimulants [90] and enhanced self-administration of depressants [91], as well as other persistent behavioral and neurological deficits [98,187,229]. Indeed, these differences comprise a unique, adolescent "nicotine abstinence syndrome" [187]. In recent studies, we focused on the long-lasting effects of adolescent nicotine treatment and withdrawal on both cholinergic and serotonergic systems as a way of understanding the biological substrates underlying some of the persistent problems seen in adolescent smokers [214,216]. Even months after discontinuing nicotine exposure, cerebrocortical cholinergic activity shows persistent reductions, in fact, just like the effects of prenatal nicotine exposure (Fig. 6A). Unlike the immediate consequences of adolescent nicotine treatment and withdrawal, which show greater effects in females, the persistent effects are more notable in males, again consistent with the greater plasticity and recovery capabilities of the female brain. These findings thus reinforce our earlier conclusions that the vulnerability of cholinergic systems to long-term deficits evoked by nicotine exposure persists from fetal stages all the way through adolescence [3,4,227].

In addition to the obvious connection between suppression of cholinergic activity and consequences for cognitive function, we also focused on serotonergic systems because of their role in affective disorders [108]. Adolescent tobacco use is highly correlated with depression [62,155,244] and is associated with higher risk of suicide [168]. Depressive symptoms are exacerbated by nicotine withdrawal and thus contribute to the failure of therapies for smoking cessation [35,176,231], especially in adolescent smokers [35,75]. It is particularly notable that, using nicotine administration to adolescent rats, we found profound suppression of serotonergic synaptic function upon cessation of nicotine administration [245]. In our earlier work for the short-term effects of adolescent nicotine exposure, we identified transient changes in the expression of serotonin receptors that were related to the immediate impact of nicotine treatment and subsequent withdrawal [213,245,246]. When we focused instead on the long-term consequences of the same treatment months later, we found permanent upregulation of serotonin synaptic proteins, including both presynaptic and postsynaptic receptors (Fig. 6B). Although some of these features are shared by prenatal nicotine exposure, this is not true for all the regionally-selective actions, suggesting that adolescent nicotine treatment produces some effects on serotonin systems that are unique to this stage, distinct from both fetal development and effects in adults. Similarly, we found persistent effects on cell signaling shared by multiple receptor inputs, evidence again for heterologous changes that produce permanent alterations in the overall response to a variety of neurotransmitters extending beyond acetylcholine and serotonin [214,216].

Taken together, these findings reinforce the distinctive attributes of the adolescent brain that render it susceptible to nicotine dependence, the equally unique withdrawal responses that dictate different behavioral outcomes, and most importantly, the persistence of the changes in patterns of synaptic

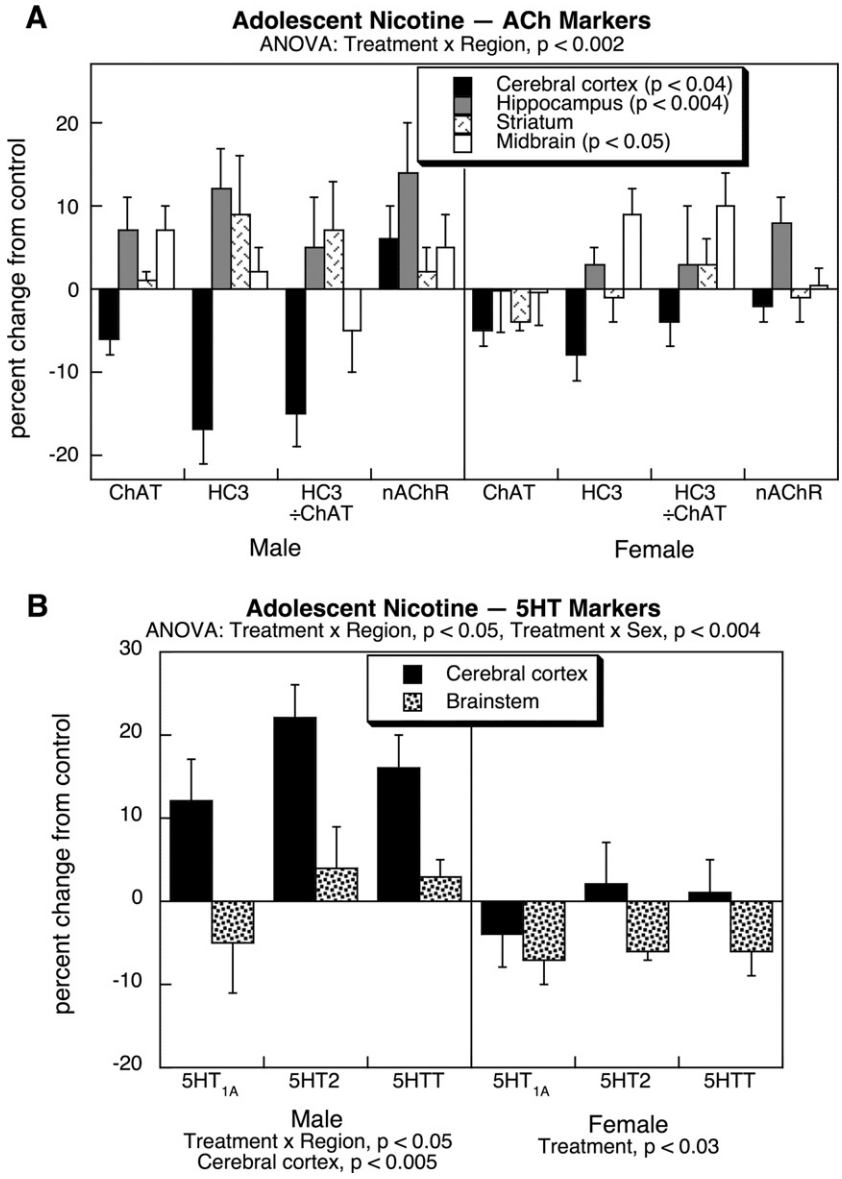


Fig. 6. Persistent effects of adolescent nicotine exposure. Rats were given nicotine infusions (6 mg/kg/day) from postnatal days 30 through 47 (NB: longer than in Fig. 5) and measurements made at six months of age; experimental details are available in the original publication [214]. Data are presented as means and standard errors. For acetylcholine systems (A), there are preferential deficits in the cerebral cortex in males. For serotonin systems (B), there is global upregulation of synaptic proteins including pre- and postsynaptic receptors and the presynaptic serotonin transporter, again with a preferential effect for the cerebral cortex in males. Abbreviations: ACh = acetylcholine; ChAT = choline acetyltransferase; HC3 = [^{3}H]hemicholinium-3 binding; nAChR = $\alpha 4\beta 2$ nicotinic acetylcholine receptor binding; 5HT = serotonin.

activity throughout the life span, despite the discontinuation of nicotine exposure. There are important ramifications to these findings. First, the impact extends beyond cholinergic systems, the immediate target of nicotine, to involve serotonergic function, providing a mechanistic underpinning for the epidemiological findings of greater susceptibility to affective, appetitive and sleep disorders in the offspring of women who smoke during pregnancy as well as in adolescent smokers [149,155,177,188,224,232,244]. Notably, though, the fact that abnormalities extend to cell signaling cascades shared by multiple neurotransmitter inputs, also suggests that there will be an even wider spectrum of behavioral disorders as outcomes of either prenatal or adolescent nicotine exposure. These findings also have profound societal implications. Smoking among adolescents is undergoing an unprecedented increase, driven in measure by advertising targeted toward this age-group, subtly embedded in films, music videos, youth-oriented magazines and the Internet, often containing powerful sexual content [50,58,71,179]. In addition, the medical community has largely failed to recognize the magnitude of the problem or to provide appropriate countermeasures [222]. The fact that nicotine in the adolescent brain, like the fetal brain, elicits neuronal and synaptic damage, and long-term alterations in synaptic function, means that there is likely to be a biological basis for increased

susceptibility to nicotine dependence and long-term, adverse consequences during this late developmental stage. And we must not overlook the fact that the persistent changes are driven by nicotine itself, not other components of tobacco smoke; obviously, this argues against the suitability of NRT for smoking cessation in this age group.

5. Prenatal nicotine exposure alters the response to nicotine in adolescence

As shown above, both prenatal nicotine exposure and nicotine in adolescence display neurotoxic properties, as well as having convergent actions on the same neural pathways. This sets the stage for a potential interaction between the actions of prenatal and adolescent nicotine, in other words, the effects of fetal exposure on the subsequent response to nicotine in adolescence. Indeed, among the factors that may predispose adolescent smokers to nicotine addiction, parental smoking provides an important contribution [15,32,144]. Perhaps most importantly, maternal smoking *during pregnancy* is a strong predictor of subsequent smoking in adolescent offspring, regardless of whether parental smoking continues during childhood [39,87,144]. Again, these point to a biological basis for prenatally-induced differences in subsequent susceptibility to adolescent nicotine addiction. Here, too, animal studies have provided important insights that show that the increased susceptibility of this subgroup reflects underlying biological alterations wrought by fetal nicotine exposure that alter the response to nicotine in adolescence. As already discussed, the prenatal effects lead to a change in the trajectory of brain development that ultimately produce permanent deficits in cholinergic and serotonergic activity that first emerge in adolescence [99,190,191,193,195,213,214, 245,253], accompanied by desensitization of nAChR-mediated responses [5,184]; this has a corresponding impact on nicotine self-administration in adolescence [92] and particularly on the ability of even a single episode of withdrawal in adolescence to trigger further increases in subsequent nicotine consumption [103].

The interaction of prenatal and adolescent nicotine goes beyond the issue of enhanced drug intake. At the level of neural cell damage and loss, as well as for persistent deficits in synaptic activity of cholinergic and serotonergic systems, the effects are enhanced by the double treatment [4,5,213,214]. Notably, the combination of prenatal and adolescent exposure removes the "protected" status of the female brain: whereas lasting effects of either treatment alone tend to be greater in males, these distinctions are lost when exposure occurs in both periods. Accordingly, although males are likely to show neurobehavioral deficits after prenatal *or* adolescent nicotine exposure, in females, we expect that the combined exposure will produce greater effects than would be anticipated from the two separate exposures. As just one example, the greater effects of prenatal nicotine exposure in males corresponds to their higher incidence of psychosocial sequelae such as learning and conduct disorders [236,237]; our findings suggest that for adolescent smokers whose mothers smoked during pregnancy, this gender selectivity will be less apparent because of an increase in corresponding outcomes for females. Indeed, this may point to the biological mechanisms underpinning the greater association for the effects of maternal smoking on the uptake and progression of adolescent tobacco use by their daughters [87,151,170]. Further, if our findings for combined prenatal and adolescent nicotine exposure in rats extend to adolescent smokers whose mothers smoked during pregnancy, there are a number of predictions that can be made that represent extensions of these findings. First, there are individuals who are prone to the rapid onset of nicotine dependence, often after smoking only a few cigarettes, with a higher incidence of vulnerability in females [47]; we anticipate that this association will be even stronger for those whose mothers smoked during pregnancy. Second, we expect that the persistent changes seen in animal models of prenatal and adolescent nicotine exposure, if paralleled in humans, would render prenatally-exposed adolescents especially vulnerable to relapse after attempts at smoking cessation [44] and again, we predict this relationship will be selectively greater for women. Third, when adolescent smokers attempt to quit, they show both cognitive impairment and depression [35,62,75,114,155,176,231,244], problems that are worse in individuals who were exposed to nicotine in utero via maternal smoking [151]. Whereas adolescent smokers whose mothers did not smoke during pregnancy show cognitive improvement during acute abstinence, those whose mothers did smoke show worsening of cognitive function [80–83]; this finding in adolescent smokers is entirely in keeping with our observations in the rodent model and indeed, the human study was predicated explicitly on the results from animal studies. Again, we expect that an examination of sex differences for this relationship will reveal a greater effect in females than males. Finally, given the targeting of serotonin systems for the lasting effects of prenatal or adolescent nicotine, alone or in combination, we would predict that treatments aimed at restoring serotonin function, such as serotonin specific reuptake inhibitors, may be particularly useful in smoking cessation therapy for adolescent smokers, with the greatest effect seen in females whose mothers smoked during pregnancy.

The results of animal studies address key issues in the persistence of nicotine addiction liability after both prenatal and adolescent nicotine exposure, either separately or together, and also account for the transgenerational nature of nicotine addiction, without requirement for underlying heritable characteristics. Nicotine exposure during either developmental period produces permanent changes in synaptic function, deficits that persist even after prolonged abstinence. These observations are entirely consistent with the view that the brain adaptations to addictive stimuli do not simply regress to normal after discontinuing drug exposure, but rather are kept in balance through lasting adjustments in synaptic activity, as postulated by the sensitization-homeostasis theory of nicotine addiction [44]. Accordingly, there are long-term sequelae that persist beyond the stage of smoking or abstinence, including enhanced susceptibility to relapse, and as found recently, emergence of depression as a consequence of adolescent smoking [217]. These results, combined with earlier work on the combined prenatal and adolescent exposure model, permit the formulation

of a hypothesis as to how smoking behaviors can be transmitted across generations [214] (Fig. 7). Prenatal nicotine exposure produces dysfunction in multiple neurotransmitter pathways, with the changes in cholinergic and serotonergic function contributing in major ways to abnormalities of cognition, reward and mood [137,190,191,193,195,253]; these may be manifest even to the extent of frank psychiatric illnesses [78]. Importantly, most of the synaptic functional deficiencies emerge in adolescence [137,190,191,193,195,253], when access to tobacco products becomes available. At that stage, nicotine intake can be expected to partially relieve the deficiencies in cholinergic function and also, because of the ability of acetylcholine to release monoamines, those in serotonergic pathways as well. Although the adolescent brain is highly responsive to nicotine [4,1,2,38,51,55,194], prenatal nicotine exposure produces lasting desensitization [5,23,105,184], so that the offspring of smokers will tend toward much higher consumption to obtain the desired effect, which in turn extends and expands the degree of damage and reprogramming of neural circuits [4,214], augmenting and cementing the permanent changes in synaptic function and behavioral performance. When these individuals attempt to quit, they are consequently thrown into a worsened degree of cognitive impairment, depression and loss of reward than if they had never smoked at all, as revealed in recent findings [82,83]. These factors then render quitting smoking far less likely, enhancing the probability that this individual, too, will smoke through pregnancy, thus ensuring that the addictive cycle extends to the next generation. These conclusions make it all the more critical that public health focus on *prevention* of tobacco use during developmental stages ranging from pregnancy through adolescence, over and above efforts toward cessation in current smokers. And we cannot overlook the fact that it is *nicotine* itself that is the trigger for these events, with important considerations for the role of NRT in smoking cessation, as will be considered next.

6. Implications for NRT in pregnancy and adolescence

The results of extensive animal studies at the morphological, neurochemical and behavioral levels all point to the fact that nicotine is a neurotoxicant that has adverse effects on brain development and synaptic function, with vulnerability displayed at stages ranging from the fetus to the adolescent. Given these facts, any potential use of NRT for smoking cessation in pregnant women, juveniles or adolescents necessitates a conclusive demonstration of three distinct requirements: successful smoking cessation, a better success rate than nonpharmacologic approaches, and safety. Unfortunately, studies to date do not support any of these three. In fact, nearly all reports show an almost complete ineffectiveness of NRT in pregnant women [13,36,59,89,183,242] but a superior result from nonpharmacologic approaches such as counseling [13,31]. Recent work [164] shows that concurrent cognitive behavioral therapy improves the effectiveness of NRT, resulting in significantly higher quit rates than with either approach alone, but the success rates were still under 20%, and more disturbingly, the trial had to be stopped when it became apparent that NRT produced a 50% increase in adverse birth or neonatal outcomes. The latter point now appears to represent an emerging problem with NRT in pregnancy; in a small, one-sample study, three out of 21 infants showed severe neonatal morbidity [183] and in another report, NRT increased the rate of congenital malformations [124]. There are two likely contributors to the adverse consequences of NRT in pregnancy. First, in the majority for whom NRT does not provide a successful route to smoking cessation, maternal smoking is likely to occur while still using NRT, resulting in an even higher delivery of nicotine to the fetus. Second, for the transdermal nicotine patch, which represents the most commonly-used form of NRT, the pharmacokinetics of fetal nicotine delivery are unfavorable relative to intermittent intake as with cigarettes, gum or other products [59,99,190,191,195]. The transdermal patch, like the minipump infusion model in animals, achieves and maintains a steady-state blood nicotine level in the mother, and accordingly, all water spaces in the maternal-fetal unit come to equilibrium [60]. In contrast, with episodic nicotine intake, the placenta delays the entry of drug into the fetal compartment until the peak blood level in the mother has declined, so that the net fetal nicotine exposure is less than for the same daily amount of nicotine delivered continuously. Indeed, animal studies with the minipump model confirm that fetal brain nicotine levels

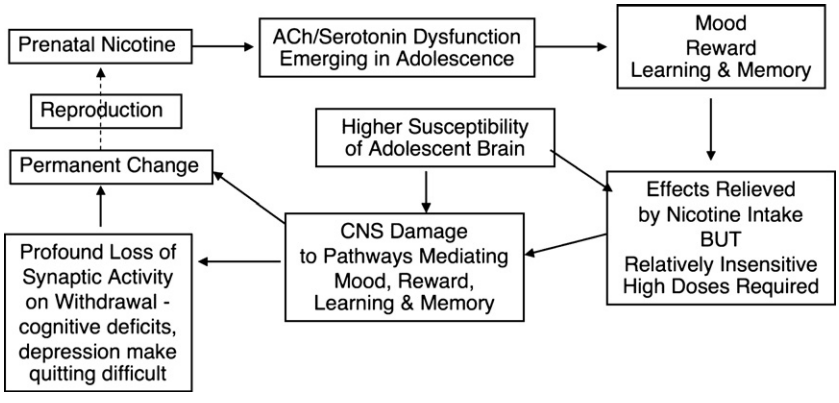


Fig. 7. How prenatal nicotine exposure predisposes the brain to nicotine addiction in adolescence and leads to transgenerational effects (see text). Abbreviation: ACh, acetylcholine.

accumulate to over twice those in maternal blood [180].[1] In light of these findings, suggestions to achieve quitting in pregnant women by delivering even higher doses of nicotine via transdermal patches [19] would appear to be inappropriate from the standpoint of fetal safety.

An upcoming, large, placebo-controlled, double-blind study of NRT in pregnancy is now underway [37] and, unless discontinued because of adverse outcomes, is likely to resolve some of the issues of effectiveness. However, the equally important safety issues may not be decided for many years, since nearly all previous and proposed studies focus on a few initial markers of the adverse effects of smoking during pregnancy, typically preterm delivery, perinatal morbidity and mortality, and most especially, low birth weight. As shown from the animal studies, the key features of neurodevelopmental damage are unrelated to growth impairment and occur at exposures that do not impede fetal growth whatsoever. Low birth weight is not itself a disorder, but instead is a surrogate marker for the risk of other morbidities. A number of studies indicate that the relationship between low birth weight and actual disorders is different for maternal smoking than for the general population. For example, although smoking during pregnancy increases the risk of preterm delivery, it actually lowers the incidence of neonatal respiratory distress syndrome, the main source of morbidity and mortality in premature infants [24], likely because of the ability of nicotine to release endogenous corticosteroids and catecholamines, along with accelerated differentiation of pneumocytes [185,234]. Further, since prenatal exposure to tobacco smoke is now known to provide a major source for obesity in later life [165,223,235], it is important to note that these outcomes involve the heaviest rather than the lightest offspring of smokers [74]. Here, too, animal studies indicate an important potential link to the effects of nicotine, rather than other components in tobacco smoke. Prenatal nicotine exposure compromises the balance of peripheral autonomic function, suppressing sympathetic in favor of parasympathetic activity [135,136,138,150,189, 198,207,204]. Studies in newborn babies indicate that the same impairment occurs in the offspring of women who smoke during pregnancy [150]. This type of imbalance would favor lower metabolic rates and promote the deposition of fat, predictions which have confirmed both in animals with prenatal nicotine exposure [57] and in children of smokers [96]. Even for birth weight itself, the importance of nonpharmacologic interventions as opposed to NRT comes into play: lack of social support is a main determinant of low birth weight in smokers, so that the effect appears to be an interaction of tobacco use with socioeconomic variables and not a sole effect of smoking [52]. Accordingly, the use of birth weight as an index for comparing the safety of NRT to tobacco consumption is probably inappropriate; instead, these studies will need to focus on the actual disorders, especially neurodevelopmental disorders, that have been identified as the important morbidities for the outcomes of maternal smoking during pregnancy, efforts which will require large cohorts and longitudinal evaluations over an extended period of time.

The main presumption of "clean nicotine" as opposed to smoking in pregnancy is that the many other constituents in tobacco smoke contribute significantly to the adverse developmental outcomes. Although nicotine has been studied far more than any of the other components, a number of animal studies of ETS exposure, both in rodents and primates, point to virtually identical outcomes to those seen with nicotine alone. This includes deficits in the numbers of neurons [63,143,211], equivalent upregulation of fetal nAChRs [54,195,209], similar patterns of neuronal and synaptic damage [63,143,211] and cognitive dysfunction [61]. Although the current review has focused on neurodevelopmental events, it is important to note that the equivalence of ETS and nicotine effects has been demonstrated for other systems or disorders as well, including adverse effects on lung development and airway reactivity [111,161,178,208,218], immune function [14,70,86,117,140,141], autonomic/cardiorespiratory function in animal models of Sudden Infant Death Syndrome or in babies born to smokers [7,27,56,66,67,72,73,121,122,150,181,192,206, 207,204], and subsequent obesity and adiposity [57,96]. In all of these cases, then, nicotine by itself is able to reproduce the net outcome from tobacco smoke exposure; that is not to say that the other components are not injurious, but rather, the replacement of tobacco with NRT is likely to produce less improvement than might otherwise be thought, and as shown above, may actually worsen some of the critical outcomes. Similar issues have emerged for studies of NRT in adolescent smokers, including relative ineffectiveness of NRT in achieving smoking cessation [123] and the added liability of NRT products as a source of substance abuse: in one survey, nearly 20% of adolescent nicotine patch users turned out to be nonsmokers [94]. Given the propensity of adolescents to experiment with addictive agents, and the permanent alterations wrought by nicotine in the adolescent brain, an outright public endorsement of "safe" nicotine products is likely to contribute to a new generation of nicotine abusers over and above adolescent smokers, or even of the use of NRT as a gateway to abuse of other drugs [110,120,215].

In conclusion, extensive studies in animal models of prenatal and adolescent nicotine exposure clearly indicate that nicotine is a neurotoxicant during stages of brain development ranging from early fetal life through adolescence. By altering the trajectory of synaptic development and function, nicotine exposure during these critical periods produces permanent changes in synaptic activity controlling critical cognitive and affective functions, including reprogramming the future reactivity to nicotine and

[1] These conclusions are based on standard pharmacokinetic models of the maternal-fetal unit [60]. To date, there is no study that directly compares neurodevelopmental outcomes with an episodic administration model that simulates smoking in humans vs. continuous nicotine administration models. Such a study would be particularly problematic in rodents because their rapid metabolism of nicotine necessitates very short dose intervals in order to simulate the swings in plasma levels found in smokers. Short intervals would simply produce a near-steady-state exposure similar to the infusion models, whereas increasing the individual doses and lengthening the intervals would produce episodic hypoxia/ischemia [191], as discussed earlier. Studies in primates are likely to be required to resolve this issue definitively. To date, evaluations have been conducted in pregnant monkeys given continuous nicotine infusions or repeated episodes of ETS exposure, both of which evoke neuronal damage to the same systems targeted by nicotine infusions in rodents [61,209–212]; however a direct comparison to a model simulating active maternal smoking patterns has not been done.

potentially other addictive drugs. Two considerations strongly argue against the use of NRT during pregnancy, childhood or adolescence. First and most important, is the weight and wealth of experimental evidence concerning nicotine's injurious and enduring effects on neuronal systems. Second is the failure to date to demonstrate any conclusive effectiveness in promoting abstinence in these vulnerable populations [59]. It is mandatory that we focus instead on nonpharmacologic interventions to achieve the important goal of smoking cessation in these groups. If we fail to do this, we will simply ensure that the adverse consequences of developmental exposure to nicotine will be passed on to succeeding generations.

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