Nicotine-induced plasticity during development: modulation of the cholinergic system and long-term consequences for circuits involved in attention and sensory processing

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Summary

Despite a great deal of progress, more than 10% of pregnant women in the USA smoke. Epidemiological studies have demonstrated correlations between developmental tobacco smoke exposure and sensory processing deficits, as well as a number of neuropsychiatric conditions, including attention deficit hyperactivity disorder. Significantly, data from animal models of developmental nicotine exposure have suggested that the nicotine in tobacco contributes significantly to the effects of developmental smoke exposure. Consequently, we hypothesize that nicotinic acetylcholine receptors (nAChRs) are critical for setting and refining the strength of corticothalamic-thalamocortical loops during critical periods of development and that disruption of this process by developmental nicotine exposure can result in long-lasting dysregulation of sensory processing. The ability of nAChR activation to modulate synaptic plasticity is likely to underlie the effects of both endogenous cholinergic signaling and pharmacologically-administered nicotine to alter cellular, physiological and behavioral processes during critical periods of development.

Keywords

nicotine; development; attention; sensory processing; thalamus; cortex

Introduction

Tobacco use causes more than 440,000 deaths and $75 billion in direct health care expenses annually in the USA alone (USDHHS, 2004). Despite considerable public awareness, 20.8% of American adults are currently smokers (CDC, 2007; USDHHS, 2004). In addition, in 2005, between 10.7% and 12.4% of pregnant women in the USA were smokers (Martin et al., 2007). Gestational tobacco exposure has numerous consequences, including intrauterine growth retardation, reduced birthweight and an increased risk for both preterm delivery and still birth (Salihu and Wilson, 2007). During infancy, exposed individuals also exhibit a generalized increased risk of morbidity and mortality, including an increased risk of sudden infant death syndrome (Salihu and Wilson, 2007).

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Children exposed to tobacco smoke *in utero* also show increased risk for psychological disorders including a 2–4 fold increased risk of attention deficit hyperactivity disorder (ADHD) (Button et al., 2007; Ernst et al., 2001; Linnet et al., 2003), conduct disorder, antisocial behavior and substance abuse (Brennan et al., 2002; Button et al., 2007; Ernst et al., 2001).

Developmental tobacco smoke exposure also has persistent effects on cognitive processes, with evidence of impairments in the verbal learning and design memory subscales of the Wide Range Assessment of Learning and Memory battery and increased perseverative responding in the Wisconsin Card Sorting Task (Cornelius et al., 2001). These observations suggest deficits in learning from auditory stimuli, impaired recall of visual stimuli and potentially impaired cognitive flexibility, an inability to learn from feedback, or a failure of attentional control in developmentally exposed 10 year olds (Cornelius et al., 2001).

Further, there is evidence of impairments in basic visuospatial function, as assessed by the Test of Visual-Perceptual Skills (TVPS) in 9–12 year old, prenatally exposed children (Fried and Watkinson, 2000) and impairments in both immediate and delayed visuospatial memory, as assessed by the Brief Visuospatial Memory Test-Revised, in gestationally exposed adolescents (Jacobsen et al., 2006). A subsequent study in adolescents identified sex differences in the sensitivity of different sensory modalities to developmental tobacco exposure, with females exhibiting impairments in tasks dependent on visual or auditory attention, while auditory dependent attention appears to be most prominently impaired in males (Jacobsen et al., 2007).

Critically, numerous studies have demonstrated impaired auditory processing in children exposed to tobacco smoke *in utero* (Fried and Makin, 1987; Picone et al., 1982; Saxton, 1978). Indeed, evidence from the Ottawa Prenatal Prospective Study has indicated deficits in the cognitive and attentional performance of tobacco exposed children which persist to 16 years of age, with particular disruptions in auditory and language related abilities (Fried and Makin, 1987; Fried et al., 1992a; Fried and Watkinson, 1988, 1990, 2001; Fried et al., 1992b, 1998b, 2003; Fried et al., 1997; Kristjansson et al., 1989; McCartney et al., 1994). It is likely that stimulus processing, rather than detection, is affected in these individuals, since there is no evidence of disrupted hearing or auditory brainstem responses in tobacco exposed neonates (Trammer et al., 1992).

Based on these human studies, it appears that developmental tobacco exposure can have deleterious effects on cognitive and attentional processes. While direct effects of developmental exposure on the higher cortical areas responsible for attentional and cognitive control cannot be excluded, it is also possible that developmental tobacco exposure may preferentially affect the neuronal circuitry responsible for the early stages of sensory processing, such as the thalamocortical neurons responsible for the gating and relay of sensory information from the thalamus to the corresponding regions of primary sensory cortex. By altering this critical cortical input, altered sensory representations could be provided to higher cortical areas, and therefore induce altered performance in tasks which rely on the detection and use of external stimuli.

Clearly, understanding the neurobiological mechanism underlying these deleterious consequences of early tobacco exposure is of great importance from a clinical and therapeutic perspective. For this, the use of animal models of developmental exposure is critical, not only to eliminate the potential confounds relating to maternal IQ, mental health, socio-economic status and education, the home environment, and the genetic susceptibility of both mother and child to psychiatric illness inherent in human studies (Shenassa et al., 2003; Winzer-Serhan, 2008), but also to determine which of the more than 4,000 constituents in tobacco smoke (Smith et al., 2003) are responsible for the effects of developmental tobacco exposure on the

nervous system at a molecular and cellular level. Of these, nicotine is one of the most likely candidates, not only because it is the main psychoactive component in tobacco, but also because the fetal brain expresses nicotinic acetylcholine receptors (nAChRs), the primary targets for nicotine in the brain, at a very early stage (Cairns and Wonnacott, 1988; Larsson et al., 1985; Navarro et al., 1989; Slotkin, 1998; Sugiyama et al., 1985; Zoli et al., 1995), providing a window of vulnerability to developmental nicotine exposure in many critical neurodevelopmental processes. We will therefore review studies conducted in animal models suggesting that developmental nicotine exposure is a critical determinant of the psychiatric and behavioral effects observed in tobacco exposed human children, and we will summarize the evidence that nicotine-mediated alterations to neuronal ensembles responsible for the processing of sensory stimuli, and in particular the relays between the sensory thalamus and cortex, are an essential underlying factor for these effects.

Rodent Models of Developmental Nicotine Exposure

Rodent exposure models typically involve maternal nicotine administration via repeated injection, osmotic mini-pump, drinking water, intravenous infusion, or inhalation to simulate *in utero* exposure in the first two human trimesters (Carmines et al., 2003; Gaworski et al., 2004; LeSage et al., 2006; Winzer-Serhan, 2008). Due to developmental differences, the first three postnatal weeks in the rodent appear to correspond to the third trimester of human pregnancy, particularly for thalamic and cortical development (Dobbing and Sands, 1979; Eppolito and Smith, 2006). Continued nicotine exposure can be achieved in this period via the milk of exposed dams (Narayanan et al., 2002), or via repeated injection, oral administration or gastrostomy of the pups (Winzer-Serhan, 2008).

When considering these models, it is important to note that studies using rats and mice are not directly comparable, as there are critical differences in nicotine metabolism between these species (Matta et al., 2007). Methods of nicotine delivery are also differentially effective across these species, with rats found to have difficulty with nicotine administration via drinking water (Murrin et al., 1987), while mice tolerate this approach well (Pauly et al., 2004; Rowell et al., 1983; Sparks and Pauly, 1999). In contrast, repeated nicotine injections in mice may induce a conditioned tolerance which elevates glucocorticoid secretion and is independent of the effects of the drug (Sparks and Pauly, 1999).

Within a species, studies using different nicotine administration routes may also be difficult to compare since the magnitude and pattern of exposure is different between them. For example, minipumps provide stable nicotine levels, while injection or maternal drinking induce cyclical, transient increases. In addition, maternal stress and fetal hypoxia are differentially induced by these methods (Pauly et al., 2004; Slotkin, 1998). The importance of route of administration is demonstrated in studies showing that injection and osmotic mini-pump administration of 6 mg/kg/day nicotine in rat dams have very different effects on open field ambulation and exposure induced neurochemical changes in the pups (Muneoka et al., 1997).

Behavioral Consequences of Developmental Nicotine Exposure in Rodents

As noted previously, one of the most prominent co-morbidities with maternal smoking is an increased risk of attention deficit hyperactivity disorder (ADHD) in the offspring (Button et al., 2007). With the widespread use of psychostimulants to control ADHD symptoms in children (Olfson et al., 2003), it is important to understand how developmental nicotine exposure may induce this disorder. This may help elucidate the etiology of ADHD and lead to the development of non-psychostimulant based therapeutics. Interestingly, a recent trial of the nAChR partial agonist ABT-089 had beneficial effects in adult ADHD (Wilens et al., 2006). In animal models, measurement of locomotor activity and analysis of performance in a variety

of cognitive tasks after developmental nicotine exposure have both been used as measures of ADHD-like symptoms.

Locomotor Activity

As noted above, there are several factors that make comparisons across animal developmental exposure studies difficult. Consequently, it is perhaps not surprising that a clear consensus on the effects of developmental nicotine exposure on locomotor activity in rodents remains elusive. In the rat, several studies have demonstrated hyperactivity following developmental exposure to nicotine (Peters et al., 1979; Richardson and Tizabi, 1994; Thomas et al., 2000; Tizabi et al., 1997; Tizabi et al., 2000; Vaglenova et al., 2004); however, no significant alteration in activity has been detected in a few studies (Gaworski et al., 2004; Paulson et al., 1993; Shacka et al., 1997) and evidence of hypoactivity (LeSage et al., 2006; Peters and Tang, 1982; Romero and Chen, 2004) has also been reported. Several factors could contribute to the significant disparity observed between these studies, including the dose of nicotine used, the route of administration selected and the length of the exposure period. In addition, the age of the exposed animals when behaviorally evaluated and the precise nature of the behavioral paradigm are also likely to be important. While indirect exposure effects, such as nicotine-induced hypoxia, could also play a significant role in determining the behavioral outcome observed, this somewhat indiscriminate and global process appears to make a relatively inconsistent contribution to locomotion, with both hyperactive (Peters et al., 1979) and hypoactive (Peters and Tang, 1982) offspring exhibiting weight deficits, indicative of exposure to hypoxia.

In contrast to the complex findings in the rat, the effects of developmental nicotine exposure on locomotor activity in the mouse appear to be more consistent and better correlated with human findings. For example, male mice of the Swiss-Webster strain exposed via repeated maternal nicotine injections are hyperactive during adolescence (Ajarem and Ahmad, 1998). Hyperactivity was also observed in 60–100 day old mice of both sexes of the C57BL6/J strain after developmental nicotine exposure via maternal drinking water administration (Paz et al., 2007). This observation is consistent with an earlier study which found both 40 and 60 day old male C57BL6/J mice show locomotor hyperactivity and enhanced stereotypy counts after nicotine exposure via the same route (Pauly et al., 2004). Interestingly, developmentally exposed female C57BL6/J mice in this study exhibited hypoactivity at 20 days of age, though this effect was not apparent at 40 or 60 days of age (Pauly et al., 2004).

These disparate findings in rodent models emphasize that it is likely that the dose, route, timing, duration and pattern of nicotine exposure are all critical factors in determining the behavioral phenotype observed. In humans, these data may suggest that differences in exposure contribute to the individual differences in the susceptibility to develop ADHD and the magnitude of the symptoms. This is of great importance as the debate over the safety of nicotine replacement therapy use by pregnant women continues (Slotkin, 2008; Winzer-Serhan, 2008).

Sensory Processing

As noted previously, studies in humans have suggested that, while detection of auditory stimuli is unaffected (Trammer et al., 1992), there is an impairment of auditory processing in children exposed to tobacco smoke *in utero* (Saxton, 1978; Picone, 1982; Fried and Makin, 1987; Fried et al., 1992a; Fried and Watkinson, 1988, 1990, 2001; Fried et al., 1992b, 1998b, 2003; Fried et al., 1997; Kristjansson et al., 1989; McCartney et al., 1994). Studies in rodents have also indicated some disruptions in tasks involving auditory processing following developmental nicotine exposure. For instance, developmentally-exposed rats show reduced pre-pulse inhibition to auditory stimuli (Popke et al., 1997), and can have reductions in peak acoustic startle responses (Gaworski et al., 2004). Significantly, both studies reported differential effects

of nicotine exposure based on stimulus magnitude. Reduced pre-pulse inhibition was observed in response to a 98 dB tone, but not a 112 or 122 dB tone (Popke et al., 1997) and startle response was reduced in response to an 80dB but not a 120dB stimulus (Gaworski et al., 2004), suggesting that developmental nicotine exposure may have minimal effects on the processing of supra-threshold auditory stimuli but would impair the processing of stimuli with a smaller magnitude. Impairment at lower stimulus magnitudes may be a consequence of a nicotine-induced reduction in the signal-to-noise ratio in the circuits responsible for auditory processing. The fact that responses to higher magnitude stimuli are not affected would suggest the circuits themselves are intact and broadly functional, and that the more intense stimuli can overcome a nicotine-induced reduction in the efficiency of the system. As the auditory brainstem responses of humans are unaffected by developmental nicotine exposure (Trammer et al., 1992), a likely locus of such a nicotine-mediated reduction in processing efficiency is the circuitry connecting the thalamus and the sensory cortex.

Attention and Cognitive Processes

As noted previously, developmental tobacco smoke exposure can induce cognitive and attentional deficits in both the visual and auditory domains in humans (Fried and Makin, 1987; Fried et al., 1992a; Fried and Watkinson, 1988, 1990, 2001; Fried et al., 1992b, 1998b, 2003; Fried et al., 1997; Kristjansson et al., 1989; McCartney et al., 1994; Jacobsen et al., 2007; Jacobsen et al., 2006). Studies using rodent models have indicated that developmental nicotine exposure may be sufficient to induce cognitive and attentional deficits in a variety of tasks.

For example, developmentally exposed rats are impaired in performing fixed ratio, variable interval discrimination and discrimination reversal schedule appetitive tasks (Martin and Becker, 1971), which is suggestive of aberrantly rigid cognitive processing. Developmental exposure also induces deficits in radial arm maze performance, suggesting deficits in learning and attentional control (Sorenson et al., 1991) and impaired spatial reference memory, with no apparent deficits in spatial working memory, as demonstrated using an Atlantis platform version of the Morris Water Maze (Eppolito and Smith, 2006). Age-dependent differences in the rate of spontaneous alternation in the T maze have also been observed in nicotine exposed rats (Levin et al., 1993). Consistent with these observations, in mice of the HS/Ibg strain, developmental nicotine exposure impairs performance in both the radial arm maze and the Morris water maze (Yanai et al., 1992).

However, as noted previously, it is apparent that the dose, route, duration and timing of exposure are critical to the development of deficits in these tasks, with some studies reporting no significant exposure effects in the radial arm maze, Morris water maze, T-maze or Cincinnati water maze tasks (Cutler et al., 1996; Huang et al., 2007; Levin et al., 1996; Paulson et al., 1993). It also appears that animals exposed to nicotine during development may be more sensitive to the effects of stress on cognitive function. For example, in one study, developmental nicotine exposure had little effect on radial arm maze performance unless the test environment was altered, thereby stressing the animals (Levin et al., 1996).

Based on these data, developmental nicotine exposure in rodents, like tobacco smoke exposure in humans, can impair cognitive and attentional function, though the magnitude of the effects can be variable and may depend on the level of stress experienced during testing. However, these data are derived from tasks in which higher cognitive processing may predominate over lower level sensory integration; thus, it is difficult to assess the contribution of sensory processing to the impaired performance in these tasks. Therefore, it is instructive to examine the effects of developmental nicotine exposure on the performance of rodents in tasks in which sensory processing is relatively more critical, such as paradigms involving aversive sensory stimuli.

In a rat study, nicotine exposed offspring acquired avoidance conditioning more rapidly than controls (Bertolini et al., 1982). A subsequent study showed that nicotine administered by injection on gestational days 1–20 improved learning in a two-way active avoidance task in females but impaired the process in male rats (Genedani et al., 1983). Similarly, adult male rats exposed to nicotine via injection on postnatal days 8–12 were impaired in learning an auditory-cued active avoidance task (Liang et al., 2006), while no significant effect on learning was observed in a visual and auditory-cued active avoidance task in female rats exposed to nicotine prenatally (Paulson et al., 1993), or in rats of either sex exposed via maternal inhalation of cigarette smoke in a passive avoidance paradigm (Gaworski et al., 2004). A similar hypersensitivity to developmental nicotine in males is also observed in mice, as the male offspring of C57BL6/J mice exposed to nicotine via drinking water showed enhanced learning in a trace fear conditioning task, with no significant alteration in learning observed in females (Paz et al., 2007). The interaction of sex, developmental nicotine and route of administration is consistent with sex differences observed in human studies showing that following maternal smoking, males were impaired in performance of an auditory attentional tasks while female subjects were not (Jacobsen et al, 2007).

The ability of developmental nicotine exposure to modulate performance in tasks relying on auditory cues suggests that nicotine may alter the strength of neurotransmission in areas of the brain responsible for transmitting sensory information for use in cognitive tasks. A selective effect of nicotine on sensory processing rather than signal detection is supported by data showing that there is no evidence of a basic auditory detection deficit in developmentally exposed rats performing an auditory-cued active avoidance task (Liang et al., 2006). This is also consistent with the absence of auditory detection deficits in tobacco-exposed humans (Trammer et al., 1992).

Significantly, mice in which the expression of nAChRs containing the β2 nAChR subunit (β2* nAChRs, where * indicates other subunits) is genetically manipulated, also show important differences in performance of avoidance tasks. In particular, β2 nAChR subunit knock-out mice, which lack all high affinity nAChRs, are hypersensitive in performance of a passive avoidance task, with no change in the unconditioned pain response to the stimulus (Picciotto et al., 1995), suggesting that these animals may find the foot-shock stimulus used in this paradigm relatively more salient than wild-type mice, despite an equivalent response to the direct sensory stimulus. The hypersensitive passive avoidance performance of β2 nAChR subunit knockout mice can be rescued by transgenic expression of the β2 nAChR subunit exclusively in corticothalamic neurons during development (King et al., 2003). These neurons are part of a corticothalamic-thalamocortical feedback relay between primary sensory cortical areas and the thalamus, and this ensemble is responsible for the transfer of sensory information to cortex for use in cognitive tasks, and cortical feedback to the thalamus for gating of sensory information (Brumberg et al., 2003; Guillery and Sherman, 2002; Sherman and Guillery, 1998, 2002). Furthermore, knocking out these corticothalamic nAChRs exclusively during adulthood has no effect on passive avoidance performance, suggesting that the critical period for nicotinic modulation of this circuit is during early postnatal development (King et al., 2003). It seems likely, therefore, that modulation of β2 subunit-containing nAChRs on corticothalamic neurons during perinatal development is important for setting the synaptic strength of these glutamatergic neurons, and that long-term alteration of signaling in corticothalamic loops is responsible for hypersensitivity to sensory stimuli leading to altered performance in tasks dependent on sensory information.

Neurobiological Consequences of Developmental Nicotine Exposure

Based on observations in both developmentally exposed and genetically modified rodents, it seems clear that nicotine, acting via nAChRs, modulates the development of neuronal

ensembles underlying the processing of sensory input, which may underlie the behavioral alterations observed in both rodents and humans. The mechanisms by which nicotine exerts these effects are largely unclear, in part due to the wide variety of effects developmental nicotine administration can have at the molecular and cellular levels, but a number of studies have provided potential pathways that may contribute to these effects.

Developmental Regulation of nAChR Number

One consequence of chronic nicotine exposure is an increase in high affinity nicotine binding (Wonnacott, 1990). As noted previously, nAChRs are expressed in the fetal brain (Cairns and Wonnacott, 1988; Larsson et al., 1985; Navarro et al., 1989; Slotkin, 1998; Sugiyama et al., 1985) and persistent increases in nicotine binding have been observed after developmental nicotine exposure in a number of rodent models (Hagino and Lee, 1985; Miao et al., 1998; Narayanan et al., 2002; Slotkin et al., 1987; Tizabi and Perry, 2000), with evidence that $\alpha4\beta2*$ nAChRs are more sensitive to upregulation than $\alpha7$ nAChRs, which is consistent with the subtype selective upregulation observed in adulthood (Huang and Winzer-Serhan, 2006). While these data indicate nAChR up-regulation may make a significant contribution to the neurobiological consequences of developmental nicotine exposure, other mechanisms are potentially more critical, as suggested by observations of relatively poor correlation between nAChR upregulation and behavioral alterations (Tizabi et al., 1997)(Liang et al., 2006) or in the presence of nAChR downregulation (Tizabi et al., 2000) and evidence of relatively poor correlation between nAChR upregulation and behavioral alterations (Tizabi et al., 1997).

Neurochemical Effects of Developmental Nicotine Exposure

Examination of the neurochemical consequences of exposure in rodents has suggested several parallels with the alterations observed in the ADHD brain. For example, psychostimulants modulate both the dopaminergic (DA) and noradrenergic (NE) systems and have significant therapeutic benefit in ADHD (Potter et al., 2006). Similarly, a number of studies have demonstrated alterations in the DA and NE systems as a result of developmental nicotine exposure. In particular, developmental nicotine can reduce DA turnover in the forebrain but not the brainstem of rats (Muneoka et al., 1997). Consistent with this study, mini-pump exposure to nicotine during prenatal development resulted in increased DA turnover at prenatal day 18 (P18), but reduced DA turnover in this region at 15 days of age (only males) and in adulthood (in both sexes) (Ribary and Lichtensteiger, 1989). Reduced neocortical DOPAC has also been observed after maternal nicotine injections in a more recent study (Muneoka et al., 1999). At the receptor level, alterations in D_2 receptor binding in the striatum and nucleus accumbens after developmental nicotine exposure have also been observed (Richardson and Tizabi, 1994; Fung and Lau, 1989).

As was seen for DA turnover, nicotine exposure can induce increased NE turnover in the forebrain at P18 (Ribary and Lichtensteiger, 1989), followed by decreased turnover at 15 days of age, an effect which persists into adulthood in males (Ribary and Lichtensteiger, 1989). It is interesting that NE turnover was affected selectively in males as a result of nicotine exposure, since an early maternal drinking water study reported elevated adrenergic receptor binding exclusively in male offspring (Peters, 1984).

The data showing that developmental nicotine exposure results in alterations in DA and NE in the neocortex is significant, since catecholaminergic signaling in the prefrontal cortex is thought to be disrupted in patients (Arnsten, 2006b). To reinforce the relevance of animal studies of nicotine exposure and the link between developmental tobacco exposure and ADHD, rats developmentally exposed to nicotine exhibit both hyperactivity and disruptions in the DA system (Richardson and Tizabi, 1994). Further, it is especially interesting that males appear to be more susceptible to changes in forebrain catecholamines, since boys are more likely to be

diagnosed with ADHD and may display a different spectrum of symptoms compared to girls (Staller and Faraone, 2006) and since boys are more susceptible to disruptions in auditory attention following developmental nicotine exposure than girls (Jacobsen et al, 2007).

Developmental nicotine exposure can also result in alterations of the serotonergic system, with age-dependent reductions in serotonin turnover observed in the forebrain, brainstem and cerebellum of exposed animals (Muneoka et al., 1997). In addition, alterations in the expression of the serotonin transporter and the $5HT_{1A}$ and $5HT_2$ receptors have been observed after developmental nicotine exposure, as has disruption of adenylyl cyclase activity, a critical downstream component of serotonin signaling (Muneoka et al., 2001; Slotkin et al., 2007a; Slotkin et al., 2007b). Alterations in the serotonergic system may contribute to some aspects of ADHD symptomology (Oades, 2007), with disruptions in the cerebellum of particular interest, given the emerging role for this structure in cognition (Arnsten, 2006a) and sensory processing (Gao et al., 1996).

While these data are suggestive of direct disruption of monoaminergic systems by nicotine exposure, it is important to note that inappropriate modulation of the endogenous cholinergic system, with its extensive cortical innervation, close association with the DA system and role in both top-down and bottom-up information processing, may also be a significant contributor to the neurochemical and behavioral deficits observed following developmental exposure (Potter et al., 2006).

Molecular and Cellular Consequences of Developmental Nicotine Exposure

While the neurochemical alterations noted are of great value, it is difficult to determine whether these changes are directly responsible for the behavioral effects observed or if they are a consequence of other nicotine-induced changes at the molecular and cellular levels. From the viewpoint of therapeutic intervention for As noted previously, neuronal nAChRs are expressed at an early stage of neurodevelopment (Zoli et al., 1995) and, as a consequence, early nicotine exposure could affect a wide variety of developmental processes. In particular, by acting as an nAChR agonist, nicotine could inappropriately mimic endogenous acetylcholine (ACh) signals, which are necessary for normal synaptic development (Liu et al., 2007). Nicotine could also disrupt ACh signaling by inducing inappropriate nAChR desensitization or upregulation, thereby modulating the magnitude of cholinergic signaling. Thus, neurodevelopmental events known to be regulated by ACh are potential targets that can be evaluated as mediators of nicotine's effects on developmental processes. For example, ACh, acting via nAChRs, is critical for growth cone turning in cultured spinal neurons from the frog *Xenopus* (Zheng et al., 1994). Thus, both activation/up-regulation or desensitization of nAChRs could influence neuronal pathfinding in the developing nervous system. Indeed, both ACh and nicotine cause neurite retraction in chick ciliary ganglion neurons that can be blocked by the α7 nAChR antagonist α-bungarotoxin (Pugh and Berg, 1994). Clearly, mistargeting of neurons in development could have significant effects on the mature nervous system; for instance, even slight mistargeting of corticothalamic neurons could disrupt the efficiency of sensory feedback from cortex to thalamus and thereby contribute to the sensory processing deficits observed following early tobacco exposure.

It has also been shown that stimulation of nAChRs by ACh is critical for the conversion of GABAergic signals from excitatory to inhibitory, which is a critical step in the maturation of the GABA system (Liu et al., 2006). Inappropriate nAChR activity mediated by developmental nicotine exposure could affect the timing of this process, which could have significant effects on the subsequent development of the nervous system, as appropriate GABAergic signaling is important in modulating neuronal precursor proliferation and migration and, at later stages, dendritic structure and therefore, the development and refinement of neuronal circuits and networks (Represa and Ben-Ari, 2005).

Indeed, nicotine exposure can clearly modulate neuronal structure, with evidence of altered axonal and dendritic branching in cultured hippocampal neurons after nicotine exposure (Audesirk and Cabell, 1999), altered prelimbic cortex pyramidal neuron dendritic length in animals after adolescent or adult nicotine exposure (Bergstrom et al., 2008) and altered motor cortex pyramidal neuron branching after exposure in adult animals (Gonzalez et al., 2005). Therefore, it is not surprising that developmental nicotine exposure can alter dendritic structure in both the somatosensory cortex (Roy and Sabherwal, 1994) and the hippocampus (Roy and Sabherwal, 1998), areas critical to sensory processing and learning and memory respectively.

From these data, it seems clear that developmental nicotine exposure can induce a variety of alterations in neurons at the molecular and cellular levels. These changes could result in altered synaptic organization, and therefore disrupted network structures. Consequently, aberrantly structured ensembles of neurons could result in altered processing of sensory input in individuals exposed to tobacco during development.

Consequences of Developmental Nicotine Exposure for Synaptic Plasticity

Given the effects of nicotine on molecular and cellular processes in developing neurons, it seems likely that developmental nicotine exposure should also result in changes in the electrophysiological properties of neurons as a result of aberrant synaptic plasticity. Consistent with this hypothesis, exposure of rat pups to nicotine in early postnatal life via gastrostomy alters the P3 component of event-related potentials (ERP) in the dorsal hippocampus in response to auditory stimulation, which may suggest an effect of nicotine on auditory stimulus evaluation and auditory memory (Ehlers et al., 1997). A subsequent study using the same exposure paradigm with a higher nicotine dose (6mg/kg/day compared to 1 or 4mg/kg/day) reported a significant decrease in power in the low delta band and a higher frequency in the hippocampal electroencephalogram and similar alterations in the hippocampal P3 component of the ERP in response to auditory stimulation (Slawecki et al., 2000). These findings are consistent with disrupted sensory processing (Slawecki et al., 2000).

Furthermore, nicotine selectively enhanced the NMDA receptor-mediated component of excitatory postsynaptic potentials (EPSPs) in glutamatergic thalamocortical neurons in slices from 8–16, but not 19–24, day old rats (Aramakis and Metherate, 1998) suggesting that there is a critical period for vulnerability to nicotine exposure. This effect involved activation of $\alpha 7$ nAChRs and enhancement of glutamate release (Aramakis and Metherate, 1998). Nicotine exposure exclusively during the second postnatal week in the rat also induced a similar enhancement of NMDA-mediated EPSPs in auditory cortex and, in addition, induced an increase in stimulus-evoked miniature EPSPs in this region (Aramakis et al., 2000). These alterations in the physiological properties of thalamic and cortical neurons were paralleled by increases in the mRNA encoding the NR2A subunit of the NMDA receptor in the auditory cortex for up to two weeks after exposure, and decreased NR2B subunit expression in the medial geniculate nucleus of the thalamus for one week after exposure (Hsieh et al., 2002). Critically, chronic nicotine exposure eliminates the ability of an acute nicotine challenge to enhance the EPSP (Aramakis and Metherate, 1998). These data therefore suggest that developmental nicotine exposure could disrupt the normal synaptic refinement of thalamocortical loops by endogenous ACh in response to sensory input that underlies the proper transmission of auditory stimuli between thalamus and cortex (Aramakis and Metherate, 1998).

In adult animals, acute nicotine administration enhanced local field potentials in the auditory cortex in response to a tone stimulus and increased the duration of the tone-evoked response while decreasing the latency of response onset in layer IV neurons of this region (Liang et al., 2006). These observations suggest that acute nicotine and, by extension, endogenous ACh, can increase the sensitivity and responsiveness of the cortex to auditory stimuli (Liang et al.,

2006). Significantly, prior nicotine exposure during the second postnatal week can largely prevent these acute nicotine induced effects (Liang et al., 2006). These data suggest that developmental nicotine exposure compromises the ability of the auditory processing circuitry to respond to both endogenous ACh and acute nicotine in adulthood, and therefore results in the loss of the ability to adjust the sensitivity and responsiveness of the system dynamically, which could be critical in the appropriate processing of auditory stimuli.

A role for nAChRs in the processing of sensory stimuli is also suggested by a recent study showing that α4β2* nAChRs on the axons of thalamocortical neurons in adult mice can modulate the transfer of stimulus-evoked neuronal activity from thalamus to cortex (Kawai et al., 2007). Acute nicotine enhanced the probability of action potential generation in response to sub-threshold stimulation, increasing the excitability of axons, reducing the latency of spiking and enhancing synchronous activity in these neurons (Kawai et al., 2007). While the effects of developmental nicotine exposure were not explicitly evaluated, it is tempting to speculate that these axonal nAChRs would also be susceptible to exposure in developing neurons, resulting in a persistent alteration in the ability to modulate sensory information transmission to the cortex in developmental tobacco exposed individuals.

Taken together, these data indicate that developmental nicotine exposure, via α7 and α4β2* nAChRs, can alter the subsequent physiological activity of thalamocortical neurons which relay auditory stimulus evoked neuronal activity from the thalamus to the primary auditory cortex, both at the synaptic and axonal levels. This inappropriate modulation could induce a sensory processing deficit, and therefore behavioral alterations in response to sensory stimuli. Indeed, it is tempting to speculate that the disruptions observed in the auditory system could be applied to other sensory modalities (Aramakis and Metherate, 1998) and therefore, these mechanisms could contribute to the altered avoidance performance of animals exposed to nicotine in development noted above.

Conclusions

From the evidence presented here, developmental nicotine exposure can clearly exert a variety of effects on the developing nervous system. These alterations, which encompass changes at all levels of analysis, from individual molecules to neuronal structure, can persist into adulthood and may underlie the behavioral, cognitive and attentional differences observed in developmentally exposed humans and animals.

In particular, a strong case can be made for nicotine-induced alterations in the development of neuronal ensembles responsible for the transmission of sensory information and feedback between primary sensory cortical areas and their corresponding thalamic nuclei. Based on observations in the rodent auditory system (Aramakis et al., 2000; Aramakis and Metherate, 1998; Hsieh et al., 2002; Liang et al., 2006), nAChRs are critical during development for the appropriate modulation of the NMDA receptor mediated component of synaptic transmission into the primary auditory cortex, via the thalamocortical relays from the medial geniculate thalamic nucleus. By disrupting the synaptic refinement of this system, developmental nicotine exposure may permanently alter the efficacy of the circuit and induce a loss of the dynamic control of the sensitivity and responsiveness of the system to stimuli modulated by endogenous ACh release in adulthood. Critically, this mechanism may have a role in the development of other sensory cortical systems beyond the auditory system (Aramakis and Metherate, 1998), thereby making them equally vulnerable to developmental nicotine exposure, consistent with the impairment in visual attention observed in human subjects exposed to tobacco during development (Jacobsen et al., 2007).

Furthermore, from observations in genetically modified mice (King et al., 2003; Picciotto et al., 1995), it is apparent that nAChRs are required on corticothalamic neurons during development for normal sensitivity to passive avoidance behavior in adulthood. These nAChRs are not necessary for normal performance of this behavior when these neurons are mature, emphasizing their critical function in the development of the feedback relay between the primary sensory cortex and thalamus. It is tempting to speculate that these β2* nAChRs perform a similar function in the synaptic refinement and modulation of the corticothalamic neurons to the α7 nAChRs on the developing thalamocortical relays. Consequently, developmental nicotine exposure could interfere with the synaptic refinement of these projections and disrupt the transmission of feedback from sensory cortex to the corresponding thalamic nuclei, compromising the ability of the thalamus to appropriately gate sensory information for transmission to the cortex in the mature organism.

In addition, in mature mouse auditory thalamocortical relays endogenous ACh, via axonal α4β2* nAChRs, also has a role in gating the transmission of neuronal activity from the thalamus to the cortex (Kawai et al., 2007). This provides another mechanism which could be perturbed by developmental nicotine exposure, since disruption of this system by inappropriate nAChR upregulation or desensitization in development could induce aberrant transmission of sensory stimulus evoked neuronal activity to the cortex in adulthood.

It is clear that developmental nicotine exposure, acting via nAChRs, can have significant effects on the development and refinement of the neuronal relays between the thalamus and cortex. Based on this observation, it is therefore reasonable to suggest that a nicotine exposed organism would exhibit the behavioral manifestations of a sensory processing deficit, with the thalamocortical branch of this circuit responsible for the transfer of sensory information to the cortex and the corticothalamic branch critical for appropriate modulation of the firing properties of these relays (Brumberg et al., 2003; Guillery and Sherman, 2002; Sherman and Guillery, 1998, 2002). Indeed, compromised communication between the cortex and thalamus may not only affect transmission and modulation of the sensory information relay to the cortex and thereby result in altered cortical computation, but may also impact this process more directly due to the potential role of the thalamus itself in computational processes (Sherman and Guillery, 2002).

Finally, it is possible that disruptions in this thalamocortical-corticothalamic circuitry could contribute to the attentional disruptions observed in ADHD, as individuals exposed to tobacco during development would be impaired in their ability to modulate the transfer and initial processing of sensory information in the cortex. In addition, endogenous ACh has a critical role in modulating attention (Rasmusson, 2000), and this could also be disrupted by developmental nicotine exposure due to alterations in nAChR number and sensitivity. Thus, it is perhaps not surprising that a cholinergic contribution to the etiology of ADHD is suspected (Potter et al., 2006) and that compounds active at nAChRs have some therapeutic benefit in these patients (Wilens et al., 2006).

In summary, developmental tobacco exposure has been associated in humans with an increased risk of deficits in cognition, attention, sensory processing and neuropsychiatric disorders such as ADHD. Animal models of developmental exposure to nicotine suggest that it is the component in tobacco responsible for many of the effects observed in humans. There is evidence to suggest that nicotine-mediated disruptions occur in the neuronal ensembles controlling the transfer of sensory information between the thalamus and primary sensory cortex, and that alterations in this circuitry contribute to the behavioral effects of developmental nicotine exposure. These studies suggest that treatments that can reverse the aberrant synaptic plasticity caused by early nicotine exposure could be useful for the treatment of the attentional and sensory processing deficits observed in tobacco-exposed individuals.

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