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Short- and Long-Term Consequences of Nicotine Exposure during Adolescence for Prefrontal Cortex Neuronal Network Function

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More than 70% of adolescents report to have smoked a cigarette at least once. At the adolescent stage the brain has not completed its maturation. The prefrontal cortex (PFC), the brain area responsible for executive functions and attention performance, is one of the last brain areas to mature and is still developing during adolescence. Smoking during adolescence increases the risk of developing psychiatric disorders and cognitive impairment in later life. In addition, adolescent smokers suffer from attention deficits, which aggravate with the years of smoking. Recent studies in rodents reveal the molecular changes induced by adolescent nicotine exposure that alter the functioning of synapses in the PFC and that underlie the lasting effects on cognitive function. Here we provide an overview of these recent findings.

Adolescence is a truly revolutionary time period in anyone's life, the age of explosive development of both emotional and cognitive sides of the mind. This is the age when passions ignite, when creativity is at its peak, bold and original ideas shake old theories, friendships and first loves are found, and important breakthroughs are made. But adolescence also has a dark side. The uncontrollable emotions create a risk zone for behavioral problems, psychopathology, and addiction. To quote John Ciardi: "You don't have to suffer to be a poet. Adolescence is enough suffering for anyone." Indeed, adolescence also marks a period of increase in the number of suicides, accidents, homicides, mood disorders, unwanted pregnancies, anorexia, bulimia, and substance abuse, such as tobacco smoking (Resnick et al. 1997; Ozer et al. 2004).

What makes adolescence such a painful period some people are happy to survive? The answer may lie in adolescent brain development. Brain development continues throughout adolescence, although the speed and timing of maturation varies for different brain areas (Gogtay et al. 2004). Subcortical limbic structures important for emotional processing, such as hypothalamus, midbrain dopamine areas, nucleus accumbens, dorsal and ventral striatum, and amygdala, experience a major developmental boost around the onset of puberty (Sowell et al. 2003; Casey et al. 2005). Their maturation is important for social and sexual

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behaviors and is triggered by pubertal hormones. In contrast, development of frontal cortical areas of the brain, responsible for cognitive control over behavior, depends on age and experience and continues throughout adolescence and into adulthood (Sowell et al. 2003; Giedd 2004). Thus, during adolescence emotional drive has already become very strong, whereas cognitive self-control and adult decision-making strategies still are developing. Thereby, brain development may be responsible for characteristic adolescent traits—uncontrollable mood swings, impulsivity, risk taking, and peer-directed social interactions (Orr and Ingersoll 1995; Spear 2000; Galvan et al. 2007). Although indispensable for transition from child to independent status of adult, these traits can backfire and cause damage. Indeed, risk-taking behavior, so typical for adolescents, is associated with high rates of mortality and morbidity among young people (Grunbaum et al. 2004).

The impulsive, peer-influenced nature of adolescent choices leads to another important health risk—experimenting with drugs of abuse. Since nicotine is one of the most socially accepted drugs in our society, the first choice usually falls on tobacco smoking. According to a recent study conducted in 41 countries in Europe and North America, 19% of 15-year-olds smoke at least once a week and 30% report experimenting with cigarettes before the age of 14 (Currie et al. 2008). Serious health risks of smoking are well known: Smoking leads to millions of premature deaths worldwide and tobacco smoking has been marked as an epidemic disease (Peto et al. 1999). Nicotine is also a psychoactive and addictive substance that directly acts on brain areas involved in emotional and cognitive processing. Early exposure to nicotine during the transition from child to adult may be harmful, since it may derange the normal course of brain maturation and have lasting consequences for cognitive ability, mental health, and even personality (Brown et al. 1996; Choi et al. 1997; Richards et al. 2003; Brook et al. 2004; Deas 2006). In this review, we will highlight recent findings that start to uncover causal relations between nicotine exposure during adolescence and cognitive deficits in later life, pinpointing the underlying functional synaptic adaptations in prefrontal networks.

SENSITIVITY TO NICOTINE OF THE ADOLESCENT BRAIN

Comparing smoking behavior of adolescents to that of adults may point to an enhanced sensitivity of the adolescent brain to addictive properties of nicotine. Adolescents report symptoms of dependence even at low levels of cigarette consumption (Colby et al. 2000; Kandel and Chen 2000). The most susceptible youth lose autonomy over tobacco intake already within 1 or 2 days of first inhaling from a cigarette. Among adolescents the appearance of tobacco withdrawal symptoms and failed attempts to stop smoking can precede daily smoking dependence and appear even before consumption reaches two cigarettes per day (DiFranza et al. 2007).

The difference in sensitivity to nicotine between adolescents and adults is also reported for laboratory animals (Slotkin 2002; Adriani et al. 2003). Rats first exposed to nicotine during adolescence self-administer more nicotine than rats exposed in adulthood and these differences in self-administration at first exposure persist into later age (Levin et al. 2003). Similarly, much lower doses of nicotine or a single injection are sufficient to establish conditioned place preference in adolescent rats, but not in adult animals (Vastola et al. 2002; Belluzzi et al. 2004; Brielmaier et al. 2007). Thus, paradigms for both self-administration and conditioned place preference in rats suggest that adolescence may be a developmental stage of particular vulnerability to the effects of nicotine exposure.

The vulnerability to rewarding effects of nicotine during adolescence may be explained by adolescent brain development. Structural and functional MRI data show earlier maturation of reward systems and much slower development of prefrontal cognitive control (Spear 2000; Chambers et al. 2003; Casey et al. 2005; Ernst et al. 2005; Ernst and Fudge 2009). Compared with adults, adolescents are generally more motivated by rewards, are less averse to risks, and are more easily influenced by peers (Spear 2000; Steinberg 2005; Galvan et al. 2006). The same

applies to estimation of health risks of smoking—adolescents have a more optimistic attitude regarding their smoking behavior than adults, believing that they "could smoke for a few years and then quit" if they wished (Arnett 2000). Lack of mature cognitive control in adolescents makes them also more susceptible to social pressure. The smoking behavior of parents, siblings, and friends leads to a higher risk of smoking among adolescents and this social influence decreases with age (Vink et al. 2003). Adolescents with ADHD symptoms, whose behavior is even more characterized by impulsive and risk-taking choices, are more likely to experiment with smoking and to become regular tobacco users (Tercyak et al. 2002; McClernon et al. 2008). Importantly, nicotine may also lead to higher levels of dependence by exerting neurotoxic effects in the prefrontal cortex (PFC) interfering with adolescent cognitive development, executive functioning, and inhibitory control. These effects are particularly evident under stressful or emotionally intense states and are most pronounced when smoking begins during early adolescence (DeBry and Tiffany 2008).

Taken together, most likely owing to its ongoing development, the adolescent brain is more vulnerable to the effects of nicotine than the adult brain. Adolescents progress faster to nicotine dependence than adults, find nicotine more rewarding, underestimate the risks of smoking, and are more influenced by smoking behavior in their social milieu. This may explain why one of five adolescents smokes regularly and up to 70% of adolescents have experimented with smoking (Currie et al. 2008; Sidransky 2010). Because nicotine acts directly on the pathways involved in cognitive control, development of the PFC during adolescence may be affected by nicotine exposure. What are the acute consequences of nicotine exposure for neuronal circuits in the PFC of the adolescent brain?

IMMEDIATE EFFECTS OF NICOTINE ON THE ADOLESCENT PREFRONTAL CORTICAL NETWORK

Once nicotine has entered the body, it is distributed quickly through the bloodstream and crosses the blood–brain barrier reaching the brain within 10–20 sec after inhalation (Le Houezec 2003). Once in the brain, it binds to its target, the nicotinic acetylcholine receptors (nAChR), which take part in cholinergic signaling in the PFC. Twelve genes have been identified encoding neuronal nicotinic receptors (for a review, see Le Novere et al. 2002; Millar and Gotti 2009). In the central nervous system nine α-subunits (α2–α10) and three β-type subunits (β2–β4) are expressed. These subunits assemble in different stoichiometries to form pentameric channels, and subunit compositions of nAChRs vary depending on the brain region (for a review, see Grady et al. 2002; Le Novere et al. 2002; McGehee 2002; Alkondon and Albuquerque 2004; Wonnacott et al. 2005; Mineur and Picciotto 2008; Millar and Gotti 2009). Nicotinic AChRs are cation selective channels that permit the flow of Na^+, K^+, and Ca^{2+} across the membrane, which leads to depolarizing currents and activate neurons (McGehee and Role 1995; Millar and Gotti 2009).

In the PFC, nAChR expression is found across all layers (Gioanni et al. 1999; Poorthuis et al. 2012). nAChRs can alter pyramidal neuron activity by enhancing glutamatergic inputs or by activating postsynaptic receptors directly (Poorthuis et al. 2009). Hippocampal pyramidal neurons express functional α7 nAChR (Ji et al. 2001). In motor cortex, somatosensory cortex, and visual cortex layers II–III and layer V pyramidal neurons do not contain nAChRs (Nicoll et al. 1996; Gil et al. 1997; Xiang et al. 1998; Porter et al. 1999; Gulledge et al. 2007). We find that PFC layers II–III pyramidal cells also do not contain nAChRs, and also glutamatergic inputs to these pyramidal neurons are not modulated by nAChRs. Hence, nAChRs do not augment the output of superficial pyramidal neurons in the PFC.

In contrast, in layer V pyramidal neurons, activation of presynaptic β2* nAChRs on glutamatergic inputs from the thalamus strongly enhances activity of these neurons (Gioanni et al. 1999; Lambe et al. 2003; Couey et al. 2007; Poorthuis et al. 2012). These presynaptic mechanisms are specific to layer V, as they are absent in layers II–III and moderate in layer VI. This

may suggest that nAChR-mediated modulation of thalamic inputs to the PFC is specifically targeting layer V pyramidal neurons, which project to the striatum and hypothalamus (Gabbott et al. 2005). Nicotinic enhancement of thalamic inputs to the cortex also plays a role in primary sensory areas, where it enhances sensory representation in the cortical target structure (Penschuck et al. 2002; Disney et al. 2007; Kawai et al. 2007). In addition to presynaptic $\beta2^*$ nAChRs that can augment its activity, layer V pyramidal neurons also contain postsynaptic $\alpha7$ nAChRs. In contrast to layer V, excitatory glutamatergic inputs to layer VI pyramidal neurons were mildly modulated by nAChRs. These neurons are modulated by $\beta2^*$ nAChRs that are responsible for the strong activation of the layer VI neuronal population (Kassam et al. 2008; Poorthuis et al. 2012). Layer VI pyramidal neurons in entorhinal cortex also have been reported to be modulated by non-$\alpha7$ nAChRs, most likely containing $\beta2$ subunits (Tu et al. 2009).

In addition to direct activation of PFC pyramidal neurons by nAChRs, PFC GABAergic interneurons are also directly activated by nAChR stimulation. Interneurons form a highly diverse group of cells with distinct roles in cortical computation (Kawaguchi 1993; Markram et al. 2004). Fast-spiking cells target the perisomatic region of pyramidal neurons (Kawaguchi and Kubota 1997; Kawaguchi and Kondo 2002) and are therefore thought to be involved in regulating the activity window of pyramidal neurons. In somatosensory areas fast-spiking cells regulate feedforward inhibition of incoming thalamic inputs (Sun et al. 2006). Feedforward inhibition in the PFC plays an important role in the integration of hippocampal inputs, which enter the PFC through superficial layers (Jay and Witter 1991; Tierney et al. 2004). Fast-spiking cells in PFC layers II–III contain $\alpha7$ nAChRs, as do about half of the fast-spiking cells in layer V (Poorthuis et al. 2012). nAChR activation on fast-spiking interneurons in PFC layer II/III may alter processing of hippocampal inputs.

Somatostatin-positive cells target distal dendritic regions (Kawaguchi and Kondo 2002; Silberberg and Markram 2007) and can mediate disynaptic inhibition between pyramidal neurons (Kapfer et al. 2007; Silberberg and Markram 2007). Regular-spiking and somatostatin-positive cells in PFC layers II–II and V are positive for nAChRs, suggesting that nAChRs play an important role in modulating feedback inhibition among pyramidal neurons in these layers (Poorthuis et al. 2012).

Increased inhibition through activation of nAChRs expressed by interneurons has been found in many different brain regions (Jones and Yakel 1997; Xiang et al. 1998; McQuiston and Madison 1999; Alkondon et al. 2000; Ji and Dani 2000; Mansvelder et al. 2002; Gulledge et al. 2007). When activated by nAChR stimulation, interneurons can alter activity and plasticity in pyramidal neurons (Xiang et al. 1998; Alkondon et al. 2000; Ji and Dani 2000; Ji et al. 2001; Couey et al. 2007). Increased inhibition can lead to blockade of long-term potentiation (LTP) induction in the hippocampus (Ji et al. 2001) and increase in the threshold for induction of spike-timing-dependent plasticity (STDP) (Couey et al. 2007). Similar mechanisms may play a role across PFC layers because we find that non-fast-spiking cells in all layers express nAChRs.

UP-REGULATION OF nAChRs AND SYNAPTIC mGluRs IN PREFRONTAL CORTEX BY NICOTINE EXPOSURE DURING ADOLESCENCE

A current hypothesis explaining why adolescents are more vulnerable to nicotine addiction is that nicotine has greater positive effects on adolescents than adults, whereas the negative effects associated with nicotine, such as withdrawal, are smaller in adolescents (O'Dell 2009). Nicotine administration during, but not following, adolescence has long-lasting effects on cognitive, addictive, and emotional behavior in rats (Adriani et al. 2003; Iniguez et al. 2008; Counotte et al. 2009, 2011). Furthermore, adolescent animals are more sensitive to nicotine-conditioned place preference than adults and show this at lower nicotine doses (Vastola et al. 2002; Belluzzi et al. 2004; Shram et al. 2006; Brielmaier et al. 2007; Kota et al. 2009).

Adolescent nicotine exposure leads to acute and longer-lasting changes in nAChR binding (Abreu-Villaca et al. 2003; Doura et al. 2008) and function (Kota et al. 2009) in brain regions such as cortex and striatum. We recently found that the adolescent rodent brain is more sensitive to nicotinic receptor up-regulation in the medial PFC (mPFC) than adults (Counotte et al. 2012). Naïve rats show an age-related decrease in ^{3}H-epibatidine labeled high-affinity nicotinic receptors in the mPFC, but not in occipital cortex. Adolescent, but not adult nicotine exposure increases ^{3}H-Epi binding of mPFC receptors on the first day of abstinence following 10 days of nicotine injections. This is paralleled by an mPFC-specific increase in expression of nAChRs containing α4 and β2 (but not α5) subunits. The increased expression of high-affinity nAChRs in adolescents is accompanied by an increase in nicotine-stimulated GABAergic synaptic transmission in the mPFC (Counotte et al. 2012).

One of the first and most common cellular adaptations following chronic nicotine exposure is the up-regulation of nicotinic receptor levels (Dani and Bertrand 2007). Especially α4β2 type of nAChRs appears to be selectively up-regulated via posttranslational mechanisms (Miwa et al. 2011). The up-regulation of α4β2 nAChRs by chronic nicotine treatment has been replicated many times in numerous systems—transfected cell lines, neurons in culture, brain slices, and smokers' brains (Wonnacott 1990; Fu et al. 2009; Lester et al. 2009; Marks et al. 2011; Miwa et al. 2011). Up-regulation is not accompanied by an increase in nAChR subunit mRNA (Marks et al. 1992); instead it leads to increased nAChR protein levels resulting from increased assembly and/or decreased degradation of nAChRs (Marks et al. 2011). Nicotine appears to act intracellularly as a selective pharmacological chaperone of acetylcholine receptor (Lester et al. 2009). It stabilizes nAChRs during assembly and maturation and this stabilization is most pronounced for the highest-affinity nAChR containing α4β2 subunits. Indeed, we found that specifically high-affinity nicotinic receptors containing the α4 and β2 subunits were up-regulated in the adolescent PFC shortly following nicotine exposure. This up-regulation was paralleled by a functional elevation in nicotine-stimulated GABAergic transmission, indicating that functional surface nAChRs are up-regulated as well (Counotte et al. 2012).

Given that pyramidal neurons and excitatory projections in layers II/III of the PFC do not express nAChRs (Poorthuis et al. 2012) the functional consequence of α4β2 nAChR up-regulation on interneurons in layers II/III will be an increased inhibitory transmission in superficial PFC layers. In the deep layers of the PFC, β2 subunits are expressed by both interneurons, as well as layer VI pyramidal neurons and excitatory inputs to layer V pyramidal neurons. An up-regulation of these receptors will lead to a combined increase in activation of pyramidal neurons and interneurons. It follows that during chronic nicotine exposure of the adolescent PFC, the pattern of activity in the prefrontal network may gradually shift toward activation of excitatory neurons in deep layers in the context of increased overall inhibition. This may affect plasticity and refinement of cortical connections (Couey et al. 2007), and because β2-containing nAChRs in the medial PFC control attention performance (Guillem et al. 2011), it may have functional implications for maturation and function of the prefrontal network.

In addition to an up-regulation of nAChRs, we recently found in a large-scale iTRAQ-based proteomics screen of synaptic protein levels in the PFC that metabotropic glutamatergic receptors type 2 (mGluR2) are significantly up-regulated during adolescent nicotine exposure (Fig. 1) (Counotte et al. 2011). These receptors are located presynaptically on glutamatergic synapses and their activation reduces the probability of glutamate release. Thereby, an up-regulation of mGluR2 receptor levels diminishes activity of excitatory glutamatergic synapses in the PFC. Thus, increases in functional nAChR on inhibitory neurons and increased nicotine-stimulated excitation in deep layers of the PFC may be counteracted by reduced excitatory synaptic activity mediated by increased mGluR2 activity.

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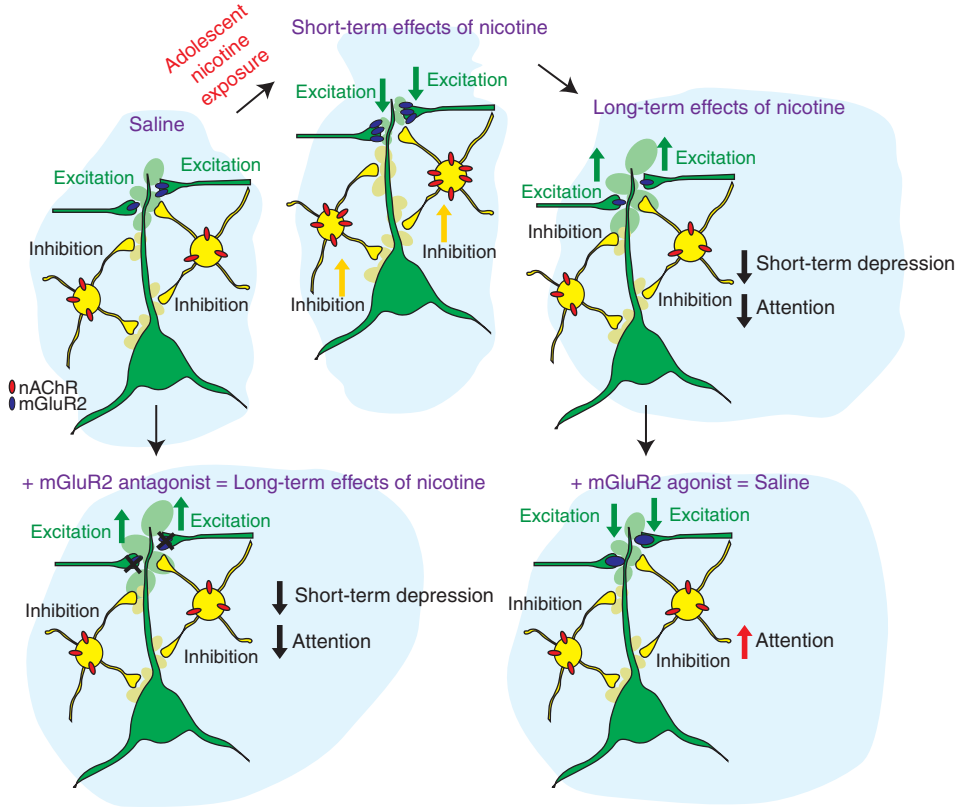

Figure 1. Schematic representation of the short-term and long-term adaptations in prefrontal cortex (PFC) neuronal networks caused by nicotine exposure during adolescence. The *upper* panels show the sequence of adaptations in nAChR and mGluR2 protein levels and the resulting changes in inhibition and excitation and attention behavior from control conditions (saline) to nicotine exposure during adolescence (short-term effects of nicotine) and 5 weeks following nicotine exposure (long-term effects of nicotine). The *lower* panels show the effects of mGluR2 agonists and antagonists in saline and nicotine-exposed animals. Applying mGluR2 antagonists to the adult medial PFC reduces mGluR2 function and short-term depression of glutamatergic synapses and reduces attention performance of the animal. Providing mGluR2 agonists to the medial PFC of adult rats that were exposed to nicotine during adolescence increases mGluR2 function at glutamatergic synapses and improves attention performance.

LONG-TERM CONSEQUENCES OF NICOTINE EXPOSURE DURING ADOLESCENCE

Several studies indicate that smoking during adolescence is associated with disturbances in working memory and attention as well as reduced PFC activation (Jacobsen et al. 2005, 2007; Musso et al. 2007). Although these studies focus on the short-term effects of adolescent smoking on cognition, they show that impaired cognitive processing in PFC already takes place during this age. Importantly, the history of smoking duration in years is correlated with the extent of diminished PFC activity, indicating a progression of deleterious effects of nicotine which may last into later life (Musso et al. 2007). Smoking is a prospective risk factor for impaired cognitive function in later life; heavy smoking predicts incident cognitive impairment and decline (Cervilla et al. 2000; Richards et al. 2003) and middle-aged smokers have a lower psychomotor speed and cognitive flexibility compared to never smokers (Kalmijn et al. 2002). Several studies have shown that adolescent tobacco use is associated with later risk of

developing mental and behavioral problems such as major depressive disorder, agoraphobia, panic disorder, addiction to other substances, antisocial personality disorder, or academic problems (Brown et al. 1996; Brook et al. 1998, 2002; Johnson et al. 2000; McGee et al. 2000; Ellickson et al. 2001).

Animal studies have shown that exposure during adolescence induces stronger changes in gene expression in the PFC than during other periods of development and adulthood (Schochet et al. 2005, 2008; Polesskaya et al. 2007). The adolescent PFC shows maximal nicotine response in gene regulation involved in vesicle release, signal transduction, cytoskeleton dynamics, and transcription, suggesting the role of chronic nicotine exposure in initiating long-term structural and functional adaptations (Polesskaya et al. 2007). The activity of specific early response genes (arc and c-fos) used as a marker for the functional activation of neurons was found to be elevated in adolescent PFC after nicotine exposure (Leslie et al. 2004; Schochet et al. 2005).

The expression of key molecules involved in plasticity is also altered in the PFC by adolescent nicotine exposure. Acute nicotine induces increases in the expression of the dendritically targeted dendrin mRNA in PFC of adolescent but not adult animals. Dendrin is an important component of cytoskeletal modifications at the synapse and therefore can lead to unique plasticity changes in the adolescent PFC (Schochet et al. 2008). Lasting synaptic adaptations involve activation of intracellular signaling pathway and such enzymes as extracellular regulated protein kinase (ERK) and cAMP response element binding protein (CREB). Specifically in the PFC, increases in phosphorylation of both these enzymes were found after repeated nicotine exposure (Brunzell et al. 2003). Also changes in macromolecular constituents indicative of cell loss (reduced DNA) and altered cell size (protein/DNA ratio) can be seen in cortical regions of rodents after adolescent nicotine treatment (Trauth et al. 2000).

Although these findings only describe direct changes after nicotine exposure, altered expression of genes involved in neuroplasticity can lead to structural changes in PFC neurons that last into adulthood. Indeed, repeated nicotine exposure also changes the structure of neurons in medial PFC: it increases both dendritic length and spine density (Brown and Kolb 2001). Long-term changes were observed in dendritic morphology of specific subpopulations of pyramidal neurons and these structural changes depended on the age of drug exposure (Bergstrom et al. 2008).

Also on the behavioral level, nicotine during adolescence leads to persisting deficits. Adolescent, but not adult, nicotine treatment reduces accuracy of correct stimulus detection in a visuospatial attentional task, with an increase in premature and time-out responding. This suggests impaired attention and lack of impulsive control, which is part of normal adolescent maturation (Counotte et al. 2009). Similar nicotine-induced deficits have been found in a serial pattern learning paradigm (Fountain et al. 2008).

Taken together, these studies in rodents show that nicotine exposure during adolescence induces significant changes in gene expression and neuronal morphology in PFC. Thus, nicotine does not only change cholinergic signaling by altering nicotinic receptor levels in the adolescent PFC, but can also lead to secondary adaptations involving structural and functional changes in cognition. What are the changes that underlie the changes in cognitive performance?

LASTING SYNAPTIC ADAPTATIONS IN THE PFC THAT AFFECT COGNITIVE PERFORMANCE IN LATER LIFE

In adult rodents that were exposed to nicotine during adolescence only a handful of proteins show long-term adaptations following adolescent nicotine exposure that persisted into later life. Nicotinic AChR levels in the PFC returned to baseline 5 weeks following adolescent nicotine exposure (Counotte et al. 2012). In contrast, mGluR2 levels show a strong down-regulation at this time (Counotte et al. 2011). Reduced mGluR2 function in medial PFC synapses resulted in impaired attention performance. Stimulating mGluR2s with specific agonists improved

attention performance in animals that were exposed to nicotine during adolescence (Counotte et al. 2011). Interestingly, the association between changes in mGluR2 signaling and nicotine exposure is not limited to the PFC. Also in other brain areas involved in reward processing such as ventral tegmental area (VTA) and the nucleus accumbens (NAcc) lasting adaptations in mGluR2 function follow nicotine exposure and were found to affect rewarding properties of nicotine (Helton et al. 1997; Kenny et al. 2003; Kenny and Markou 2004; Liechti et al. 2007). In these brain areas, activation of mGlu2/3 receptors decreases nicotine self-administration (Liechti et al. 2007), and they play an important role in the development of drug dependence and the expression of the negative affective state observed during withdrawal (Kenny and Markou 2004). However, the role of group II mGlu receptors in withdrawal appears complex and most likely depends on changes in multiple brain areas.

Although the sequence of events linking mGluR2 adaptations to nAChR activation is unknown, it seems that the reasons for its up- and down-regulation pattern after adolescent nicotine exposure may lie in its function. Metabotropic GluR2 receptors are located on presynaptic glutamatergic terminals where they are activated by glutamate spillover to inhibit glutamate release (Mateo and Porter 2007). It was shown that activation of mGluR2s can also regulate release of other neurotransmitters: it can inhibit GABA release via a presynaptic mechanism (Bradley et al. 2000; Pilc et al. 2008). Given the inhibitory role of mGluR2 in neurotransmitter release, its function seems to counteract that of nAChR, which enhances both excitatory and inhibitory synaptic transmission (Lambe et al. 2003; Couey et al. 2007; Poorthuis et al. 2012). The short-term effects of adolescent nicotine exposure most likely involve enhanced levels of inhibition in prefrontal network. Accordingly, we found an initial and transient upregulation of inhibitory mGluR2 receptor directly following nicotine exposure during adolescence (Counotte et al. 2011), which would contribute to the same effect.

In general, factors that lead to enhanced excitation can cause alterations in mGluR2 transmission and cause cognitive deficits (Melendez et al. 2004; Pozzi et al. 2011). Enhanced glutamate release in PFC was found to be associated with attention deficit and loss of impulse control (Pozzi et al. 2011). MGluR2 agonists are effective in improving cognitive deficits if enhanced glutamate release is caused by NMDA receptor antagonists (Pozzi et al. 2011). Furthermore, the important role of prefrontal mGluR2 signaling in cognition is stressed by its link to brain disorders such as depression and schizophrenia. Activation of this receptor has even been proposed as a novel treatment approach for these disorders (Gupta et al. 2005; Palucha and Pilc 2005; Pilc et al. 2008; Conn et al. 2009). Thus, mGluR2 signaling seems to be a good candidate for shaping cognitive behavior and its impairment leads to disturbances in cognitive function.

At the level of synapse function, alterations in mGluR2 levels affect short-term synaptic plasticity in later life. Short-term depression (STD) is reduced in adult animals as a result of nicotine exposure during adolescence (Counotte et al. 2011). In control animals, blocking mGluR2 signaling with mGluR2 antagonists also results in reduced STD. Reduced mGluR2 signaling after nicotine exposure has a similar effect on STD as mGluR2 block by antagonist (Fig. 1). Thereby, mGluR2 may act as an inhibitory feedback mechanism in conditions of excessive excitation and high glutamate release, as occurs when a neuron fires a train of action potentials. Especially at high-frequency stimulation the effect of mGluR2 on STD was most prominent at excitatory synapses on layer V pyramidal neurons in the PFC. The lasting reduction of mGluR2 levels and function after adolescent nicotine exposure leads to reduced inhibitory feedback on pyramidal cells and reduces the regulatory role of this receptor in short-term plasticity. Most likely, activation of mGluR2s affects presynaptic calcium channel function as was found in the calyx of Held, by direct electrophysiological recordings from presynaptic terminals (Takahashi et al. 1996). Agonists of mGluRs suppressed high voltage-activated P/Q-type calcium channels in the presynaptic terminal, thereby inhibiting

transmitter release (Takahashi et al. 1996). Because presynaptic Ca^{2+} dynamics play a key role in short-term plasticity (Zucker and Regehr 2002), decrease in Ca^{2+} current may explain mGluR-dependent modulation of STD.

STD may equip the synapse with low-pass filtering properties, by which the synapse will pass on the first of stimulus in a train of stimuli unaltered, whereas the rest are attenuated. In this manner it shapes the information transfer by synaptic networks and gives rise to sensory and behavioral phenomena (Zucker 1989). For example, in the somatosensory cortex of rat, in vivo whole-cell recordings in cortical neurons during whisker deflection directly showed that synaptic depression of thalamic input to the cortex contributes to rapid adaptation of sensory responses (Chung et al. 2002). Selective attention, the ability of an organism to filter out relevant information in the face of distractors, can build on just such a synaptic process. Layer V pyramidal neurons in PFC handle diverse incoming information from mediodorsal thalamus and from local neurons, and these connections are important in mediating executive functions such as, for example, working memory (Floresco et al. 1999). STD on this level may represent a higher level of sensory adaptation that can be expressed as decreased levels of attention and responsiveness. Reduced short-term plasticity after nicotine exposure compromises the ability of prefrontal neurons to efficiently filter out irrelevant information.

CONCLUDING REMARKS

The prefrontal cortex, the brain area responsible for executive functions and attention performance, is one of the last brain areas to mature and is still in the process of developing during adolescence. This places the adolescent brain in a vulnerable state of imbalance, susceptible to the influence of psychoactive substances such as nicotine. In prefrontal networks nicotine modulates information processing on multiple levels by activating and desensitizing nicotine receptors on different cell types and in this way affects cognition. The adolescent brain is particularly sensitive to the effects of nicotine. Studies in human subjects indicate that smoking during adolescence increases the risk of developing psychiatric disorders and cognitive impairment in later life. In addition, adolescent smokers suffer from attention deficits, which aggravate with the years of smoking.

From studies in the rodent brain it is becoming clear that on the short-term, adolescent, but not adult, nicotine exposure increases the expression of nAChRs containing α4 and β2 subunits in the medial PFC, which leads to an increase in nicotine-induced GABAergic synaptic transmission. In addition, mGluR2 levels on presynaptic glutamatergic terminals in the PFC are increased, causing a reduction in glutamatergic synapse strength (Fig. 1). Changes in nAChR levels are reversible: In the adult rodent brain, weeks after nicotine levels have subsided, nAChR levels in the PFC return to baseline levels. In contrast, at this stage, mGluR2 levels have reduced significantly below baseline levels, thereby altering mGluR2 signaling during short-term plasticity and hampering attention performance. This reduction in mGluR2 signaling underlies the reduced attention performance observed in animals after nicotine exposure during adolescence (Counotte et al. 2011).

New questions and opportunities arise from these recent findings. The long-term adaptations involving mGluR2s can have profound implications for network functioning and affect more complex levels of information processing. A consequence of increased glutamatergic transmission in adult PFC caused by reduced mGluR2 function could be the impairment of other types of plasticity than STD, such as mechanisms of long-term plasticity. Changes in inhibitory tonus and excitatory transmission following adolescent nicotine exposure may have different short- and long-term effects on long-term plasticity.

Another interesting question would be whether mGluR2 signaling is involved in a broader spectrum of attention impairments with different etiology. If change in mGluR2 signaling is a common underlying mechanism for attention malfunction it would make it a suitable pharmacological target for therapy.

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