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Molecules and circuits involved in nicotine addiction: the many faces of smoking

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Abstract

Tobacco smoking in humans is one of the most persistent and widespread addictions and is driven by nicotine in tobacco smoke. Over the last several decades, understanding of the molecular and cellular basis for nicotine addiction has increased tremendously as a result of pharmacological, molecular genetic, electrophysiological and behavioral studies of nicotine reinforcement. Studies of the biological basis for nicotine reinforcement has helped in the design of new treatments for smoking cessation such as varenicline; however, smokers report that they smoke for many reasons, including the ability to control symptoms of anxiety and depression or the desire to control appetite. Further, developmental exposure to tobacco smoke increases the likelihood of adult smoking. Here we review what is known about the molecular and circuit basis for a number of behaviors related to tobacco smoking. Leveraging the knowledge from studies of different behaviors mediated by nicotine receptors in multiple brain circuits could provide points of convergence that will inform future therapeutic development for smoking cessation.

Keywords

tobacco; smoking; molecular basis; animal models

Introduction

There is an essential paradox at the heart of smoking behavior. Among humans, tobacco is a highly addictive drug, however, in animal models, the primary addictive component of tobacco, nicotine, is less reinforcing than some other drugs of abuse, such as cocaine (Risner and Goldberg, 1983). There are likely to be many reasons for this discrepancy. First, tobacco is legal and access is almost universal, so there is more chance of exposure to tobacco than to illicit drugs, and the stigma of use may be lower. Second, there are more than 4,000 constituents of tobacco smoke, and other constituents in addition to nicotine may contribute to tobacco use. Third, and perhaps most important, nicotine has many effects on brain circuits and behavior in addition to its ability to stimulate neuronal systems involved in primary reinforcement, and the complex actions on these systems may contribute to smoking behavior and relapse in human tobacco users. In addition to the rewarding and reinforcing effects of nicotine, several other factors contribute to the initiation and maintenance of

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tobacco intake. Smokers report that they use tobacco because is it pleasurable, but they also report that that they use it to control appetite, to help with mood symptoms and to focus their attention. For instance, weight control is cited as the primary reason for initiation of cigarette use in teenage girls in the United States (Fulkerson and French, 2003). Given the current high rates of obesity and the focus on limiting food intake, this connection is alarming. Further, the rate of smoking in depressed patients is twice that of the average population (Kalman et al., 2005). While the connection between mood disorders and tobacco addiction is not fully understood, it is clear that depression, which affects up to 10% of the population, is a significant risk factor for tobacco use. Finally, maternal smoking is associated with an increased risk of attention hyperactivity disorder (ADHD) in children exposed to tobacco smoke *in utero*, and this points to one potential link between smoke exposure and circuits involved in attention (Heath and Picciotto, 2009; Picciotto et al., 2012). The deleterious effects of developmental smoke exposure also highlight the fact that tobacco use can have long lasting, transgenerational effects due to changes in the developing brain that can last many years after exposure.

Therefore, while there are many behavioral consequences of smoking, this review will focus on the multivariate effects of nicotine on behaviors related to depression and food intake, as well as the more classical brain systems and behaviors related to addiction. In addition, since one of the risk factors for tobacco smoking is parental tobacco use, we will review the effects of nicotine on brain development. It is clear that there are social and societal factors that support smoking and contribute to relapse, but in addition, there are molecular and neurobiological mechanisms that make it difficult to quit smoking. It is these diverse mechanisms that we will review here.

Molecular and anatomical basis for nicotine reinforcement

The primary reason that people smoke is that the nicotine in tobacco is addictive. Like other drugs of abuse, nicotine stimulates dopamine (DA) release from neurons in the mesolimbic system originating in the ventral tegmental area (VTA) and terminating in the nucleus accumbens (NAc). Nicotine can stimulate the firing rate of VTA neurons (Grenhoff et al., 1986; Picciotto et al., 1998), induces DA release from isolated nerve terminals (synaptosomes) (Grady et al., 1992) and increases the excitatory glutamatergic drive onto DA cell bodies in the VTA (Mansvelder et al., 2002; McGehee et al., 1995). Consistent with the ability of nicotine to potentiate DA signaling, peripheral nicotine administration can increase extracellular DA levels in the NAc of rodents for more than an hour (Benwell and Balfour, 1992; Picciotto et al., 1998). The ability of nicotine to potentiate glutamatergic signaling onto DA neurons in the VTA has been proposed as a mechanism underlying this prolonged nicotine-induced DA release, that outlasts the acute effects of nicotine on firing rate of DA neurons (Mansvelder and McGehee, 2000; Tang and Dani, 2009). Thus, nicotine is highly effective at stimulating the DA system, a circuit necessary for drug reinforcement (Koob, 1992).

If nicotine is so effective at stimulating the DA system, why isn't it as effective as other psychostimulants in supporting drug self-administration in rodents? One reason may be that nicotine stimulates both glutamatergic and GABAergic inputs onto VTA DA neurons, resulting in a mixed excitation and inhibition of this circuit (Mansvelder et al., 2002; Wooltorton et al., 2003). Thus, nicotine efficiently activates the mesolimbic system, but the action of nicotine on many neuronal subtypes can mitigate the ability of nicotine to drive DA signaling (Picciotto, 2003).

Another reason may be that nicotine can stimulate its molecular targets in the brain, the nicotinic acetylcholine receptors (nAChRs), but also rapidly desensitizes these receptors

(Grady et al., 1994; Picciotto et al., 2008; Pidoplichko et al., 1997). Therefore, nicotine can limit its own actions in the mesolimbic system. Repeated nicotine exposure results in decreased stimulation of DA neuron firing rate (Pidoplichko et al., 1997) and nicotine-elicited DA release from synaptosomes (Grady et al., 1994). Despite the limiting consequences of repeated nicotine administration, a number of studies have now shown that nAChR desensitization can promote DAergic signaling in the VTA by decreasing nicotine-stimulated GABA release (Mansvelder et al., 2002; Wooltorton et al., 2003), and by increasing signal to noise in the NAc through decreased tonic DA release but maintained phasic DA signaling (Rice and Cragg, 2004; Zhang and Sulzer, 2004). The complex interaction between nAChR stimulation and desensitization varies across nAChR subtypes, and therefore across brain regions and neuronal subtype (Picciotto et al., 2008), potentially contributing to individual differences in susceptibility to nicotine addiction. For example, even though nAChRs containing the α7 subunit desensitize very rapidly *in vitro* in response to high concentrations of nicotine (reviewed in (Picciotto et al., 2008)), this nAChR subtype mediates the ability of low concentrations of nicotine to stimulate glutamate release from terminals in VTA slices, even after several minutes of exposure. Thus, nAChR desensitization rates can vary depending on the cellular context in which they are measured, and the dose of nicotine used.

The nAChR subtypes that contribute to the ability of nicotine to stimulate the DA system and to support behaviors related to nicotine addiction have been characterized using transgenic mice with mutations in specific nAChR subunits (Table 1). Mouse VTA DA neurons express mRNAs encoding many different nAChR subunits, including α3, α4, α5, α6, α7, β2, β3 and β4 (Klink et al., 2001). In the rat NAc, the primary subtypes of nAChRs on DA terminals include α4/α5/β2, α4/α6/β2/β3 and α6/β2/β3 nAChRs (Zoli et al., 2002). Studies of transgenic mice expressing hypersensitive nAChRs subunits have shown that activation of receptors containing the α4 or α6 subunits is sufficient for nicotine-mediated stimulation of DA neuron firing and for nicotine preference in conditioned place preference paradigm (Drenan et al., 2008; Tapper et al., 2004). Similarly, knockout studies have shown that β2 subunit-containing (β2*) nAChRs are necessary for nicotine-elicited DA neuron firing, DA release from synaptosomes, locomotor activation, conditioned place preference, conditioned reinforcement and self-administration (Brunzell et al., 2009; Brunzell et al., 2006; Grady et al., 2001; King et al., 2004; Mineur et al., 2009a; Picciotto et al., 1998). The brain areas and neuronal subtypes involved in the ability of α4/β2* nAChRs to support nicotine-induced DA neuron firing and self-administration have been elucidated using viral-mediated rescue throughout the VTA (Maskos et al., 2005; Pons et al., 2008) or in specific VTA cell types (Tolu et al., 2012). Interestingly, these studies show that β2* nAChR expression in VTA is sufficient for neuronal firing and nicotine reinforcement (Maskos et al., 2005), but that these nAChRs must be expressed in both DA and GABA neurons of the VTA for nicotine to induce burst firing of DA neurons and to support nicotine self-administration (Tolu et al., 2012). Similarly, knockout of the α4 nAChR subunit only in DA neurons shows that α4/β2* nAChRs in DA neurons are required for nicotine reinforcement (McGranahan et al., 2011). Finally, recent studies using constitutive knockout mice or highly selective conotoxins have shown that α6* nAChRs are critical for nicotine-elicited dopamine release and self-administration in both mice and rats (Brunzell et al., 2010; Gotti et al., 2010; Pons et al., 2008). Taken together, a combination of pharmacological, molecular genetic, electrophysiological, neurochemical and behavioral approaches has identified α4/α6/β2* nAChRs in DA neurons of the VTA as essential for nicotine reinforcement, and suggests an important contribution of β2* nAChRs in GABA neurons of the VTA to this circuit (Table 1). Thus, medications targeted to these nAChR subtypes are likely to be the most effective for smoking cessation. Varenicline, a partial agonist at α4/β2* nAChRs currently in use for smoking cessation (Rollema et al., 2007), is therefore an example of molecular-based drug design that has helped in smoking cessation

Molecular and anatomical basis for effects of nicotine on mood and depression

One critical risk factor that greatly decreases the success of smoking cessation is a history of major depression (Glassman et al., 1990). Smokers have twice the rate of depressive disorders than non-smokers (Diwan et al., 1998; Glassman et al., 1990) and common etiological factors, including shared genetic susceptibility (Cinciripini et al., 2004; Lerman et al., 1998), are likely to underlie this connection. It has been suggested that some smokers use tobacco to control their mood symptoms, and that smoking cessation can exacerbate symptoms of depression (Glassman et al., 1990); however, recent epidemiological studies suggest that the use of nicotine may lead to development of depressive symptoms.

In a computational analysis investigating the behavior of young adults between the ages of 18 and 25, the best fitting causal model suggested that depression symptoms are precipitated by regular use of nicotine (Boden et al., 2010). There is also strong evidence for a bidirectional relationship between smoking and depression. In a longitudinal study of adolescents, those with major depression at the first measurement had an increased risk for daily smoking at follow up, while daily smoking in early adolescence increased the risk for major depression at follow up (Breslau et al., 1998). Whereas acute withdrawal increases stress and the likelihood of depression, measures of stress have been reported to be lower following prolonged smoking cessation (Parrott, 1995, 2000), supporting the idea that smoking can actually increase negative affect (Munafo and Araya, 2010). The timing of smoking initiation, duration of smoking behavior and duration of abstinence are critical elements that determine self-rated mood status. Smokers report increased feelings of anxiety and stress between cigarettes (Hughes et al., 1990). Nicotine delivery can alleviate these negative effects of short term withdrawal, resulting in self-report that smoking is perceived as a positive experience (Parrott, 1999). These mood changes are positively correlated with the quantity of tobacco used, even in people with no history of depression (Parrott and Murphy, 2012). Thus, smokers may perceive a positive effect of smoking on mood because nicotine delivery counteracts the negative effects of withdrawal, but over the course of the day, the cyclical mood changes reported by smokers may mask a longer term increase in depression symptoms. But, despite these clinical and epidemiological studies, the direction of causality between nicotine exposure and depression remains an open question (Morrell et al., 2010). Although there is no conclusive evidence that depression drives initiation of smoking, a constellation of studies suggests that, as for most drugs of abuse, smokers continue to smoke to avoid negative affect (Baker et al., 2004a; Baker et al., 2004b)

The possibility that smoking could induce signs of depression is in line with studies of acetylcholine (ACh), the endogenous ligand for nAChRs, which demonstrate that a balance exists between cholinergic and noradrenergic systems, such that hyperactivation of cholinergic signaling, as could be induced by nicotine in tobacco, could lead to, or worsen, depressive symptoms (Janowsky et al., 1972; Oppenheim et al., 1979). Clinical observations demonstrate that administration of physostigmine, a cholinesterase antagonist that increases ACh levels in brain, to patients or volunteer healthy subjects resulted in negative effects on mood (Janowsky et al., 1974). From these observations, it was suggested that cholinergic hypersensitivity could represent a risk factor for the development of depression (Janowsky et al., 1994). Based on this hypothesis, a rat model of depression was developed (the Flinders sensitive line) by selecting for vulnerability to a depressive-like response to a cholinesterase antagonist (Overstreet, 1993). Human imaging studies have also shown that depressed patients have increased central concentrations of choline, the precursor of ACh (Charles et al., 1994), and patients with depression have decreased brain nAChR availability with no change in receptor number, suggestive of increased endogeneous ACh levels (Saricicek et al., 2012).

Initial studies used the muscarinic cholinergic antagonist scopolamine to reverse the effects of physostigmine on depressive symptoms (Janowsky et al., 1983), but rodent experiments demonstrated that nicotinic receptors are critical in the ability of scopolamine to reverse the depression-like effects of physostigmine (Rhodes et al., 2001). These data suggest that regulation of mood by ACh is complex, could be altered by nicotine in tobacco, and involves multiple receptor subtypes. Likely, multiple AChR subtypes and brain circuits are involved, and the net homeostatic balance of activity in these pathways influences mood. For instance, an increase in cholinergic tone in amygdala by stimulation with nicotine from tobacco could be sufficient to induce depression-like symptoms (Mineur and Picciotto, 2010), but a study in mouse has suggested that decreasing cholinergic tone in striatum can also lead to depression-like symptoms (Warner-Schmidt et al., 2012). These results highlight the likelihood that nicotine in tobacco smoke induces heterogeneous effects in different brain areas, with potentially opposing behavioral consequences. In addition, nAChRs are largely neuromodulatory, so effects of these receptors on ACh signaling in the brain depend on the baseline activity of individual circuits.

The integration of nicotinic signaling across brain regions with different levels of activity under conditions of stress could also explain the apparent discrepancy between the idea that smoking induces depressive symptoms and that smoking ameliorates depressive symptoms. Depressed smokers are thought to use cigarettes as a method of nicotine delivery in an effort to self-medicate their mood symptoms. Smokers report a decrease in symptoms immediately after using tobacco products, however, these positive effects are only observed after abstinence, when withdrawal-induced depression symptoms are high (Perkins et al., 2010).

At the molecular level, nicotine enters the brain rapidly and acts as an agonist at nAChRs, but it subsequently desensitizes most subtypes, particularly those containing the β2 subunit (Picciotto et al., 2008). Significant nAChR desensitization would mimic the effects of a nicotinic antagonist or low-efficacy partial agonist, and may therefore underlie at least some of the antidepressant-like effects of nicotinic drugs. The potent antidepressant-like effects observed with nicotinic agonists (Ferguson et al., 2000; Gatto et al., 2004), partial agonists (Mineur et al., 2009b; Mineur et al., 2007; Rollema et al., 2009), and antagonists (Ferguson et al., 2000; Shytle et al., 2002) is puzzling unless one recognizes that all these agents can decrease ACh activity by desensitizing, limiting activity of, or blocking nAChRs, respectively. This would also be consistent with the state-dependent effects of smoking on mood. Chronic nicotine delivery, by smoking or nicotine patches, leads to long term desensitization of nAChRs (Reitstetter et al., 1999), and functional antagonism of most nAChRs over time (Quick and Lester, 2002). However, chronic smoking also leads to long-term upregulation of high affinity nAChRs containing the β2 subunit (Staley et al., 2006), potentially increasing nAChR activity once nicotine-induced desensitization is relieved following abstinence. This increase in ACh-mediated signaling could contribute to depressive symptoms associated with smoking withdrawal.

While a broad nicotinic antagonist has antidepressant-like effects in animal models (Caldarone et al., 2004; Rabenstein et al., 2006), it is likely that multiple nAChR subtypes have effects on depression-like behaviors. For example, mice lacking either the β2 or the α7 subunit do not exhibit the antidepressant-like effects of mecamylamine (Rabenstein et al., 2006). Both α7- (Pichat et al., 2007) and β2- (Mineur et al., 2009b; Mineur et al., 2007; Rollema et al., 2009) selective partial agonists have antidepressant-like properties in rodents, suggesting that decreasing ACh signaling through either subtype is effective; however, in rats, the ability of nicotine to act like an antidepressant can be antagonized by mecamylamine (Tizabi et al., 2000) and nicotine agonism can potentiate the effects of the antidepressant citalopram (Andreasen and Redrobe, 2009), supporting the idea that nAChRs can have complex effects on circuits involved in depression-like behavior.

The co-morbidity between depression and smoking has also influenced antidepressant drug development. Despite the failure of a recent clinical trial, nAChR antagonists or partial agonists can show antidepressant effects in combination with ineffective regimens of selective serotonin reuptake inhibitors in human depressed patients (George et al., 2008; Philip et al., 2009). Both α7 and β2 nAChRs are located throughout the brain, so the neuroanatomical basis for the antidepressant effects of nicotinic drugs is not yet known. Recent studies in subjects with a history of depression indicated that nicotine restored functional asymmetry in frontal cortical areas following tryptophan depletion, a model of induced depressive symptoms (Knott et al., 2012). Nicotine acting through presynaptic α4β2 nAChRs (Garduno et al., 2012) also increases the firing rate of serotonergic neurons projecting to the nucleus accumbens, which is suspected to improve mood and affect (Chang et al., 2011). Doses of nicotinic antagonists and partial agonists that have antidepressant properties also decrease neuronal activity (as measured by cfos activity) in the amygdala (Mineur et al., 2007), a brain region that is often hyperactive in depressed patients (Drevets et al., 2008). Finally, increased ACh activity decreases resilience to stress and results in depressant-like effects (Mineur et al., 2013). Taken together, these studies identify a potential molecular basis for the co-morbidity between depression and smoking, and provides potential avenues for medication development to help depressed smokers quit smoking.

Molecular and anatomical basis for effects of nicotine on appetite

A frequent reason cited by smokers for ongoing cigarette use is appetite control, and among smokers, female teenagers reported that their motivation to smoke was primarily to control body weight (Voorhees et al., 2002). Following the intake of nicotinic drugs, immediate effects are observed on food intake, appetite, hunger and fullness (Grebenstein et al., 2013), likely due to the activation of melanocortin system (Huang et al., 2011; Mineur et al., 2011). These effects seem to be maintained over time, suggesting that long-term smoking does not lead to tolerance to the appetite suppressing effects of nicotine. This is in line with data demonstrating that, in the aggregate, smokers are leaner than non-smokers, and why nicotine decreases weight gain over long periods of time in animals models (Mineur et al., 2011; Grebenstein et al., 2013). Conversely, smoking cessation often leads to weight gain. Nicotine administration limits weight gain and food intake in former smokers and in laboratory rodents (Bellinger et al., 2005; Blaha et al., 1998; Filozof et al., 2004; Hughes and Hatsukami, 1997; Perkins, 1993). As in human ex-smokers, rodents gain weight after cessation of a chronic nicotine administration regimen (Bishop et al., 2004; Filozof et al., 2004; Fornari et al., 2007). Nicotine contained in tobacco products can act at many different levels throughout the body and brain, therefore it is likely to include alteration of metabolism, caloric intake and feeding behaviors (Zoli and Picciotto, 2012). Other factors including oral stimulation (smoking instead of snacking, for instance) likely also contribute to the effects of cigarettes on weight and feeding, but we will focus on the physiological and neuronal basis of nicotine's impact on food intake.

Calorie intake is only one part of the complex homeostatic regulation of the balance between energy expenditure and food intake, and the nicotinic system can act on each of these levels. Humans and animals tightly regulate nicotine intake (Gritz et al., 1976; Vieyra-Reyes et al., 2008), and this likely allows for careful titration of the effects of nicotine on different nAChR subtypes and circuits. The arcuate nucleus (ARC), located at the bottom of the ventral hypothalamus, is the main brain structure that controls energy expenditure, food intake and feeding patterns (Sainsbury and Zhang, 2010). Neuropeptide Y (NPY) and proopiomelanocortin (POMC) expressing neurons are the two main neuronal populations in the ARC and activation of these neuronal pathways stimulate or inhibit feeding, respectively. Equilibrium binding experiments have identified multiple nAChR subclasses in

ARC, including α7 and β2* nAChRs, the most widely expressed subtypes (Han et al., 2000; Han et al., 2003). *In situ* and rtPCR experiments have indicated that other, less widely expressed, subunits are also expressed in these neurons (Gotti et al., 2006; Han et al., 2000; Mineur et al., 2011), likely in discrete cell types, providing a potential molecular target for nicotine in the ARC in regulation of food intake.

Rat studies have shown that nicotine administration can decrease food intake and body weight, with greater effects in female animals (Grunberg et al., 1987). A similar nicotine regimen also decreases body weight and fat mass in mice as a result of β4* nAChR-mediated activation of POMC neurons and subsequent activation of MC4 receptors on second order neurons in the paraventricular nucleus of the hypothalamus (Mineur et al., 2011). NPY neurons are also activated by nicotine acutely, however, consistent with the continued ability of nicotine to decrease food intake after chronic administration, repeated stimulation by nicotine potentiates signaling in POMC, but not NPY, neurons (Huang et al., 2011). The fact that nicotine-induced firing of NPY neurons was not as sustained as the effects on POMC neurons may also explain why nicotinic-induced cfos activation was observed primarily in POMC neurons (Mineur et al., 2011). More indirect effects of nicotine are also likely to modulate feeding by altering ARC neuron activity. For instance, activation of nAChRs located on orexin-positive neurons in the lateral hypothalamus can trigger the release of glutamate and ACh, two neurotransmitters that could then induce a feed-forward stimulation of the LH-ARC pathway once primed by nicotine (Pasumarthi and Fadel, 2010). These data suggest that nicotine effects on hypothalamic nAChRs may decrease food intake in a receptor subtype- and cell type-specific manner and raises the possibility that medications targeting specific nAChR subtypes could help moderate weight gain following smoking cessation.

Effects of nicotine on neuronal development

The contribution of parental smoking to initiation of tobacco use in children is likely to involve greater access to cigarettes, effects of socio-economic status and other social factors. In animal models, nicotine exposure during early development and adolescence also promotes later nicotine reinforcement. For example, nicotine administration to pregnant dams or to adolescent rodents increases later nicotine preference and potentiates the acquisition of nicotine self-administration (Adriani et al., 2003; Klein et al., 2003), suggesting that biological effects of nicotine during development in children exposed to tobacco smoke also contribute to susceptibility to tobacco addiction. It is clear that nAChRs contribute to normal neuronal development and that nicotine can perturb the maturation of neurons (Role and Berg, 1996), likely leading to these long-term changes in behavior. While the specific molecular and cellular basis of the effects of developmental nicotine exposure on susceptibility to nicotine reinforcement is not yet established, it is clear that nAChR stimulation affects the maturation of a number of neuronal subtypes, and that nicotine can alter neuronal function at several stages of development. Thus, parental smoking can increase risk of smoking by their children, and the effects of nicotine in tobacco on neuronal development is likely to be one important factor underlying that risk.

At early stages of neuronal development, nAChRs are critical for the timing of maturation of GABA signaling in the CNS (Liu et al., 2006). Whereas GABA signaling is inhibitory in adult neurons, GABA depolarizes and stimulates firing of immature neurons. The switch from GABA-mediated excitation to inhibition results from the expression of an adult isoform of the chloride transporter which is induced by β2* nAChR signaling (Liu et al., 2006). This finding suggests that fetal nicotine exposure could accelerate the transition to inhibitory GABA signaling, potentially altering the timing of neuronal maturation events dependent on GABA-induced depolarization. With respect to addiction, alterations in the

balance of GABA signaling in brain areas involved in nicotine reinforcement, such as the VTA, could result in greater susceptibility to nicotine reward later in life.

At the synaptic level, recent studies have identified nAChR-dependent alterations in development of glutamatergic synapses (Lozada et al., 2012a, b). Activation of postynaptic α7 nAChRs in cultured neurons or organotypic slices promotes glutamatergic synapse formation, whereas knockout of the α7 subunit in mice decreases the number of dendritic spines (Lozada et al., 2012b) and glutamatergic synapses, although the number of GABAergic synapses was unchanged, suggesting that cholinergic signaling through this nAChR subtype is normally important in modulating the number of excitatory synapses and can modulate the ratio of excitatory to inhibitory inputs (Lozada et al., 2012a). As above, alterations in this ratio could alter susceptibility to the rewarding and reinforcing effects of nicotine later in life.

The effects of nicotine on neuronal development can also be seen at the circuit level. One well-studied site for developmental actions of nicotine is the cortico-thalamo-cortical connections that are critical for the gating of sensory information (Heath and Picciotto, 2009). Prospective studies of children exposed to tobacco smoke *in utero* through maternal smoking have identified early changes in auditory processing (Fried and Watkinson, 1988) and long lasting changes in performance of auditory and other sensory attention tasks (Fried et al., 2003; Jacobsen et al., 2007b). Some smokers report that they use tobacco to help focus their attention; therefore the ability of developmental nicotine exposure to perturb these circuits could contribute to later smoking to attempt to self-medicate attentional deficits.

The circuits important for the developmental effects of tobacco exposure on sensory attention have been investigated with *in vivo* imaging techniques in human subjects (Jacobsen et al., 2007a) and in animal models (Aramakis et al., 2000; Heath et al., 2010b; King et al., 2003; Liang et al., 2006; Liang et al., 2008), and appear to involve altered signaling in the connections between cortical and thalamic neurons. A number of molecular and electrophysiological studies have implicated α7 nAChR signaling in thalamocortical neurons (Aramakis and Metherate, 1998; Aramakis et al., 2000) and β2* nAChR signaling in layer 6 cortical pyramidal neurons (Heath et al., 2010b; King et al., 2003) as important for development of cortico-thalamo-cortical loops (Heath and Picciotto, 2009). Layer 6 pyramidal neurons projecting to the thalamus express high levels of α5* nAChRs during early postnatal development that are critical for maturation of cortico-thalamic communication (Bailey et al., 2010; Kassam et al., 2008). In mice, pharmacological disruption of nAChR signaling during development by administration of nicotine during the postnatal period, or genetically by knocking out the β2 nAChR subunit results in impaired performance in an auditory discrimination task (Horst et al., 2012) and hypersensitive passive avoidance learning that is dependent on expression of β2* nAChRs in layer 6 cortical neurons that project to the thalamus (Heath et al., 2010b; King et al., 2003; Picciotto et al., 1995). Nicotine administered through the dam does not result in changes in maternal behavior, suggesting that altered neurodevelopment is likely to explain the behavioral consequences of early nicotine exposure (Heath et al., 2010a). Thus, specific nAChR subtypes and a potential neuronal circuit have been implicated in the effects of developmental tobacco and nicotine exposure on sensory attention.

In addition to effects on sensory processing, early tobacco exposure also alters later likelihood of smoking in humans (Ernst et al., 2001), whereas developmental nicotine exposure increases later nicotine self-administration in rodents (Adriani et al., 2006). While a number of molecular consequences of developmental nicotine exposure have been identified (Heath and Picciotto, 2009), there are not studies identifying a causal link between these molecular changes and altered nicotine reinforcement. One hint may come from a

recent study showing that nicotine can result in epigenetic alterations that lead to increased drug reinforcement (Levine et al., 2011). This study identified a nicotine-dependent decrease in histone deacetylase activity and a concomitant increase in ΔfosB expression in the striatum that potentiated the effects of another drug of abuse (cocaine) on plasticity in medium spiny neurons. This was associated with an increase in drug place preference. Similar molecular mechanisms acting as a result of nicotine exposure during critical periods of development could potentially be involved in alterations in nicotine and tobacco preference.

Taken together, the human epidemiological data and the rodent behavioral data suggest that early exposure to nicotine in tobacco smoke can increase the likelihood of later nicotine addiction. The molecular and cellular events mediated through nAChR signaling alter neural development and result in plasticity in a number of brain areas that could contribute to increased susceptibility to smoking in children exposed to tobacco during development.

Integration of systems level effects of nicotine: common and disparate molecular mechanisms

It is now very clear that the nicotine in tobacco interacts with nAChRs in the brain, and alters their function. It is therefore important to understand the role of these receptors in the brain if we are to understand how nicotine supports tobacco addiction. We have briefly reviewed the effects of nicotine on reward circuits, appetite, stress-related behaviors and neuronal development. While the subtypes of nAChR and the cell type on which they exert their effects differ across the behaviors and developmental time points discussed here, a number of fundamental mechanisms have been identified that likely operate at many sites throughout the brain to mediate the effects of nicotine. For example, one common mechanism that contributes to all the behavioral effects of nicotine is the the ability of nicotine to potentiate neurotransmitter release from presynaptic sites as a key electrophysiological function of nAChRs (McGehee and Role, 1996; Wonnacott, 1997). The ability of nAChRs to increase DA, ACh, GABA and glutamate release (Dickinson et al., 2008; Grady et al., 1992; Grady et al., 2001; Lu et al., 1998; Radcliffe and Dani, 1998) is likely to underlie at least some of its effects on behavior. Another common mechanism is the ability of nicotine to desensitize, as well as activate, its receptors. The differential desensitization of different presynaptic nAChR subtypes is likely to shape the postsynaptic consequences of nicotine application in many brain areas, as has been shown in both the VTA, where desensitization results in maintained glutamate release but less GABA release following extended nicotine exposure (Mansvelder et al., 2002), and the striatum, where desensitization decreases tonic DA release while leaving phasic DA signaling intact (Rice and Cragg, 2004; Zhang and Sulzer, 2004). These mechanisms have been studied in specific brain areas, but are likely to be common across many brain areas, and to mediate the effects of nicotine in other circuits in which nAChRs are expressed, such as those involved in appetite (Huang et al., 2011) or affective behaviors.

In addition to the broad themes of presynaptic action on neurotransmitter release and the relevance of desensitization to nicotine's actions, it is important to emphasize that activation of nAChRs coordinates the firing of ensembles of neurons to modulate the output of circuits involved in reinforcement, appetite and stress response. Nicotine depolarizes and increases the firing of neurons in the VTA, thalamus, cortex and hippocampus (Grenhoff et al., 1986; Gu and Yakel, 2011; Kassam et al., 2008; Picciotto et al., 1995; Picciotto et al., 1998). Nicotine can coordinate the firing of neuronal ensembles by decreasing the threshold for action potential firing (Kawai et al., 2007). This ability of nicotine to coordinate the firing of neurons in brain areas relevant for behaviors related to reinforcement, attention and stress involves a combination of pre- and post-synaptic effects of nAChRs shape the output of

brain circuits that mediate nicotine-dependent behaviors. In the mesolimbic system, the multiple levels of nicotine effects on nAChR activity result in increased burst firing of DA neurons (Grenhoff et al., 1986), potentiation of excitatory input onto VTA DA neurons (Mansvelder and McGehee, 2000) but decreased GABA input (Mansvelder et al., 2002; Wooltorton et al., 2003), increased DA release from NAc DA terminals (Grady et al., 1992), and decreased salience of tonic DA release (Exley et al., 2008; Grady et al., 2012), all of which combine to result in long-term increases in nicotine-induced DA signaliing (Balfour et al., 1998), likely strengthening association between nicotine administration and salient environmental cues that drive ongoing nicotine intake (Palmatier et al., 2007). Thus, actions of nicotine at each of these points in the mesolimbic circuit come together to mediate the ability of nicotine in tobacco to drive ongoing smoking.

While extensive research at the molecular, electrophysiological and behavioral levels has begun to provide a coherent picture of how effects of nicotine at multiple points in the mesolimbic system coordinates DA dynamics, there is still more work to do to understand how the nicotine in tobacco promotes behaviors that contribute to ongoing smoking. For example, ACh in hippocampus may be important for the association between smoking and depression (Mineur et al, 2013) and the effects of nicotine on corticothalamic loops may explain why smokers report that smoking focuses their attention (Heath and Picciotto, 2009), whereas the ability of nicotine to stimulate neurons in the ventral hypothalamus may contribute to the perception that smoking can be used to regulate appetite (Mineur et al, 2011). Nicotine-induced changes in hippocampal GABA and glutamate neuron activity and plasticity are mediated through a number of different nAChR subtypes acting at different cell types and subcellular locations in the hippocampus (Fujii and Sumikawa, 2001; Ge and Dani, 2005; Ji et al., 2001; Jones and Yakel, 1997; Leao et al., 2012; Nakauchi et al., 2007; Radcliffe and Dani, 1998; Shao and Yakel, 2000). Similarly, $\alpha 7$ and $\beta 2$ nAChRs can modulate cortico-thalamic signaling at multiple different points in the circuit (Heath and Picciotto, 2009; Kawai et al., 2007; Metherate and Hsieh, 2004). Finally, postsynaptic effects of nicotine in the ventral hypothalamus (Mineur et al., 2011), and differential desensitization of nAChRs on NPY- and POMC-expressing neurons (Huang et al., 2011) contribute to effects of nicotine on this brain center critical for food intake. In each of these brain areas, some of the mechanisms that have been identified in the mesolimbic system have not yet been investigated. As a result, studies of the effects of nicotine on circuits involved in addiction could be extended to these brain areas, particularly studies of how differential desensitization of nAChR subtypes contributes to the ability of nicotine to alter the output of hippocampal, corticothalamic or hypothalamic circuits. Overall, while there have been significant advances in the understanding of nicotine's effects on circuits related to nicotine reinforcement, a more complete understanding of the mechanisms underlying effects of nicotine on circuits involved in effects of nicotine on other behaviors that also drive tobacco smoking will allow more targeted interventions for smoking cessation.

Conclusions

Over the last several decades there has been a great deal of progress understanding the molecular and cellular basis of behaviors related to nicotine addiction (Changeux, 2010), and this understanding has led to targeted drug discovery leading to new therapeutics for smoking cessation such as varenicline (Coe et al., 2005). These advances show that fundamental studies of the neurobiological basis of drug abuse can increase our knowledge of why individuals become addicted and what drives ongoing smoking, but can also lead to novel methods of intervention to help people quit and stay abstinent. The knowledge that has been gained about the mechanisms underlying nicotine reinforcement has been applied to understanding other behaviors that drive ongoing smoking. Targeting the multimodal basis

for nicotine intake may therefore result in more effective treatments for smoking cessation going forward.

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Highlights

- Many behaviors contribute to tobacco smoking.
- Nicotine is addictive, but can affect mood and appetite as well.
- Developmental effects of nicotine can promote later smoking.
- We review advances on molecular and cellular basis of nicotine-related behaviors.
- Molecular knowledge could help design novel smoking cessation therapies.

Table 1

role of nAChR subunits in nicotine-related behaviors.

	β2* activation	**β2* blockade**		**β4***	**α4***	**α5***	**α6***	**α7**
VTA (DA neurons)	↑ CPP, self-admin (Tolu et al., 2013), DA drive (Mansvelder et al., 2002; Wooltorton et al., 2003) and release (Grady et al., 1992; Tolu et al., 2013)	↓ DA release (Grady et al., 2001; Maskos et al., 2005; Picciotto et al., 1998)	↓ CPP and locomotion (Brunzell et al., 2009; Maskos et al., 2005; Mineur et al., 2009a; Walters et al., 2006)		↑ self-admin (Pons et al., 2008), CPP and DA release (McGranahan et al., 2011; Tapper et al., 2004)		↑ self-administration (Pons et al., 2008), CPP and DA release (Drenan et al., 2008)	
VTA (DA neurons)	↑ CPP, self-admin (Tolu et al., 2013), DA drive (Mansvelder et al., 2002; Wooltorton et al., 2003) and release (Grady et al., 1992; Tolu et al., 2013)	↓ DA release (Grady et al., 2001; Maskos et al., 2005; Picciotto et al., 1998)	↓ CPP and locomotion (Brunzell et al., 2009; Maskos et al., 2005; Mineur et al., 2009a; Walters et al., 2006)					
VTA (GABA neurons)	↑ Self-admin (when â2 also in DA neurons) (Tolu et al., 2013)	↓ GABA release (Lu et al., 1998)						
Striatum	↓ nAChR binding in model of depression (Tizabi et al., 2009)						↑self-admin (Brunzell et al., 2010)	
PPtg								↑ VTA neuron stimulation (Mansvelder and McGehee, 2000)
Habenula						Nicotine aversion (Fowler et al., 2011)		
Amygdala		↓ depression-like behavior (Mineur et al., 2007)						
Hippocampus		↑ depression-like behavior and anxiety (ACh; Mineur et al, 2013)						↓ anxiety (5HT terminals) (Andreasen et al., 2012; File et al., 2000; Tucci et al., 2003)
OFC	↓ binding in depressed patients (Saricicek et al., 2012)							
Dorsal raphe	↑anxiety (w/low level nic) (Tucci et al., 2003)							

	β2* activation	β2* blockade	β4*	α4*	α5*	α6*	α7
Arcuate Nucleus			↓ feeding (Mineur et al., 2011)				