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Invited review

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.

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1. 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 4000 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 tobacco intake. Smokers report that they use tobacco because it is 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

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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.

2. 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

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 (GABA neurons)	↑ Self-admin (when β2 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	↓ nAChR availability in depressed patients (Saricicek et al., 2012)						
Dorsal raphe	↑ Anxiety (w/low level nic) (Tucci et al., 2003)						
Arcuate nucleus			↓ Feeding (Mineur et al., 2011)				