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Nicotinic Acetylcholine Receptors and Nicotine Addiction: A Brief Introduction

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Abstract

Nicotine is a highly addictive drug found in tobacco that drives its continued use despite the harmful consequences. The initiation of nicotine abuse involves the mesolimbic dopamine system, which contributes to the rewarding sensory stimuli and associative learning processes in the beginning stages of addiction. Nicotine binds to neuronal nicotinic acetylcholine receptors (nAChRs), which come in a diverse collection of subtypes. The nAChRs that contain the α4 and β2 subunits, often in combination with the α6 subunit, are particularly important for nicotine's ability to increase midbrain dopamine neuron firing rates and phasic burst firing. Chronic nicotine exposure results in numerous neuroadaptations, including the upregulation of particular nAChR subtypes associated with long-term desensitization of the receptors. When nicotine is no longer present, for example during attempts to quit smoking, a withdrawal syndrome develops. The expression of physical withdrawal symptoms depends mainly on the α2, α3, α5, and β4 nicotinic subunits in the epithalamic habenular complex and its target regions. Thus, nicotine affects diverse neural systems and an array of nAChR subtypes to mediate the overall addiction process.

Introduction:

Nicotine addiction (Dani and Heinemann, 1996; De Biasi and Dani, 2011; Mansvelder and McGehee, 2002) causes more than 7 million deaths each year worldwide (WHO, 2017). This number is rising (Prochaska and Benowitz, 2016), making it the leading cause of preventable death in the world (Gowing et al., 2015). Approximately 50 million people in the United States alone are addicted to tobacco products (Creamer et al., 2019), resulting in tremendous public health, societal, and economic costs. Nicotine is the main addictive component of tobacco products (Dani et al., 2019), but there are multiple constituents that

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contribute to its reinforcing properties (Brennan et al., 2015). While the rate of cigarette smoking has fallen in recent years, the rise of e-cigarettes has led to a renewed use of nicotine, particularly among adolescents and young adults (CDC, 2019). This resurgence has many harmful consequences and highlights the importance of understanding the pharmacology of nicotine (Dani et al., 2019) and the properties of neuronal nicotinic acetylcholine receptors (nAChRs) (Dani and Bertrand, 2007) for devising effective addiction treatments.

Nicotine is a naturally occurring alkaloid in many plants where it serves as an insecticide (Dani et al., 2019). Nicotine is a tertiary amine that occurs in two stereoisomers and consists of a pyridine and a pyrrolidine ring. The (S)-nicotine form is found in tobacco, and is the active form that binds to diverse nAChR subtypes throughout the central and peripheral nervous systems. During smoking or heating of tobacco, some racemization of nicotine takes place and small quantities of the (R)-nicotine isoform can also be found in the consequent smoke. In addition, because nicotine is a tertiary amine, it can exist in both a charged and an uncharged form. In its uncharged state, nicotine is membrane-permeable and can enter the brain, where it then converts to the charged form and binds to receptors (Dani and Bertrand, 2007; De Biasi and Dani, 2011). Nicotine thus influences intracellular processes indirectly by acting on nAChRs, but it may also directly influence these processes when it enters into the cytoplasm (Henderson and Lester, 2015; Rezvani et al., 2007). This chapter will focus exclusively on nicotine's actions on nAChRs on the cell surface.

Nicotinic Receptor Structure and Subtypes

Nicotinic acetylcholine receptors are ligand-gated cation channels that are widely distributed throughout the nervous system and body (Papke, 2014), but this section will focus on neuronal nAChRs (Dani and Bertrand, 2007). They are expressed in nearly every region of the brain, both pre- and post-synaptically and can be found on axon terminals, axons, dendrites, and somata (Grady et al., 2007; Henderson and Lester, 2015; McGehee et al., 1995; Nashmi and Lester, 2006). Nicotinic receptors are pentameric structures made up of five distinct subunits that together form a central aqueous pore that allows cation influx when the receptor is activated (Cooper et al., 1991; Morales-Perez et al., 2016). Each subunit is comprised of an extracellular N-terminus that contributes to ligand-binding, three hydrophobic transmembrane domains (M1-M3), an intracellular loop, a fourth hydrophobic transmembrane domain (M4), and an extracellular C-terminus. Activation of nAChRs is achieved by the binding of the endogenous neurotransmitter acetylcholine or exogenous ligands like nicotine (Karlin, 1993).

There are 12 homologous neuronal nAChR subunits found in vertebrates, resulting in an enormous amount of diversity in the subunit compositions of these receptors (Albuquerque et al., 2009; Dani and Bertrand, 2007; Zoli et al., 2015). Among them are nine α-subunits (α2-10) and three β-subunits (β2-4), and diverse combinations of these subunits form functionally distinct receptors that can vary widely in their pharmacological and biophysical properties (Figure 1). All α subunits share a highly conserved set of six amino acids, including two adjacent cysteine residues that share a disulfide bond that is important in forming the ligand-binding site (Karlin, 1993; McGehee and Role, 1995). Importantly, the β

subunits lack this pair of cysteine residues (Cooper et al., 1991; McGehee and Role, 1995). As a result, at least two alpha subunits are necessary to form a functional receptor.

The resultant nAChR subtypes can be classified (Figure 1B) as either homopentameric (consisting of 5 identical subunits) or heteropentameric (consisting of at least 1 α and 1 β subunit type). Homopentameric receptors are thought to have five identical ligand binding sites, one between each pair of neighboring subunits, but it seems that only one binding site needs to be occupied to achieve some receptor activation (Figure 2) (Andersen et al., 2013). Heteropentameric receptors are believed to have only two binding sites that are located between neighboring pairs of α and β subunits (Gotti et al., 2006; Palma et al., 1996; Taly et al., 2009; Zoli et al., 2018) but unorthodox binding sites have recently been reported (Wang and Lindstrom, 2018). These receptors typically contain two αβ subunit pairs and a fifth accessory subunit. Each subunit is not entirely symmetrical and, thus, the placement of different subunits in a variety of positions within the pentameric complex can result in a wide variety of different nAChR subtypes, each with potentially different roles. Both α5 and β3 subunits function only as accessory subunits, at least in native nAChRs (Groot-Kormelink et al., 1998; Jain et al., 2016; Ramirez-Latorre et al., 1996; Wang and Lindstrom, 2018; Zoli et al., 2018). As such, they do not contribute to the agonist-binding site, but instead modify the functional properties of the nAChR complex and modify the receptor's regulation by agonists (Kuryatov et al., 2008). For example, the α5 subunit has a regulatory role as its presence blunts the desensitization of nAChRs following nicotine exposure and is thought to be critical for controlling the expression and function of α4-containing nAChRs in the VTA (Chatterjee et al., 2013).

Despite this diversity, all mammalian neuronal nAChR subtypes share the functional property of being permeable to Na^+, K^+, and Ca^{2+} (Gotti et al., 2007; Gray et al., 1996; Shen and Yakel, 2009; Vernino et al., 1992; Vernino et al., 1994). Nicotinic receptors, like most ligand-gated ion channels, can exist in multiple conformational states (Figure 2): closed and able to be activated by ligand, open and conducting to small cations, or desensitized and closed and not able to be activated by ligand. When nicotine binds to the receptor, the ion channel is open and briefly stabilized in that conformation, allowing cation flux, which will move the membrane potential toward 0 mV, usually depolarizing the membrane. The channel then either returns to its resting state (closed and able to be activated) or enters a desensitized state in which it cannot be activated by nicotine or other agonists. The subunit composition governs the kinetics of these conformational states, the selective cationic permeability of the nAChR's pore, and the pharmacological affinities of various agonists (Dani et al., 2019; Giniatullin et al., 2005; Picciotto et al., 2008; Quick and Lester, 2002; Wang and Lindstrom, 2018; Zoli et al., 2018). Therefore, the extraordinary diversity of nAChR subtypes results in numerous functional responses to nicotine. Among the wide array of nAChR subtype combinations in the brain, the most commonly expressed homomeric receptors are the α7 type, and the most commonly expressed heteromeric receptors are those containing the α4 and β2 subunits (Feduccia et al., 2012; Gotti et al., 2006).

Because the α7 nAChRs are the most common homomeric subtype, and because α7 subunits form heteromeric receptors relatively rarely (Gotti et al., 2006; Zoli et al., 2018), a

short-hand for receptor classification is whether the receptor is an α7 nAChR or a non-α7 nAChR. Pharmacologically, this determination can be made by observing sensitivity to α-bungarotoxin (α-BTX), which in the brain is a potent and selective antagonist of the neuronal α7 homomeric receptors. Receptors sensitive to α-BTX have a relatively low affinity for nicotine and fast kinetics, while receptors insensitive to α-BTX generally have a higher affinity for nicotine, slower kinetics, are heteromeric, and desensitize to low agonist concentrations (Dani, 2015; Gotti et al., 2006). These distinct receptor properties result in different temporal, physiological, and biochemical responses to nicotine, and the significance of those different responses will be discussed in the next section.

Genetic Factors Mediating Nicotine Effects

While a complex array of environmental, pharmacological, and individual factors influence nicotine dependence and smoking behaviors, many studies have also investigated the genetics of nicotine addiction. Genetic factors are thought to play an important role in smoking initiation, progression to heavy use, and persistence of use (Fowler et al., 2007; Kendler et al., 1999; Lessov et al., 2004; Munafo and Johnstone, 2008; Sullivan and Kendler, 1999). One meta-analysis reports that genetic elements were responsible for 50% of the variation in nicotine initiation and persistence of usage (Li et al., 2003). Although gene-wide association studies (GWAS) and candidate gene studies have identified a large number of genes that can influence tobacco use, many associations between gene variants and nicotine phenotypes have not been reliably replicated. However, risk alleles in the *CHRNA5-A3-B4* gene cluster of nicotinic receptor subunit genes on chromosome 15q25, which encodes the α5, α3, and β4 nAChR subunits, have consistently been associated with nicotine addiction (Bühler et al., 2015). Polymorphisms in this gene cluster have been linked to multiple smoking-related phenotypes, including nicotine dependence (Bierut et al., 2008; Chen et al., 2009a; Grucza et al., 2007; Saccone et al., 2007; Spitz et al., 2008; Thorgeirsson et al., 2008), smoking quantity (Amos et al., 2008; Berrettini et al., 2008; Keskitalo et al., 2009; Lips et al., 2010; Stevens et al., 2008; Thorgeirsson et al., 2008), smoking cessation (Freathy et al., 2009), and smoking-related diseases (Amos et al., 2008; Hung et al., 2008; Lips et al., 2010).

A number of single nucleotide polymorphisms (SNPs) in this gene cluster have been identified, but rs16969968 in *CHRNA5* and rs1051730 in *CHRNA3* have generated particular interest with respect to nicotine-related phenotypes, though the rs16969968 SNP has been studied in more detail. This SNP is a functional missense mutation G/A (D398N) in exon 5 and is the only SNP that has been implicated in nicotine behaviors thus far that results in a non-synonymous amino acid change in the resulting protein. The major allele produces α5 subunits with an aspartate (D) in position 398, which is swapped for an asparagine (N) in the minor allele. The minor allele (N398) has been shown to be highly associated with heavy smoking, intense craving for nicotine, and nicotine dependence (Bierut et al., 2008; Breetvelt et al., 2012; Buczkowski et al., 2015; Chen et al., 2012; Liu et al., 2010; Olfson et al., 2015; Sherva et al., 2008; Stevens et al., 2008). This polymorphism is also known to be of functional significance because *in vitro* studies have shown that α4β2α5 receptors with the asparagine allele show a decreased response to a nicotinic agonist, reduced calcium permeability, and faster desensitization (Bierut et al., 2008).

SNP 1051730, located within the *CHRNA3* gene, has also been associated with nicotine dependence and smoking quantity (Chen et al., 2009b; Saccone et al., 2007; Thorgeirsson et al., 2008). This SNP is in perfect linkage disequilibrium with rs16969968 and the two SNPs are considered to be interchangeable, although this requires further investigation. An additional non-synonymous variant located in *CHRNB4* (rs12914008) has been shown to mediate the fast transition from initial smoking to nicotine dependence, but it is a less common SNP and has been studied in much less detail. This SNP causes a missense mutation in *CHRNB4* from threonine to isoleucine. While these rarer variants have been linked with nicotine dependence and susceptibility, it is currently unknown whether they represent risk factors independent of the other SNPs in the same gene cluster (Saccone et al., 2009).

Many other genes for nAChRs have also been implicated in various ways in nicotine addiction-related phenotypes (for review, see Ware et al., 2012; Yang and Li, 2016), and these findings from human genetic studies have formed the basis for a variety of animal models that have been used to study the circuit and molecular effects of these mutations. The following sections will refer to these and other animal models when discussing nicotine's effects on various neural pathways and behaviors.

Nicotine Acts on the Mesolimbic Reward Circuit

All drugs of abuse, including nicotine, activate the ventral tegmental area (VTA) dopamine neurons that project to the nucleus accumbens (NAc). Activation of this mesolimbic pathway results in dopamine efflux in the NAc, which is important for nicotine reward-based learning and the initiation of the addiction process (De Biasi and Dani, 2011; Di Chiara and Imperato, 1988). A variety of nAChR subtypes are expressed in the neuronal populations in the VTA, as well as on the axon terminals of afferents from a number of brain regions. Therefore, nicotine's effects in the VTA are complex. However, a variety of studies have shed some light on the mechanisms by which nicotine acts in the VTA to cause dopamine neuron activation.

Nicotine can directly activate dopamine neurons by binding to their high-affinity, β2-containing nicotinic receptors, thereby causing a net influx of cations that depolarizes the neuron (Dani and Bertrand, 2007; Mao et al., 2011; Pidoplichko et al., 1997). These effects increase dopamine neuron firing rates and phasic burst activity, elevating dopamine levels in the NAc (Placzek et al., 2009; Tsai et al., 2009; Zhang et al., 2009). As a result, the β2 subunit may be crucial in mediating the rewarding effects of nicotine since nicotine stimulates dopamine release in wild-type mice, but mice lacking the β2 subunit do not show an increase in extracellular dopamine following nicotine administration (Picciotto et al., 1998). However, VTA GABA neurons that inhibit the dopamine neurons also express β2-containing nAChRs, so GABAergic drive to the VTA dopamine neurons is transiently enhanced at the same time that the dopamine neurons themselves are directly activated by the presence of nicotine. Because the α4β2 nAChRs rapidly desensitize, GABAergic drive to the dopamine neurons is functionally reduced over a longer time frame when low levels of nicotine are continually present (Dani et al., 2019; Grieder et al., 2019; Mansvelder et al., 2002). Simultaneously, glutamatergic drive to the dopamine neurons is enhanced by

activation of pre-synaptic α7 nAChRs, which are less prone to desensitization at nicotine concentrations achieved by smokers due to their low affinity for nicotine (Dani et al., 2000; Pidoplichko et al., 1997; Wooltorton et al., 2003), thus resulting in a long-lasting increase in excitatory drive to the dopamine neurons in the presence of nicotine (Mansvelder et al., 2002; Mansvelder and McGehee, 2002; Pidoplichko et al., 2004). This increased excitatory drive combined with the reduced inhibitory drive enhances activity in the dopamine neurons and facilitates Hebbian long-term potentiation of glutamatergic afferents onto the midbrain dopamine neurons (Mansvelder and McGehee, 2000; Mao et al., 2011; Ostroumov and Dani, 2018; Saal et al., 2003), which is thought to be a critical step in the initiation of addiction.

Nicotine dependence also critically involves striatal dopamine. VTA dopamine neurons express nAChRs on their presynaptic terminals in the striatum. Therefore, in addition to increasing the activity of the dopamine neurons themselves, nicotine also modulates striatal dopamine release via activation of these receptors. In the nucleus accumbens, nicotine acts via heteromeric presynaptic nAChRs that contain the α6β2 and/or α4β2 subunits (Exley et al., 2013; Gotti et al., 2010). The β2 subunit regulates dopamine release probability in the NAc core as well as in the dorsal striatum (Zhang et al., 2009; Zhou et al., 2001). Specifically in the NAc core, dopamine is predominantly regulated by α6α4β2β3 nAChRs (Exley et al., 2011). Multiple studies have shown that nicotine rapidly desensitizes these receptors, resulting in reduced tonic dopamine tone. However, this reduction in background dopamine “noise” allows for an improved signal to noise ratio when a phasic dopamine signal is transmitted (Rice and Cragg, 2004; Threlfell and Cragg, 2011; Zhang et al., 2009).

Effects of Chronic Nicotine

Chronic nicotine exposure leads to a number of neuroadaptations that can influence diverse signaling pathways and circuits, including the mesolimbic reward pathway. One such neuroadaptation is the subtype-specific upregulation of nAChRs that occurs in response to persistent desensitization of the receptors (Henderson and Lester, 2015). This desensitization occurs because unlike acetylcholine, nicotine cannot be removed from the synapse via rapid hydrolysis by acetylcholinesterase (Baker et al., 2013; De Biasi and Dani, 2011; Nashmi et al., 2007; Picciotto et al., 2008). Nicotine’s long-lasting presence in the synapse desensitizes nAChRs, rendering them unresponsive to further binding by nicotine or acetycholine and functionally inhibiting the nAChRs (Dani et al., 2000; Picciotto et al., 2008; Pidoplichko et al., 1997; Wooltorton et al., 2003). Accordingly, nAChR levels are upregulated to maintain homeostasis following chronic nicotine (Feduccia et al., 2012; Fenster et al., 1999a; Fenster et al., 1999b; Giniatullin et al., 2005).

The α4β2 nAChR is the predominant high-affinity nicotinic receptor in the brain and its upregulation has been the most thoroughly-studied (Bertrand and Terry, 2018; Feduccia et al., 2012; Henderson and Lester, 2015; Zoli et al., 2018). Comparing other nAChR subtypes to the α4β2 nAChR can therefore be useful in understanding how different nAChRs are differentially regulated by nicotine. For example, α4β2 nAChRs are upregulated by low, physiologically-relevant nicotine concentrations (Henderson et al., 2014; Peng et al., 1994), whereas α3β4 nAChRs are usually upregulated only by high nicotine concentrations that are outside of the normal range obtained by smoking (Matta et al., 2007; Mazzo et al., 2013).

These changes begin within days of nicotine exposure and are thought to be significant mediators of nicotine addiction (Henderson et al., 2014; Matta et al., 2007; Nashmi et al., 2007).

The upregulation of nAChRs can be achieved by multiple processes, including changes in receptor assembly, trafficking, and degradation (Henderson and Lester, 2015; Henderson et al., 2014; Mazzo et al., 2013; Rezvani et al., 2010; Rezvani et al., 2007). It is important to note that nAChR upregulation and the mechanisms underlying this phenomenon can vary, not only for different nAChR subtypes, but also for different brain regions and nicotine administration paradigms (Baker et al., 2013; Henderson et al., 2017; Marks and Pauly, 1992; Nashmi et al., 2007; Pistillo et al., 2016; Renda and Nashmi, 2014).

In addition to altering nAChR expression levels in specific brain regions, repeated nicotine exposure can also produce a variety of additional neuroadaptations throughout the brain, including strengthening glutamatergic synapses onto dopamine neurons and onto the projection neurons of the NAc (Kenny et al., 2009; Mansvelder and McGehee, 2000; Mao et al., 2011; Ostroumov and Dani, 2018; Pidoplichko et al., 2004; Pistillo et al., 2015; Saal et al., 2003). Chronic nicotine can also dysregulate neuronal homeostatic mechanisms, modulate midbrain GABAergic circuitry, upregulate the high-affinity D2 dopamine receptors in the NAc, modulate neuronal scaffolding proteins, and alter epigenetic processes (Grilli et al., 2012; Hayase, 2017; Hwang and Li, 2006; Novak et al., 2010; Rezvani et al., 2007; Thomas et al., 2018).

Withdrawal from Chronic Nicotine

After chronic nicotine exposure, abstinence from the drug can cause unpleasant withdrawal symptoms (De Biasi and Dani, 2011; De Biasi and Salas, 2008; Mclaughlin et al., 2015). Withdrawal is defined as a combination of affective and somatic symptoms that appear soon after nicotine abstinence, reflecting a change in neurochemistry caused by the absence of the drug. In humans, the symptoms used to assess nicotine withdrawal according to the DSM-V are: irritability/frustration, anxiety, depression, increased appetite, impatience, insomnia, and restlessness (Wenzel, 2017). Because the half-life of nicotine in humans is roughly 20 hours (Matta et al., 2007), withdrawal symptoms typically peak within a week of cessation and subside over the following 3–4 weeks (Hughes, 2007). In mice, symptoms can be assessed by observing somatic signs of withdrawal, which include increased shaking, paw tremors, and scratching (Damaj et al., 2003; De Biasi and Salas, 2008; Isola et al., 1999; Salas et al., 2004), and affective withdrawal symptoms, which include anhedonia, aversion, and anxiety. These affective symptoms are probed using a variety of behavioral assays. For example, an increase in intracranial self-stimulation (ICSS) reward thresholds or reduced sucrose preference can indicate anhedonia, and reduced time spent in the open arms of an elevated-plus maze can indicate increased anxiety. Because the half-life for nicotine in mice is approximately 6 minutes, withdrawal symptoms typically peak 12-36 hours after abstinence (Matta et al., 2007; Perez et al., 2015).

While not the main focus of this section, it is interesting to note that different nAChR subtypes appear to differentially mediate the somatic vs. affective components of withdrawal

(for extensive review, see Jackson et al., 2015; Mclaughlin et al., 2015). For example, β4 KO is sufficient to prevent somatic signs of nicotine withdrawal in mice, while β2 KO results in no change to somatic withdrawal signs compared to controls (Salas et al., 2004). However, β2 KO is sufficient to reduce the affective components of withdrawal (Jackson et al., 2008), and interestingly, β4 KO also prevents withdrawal-induced anhedonia (Stoker et al., 2012). Thus far, β2 (Jackson et al., 2009a; Jackson et al., 2008) and α6 (Jackson et al., 2009b) nAChRs have been implicated in the affective components of nicotine withdrawal, while α7, α3 (Jackson et al., 2013), α5 (Jackson et al., 2008; Salas et al., 2009), β4 (Jackson et al., 2013; Salas et al., 2004; Stoker et al., 2012), and α2 (Lotfipour et al., 2013; Salas et al., 2009) nAChRs have been implicated in the somatic aspects of nicotine withdrawal (De Biasi and Salas, 2008; Mclaughlin et al., 2015).

In addition to understanding the roles of various nAChR subtypes in different aspects of nicotine withdrawal, it is important to consider how neural circuits mediate withdrawal and how withdrawal serves to maintain addiction-related behaviors. Nicotine withdrawal contributes to continued nicotine use through negative reinforcement mechanisms, suggesting that both rewarding and aversive motivational signals and brain circuits are important for maintaining chronic nicotine use (Bromberg-Martin et al., 2010; Hikosaka, 2010; Matsumoto and Hikosaka, 2007). In fact, aversive nicotine withdrawal symptoms may be required to produce escalated intake of nicotine (George et al., 2007; Gilpin et al., 2014), a hallmark feature of addiction. While the positive motivational effects of nicotine are achieved by activation of the mesolimbic dopamine pathway, the negative motivational effects of nicotine withdrawal are mediated by the habenulo-interpeduncular pathway (Mclaughlin et al., 2015; McLaughlin et al., 2017; Pang et al., 2016). The habenula is an epithalamic nucleus involved in fear, anxiety, depression, and other forms of negative affect (De Biasi and Dani, 2011; Ikemoto, 2010; Lecca et al., 2014; Meye et al., 2017; Winter et al., 2011). Anatomically, the habenula is divided into medial (MHb) and lateral (LHb) nuclei, but the MHb has been most strongly implicated in nicotine withdrawal (Dao et al., 2014; Mclaughlin et al., 2015; McLaughlin et al., 2017). The MHb receives its primary inputs from the limbic system and sends almost all of its cholinergic and glutamatergic projections to the interpeduncular nucleus (IPN) (Hikosaka, 2010; Ren et al., 2011).

The MHb-IPN axis is unique in that it densely expresses almost all neuronal nAChR subtypes (Grady et al., 2009; Marks and Pauly, 1992) and many studies have established its important role in mediating the symptoms of nicotine withdrawal. For example, microinjections of the nAChR antagonist mecamylamine into the MHb or IPN of mice treated with chronic nicotine are sufficient to precipitate nicotine withdrawal symptoms (Damaj et al., 2003; De Biasi and Salas, 2008; Hildebrand et al., 1997; Malin and Goyarzu, 2009; Malin et al., 1992; Salas et al., 2004; Salas et al., 2009), and mice lacking the α2, α5 and β4 nAChR subunits, which are most densely expressed in the MHb-IPN pathway, exhibit reduced withdrawal responses after chronic nicotine. These findings indicate both the role of the MHb-IPN circuit and the role of these receptor subtypes in mediating nicotine withdrawal (Salas et al., 2004; Salas et al., 2009). More recent studies have also shown that cholinergic habenular signaling is required for nicotine withdrawal (Frahm et al., 2015), that optogenetic activation of IPN GABA neurons is sufficient to elicit withdrawal-like symptoms (Zhao-Shea et al., 2013), and that increased nAChR activity in the MHb underlies

anxiety-related symptoms of nicotine withdrawal (Pang et al., 2016). Interestingly, studies have also shown that different sub-regions of the MHb and the IPN are implicated in different aspects of the nicotine withdrawal syndrome (Shih et al., 2014; Shih et al., 2015).

Although the MHb-IPN axis and its role in nicotine withdrawal are usually studied in parallel to the mesolimbic circuit that regulates nicotine reward, these pathways likely interact with each other. In addition to altering the MHb-IPN pathway, withdrawal from chronic nicotine also leads to reduced basal dopamine levels in the NAc (Zhang et al., 2012). Furthermore, many of the nAChR subtypes that are important for withdrawal-related behaviors are also expressed in the mesolimbic circuit, and a variety of studies have shown direct and indirect anatomical connections between these aversive and rewarding pathways (Quina et al., 2017; Wolfman et al., 2018; Zhao-Shea et al., 2015).

Conclusion

Nicotine addiction results from a complex and wide-ranging series of neuroadaptations in many brain regions and neurotransmitter systems. These adaptations include alterations in nicotinic receptor expression and modulation of neurotransmitter release. A great deal of preclinical research has focused on the circuits that underlie both the rewarding effects of acute nicotine exposure and the aversive effects of withdrawal from chronic nicotine exposure. These studies have confirmed the role of the mesolimbic reward pathway in the development and maintenance of nicotine addiction as well as the role of the MHb-IPN axis in mediating the nicotine withdrawal syndrome.

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Highlights

1. Nicotine is highly addictive and is a leading cause of premature death worldwide.
2. Great diversity in neuronal nicotinic acetylcholine receptors arises from their subunit composition.
3. Genetic factors, especially within the CHRNA5-A3-B4 gene cluster, play an important role in nicotine addiction.
4. Midbrain dopamine systems play an important role especially in the initiation of nicotine use.
5. Aspects of nicotine withdrawal are mediated by the habenulo-interpeduncular pathway.

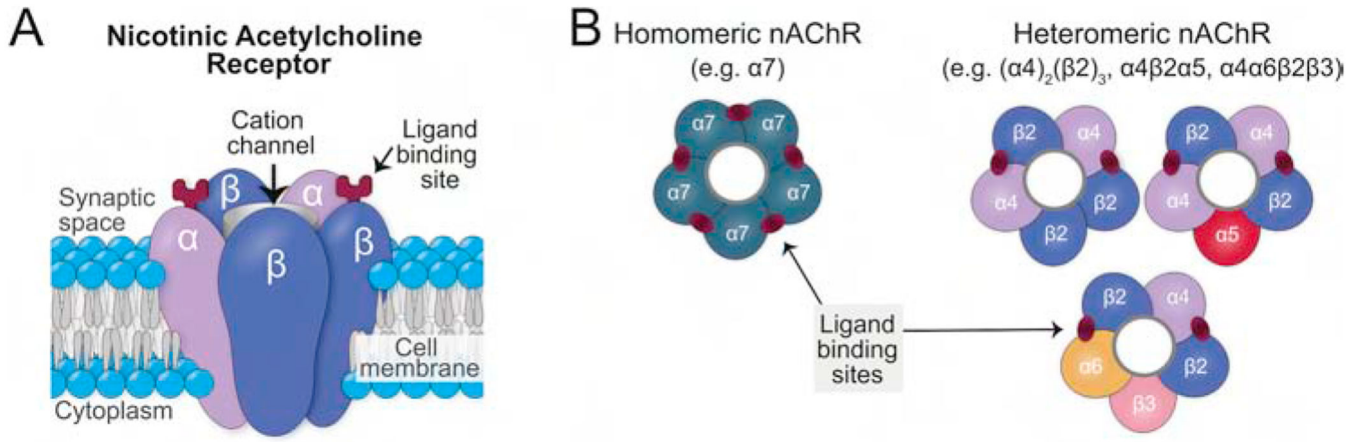

Figure 1.

Didactic structure of nAChR subtypes. (A) A side view of the subunits' arrangement like the staves of a barrel around the central water-filled pore. In the generic heteromeric nAChR subtype shown, there are two alpha subunits and three beta subunits with the ACh binding sites located at the interfaces between α-β subunits. Note that for clarity, this schematic illustration is not drawn to scale and shows the ligand binding-sites at the apex of the subunits rather than at their actual positions deep within the structure. (B) These top down views of subunit arrangements for a homomeric α7-nAChR and for 3 of the myriad potential heteromeric nAChRs.

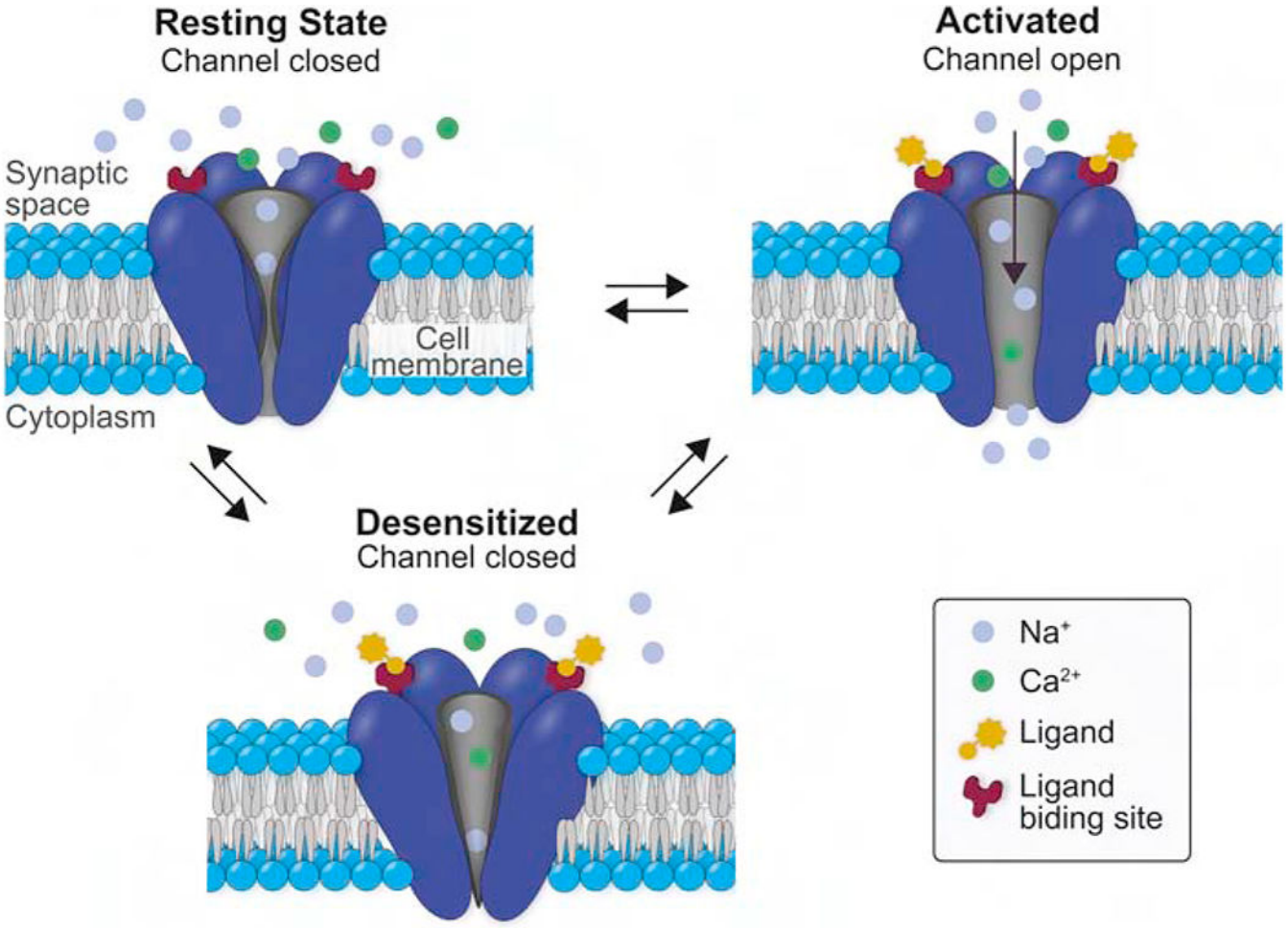

Figure 2.

Didactic representation of the three main functional states of the nAChR. In the resting state, the ACh binding sites are not occupied, and the water-filled pore is closed and non-conducting to cations. In the open, activated state, the ion channel is open, providing a water-filled pore through the membrane that is permeable to small cations. In the desensitized state, the ACh binding sites are (usually) occupied, but the pore is closed and non-conducting. Note that for clarity, sodium to calcium ratios are lower in this schematic than in actuality and that the arrows do not indicate rate constants of conformation changes.