Neurophysiology of Nicotine Addiction

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Abstract
Tobacco use is a major health problem, and nicotine is the main addictive component. Nicotine binds to nicotinic acetylcholine receptors (nAChR) to produce its initial effects. The nAChRs subtypes are composed of five subunits that can form in numerous combinations with varied functional and pharmacological characteristics. Diverse psychopharmacological effects contribute to the overall process of nicotine addiction, but two general neural systems are emerging as critical for the initiation and maintenance of tobacco use. Mesocorticolimbic circuitry that includes the dopaminergic pathway originating in the ventral tegmental area and projecting to the nucleus accumbens is recognized as vital for reinforcing behaviors during the initiation of nicotine addiction. In this neural system β2, α4, and α6 are the most important nAChR subunits underlying the rewarding aspects of nicotine and nicotine self-administration. On the other hand, the epithalamic habenular complex and the interpeduncular nucleus, which are connected via the fasciculus retroflexus, are critical contributors regulating nicotine dosing and withdrawal symptoms. In this case, the α5 and β4 nAChR subunits have critical roles in combination with other subunits. In both of these neural systems, particular nAChR subtypes have roles that contribute to the overall nicotine addiction process.

Introduction
It is estimated that 1/3 of the world’s adult population smokes tobacco [1–3]. In developed countries, tobacco use is estimated to be the largest single cause of premature death, and about 1/2 of those who smoke from adolescence throughout life will die from smoking-related diseases [4]. In less developed countries, tobacco use is on the rise; thus, it is one of the few causes of mortality that is increasing worldwide [2]. Tobacco is projected to be responsible for 10% of all deaths globally by 2015 [2,3].

When studied under laboratory conditions in the absence of other factors, nicotine elicits classically defined addictive behaviors. In animal studies at a narrowly defined dose, nicotine reinforces self-administration, elicits drug-seeking behavior, induces conditioned place preference, increases locomotor activity, and enhances reward from intracranial stimulation [5–9]. In drug discrimination tasks there is some cross-generalization between nicotine and other addictive drugs. That is, nicotine is in some cases mistakenly chosen in place of a different addictive drug [7,10]. Similar to other addictive drugs, nicotine cessation after chronic use also produces a withdrawal syndrome, and those symptoms can be relieved by nicotine replacement [9,10]. Although other substances and factors are important during the tobacco addiction process, nicotine is the major addictive component [11]. This issue was directly examined recently, supporting the conclusion that nicotine is the main substance reinforcing the use of tobacco [12].

Nicotine from smoke to the brain
Nicotine is an alkaloid and a tertiary amine that consists of a pyridine and a pyrrolidine ring. The unprotonated (uncharged) form of nicotine is absorbed from cigarette smoke through the mucous membranes, and the protonated form deposited in the lungs during smoking is buffered to the physiological pH and then absorbed [13–15]. The uncharged form of nicotine passes through lipid barriers, such as cellular membranes and enters the intracellular space, where the charged form may be held longer. Nicotine begins to reach the brain quickly, in tens of seconds after inhalation, but the concentration continues to increase gradually. PET imaging indicates that the distribution of nicotine onto nAChRs is slower than the rise in the blood stream [16]. Thus, nicotine blood concentrations undergo peaks and troughs following each cigarette, but those variations are significantly smoothed out within the brain. Because multiple nicotine doses are obtained by repeated smoking throughout the day and the half-life of nicotine is two hours or more in humans, the background level of nicotine rises during the day for a regular smoker, which leads to considerable accumulation of nicotine in the brain and body tissues [17]. In the early afternoon, the plasma nicotine level usually nears a plateau typically ranging between 10 and 50 ng/mL [15]. Smoking a single cigarette increases the blood nicotine concentration from roughly 5 to 30 ng/mL, depending on how the cigarette is smoked [18]. The widespread use of cigarettes likely arises because it is an easily controlled dosing device that smokers use to achieve their desired, and narrowly defined, nicotine dose. Although smoking habits vary, it is not uncommon for smokers to manipulate their nicotine intake to maintain a consistent level from day to day [19].

Nicotine interaction with nicotinic acetylcholine receptors
Neuronal nicotinic acetylcholine receptors (nAChRs) provide the main binding sites and primary site of action of nicotine [9,20], but other sites of action influencing intracellular events are likely [21]. Neuronal nAChRs are assembled from α and β subunits that are arranged around a central water-filled pore [20,22,23]. The α2–α6 and the β2–β4 subunits form nAChRs in combinations. The α7–α9 subunits are capable of forming homomeric nAChRs, but of these only the α7 subunit is widely distributed in the mammalian brain. The α4β2-containing (α4β2*) nAChRs often in combination with α5 or α6 provide the higher affinity binding sites for nicotine [24,25].

Nicotinic AChRs have complex kinetic behavior that is dependent on their subunit composition. The activation, closure, and

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Desensitization of nAChR subtypes are influenced by the exact amino acid sequence of the subunits, and the dose and kinetics of agonist application or arrival. Both the endogenous acetylcholine arriving from neuronal sources and the exogenous nicotine arising from tobacco use have to be considered. The kinetic response of nAChRs depends on the agonist dose-response profile. As nicotine arrives in the brain, occupancy of nAChRs increases over a period of many minutes, and the high affinity nAChRs are significantly occupied out to the time scale of hours. Desensitization of nAChRs becomes a more important issue as low levels of nicotine linger in the brain for many minutes or hours.

Desensitization is mainly an agonist-dependent conformational transition of the receptor to an inactive state that cannot be activated by agonist [20,26-28]. At a cholinergic synapse, vesicular neurotransmitter release usually produces a high ACh concentration in the synaptic cleft that lasts for only a few milliseconds before diffusion and acetylcholinesterase removes the neurotransmitter. Under these conditions, desensitization is not strong. However, the slowly rising and falling, low concentrations of nicotine obtained from tobacco will cause some desensitization over time. Because of desensitization, acute tolerance occurs to multiple cigarettes in an episode of smoking. Because the background level of nicotine rises throughout the day, the effects of individual cigarettes tend to lessen as the day (and smoking) progresses. Overnight abstinence from tobacco/nicotine allows considerable, but not necessarily complete, recovery from desensitization [15,17].

Reinforcement of rewarding behaviors by nicotine

Mesocorticolimbic circuitry that is normally critical for reinforcing successful behaviors also participates in the addiction process [9,29-31]. The dopaminergic centers of the midbrain and their targets have received much attention because of their roles in arousal, motivation, cognition, motor function, and processes associated with reinforcing behaviors that lead to reward. One of the important dopaminergic pathways originates in the ventral tegmental area (VTA) of the midbrain and projects to forebrain structures, including the prefrontal cortex, and areas such as the olfactory tubercle, the amygdala, the septal region, and the striatum, which includes a particularly important target, the nucleus accumbens.

The accumulation of evidence implicates these mesocorticolimbic circuits in addiction [7,9,32-34]. Many addictive drugs, including nicotine, elevate dopamine (DA) in the nucleus accumbens, and that elevation correlates with the reinforcement of drug use, particularly during the acquisition phase [7,9,35-38]. Blocking dopamine release in the nucleus accumbens with antagonists or lesions reduces nicotine self-administration in rats, which is interpreted to mean that inhibited dopamine release attenuates the rewarding effects of nicotine [8,36]. Nicotine administration activates dopamine neuron firing as has been shown using rodent brain slices [39] and using in vivo recordings from freely-moving rodents [40,41]. Thus, the concentration of nicotine obtained from tobacco can activate nAChRs on midbrain dopamine neurons and influence associated excitatory and inhibitory circuitry and, thereby, increase dopamine neuron firing.

The midbrain DA area receives afferent cholinergic innervation from the nearby pedunculopontine tegmentum (PPT) and the laterodorsal tegmentum (LDT), which are a loose collection of cholinergic neurons interspersed with GABAergic and glutamatergic neurons [42]. The midbrain DA area expresses diverse nAChR subtypes [25,39,43], and particularly nAChRs containing the β2 subunit, usually in combination with α4 and/or α6 subunits, mediate nicotine-induced dopamine signals [44–48]. Activation of nAChRs directly depolarizes DA neurons [39] and, consequently, increases their firing [40]. In addition, nicotine influences excitatory and inhibitory circuitry and local synaptic plasticity, which have longer lasting influences over midbrain activity [40,46,49-51]. In this manner, nicotine supercedes the actions of normal environmental events that act upon the midbrain circuitry. The drug acts directly upon this circuitry, as if a reward-related sensory input has been received.

DA neurons fire in different modes [52-54], commonly firing at low tonic frequencies interspersed with higher frequency phasic bursts that can be induced by unpredicted reward or unanticipated cues that have been conditioned to a known reward [55,56]. Disrupting phasic bursts diminishes the ability to learn cues about reward and impairs the processing of reward [56]. Nicotine administration increases the firing of DA neurons and increases the number and length of phasic bursts [40,46,57], which particularly boosts DA concentrations in the nucleus accumbens [40]. This action by nicotine requires β2-containing nAChRs. In mice lacking the β2 nAChR subunit (β2 -/-), nicotine does not produce burst firing from DA neurons [46] and does not support self-administration [44]. In β2 null mice, when β2 is re-expressed in the ventral tegmental area, nicotine self-administration is reinstated [48,58]. In addition, nicotine self-administration also is influenced by the α4 and the α6 nAChR subunits, and those two subunits cannot completely substitute for each other even though they are abundantly expressed in VTA neurons [59,60]. The results are consistent with the expression of α4β2 and α4α6β2 nAChRs in the VTA [48] and consistent with the importance of these receptors in the VTA for the reinforcing properties of nicotine.

Chronic nicotine induces neuroadaptations

Prolonged exposure to the exogenous drug, nicotine, produces neuroadaptations that influence diverse signaling pathways and circuits [61]. The most well studied neuroadaptation is the subtype-specific upregulation of nAChRs [21,24,62-71]. The populations of nAChR subtypes begins to change as molecular mechanisms involving neuroadaptations come into play after days and weeks of tobacco use [32,72,73]. Various molecular mechanisms have been proposed to underlie nAChR upregulation [73-79], which may be viewed as a homeostatic adaptation [68]. Unlike ACh, nicotine is not hydrolyzed by acetylcholinesterase, and nicotine’s long-lasting presence favors nAChR desensitization (i.e., turning down nAChR tone). The homeostatic response to desensitized receptors is upregulation [68,80,81]. Nicotinic receptor upregulation differs among the diverse nAChR subtypes, varies among brain regions for the same nAChR subtype, and depends on the contingency of nicotine administration [62,63,82-86].

Chronic nicotine also causes a number of other heterologous neuroadaptations: changes in glutamate receptors often associated with synaptic plasticity [51,87], changes in DA receptor subtype densities [88], changes in scaffolding proteins [21,89], changes in protein turnover [21], and others. Because nAChRs affect the release of virtually every major neurotransmitter [20,90-95], these overall neuroadaptations can have far-reaching effects and contribute to the mechanisms that maintain nicotine consumption, as well as underlying the nicotine-withdrawal syndrome [95,96].
Withdrawal from chronic nicotine

The withdrawal syndrome arises when the abrupt absence of nicotine disrupts homeostasis maintained in the presence of chronic nicotine. Specifically, withdrawal from nicotine produces somatic effects such as twitches, tremors, and bradycardia, as well as affective symptoms such as elevated anxiety levels. The withdrawal of nicotine begins a new process of neuroadaptations to counteract the negative state. Just as specific nAChR subtypes support the induction of nicotine addiction, other specific nAChR subtypes underlie the withdrawal syndrome. For instance, α5, α3, and β4 subunits are all found in the same gene cluster, and all of these subunits seem to help regulate consequences of nicotine withdrawal [97,98]. α5-null and β4-null mice lack the somatic signs of withdrawal [99,100]. Consistent with the role of anxiety and stress in relapse [96], both α5-null and β4-null mice have reduced anxiety-related behaviors [101,102], but β2-null mice show normal anxiety-like responses [103]. The α2 subunit also contributes to the somatic signs of withdrawal [100], and this role likely arises from its expression in the interpeduncular nucleus (IPN) of rodents [104,105].

In the mouse, the α5, α2, and β4 nAChR subunits are expressed at high levels in the medial habenula (MHb) and in its main target the IPN [96,106]. The MHb projects to the IPN via the fasciculus retroflexus, forming an axis involved in the somatic signs of withdrawal. Withdrawal symptoms are reduced when nAChRs in the Hb/IPN are inhibited [100], and α5-null mice self-administer nicotine at high doses that elicit aversion in wild-type mice, indicating that α5-containing nAChRs in the Hb regulate the upper limit of the self-administered nicotine dose [107]. It is intriguing and likely not a coincidence that a single nucleotide polymorphism (SNP) within the α5 gene (CHRNA5) reduces α5-nAChR function and correlates with greater nicotine dependence risk, heavier smoking, and increased pleasurable sensation from cigarettes [108-111]. The MHb/IPN axis helps to mediate the CNS component of the aversive effects of nicotine, and the α5 receptors within this axis are important contributors to the nicotine withdrawal symptoms.

Taken together the results suggest reward and withdrawal circuits have partially overlapping functions. The VTA/NAc and the dopaminergic system are established in reinforcement of rewarding drug seeking to reverse the nicotine-induced DA deficiencies because the majority of people who attempt unaided to quit smoking relapse within the first 2 weeks [116,117]. Those results suggest that the early withdrawal period is a critical time for relapse and, potentially, for intervention.

The most commonly used aid to quitting is nicotine replacement therapy, which partially relieves withdrawal symptoms and tobacco (mainly nicotine) craving [112,118]. Nicotine replacement therapy is most successful with smokers willing to attempt an abrupt cessation with this aid: the success rate is around 16% with replacement versus 10% with placebo [119].

Bupropion, an atypical antidepressant, acts upon multiple targets as an aid to smoking cessation [120]. One action of bupropion is inhibition of catecholamine reuptake, which increases extracellular concentrations of norepinephrine and DA, thereby, helping to relieve the hypo-dopaminergic state of withdrawal [121]. Another action of bupropion that may contribute to its efficacy is that it functions as a non-competitive antagonist of various nAChR subtypes [122]. In addition, animal studies suggest that bupropion may exert some systems-level effects similar to nicotine. Both drugs are psychomotor stimulants [123] and both increase catecholamine concentrations in mesolimbic regions [120]. Bupropion on its own improves abstinence rates, and it is most effective combined with nicotine replacement therapy, which augments cessation to about 29% [124,125].

Another approved smoking cessation therapy is varenicline, which is a derivative of the nAChR agonist cytisine. Originally it was thought to act as a selective agonist for α4β2 nAChRs, but further preclinical studies indicated it has agonist action at many nAChR subtypes [126,127]. Varenicline's partial agonist action at α4β2 nAChRs is thought to decrease withdrawal and cravings [128]. In addition, varenicline inhibits nicotine-induced decreases in brain stimulation thresholds, suggesting that it makes smoking less rewarding [129]. Just over 20% of patients taking varenicline for 12 weeks maintained abstinence when examined at 52 weeks, which was an improvement over bupropion alone or placebo, but the rates of cessation were not consistently better than nicotine replacement therapy [130].

Although a causal relationship has not been established between bupropion and varenicline therapies and serious adverse effects, safety concerns have arisen and warnings have been added to the prescribing information of the two drugs. Adverse events in patients treated with bupropion or varenicline include changes in behavior, depression, and suicidal behavior [131]. The occurrence of serious side effects and the relatively small long-term improvements in cessation rates serves as a spur to develop improved therapeutic approaches [128].

Disclosure Statement

The authors are not aware of any affiliations, memberships, funding, financial holdings, or any other conflicts of interests that might be perceived as affecting the objectivity of this review.

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