Molecular Mechanisms Associated with Nicotine Pharmacology and Dependence

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Contents

Abstract

Tobacco dependence is a leading cause of preventable disease and death worldwide. Nicotine, the main psychoactive component in tobacco cigarettes, has also

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been garnering increased popularity in its vaporized form, as derived from e-cigarette devices. Thus, an understanding of the molecular mechanisms underlying nicotine pharmacology and dependence is required to ascertain novel approaches to treat drug dependence. In this chapter, we review the field's current understanding of nicotine's actions in the brain, the neurocircuitry underlying drug dependence, factors that modulate the function of nicotinic acetylcholine receptors, and the role of specific genes in mitigating the vulnerability to develop nicotine dependence. In addition to nicotine's direct actions in the brain, other constituents in nicotine and tobacco products have also been found to alter drug use, and thus, evidence is provided to highlight this issue. Finally, currently available pharmacotherapeutic strategies are discussed, along with an outlook for future therapeutic directions to achieve to the goal of long-term nicotine cessation.

Keywords
Neurobiology nicotine dependence · Nicotine · Nicotinic receptors · Smoking cessation

1 Introduction

Cigarette smoking is the principal cause of premature death and disability in the United States. In 2014, about 480,000 deaths in the United States were caused by cigarette smoking. Globally, smoking-related illnesses result in over four million deaths annually. However, despite enormous educational efforts about the health hazards of smoking and other tobacco control efforts, many smokers continue to encounter extreme difficulty quitting and staying tobacco-free in the long-term. The 2017 CDC report estimated that 15.1% of the US population was "current smokers," (11.2% (75%) of them are daily smokers).

Addiction to tobacco smoking depends not only on the positive reinforcing and hedonic actions of nicotine but also on escape from the aversive consequences of nicotine withdrawal. Many studies suggest that avoidance of the negative emotional state produced by nicotine withdrawal represents a motivational component that promotes continued tobacco use and relapse after smoking cessation. The difficulty in overcoming nicotine dependence is illustrated by the poor success rates among smokers who try to quit. While the majority of smokers (~70%) report an interest in quitting, and around 55% have attempted to quit in the previous year, ~7% of smokers are abstinent at 1 month after their quit date, and fewer than 2% are abstinent 1 year after quitting when they do not receive assistance in smoking cessation (CDC 2015).

While several smoking cessation therapies are available, the success rate of these therapies after 1 year remains only about 20–25% (Gonzales et al. 2006). Therefore, understanding the various mechanisms and factors involved in the different aspects of nicotine dependence is crucial to develop successful prevention and intervention approaches, including newer and more effective pharmacotherapies.

2 Basic Neurocircuitry of Nicotine Addiction

Tobacco smoke contains about 9,000 chemicals, among which about 70 are known carcinogens. However, nicotine is the major psychoactive ingredient in tobacco smoke and the component most associated with tobacco dependence. The development and persistence of dependence on tobacco is due to the actions of nicotine, acting at neuronal nicotinic acetylcholine receptors (nAChRs). nAChRs belong to the Cys-loop receptor family, which are ligand-gated ion channels that form pentamers arranged around a water-filled pore and allow for the influx of both Na+ and Ca^{2+} (Changeux et al. 1998). The subunits of mammalian neuronal nAChRs range from α2–α7, α9, α10, to β2–β4, which form multiple combinations of homomeric and heteromeric receptor subtypes having varying function (Changeux et al. 1998). These receptors have three broad conformational states: resting closed states, open states, and desensitized states (Changeux et al. 1998). The typical resting closed state is induced when the orthosteric site (traditional ligand binding site) is unoccupied and the cation channel is closed. Upon binding of an orthosteric agonist, the cation channel is opened, allowing for cation influx into the cell. Following the open state, the receptor is then desensitized; despite agonist binding, the cation channel is closed, rendering the receptor inactive (Changeux et al. 1998). Due to their predominant presynaptic location, nAChRs in the CNS primarily function via modulation of neurotransmitter release (Mansvelder and McGehee 2000). This modulation, in turn, results in long-term synaptic plasticity, which is a prominent neuronal signature of exposure to nicotine (Ji et al. 2001). The most abundant nAChRs found in the mammalian brain are the low-affinity homomeric α7 and the high-affinity heteromeric α4β2 containing (α4β2∗), which have diverse characteristics (Hill et al. 1993). The α7 nAChR has high calcium permeability, low probability of opening, and rapid desensitization (in milliseconds) (Williams et al. 2011). In contrast, the α4β2∗ nAChR has a high probability of opening and desensitizes at a slower rate (in seconds) (Li and Steinbach 2010). These differing characteristics, however, do not necessarily drive divergent effects on neuronal plasticity. For example, previous studies have shown that both α4β2∗ and α7 nAChR activation can either elicit (Lagostena et al. 2008; Tang and Dani 2009; Welsby et al. 2009) or prevent (Alkondon and Albuquerque 2001; Alkondon et al. 1997; Ji et al. 2001) long-term potentiation (LTP) in the hippocampus, with these variable effects attributed to activation of differing subtypes on specific interneuron populations. Further, accessory nAChR subunits, such as α5 and β3, can integrate into the α4β2, α3β4, or α3β2 nAChR subtypes to alter receptor function. For instance, insertion of the α5 subunit into the α4β2 or α3β2 nAChR subtypes results in increased ligand-mediated receptor activation, rate of desensitization, and conductance (Gerzanich et al. 1998; Ramirez-Latorre et al. 1996).

Nicotine initiates its rewarding effects by activating nAChRs in the natural reward system of the brain, the mesolimbic pathway. This pathway is comprised of dopaminergic neurons originating in the ventral tegmental area (VTA) that project to regions such as the nucleus accumbens (NAc), prefrontal cortex (PFC), amygdala, and hippocampus (De Biasi and Dani 2011; Lisman and Grace 2005).

Dopamine release, especially in the NAc, is associated with the rewarding and reinforcing effects of all drugs of abuse. nAChRs are localized throughout the mesolimbic circuitry and when activated, increase dopaminergic firing and release (De Biasi and Dani 2011; Di Chiara 2000). Further, infusion of nAChR antagonists directly into the VTA attenuates nicotine self-administration (Corrigall et al. 1994). This pathway has a complex circuitry that also involves other neurotransmitters; for instance, glutamatergic, GABAergic, and cholinergic inputs converge on dopamine neurons to modulate dopamine release (Dani and Bertrand 2007). Cholinergic neurons in the laterodorsal tegmentum and the pedunculopontine tegmentum initiate excitation of dopamine neurons in VTA that project to the NAc (Maskos 2010; Omelchenko and Sesack 2005), and these cells in the pedunculopontine tegmentum have been shown to regulate nicotine self-administration (Lanca et al. 2000). In opposition to reward-related signaling, dense nAChR expression is also found in the projection from the medial habenula (MHb) to the interpeduncular nucleus (IPN), a circuit involved in aversive processing and nicotine withdrawal (Fowler et al. 2011; Salas et al. 2009). The major neurotransmitters of this pathway are acetylcholine, glutamate, and substance P, and it is thought that presynaptic nAChRs on MHb axons facilitate glutamate release from cholinergic and glutamatergic coexpressing axons in the IPN to mediate the aversive signal to high doses of nicotine (Fowler et al. 2011; Girod and Role 2001), which serves to limit drug intake.

3 Role of Nicotinic Receptors in Nicotine Dependence and Brain Function

The utilization of genetically mutant mice, pharmacological interventions, and viral reexpression approaches have implicated particular brain areas and specific nAChR subtypes in nicotine dependence. For instance, in a β2 knockout mouse model, the β2∗ nAChRs have been shown to be required for nicotine reward and reinforcement, as revealed in nicotine conditioned place preference (CPP) and intravenous self-administration studies (Orejarena et al. 2012; Picciotto et al. 1998; Walters et al. 2006). The β2 subunit co-assembles with the α6 and α4 subunits to form several α6β2∗, α4β2∗, and α4α6β2∗ nAChR subtypes, which are notably expressed in the VTA-NAc circuit (Champtiaux et al. 2003; Klink et al. 2001; Salminen et al. 2004). These findings are consistent with the fact that stimulation of α4β2∗ high-affinity nAChRs located on the dopaminergic cells in the VTA shifts firing from tonic to phasic modes, resulting in increased DA release in both the NAc and the PFC (Dani et al. 2011). Nicotine CPP revealed a critical role of the α4, α6, and β2 subunits in the NAc via genetic mutant mice and site-specific infusions (Sanjakdar et al. 2015). In addition, genetic ablation of the β2, α6, and α4 nAChR subunits attenuated nicotine self-administration in mice, an effect which could be rescued by reexpression of these subunits in the VTA via a lentiviral vector (Picciotto et al. 1998; Pons et al. 2008). Furthermore, α4 "knock-in" mice (Leu9' Ala mutation renders animals hypersensitive to nicotine) demonstrated a preference for nicotine at a dose 50-fold

lower than the typical nicotine dose that induces a preference in wild-type (WT) mice in the CPP test (Tapper et al. 2004).

Reward systems in the brain undergo neuroadaptations after chronic exposure to nicotine in tobacco products, which likely underlie nicotine dependence. Cessation from cigarette smoking induces a withdrawal syndrome comprised of physical, affective, and cognitive symptoms. The severity of these symptoms is a risk factor for relapse (Le Foll and Goldberg 2005; Markou and Kenny 2002), and nAChRs are important mediators of nicotine withdrawal symptoms. The nonselective nAChR antagonist mecamylamine is known to precipitate nicotine withdrawal signs in nicotine-dependent rodents (Damaj et al. 2003). Pharmacological interventions and mouse knockout studies have revealed that nAChR subunits modulate different aspects of the nicotine withdrawal syndrome. For example, some affective signs of withdrawal such as aversion-, anxiety-, and anhedonia-like measures are mediated by the β2, α6, β4, and α7 nAChR subunits (Jackson et al. 2008, 2009). The physical signs of the nicotine withdrawal syndrome are mediated by α3, α5, α2, and β4 (Jackson et al. 2008, 2013; Salas et al. 2009), and a subset are mediated by α7 subunits (Stoker et al. 2012). One interesting feature of chronic nicotine exposure is the upregulation of nAChRs, most notably α4β2∗ (Flores et al. 1992). This phenomenon has been observed both in vitro and in vivo and in human imaging studies (Kassiou et al. 2001; Marks et al. 1983; Perry et al. 1999). Interestingly, rodent and human studies suggest a positive correlation of nicotine withdrawal signs with upregulation of α4β2∗ nAChRs (Cosgrove et al. 2010; Turner et al. 2011). Furthermore, the MHb-IPN pathway has been selectively implicated in withdrawal-induced somatic signs with α5∗ and β4∗ nAChRs (Salas et al. 2009). In addition, infusion of the α6∗ nAChR-selective antagonist α-conotoxin MII in the MHb attenuated anxiety-like behavior in nicotine-withdrawn mice (Pang et al. 2016). Aberrant synaptic and circuitry function is also thought to underlie abnormal behavioral phenotypes, including nicotine withdrawal phenotypes like cognitive impairments and affective dysfunction (Ashare et al. 2014; Turner et al. 2013). For example, the hippocampus and the orbitofrontal cortex (OFC) are two well-described circuits impinging upon these nicotine withdrawal symptoms (Schoenbaum et al. 2016; Turner et al. 2011; Zhou et al. 2018), including impulsivity, altered affect, and cognition in humans. Supporting data in human (Dani and Harris 2005) and animal (Jackson et al. 2008) models link hippocampal function with nicotine withdrawal-induced symptoms, which are reliable determinants for smoking cessation outcomes. Functional imaging studies in smokers have shown that activation of the hippocampus can be correlated with both cognitive and affective withdrawal symptoms (Froeliger et al. 2010; McClernon and Gilbert 2004). Additionally, human studies report a correlation between hippocampal volume and successful quit attempts (Froeliger et al. 2010). This link may be due to nAChRs present at both excitatory and inhibitory terminals (Alkondon and Albuquerque 2001; Jones and Yakel 1997; Wada et al. 1989), well-positioning nicotinic signaling to influence the balance of excitatory and inhibitory transmission within the hippocampus (John and Berg 2015). The OFC regulates impulsivity, affective value of reinforcers, and emotion-attention interactions (Schoenbaum et al. 2016). Previous studies reported that

nicotine self-administration in rodents alters synaptic morphology in the OFC (Vazquez-Sanroman et al. 2016), while tobacco smokers display both morphological and functional connectivity changes within this region (Claus et al. 2013; Li et al. 2015). For example, smoking has been consistently shown to reduce the thickness of gray matter volume in the OFC (Kuhn et al. 2010; Li et al. 2015), and acute nicotine increases blood oxygen level-dependent fMRI signal in the striato-thalamo-orbitofrontal circuit (Ashare et al. 2014). However, the neuronal mechanisms underlying these effects are not easily examined, given that nicotine modulates the release of a number of neurotransmitters, including glutamate, GABA, and dopamine, and can lead to both facilitation and suppression of neuronal firing. For example, electrophysiological experiments have shown that nicotine impacts long-term potentiation (LTP) generation in the orbitofrontal cortex (Couey et al. 2007; Zhou et al. 2018). Classical LTP is based on the observation that a neuron's excitability to a particular synaptic input is increased following high-frequency stimulation, representing the molecular basis for Hebb's postulate, which states that when two connected cells fire simultaneously, the connection between them is strengthened. Previous studies examining nicotine's effect on this phenomenon have reported enhancement of LTP in a number of brain regions, such as the hippocampus (Nakauchi and Sumikawa 2012), amygdala (Huang et al. 2008), and VTA (Mansvelder and McGehee 2000). However, these effects diverge in the OFC. Zhou and colleagues (Zhou et al. 2018) demonstrated that acute nicotine application to the OFC during LTP induction resulted in nicotine-mediated conversion of LTP to LTD, a form of "metaplasticity," due to enhanced GABAergic transmission. These effects were in agreement with studies in nearby frontal cortical regions, where nicotine was observed to raise the threshold for LTP induction via enhancing GABAergic transmission (Couey et al. 2007). As appreciation grows for the importance of frontocortical excitatory/inhibitory balance in nicotine dependence (Pittaras et al. 2016), understanding nicotine's effects in this region may not only lead to better understanding of circuit-level mechanisms of nicotine dependence but also to potential therapeutic interventions.

4 Modulatory Factors That Influence nAChR Expression and Signaling

Several mechanisms that regulate nAChR expression, assembly, and trafficking were reported in the last two decades. Recent studies have shown that nicotine can act as a "chaperone" which expedites the transport of nAChR subunits, including α4 and β2 nAChRs, to the endoplasmic reticulum and facilitates the passage and insertion of assembled nAChRs to the plasma membrane (Henderson et al. 2014; Srinivasan et al. 2011). In this context, this pharmacological chaperone mechanism may represent an important molecular mechanism of the first step in neuroadaptation to chronic nicotine and possibility of the emergence of neuronal adaptations underlying nicotine dependence. Another class of nAChR signaling modulators is represented by the Ly-6/neurotoxin gene superfamily of proteins that exhibit cellular

specific expression patterns in the brain and include Lynx1, Lynx2, and Lypd6. These proteins are negative modulators of nAChR signaling and feature a three-looped fold, a structural characteristically shared with the snake venom toxin α-bungarotoxin. Thus, as endogenous prototoxins, these proteins can bind directly to the extracellular face of nAChRs (Arvaniti et al. 2016; Miwa et al. 1999). The presence of Lynx1 and Lynx2 increases the desensitization rate and decreases ligand binding efficiency for multiple nAChR subtypes (George et al. 2017; Ibanez-Tallon et al. 2002; Lyukmanova et al. 2011; Tekinay et al. 2009). In cortex, Lynx1 is expressed in both glutamatergic and γ-aminobutyric acid-ergic (GABAergic) neurons, whereas Lynx2 has been mainly localized in glutamatergic neurons (Demars and Morishita 2014). Results suggest that lynx proteins can modulate nAChR function in the brain with important consequences for cholinergic-dependent synaptic plasticity (reviewed in Miwa et al. 2011; Miwa and Walz 2012; Thomsen and Mikkelsen 2012). Recently, Nissen and colleagues reported that the antinociceptive effect of nicotine and epibatidine in acute thermal pain tests is enhanced in Lynx1 knockout mice (Nissen et al. 2018). Further, computer simulations predict preferential binding affinity of Lynx1 to the α:α interface that exists in the stoichiometry of the low sensitivity (α4)3(β2)2 nAChRs.

5 Genomics and Genetics of Nicotine Dependence

5.1 Overview

Nicotine addiction is a complex disorder with multiple factors contributing to its dependence. Though a large host of factors contribute to nicotine dependence, reward, withdrawal effects, and relapse, twin studies have shown that genetics play a pivotal role (Li et al. 2003; Sullivan and Kendler 1999). Approximately 70% of the variability in nicotine dependence and smoking persistence has been attributed to genetic influences (Broms et al. 2006; Carmelli et al. 1992; Kendler et al. 2000; Li et al. 2003). Furthermore, twin studies have shown that ~50% of the individual differences that contribute to smoking relapse can be attributed to heritability (Xian et al. 2003). Ongoing studies examining not only genetics, but genomics and epigenetics, are increasing our understanding of how individual differences drive vulnerability or resilience to nicotine dependence.

5.2 Human and Animal Genetic Studies

In recent years, genome-wide association studies in humans revealed that a variant in the CHRNA5/A3/B4 gene cluster (encodes α3, α5, β4 nAChR subunits), located in chromosome region 15q25, serves as a risk factor for lung cancer and nicotine dependence (Berrettini et al. 2008; Liu et al. 2010; Saccone et al. 2009). More specifically, a single nucleotide polymorphism (SNP) in the CHRNA5 gene (rs16969968) (D398N), which encodes the α5 nAChR subunit, has been repeatedly

linked to increased risk for tobacco dependence (Bierut et al. 2008; Kuryatov et al. 2011). The mechanisms behind this increased risk have been investigated in in vitro and in vivo functional studies. The α5 SNP was shown to reduce the function of the α3β4 and α4β2 nAChR subtypes that incorporate the mutant subunit (Bierut et al. 2008), a loss of function that subsequently was shown to influence addiction-like behaviors in vivo. Initial studies were conducted in α5 nAChR subunit gene knockout mice (Fowler et al. 2011). The α5 knockout mice were found to exhibit far greater motivation to consume large quantities of nicotine, and reexpression of α5 subunits within this pathway attenuated nicotine intake to wild-type levels (Fowler et al. 2011). Further, decreased expression of α5 subunits in rats similarly increased nicotine intake while decreasing the inhibitory effects of higher nicotine doses on brain reward circuitries (Fowler et al. 2011, 2013). Similar observations occurred in the nicotine CPP paradigm where α5 knockout mice exhibited a maintained nicotine preference at higher doses not maintained by α5 wild-type mice (Jackson et al. 2010). In addition, in mice expressing the α5 human mutation, an increase in nicotine self-administration was reported (Wilking and Stitzel 2015). Furthermore, using rats carrying the α5 human mutation, Forget et al. (2018) found greater nicotine intake in the SNP-expressing mutant rats compared with wild-type rats, as well as an increase in nicotine motivation mutant rats. In addition, the SNP-expressing rats exhibited a higher reinstatement of nicotine-seeking lever-pressing responses than the wild-type rats (Forget et al. 2018). Collectively, these studies suggest that the α5 subunit acts as an inhibitory signal that limits nicotine consumption and rewarding effects in smokers.

5.3 Transcriptionally Adaptive Changes

A potential way smoking and genetics may interact is through transcriptionally driven adaptive changes. It is now clear that continued drug use induces adaptive changes in the central nervous system that lead to drug dependence. Long-term adaptations in cellular signaling mechanisms are likely part of the maintenance of drug dependence, which may be necessary for their development and persistence. One well-characterized protein responsible for regulating gene expression is the transcription factor cAMP response element binding protein (CREB). Both human and animal studies have shown that CREB-dependent transcription is an important molecular mechanism underlying dependence on multiple drugs of abuse, including nicotine (Nestler 2005). In human studies, CREB expression correlates with the number of cigarettes smoked per day (Lenz et al. 2010). In adult mice, CREB activation is necessary for nicotine reward (Walters et al. 2005). These studies and others suggest a role for CREB in mediating the neuroplasticity changes that characterize nicotine dependence (Kenney et al. 2012; Portugal et al. 2012; Turner et al. 2014). For example, Turner and colleagues (Fisher et al. 2017; Turner et al. 2014) showed that hippocampal CREB signaling and the associated changes in synaptic plasticity impacted nicotine withdrawal phenotypes in mice. Further studies (Fisher et al. 2017) then demonstrated that site-specific CREB deletion in the

hippocampus impacted both cognitive and affective nicotine withdrawal phenotypes due to reduced CREB-mediated transcription of neuroplasticity-related genes, such as Arc and TrkB. However, while CREB is an important regulator of transcription, its widespread function precludes its use for development of targeted therapeutics. Instead, current studies are examining genomic CREB targets as potential therapeutics. For example, CREB ChIP-Seq data show that CREB's activation by chronic nicotine and withdrawal differentially modulate its binding to the genome and network pathway analyses of these data highlight the importance of different families of neuroplasticity genes, such as neurotrophin, netrin, and neuregulin family members (Turner et al. 2014).

Genes encoding a member of the epidermal growth factor family, neuregulin 3 (NRG3), and its receptor, ErbB4, have been recently linked to smoking cessation outcomes (Loukola et al. 2014; Turner et al. 2014). NRG3 is present on excitatory cells and signals transsynaptically through the ErbB4 receptor, which is found on select inhibitory cell types (Vullhorst et al. 2017). Genetic variation in this pathway has been demonstrated to impact multiple dimensions of smoking behavior, including smoking initiation, amount smoked, and nicotine dependence (Loukola et al. 2008, 2014). In particular, single nucleotide polymorphisms in the gene for NRG3 result in impaired ability to quit smoking in the clinical population (Turner et al. 2014). Conserved and consistent association of variants in this pathway with nicotine dependence measures lends confidence to future mechanistic evaluation of these associations. Furthermore, these data suggest that while therapeutic interventions for molecules such as CREB are unlikely, evaluation of those gene families regulated by CREB has great potential for future therapeutic development. For example, compounds targeting downstream effectors of ErbB4, the receptor for the CREB target gene NRG3, are already being developed for clinical use in psychiatric conditions such as schizophrenia (Law et al. 2012), a condition highly comorbid with nicotine dependence.

6 Other Constituents in Nicotine and Tobacco Products Mediating Dependence

While the field has focused on nicotine as the main psychoactive constituent in cigarettes and e-cigarettes, it is important to consider other compounds in the products that may alter the pharmacokinetics of nicotine and/or exert independent reinforcing effects on the substance user. Accumulating research has provided evidence that some non-nicotine constituents have innate reinforcing properties, which may thereby increase product use. For instance, anatabine, anabasine, cotinine, and myosmine have all been shown to increase the reinforcing properties of nicotine (Clemens et al. 2009; Hall et al. 2014). Mesolimbic dopamine levels are also increased in the presence of cotinine, acetaldehyde, and nornicotine at a level similar to that found for other substances of abuse (Bardo et al. 1999; Dwoskin et al. 1993, 1999; Foddai et al. 2004). Acetaldehyde and several minor alkaloids have also been shown to act as reinforcers (Myers et al. 1982; Peana et al. 2010; Smith et al. 2015),

although it is debatable as to whether this potentiative effect occurs at the concentrations of product consumed by humans. Another potential candidate mediating the enhanced reinforcing effect of nicotine in tobacco cigarettes is MAO inhibition with chronic exposure (Fowler et al. 1996, 2000). Consistent with the findings in humans, pharmacological inhibition of MAO in rodents has been shown to increase low-dose nicotine self-administration (Smith et al. 2015). Furthermore, the β-carbolines, harman and norharman, appear to inhibit MAO and may partially explain the effects found with tobacco consumption (Truman et al. 2017). With specific regard to e-cigarettes, several factors may interact to affect nicotine absorption and bioavailability, including pH, concentration of propylene glycol to glycerine vehicle, alcohol, nicotyrine, temperature, concentration of nicotine, and user characteristics (e.g., puff topography, level of experience) (DeVito and Krishnan-Sarin 2018). In addition, propylene glycol has been shown to decrease the aversive effects of high-dose nicotine, which may subsequently promote higher levels of nicotine consumption (Harris et al. 2018).

Various flavorant additives are also found in tobacco and e-cigarette products, and this topic has garnered recent attention since product flavor has been reported to be a main reason for the initiation of e-cigarette use among adolescents (Kong et al. 2015). Interestingly, a fMRI study found that e-cigarette advertisements showing sweet- and fruit-flavored products elicited a greater increase in nucleus accumbens activity compared to tobacco e-cigarette advertisements or control images of sweets and fruits (Garrison et al. 2018), thus demonstrating the strong cue-associated effects of these flavorants on brain reward circuity. In addition to enhancing the attractiveness and palatability of the cigarette, the additives may additionally interact with nicotine or other constituents at a biological level. For instance, menthol, a common flavoring additive to cigarettes and e-cigarettes, has garnered much attention recently given the preferential use of mentholated products among youth, adult women, and racial/ethnic minorities (FDA 2013; Villanti et al. 2017). In addition to focused marketing in targeted communities, the disproportional use by these populations has been proposed to be due to underlying genetic or biological factors, such as differences in nAChR expression or nicotine metabolism. Indeed, the presence of menthol in cigarettes has been demonstrated to alter nicotine's effects in smokers (Benowitz et al. 2004; Williams et al. 2007), which may be due to menthol-mediated inhibition of nicotine metabolism (Caraballo et al. 2011; Fagan et al. 2016) and potentiative effects on nicotine-mediated dopamine release in brain reward pathways (Zhang et al. 2018). Furthermore, menthol has also been shown to allosterically modulate α7 nAChRs (Ashoor et al. 2013) and can further upregulate nAChR expression (Alsharari et al. 2015). Thus, the pharmacological and addictive properties of nicotine may be enhanced and prolonged in the presence of menthol. This is further evidenced by the finding that mentholated cigarette smokers are less successful in maintaining abstinence following cessation (Caraballo et al. 2011; Fagan et al. 2016; Okuyemi et al. 2007).

7 Therapeutic Approaches for Tobacco and Nicotine Dependence

7.1 Nicotine Replacement Therapies

Nicotine replacement therapies (NRT) represent one of the first effective strategies to promote smoking cessation. In most formulations, nicotine is slowly administered over a prolonged period of time; this approach is thought to attenuate the negative somatic and cognitive effects found during drug withdrawal, while minimizing the reinforcing properties of the drug. A variety of available products include nicotine containing gums, lozenges, and patches. In controlled studies, NRT has been shown to be moderately efficacious in the short-term (days to weeks) (Hartmann-Boyce et al. 2018). However, over longer periods, relapse is often found in most individuals (Hartmann-Boyce et al. 2018), thus necessitating the development of alternate approaches. Along these lines, e-cigarette devices were developed as an NRT and harm reduction product. Compared to the traditional tobacco cigarette, e-cigarettes have been promoted as reducing exposure to carcinogens while providing reinforcing properties of nicotine via inhalation and quick delivery of the drug to the brain. Although e-cigarettes have been reported to assist some individuals in tobacco cessation, the emerging incidence of e-cigarette use among never smokers has represented a concerning trend for the promotion of nicotine dependence, especially among adolescents (Miech et al. 2019). Indeed, while e-cigarettes may be less harmful than tobacco cigarettes, they are by no means harmless, as evidenced by the multitude of chemicals and carcinogens emitted (Goniewicz et al. 2018). It is currently debatable as to whether electronic nicotine delivery devices should be employed by physicians for tobacco cessation since inconsistent findings have been reported with effectiveness and the potential harmful effects with short- and long-term use remain to be resolved (Livingston et al. 2019).

7.2 Varenicline and Bupropion

Given the direct action of nicotine on α4β2∗ nAChRs to mediate the reinforcing properties of the drug, it is perhaps not surprising that the most efficacious pharmacotherapeutics available is varenicline, a partial agonist of α4β2∗ nAChRs. Varenicline also has full agonist, but less potent, effects at α7 and α3β4∗ nAChRs and serotonin 5-HT_3 receptors. Approved by the FDA in 2006, varenicline has been shown to have similar or greater effectiveness in promoting smoking cessation compared to NRT and other approved therapeutics, such as bupropion (Gonzales et al. 2006). Bupropion was first characterized as a dopamine and norepinephrine reuptake inhibitor with antidepressant actions but more recently became approved as a first-line treatment for tobacco cessation. In addition to its actions as a catecholamine reuptake inhibitor, bupropion has also been shown to result in noncompetitive antagonism of α4β2∗ and α3β4∗ nAChRs (Carroll et al. 2014) and negative allosteric modulation of serotonin $5HT_{3A}$ receptors (Pandhare et al. 2017), either of which

may underlie the beneficial effects found for smoking cessation. In addition to NRT, varenicline, and bupropion, the tricyclic antidepressant nortriptyline and the α-adrenergic agonist clonidine have also been prescribed for smoking cessation, although studies have generally found them to be less effective than the aforementioned therapeutics (Dodd et al. 2018).

7.3 Novel Approaches

With advances in our understanding of the biological mechanisms underlying nicotine's physiological, reinforcing, and aversive effects, novel approaches for therapeutic development hold the promise of achieving substantial long-term clinical outcomes. Since α5∗ nAChRs in the MHb-IPN pathway have been demonstrated to mediate the aversive properties of nicotine that limit intake (Fowler et al. 2011), drug development efforts are focused on generating positive allosteric modulators of these receptors, with the idea of enhancing aversive processing in the presence of nicotine to decrease further drug intake (Jin et al. 2014). Another compound, AT-1001, which is an α3β4 partial agonist, has been shown to reduce nicotine relapse-related behaviors in rodents (Yuan et al. 2017), likely through action on the α3β4∗ nAChRs expressed in the MHb. GLP-1 receptor signaling has also been implicated in MHb-IPN modulation of nicotine intake (Tuesta et al. 2017), and a GLP-1 receptor agonist, liraglutide, is currently being tested for smoking cessation in a clinical trial (Ashare 2019). Another potentially beneficial strategy is to inhibit the main enzyme responsible for metabolizing nicotine, CYP2A6. The foundation of this approach is based on the observation that individuals with allelic variation in the CYP2A6 enzyme exhibit lower levels of nicotine consumption and greater abstinence rates when attempting to quit (Strasser et al. 2007). With CYP2A6 inhibition, lower levels of drug consumption would result in higher levels of nicotine intake, which may thereby lead either to an aversive effect with moderate levels of nicotine consumption or a reinforcing effect at lower levels of nicotine. Methoxsalen, a CYP2A5/CYP2A6 inhibitor, was a promising candidate as it was shown to decrease nicotine dependence-associated behaviors in rodents (Alsharari et al. 2014; Bagdas et al. 2014), but this drug was not further advanced for smoking cessation due to carcinogenic side effects that were unrelated to the CYP2A6 inhibitor actions. As such, current drug development efforts are ongoing to derive alternative CYP2A6 inhibitors. In addition to pharmacotherapeutics, nicotine vaccines have been under development. Conceptually, vaccination results in the generation of antibodies that bind to nicotine in the blood, thereby reducing the amount of nicotine capable of entering the brain. However, double-blind randomized trials have failed to demonstrate sustained benefit in long-term cessation (Hartmann-Boyce et al. 2012; Tonstad et al. 2013), likely due to insufficiently sustained antibody levels. In another approach to minimize nicotine entry into the brain, NicA2-J1 has been developed as a reengineered nicotine-degrading enzyme (Kallupi et al. 2018). Interestingly, while NicA2-J1 did not induce significant differences from the control in nicotine

intake, an attenuation of withdrawal and relapse-related behaviors was found in rats (Kallupi et al. 2018).

8 Conclusion

Tobacco use disorder is the leading cause of preventable disease and death in the United States and worldwide. The health consequences of nicotine addiction resulting from prolonged drug use are tremendous and devastating. After more than three decades of research on the neurobiology of nicotine dependence, health professionals can now turn to several efficacious pharmacotherapies to treat smoking. These agents often double the odds for quitting over placebo and in some cases (i.e., varenicline) almost triple the odds of quitting over those of placebo. However, despite these advances, many smokers relapse, and unfortunately the long-term abstinence rates among smokers attempting to quit remain low. Therefore, a better understanding of the various genetic, behavioral, and biological mechanisms mediating the various aspects of nicotine dependence is paramount.

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