Biochemical Pharmacology 82 (2011) 984–995

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Review

Recent advances in understanding nicotinic receptor signaling mechanisms that regulate drug self-administration behavior

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ARTICLE INFO

Article history:
Received 21 April 2011
Accepted 16 June 2011
Available online 29 June 2011

Keywords:
Nicotine
Nicotinic acetylcholine receptor
Tobacco smoking
Cocaine
Alcohol
Opiates
Cannabinoids
Intravenous self-administration
Knockout mice

ABSTRACT

Tobacco smoking is one of the leading causes of disease and premature death in the United States. Nicotine is considered the major reinforcing component in tobacco smoke responsible for tobacco addiction. Nicotine acts in the brain through the neuronal nicotinic acetylcholine receptors (nAChRs). The predominant nAChR subtypes in mammalian brain are those containing α4 and β2 subunits. The α4β2 nAChRs, particularly those located in the mesoaccumbens dopamine pathway, play a key role in regulating the reinforcing properties of nicotine. Considering that twelve mammalian nAChR subunits have been cloned, it is likely that nAChRs containing subunits in addition to, or other than, α4 and β2 also play a role in the tobacco smoking habit. Consistent with this possibility, human genome-wide association studies have shown that genetic variation in the *CHRNA5–CHRNA3–CHRNB4* gene cluster located in chromosome region 15q25, which encode the α5, α3 and β4 nAChR subunits, respectively, increases vulnerability to tobacco addiction and smoking-related diseases. Most recently, α5-containing nAChRs located in the habenulo-interpeduncular tract were shown to limit intravenous nicotine self-administration behavior in rats and mice, suggesting that deficits in α5-containing nAChR signaling in the habenulo-interpeduncular tract increases vulnerability to the motivational properties of nicotine. Finally, evidence suggests that nAChRs may also play a prominent role in controlling consumption of addictive drugs other than nicotine, including cocaine, alcohol, opiates and cannabinoids. The aim of the present review is to discuss recent preclinical findings concerning the identity of the nAChR subtypes that regulate self-administration of nicotine and other drugs of abuse.

Contents

1. Introduction

The burden of disease and negative economic impact of tobacco addiction on society is staggering. It is predicted that approximately 0.6 billion current smokers worldwide will die from

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0006-2952/$ – see front matter © 2011 Elsevier Inc. All rights reserved.
doi:10.1016/j.bcp.2011.06.026

smoking-related illnesses, such as chronic obstructive pulmonary disorder (COPD), lung cancer, and cardiovascular disease [1–4]. Indeed, if current trends in tobacco use persist, by 2020 smoking will become the largest single health problem worldwide, causing an estimated 8.4 million deaths annually [5]. The World Bank estimates that in high-income countries, smoking-related health-care accounts for between 6 and 15% of all healthcare costs, ~$160 billion annually. Smokers who quit before the onset of tobacco-related illness can largely avoid the increased mortality risk [6,7]. Nevertheless, approximately 80% of smokers currently attempting to quit will relapse within the first month of abstinence [8]. The development of efficacious smoking cessation aids is perhaps the most cost-effective intervention possible within the health-care systems of developed countries [9]. Although clinically efficacious, current smoking cessation agents approved by the US Food and Drug Administration (FDA) have limited utility. In smokers attempting to quit, 23% treated with Chantix (varenicline) and 16% treated with Zyban (bupropion) remain abstinent after 1 year, compared with 9% of those treated with placebo [9]. Pharmacotherapy is therefore an effective strategy to aid smoking cessation efforts, but there remains considerable risk of relapse even when treated with the most efficacious medications currently available. This highlights the pressing need to better understand the neurobiological mechanisms underlying tobacco addiction and to facilitate the development of more effective therapeutics.

Nicotine is considered the major reinforcing component in tobacco smoke responsible for addiction [10]. Nevertheless, other components of tobacco smoke, such as those that inhibit the activity of monoamine oxidases in brain, are also likely to contribute to tobacco dependence [11–13]. The addiction-relevant actions of nicotine are related to its stimulatory effects on neuronal nicotinic acetylcholine receptors (nAChRs) in the central nervous system (CNS) [14]. As such, nAChRs are key targets for the development of therapeutic agents for smoking cessation efforts. Indeed, varenicline was rationally designed as a smoking cessation aid based on its action as a partial agonist at nAChRs. In contrast, bupropion is the only smoking cessation medication approved by the FDA that does not have nAChRs as its primary site of action (atypical antidepressant considered to act through norepinephrine/dopamine reuptake inhibition). Nevertheless, bupropion acts as an antagonist at nAChRs [15]. Thus, identification of the nAChRs that control the addiction-related actions of nicotine may provide valuable insights into the neurobiology of the nicotine habit in smokers and facilitate the development of novel therapeutic strategies for the treatment of tobacco addiction [16].

The nAChRs are composed of five distinct membrane-spanning subunits (α and β subunits) that combine to form a functional receptor [17,18]. There are nine isoforms of the neuronal α subunit (α2–α10), and three isoforms of the neuronal β subunit (β2–β4) [19–21]. These nAChR subunits arrange in various combinations to form distinct pentameric nAChR subtypes [22,23]. Typically, α7, α8 and α9 subunits form homopentameric complexes lacking β subunits, with only the α7 pentamer expressed in the CNS. Because of the large number of subunits, many nAChR subtypes could exist, each composed of various combinations of α and βsubunits. However, the number of functional nAChR subtypes appears to be far less than could potentially be generated, suggesting that tight regulatory mechanisms control the incorporation of nAChR subunits into functional nAChR subtypes. The predominant nAChR subtypes in mammalian brain, which account for most of the high-affinity nicotine binding sites, are nAChRs containing the α4 and β2 subunits (α4β2* nAChRs, where the asterisk denotes a nAChR that contains the indicated subunits but the complete subunit composition is unknown) [24]. Because of a lack of receptor agonists and antagonists with selectivity for all putative nAChR subtypes, the precise identification of functional nAChR subtypes that regulate the behavioral and physiological actions of nicotine *in vivo* remain unclear. However, recent studies identifying nAChR subunits expressed by individual neurons in the brain are beginning to shed light on the functional nAChR subtypes likely expressed in these cells. For example, approximately 90–100% of neurons located in the medial habenula (MHb) express α3, α4, α5, β2 and β4 nAChR subunits [25]. Further, it is hypothesized that ~20% of nAChRs in rat MHb neurons that project to the interpeduncular nucleus (IPN) contain α4β2α5* nAChRs, whereas only about 5% of the receptor population in this pathway are α3β4α5* nAChRs [26] (refer to Fig. 1 for schematic representation of nAChR subtypes expressed in addiction-relevant brain regions). A major goal of tobacco addiction research is to identify the precise subtypes of nAChRs that regulate the addictive properties nicotine and thereby drive tobacco dependence. Such information may facilitate the development of subtype-selective nAChR ligands that can aid smoking cessation efforts. Nicotine elicits many behavioral effects that may contribute to the development and maintenance

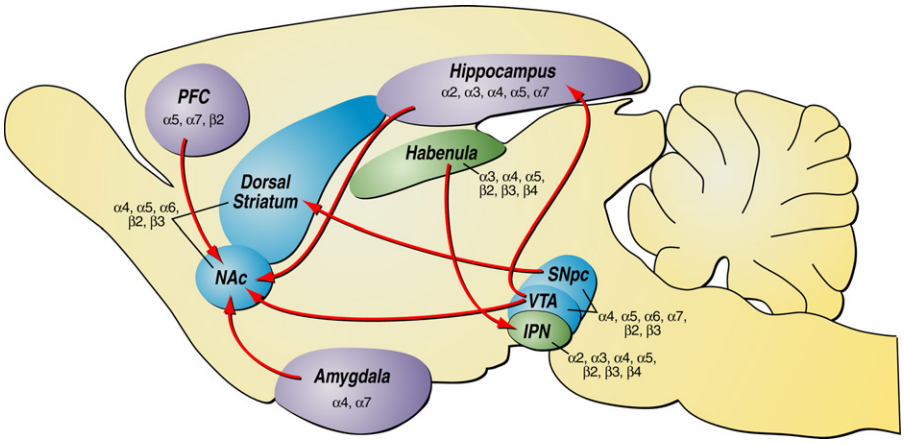

Fig. 1. Expression MRNA and protein of nAChR subunits in brain regions relevant to nicotine reinforcement. Graphical representation of nAChR subtypes expressed in brain regions implicated in the rewarding and reinforcing properties of nicotine and other drugs of abuse. The red arrows indicate neuronal projections. There is dense expression of nAChR subtypes in the ventral tegmental area (VTA) and substantia nigra pars compacta (SNpc) [63,60,112,111,147,149,257,258,259], which are two major sites of ascending dopamine projections. Sites of dopaminergic input, including the nucleus accumbens (NAc), dorsal striatum, prefrontal cortex (PFC) and hippocampus [126,112,163,254,255,262] are also enriched in nAChR subtypes. Other brain sites that have dense nAChR expression and that have been implicated in regulating nicotine self-administration behavior include the medial habenula, interpeduncular nucleus (IPN), and amygdala [25,26,41,112,163,256,257,260,261]. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

of tobacco addiction, including an ability to amplify secondary reinforcers in the environment [27,28], cognitive-enhancing effects [29–32], and also the expression of an aversive withdrawal syndrome including deficits in brain reward function and cognition [14]. Indeed, it is not quitting but avoiding relapse that presents the greatest challenge for smokers to achieving long-term abstinence. Hence, understanding the contribution of nAChRs to relapse-like behaviors will be critical to developing novel approaches to help smokers achieve long-term cessation of the tobacco habit. However, considering the many recent advances in the area, we will focus our review on new insights into the nAChR subtypes that regulate the reinforcing properties of nicotine and other major drugs of abuse, which may also contribute to relapse during periods of abstinence. For a discussion advances in understanding the mechanisms of reinstatement of extinguished drug-seeking behaviors, readers are referred to excellent recent reviews on this subject, e.g., [33–35].

The reinforcing properties of nicotine and other drugs of abuse can be assessed in laboratory animals by means of the intravenous (IV) self-administration procedure, which is generally considered the most reliable and direct measure of drug reinforcement in animals. Indeed, nicotine is self-administered by humans [36], nonhuman primates [37], dogs [38], rats [39,40], and mice [41–44]. When access to a range of doses is provided, IV nicotine infusions are invariably self-administered according to an inverted 'U' shaped dose–response (D–R) curve across species. The shape of the D–R curve likely reflects the combinatorial outcome of the competing positive and aversive properties of nicotine at the different doses available with the motivation to respond for the drug. The ascending limb of the D–R curve is hypothesized to reflect the increasing reinforcing effects of nicotine as the unit dose increases, motivating greater responding for the drug [45]. In contrast, the decreased responding for nicotine on the descending limb of the D–R curve, as the unit dose of nicotine increases, represents increasingly aversive drug effects or more rapid development of drug satiation, which act to limit responding [45–47]. Blockade of nAChR signaling with the relatively general nAChR antagonist mecamylamine decreases nicotine intake in nonhuman primates, rats and mice [48–50]. In human tobacco smokers, mecamylamine treatment can also provoke a transient increase in tobacco smoking [51] and IV self-administration behavior [52,53]. Interestingly, mecamylamine can also transiently increase nicotine self-administration behavior in rats with extended daily access to the drug (12 h/day) (Kenny, unpublished observations). Hence, blockade of nAChRs generally decreases nicotine intake, verifying an essential role for nAChRs in regulating IV nicotine self-administration behavior. However, in the case of human smokers and nicotine-dependent rats, blockade of nAChRs can also trigger a brief increase in nicotine intake, likely reflecting an attempt to overcome the inhibitory effects of mecamylamine on nAChR signaling through increased consumption of the drug.

1.1. α4β2* nAChRs in nicotine self-administration

Similar to other major drugs of abuse, nicotine enhances mesoaccumbens dopamine transmission, which comprises dopamine-containing neurons that arise in the ventral tegmental area (VTA) and project to the nucleus accumbens (NAc). This stimulatory action of nicotine on midbrain dopamine systems is hypothesized to play an important role in its positive reinforcing effects that drive the initiation and maintenance of the tobacco smoking habit [54–59]. There is now considerable evidence that α4β2* nAChRs regulate the stimulatory effects of nicotine on midbrain dopamine systems, and also the positive reinforcing effects of the drug. α4β2* nAChRs are expressed by the majority of VTA neurons [60,61]. In addition, α4β2* nAChRs are also located on GABAergic neurons in VTA [60–62]. This suggests that α4β2* nAChRs play a key role in coordinating the actions of nicotine and also endogenous cholinergic transmission on local GABAergic transmission in VTA and on dopamine transmission throughout the mesoaccumbens pathway. It has been shown that nicotine can activate and then rapidly desensitize α4β2* nAChRs on GABAergic interneurons in the VTA [63], suggesting that the reinforcing properties of nicotine may be related, in part, to disruption of inhibitory GABAergic transmission in the VTA. In addition, chronic exposure to nicotine upregulates α4 and β2 nAChR subunit expression throughout rodent brain [64,65], an effect also observed in postmortem brain tissues from human smokers [66,67]. In future studies it will be important to determine the precise contribution of α4β2* nAChRs located on dopaminergic and GABAergic neurons in the VTA.

The putatively selective agonist of β2* nAChRs, 5-iodo-A-85380, is actively self-administered by rats [68]. Partial agonists of α4* and β2* nAChRs, such as SSR591813, UCI-3002 and varenicline, decrease nicotine self-administration in rats [69–72]. However, it should be noted that UCI-30002 also demonstrates an affinity for α7* and α3β4* nAChR receptors [70], and varenicline is a full agonist at α7* nAChRs [71]. Thus, alteration in the reinforcing properties of nicotine may be due to singular or cumulative effects of these drugs on different subtypes of nAChRs. SSR591813 has undergone phase III clinical trials for smoking cessation in humans but was ineffective in promoting abstinence; however, subjective reports of cigarette craving and withdrawal symptoms were reportedly reduced [73]. Varenicline (Chantix) is an FDA-approved anti-smoking therapeutic with moderate efficacy, but significant adverse effects including nausea, depressed mood, agitation and suicidal ideation have been reported [74,75]. Bupropion (Wellbutrin, Zyban) is another commonly prescribed smoking cessation therapeutic that primarily acts as a blocker of norepinephrine and dopamine transporter systems, but also acts as a noncompetitive antagonist at α4β2* and α3β2* nAChRs [15,76]. In mice, bupropion did not attenuate the rewarding effects of nicotine, as measured in a place conditioning procedure [78]. In rats, however, bupropion decreases nicotine self-administration and the somatic and effective aspects of nicotine withdrawal [79,80]. Finally, the competitive nAChR antagonist dihydro-β-erythroidine (DHβE), which is relatively selective for α4β2* nAChRs [81,82], decreases nicotine self-administration in rats following systemic or intra-VTA administration [39,49].

The above findings provide strong pharmacological evidence supporting a role for β2* nAChRs in VTA in regulating nicotine self-administration behavior. More direct evidence has been generated using genetically modified mice. In knockout (KO) mice with a null mutation of the β2 nAChR subunit gene (β2 KO mice), dopaminergic neurons in the VTA exhibit decreased levels of basal firing, are less responsiveness to nicotine-induced changes in neuronal activity, and have less nicotine-evoked increases in dopamine release in the NAc compared to wildtype mice [62,83,84]. Further, varenicline increases mesoaccumbens dopamine transmission in wildtype but not in β2 KO mice [85]. Moreover, when intra-VTA infusions of nicotine were delivered to mice upon entry into the correct arm of a Y-maze, β2 KO mice did not learn to direct their behavior toward obtaining nicotine infusions. Hence, the β2 KO earned far less nicotine than wildtype mice and appeared resistant to the reinforcing properties of the drug [86,87]. Responding for IV nicotine infusions has also been examined in β2 KO mice after they had first acquiring responding for IV cocaine infusions [83,88]. Whereas wildtype mice persisted in responding after cocaine was substituted with nicotine infusions, the β2 KO mice rapidly decreased their responding and established a level of responding equivalent to that seen in wildtype mice with access to saline infusions [83,88]. The β2 KO

mice also displayed deficits in nicotine discrimination [89] and in developing a nicotine-induced conditioned place preference [90]. Importantly, virus-mediated re-expression of β2 nAChR subunits specifically in the VTA, but not the adjacent substantia nigra pars compacta (SNpc), of the β2 KO mice "rescued" the deficits in dopaminergic transmission, responding for nicotine via intra-VTA infusions, and sensitivity to developing nicotine-conditioned place preferences [86,87,91]. It is important to note that the place conditioning procedure is dependent on the ability of the mice to form, store and recall a drug-related memory. However, cholinergic transmission at nAChRs is known to modulate these processes [30,92]. Hence, it is possible that disruption of drug-related memories rather than nicotine reward *per se* may contribute to alterations in the performance of nAChR subunit KO mice in the conditioned place preference procedure.

Similar to the β2 KO mice, α4 subunit KO mice do not acquire nicotine self-administration behavior [91]. In these studies, nicotine self-administration in wildtype and α4 KO was measured using a procedure in which mice are placed into an apparatus to restrain their movement and prepared with a temporary catheter in their lateral tail vein through which nicotine infusions are delivered contingent upon nose-poke responses [91,93–95]. Although this procedure has a number of notable confounds that limit its utility, particularly the high level of restraint and the fact that typically only a single self-administration session can be assessed for each mouse using the temporary tail-vein catheter, these studies nonetheless suggest that α4 nAChRs play a key role in nicotine reinforcement. Interestingly, virus-mediated re-expression of α4 nAChR subunits in the VTA of the KO mice "rescued" their deficient nicotine intake in this procedure similar to the effects β2 re-expression in the VTA of the β2 KO mice [91]. In contrast to these findings, Lawrence and co-workers found that α4 KO mice responded for nicotine infusions at similar rates as their wildtype littermates in a more traditional self-administration procedure in which the mice received IV nicotine infusions through chronic indwelling IV catheters in the jugular vein [96]. Knock-in mice expressing hypersensitive α4* nAChRs, generated by replacing an endogenous exon of the α4nAChR gene with one containing a single point mutation (Leu 9′ Ala 9′) that increases the function of the subunit [54], show dramatically increased sensitivity to nicotine reward. Indeed, these α4 knock-in mice demonstrate a place preference for nicotine at doses far lower (~50-fold) than those necessary to support a place preference in wildtype mice [54]. VTA dopamine neurons from the α4 knock-in mice are similarly far more sensitive to nicotine than dopamine neurons in wildtype mice [54]. More recently, a second line of hypersensitive α4 knock-in mice was developed by replacing the serine with phenylalanine at amino acid residue 248 in the α4 subunit (Ser248′ Phe248′). This line of α4 hypersensitive knock-in mice self-administered IV nicotine infusions far more vigorously than wildtype controls when a low unit dose of the drug was available (0.03 mg kg^{-1} per infusion) [96]. Taken together, these data suggest that α4β2* nAChRs, particularly those located in the VTA, play a key role in regulating the reinforcing properties of nicotine.

1.2. α5* nAChRs in nicotine self-administration

Genome-wide association studies have revealed a strong link between allelic variation in the α5/α3/β4 nAChR gene cluster and increased vulnerability to tobacco addiction in humans [97–101]. For example, a non-synonymous single nucleotide polymorphism (SNP) in *CHRNA5* (rs16969968), the gene encoding the α5 nAChR subunit, results in an aspartic acid to asparagine substitution at amino acid residue 398 (D398N), and decreases the function of α5* nAChRs incorporating this risk allele [99]. This SNP, which is relatively common in those of European descent (minor allele frequency = 0.42), increases the risk of tobacco dependence by approximately 30% in individuals carrying a single copy of the variant, and more than doubles the risk in those carrying two risk alleles [98,99,102–104]. The D398N major risk allele is associated with heavy smoking [98,99,103,104], early onset of smoking behavior [105], and "pleasurable buzz" from tobacco [106]. In addition, the D398N allele is also a major risk factor for lung cancer and COPD in smokers [107–109], likely reflecting higher levels of tobacco dependence in individuals carrying risk alleles and consequently greater exposure to carcinogens contained in tobacco smoke [101,110]. As such, considerable interest has arisen into how α5 nAChR subunits may influence the reinforcing properties of nicotine. The α5 nAChR subunits demonstrate a relatively discrete mRNA expression profile in the brain, with the highest densities of expression found in the medial habenula (MHb), interpeduncular nucleus (IPN), VTA, SN, hippocampus and deep layers of the cortex [25,111,112]. The MHb projects almost exclusively to the IPN via the fasciculus retroflexus [113], and high, but not low, nicotine doses activate the habenulo-interpeduncular pathway, as measured by an increased local glucose utilization in rats [114]. The α5 nAChR subunit is incorporated into functional nAChRs in the MHb–IPN pathway, and presynaptic α5* nAChRs on MHb afferents to the IPN are thought to regulate glutamate, but not acetylcholine, release in the IPN [26,115,116]. Incorporation of the α5 subunit is known to alter the nicotine binding and desensitization kinetics of α4β2*, α3β2* or α3β4* nAChR receptors [117,118], suggesting that incorporation of wildtype or risk alleles of the α5 nAChR subunit into habenulo-interpeduncular nAChRs may profoundly alter the sensitivity of this tract to nicotine. There are no available pharmacological compounds that selectively modulate the activity ofα5* nAChRs, which thus necessitates the use of genetically modified mice to assess the role for α5* nAChRs in nicotine reinforcement.

The α5 subunit KO mice are known to have decreased sensitivity to nicotine-induced seizures and hypolocomotion, and display reduced expression of the somatic aspects of nicotine withdrawal [119–121]. Intriguingly, α5 KO mice demonstrate a place preference for high nicotine doses that are otherwise aversive in wildtype mice [121]. Recently, our laboratory has shown that the α5* nAChRs play a critical role in regulating nicotine self-administration behavior [41]. When we assessed nicotine self-administration behavior in α5 KO mice, we found that the ascending portion of the D–R curve was similar between the KO mice and their wildtype counterparts [41]. However, the α5 KO mice continued to consume far more nicotine than wildtype mice when higher unit doses of nicotine were made available [41], and as a result the descending portion of the D–R curve failed to decline as rapidly in the KO mice [41]. The α5 KO mice also responded far more vigorously for nicotine when tested under a progressive ratio schedule of reinforcement that is thought to better reflect the motivational aspects of nicotine compared with fixed ratio reinforcement schedules typically used in nicotine self-administration studies [122]. Again, this effect in the α5 KO mice was most apparent when higher nicotine doses were made available for self-administration [41]. As noted above, the increased responding for nicotine over the ascending portion of the D–R curve is thought to reflect increasing rewarding properties of the unit dose available for consumption, motivating greater responding for the drug. In contrast, decreased responding over the descending portion of the D–R curve as the unit dose of nicotine further increases is thought to reflect the emergence of aversive drug effects or more rapid drug satiation. As such, it appears that α5 KO mice are less sensitive to the aversive effects of nicotine that serve to limit responding for the drug [41].

Re-expression of the α5 subunit in the habenulo-interpeduncular pathway of the α5 KO mice, achieved through infusion of an

α5 nAChR subunit-expressing lentivirus directly into the MHb, "rescued" the increased nicotine intake observed in the KO mice at higher doses, and normalized their intake relative to the wildtype mice [41]. Conversely, knockdown of α5 nAChR subunits in the habenulo-interpeduncular pathway of rats, achieved through intra-MHb infusion of a lentivirus expressing a short hairpin RNA (shRNA) against α5 nAChR subunits, increased nicotine intake, particularly at high doses of the drug [41]. Interestingly, knockdown of α5 subunits in the habenulo-interpeduncular pathway did not alter the stimulatory effects of nicotine on brain reward systems (i.e., increased reward), as measured by nicotine-induced lowering of intracranial self-stimulation (ICSS) reward thresholds in rats [41]. However, deficient α5* nAChR signaling in the habenulo-interpeduncular tract greatly diminished the inhibitory effects of higher nicotine doses on brain reward function (i.e., decreased reward), as measured by nicotine-induced elevations of ICSS thresholds in rats [41]. This again is consistent with the shape of the nicotine D–R curve in the knockout mice and knockdown rats, in which it appears that aversive effects of higher nicotine doses that limit its intake are greatly diminished when α5* nAChR signaling in the habenulo-interpeduncular tract is disrupted. Finally, using Fos immunoreactivity as a measure of neuronal activation, we found that aversive doses of nicotine robustly activated the IPN in WT mice, an effect that was completely abolished in α5 KO mice [41]. In contrast, nicotine-induced activation of the VTA was similar in WT and α5 KO mice [41]. This suggests that α5* nAChRs preferentially control the sensitivity of the MHb–IPN tract, but not VTA, to nicotine. Moreover, lidocaine-induced inactivation of MHb or IPN, or inhibition of NMDA glutamate receptors in MHb or IPN, increased nicotine self-administration behavior in rats [41]. Strikingly, these same manipulations in the VTA had opposite effects by decreasing nicotine intake [41]. Taken together, we hypothesize that nicotine stimulates the MHb–IPN tract through α5* nAChRs, and perhaps through other nAChR subtypes expressed in this tract. Activation of this pathway decreases the motivation to further consume nicotine, thereby limiting its intake. Disrupted sensitivity of the MHb–IPN to nicotine in the α5 KO mice diminishes this negative motivational signal and results in greater levels of nicotine intake. It will therefore be important to examine if a similar mechanism explains the increased vulnerability to tobacco addiction in humans carrying *CHRNA5* risk alleles. As noted above, α5 nAChR subunits are also expressed in many other addiction-relevant brain regions, in addition to their dense concentration in the MHb–IPN tract [61,123,60,124–126]. Changeux and co-workers reported that a high percentage of nAChRs in VTA express α5 nAChRs [60]. Further, Lambe and co-workers have shown that excitatory glutamate transmission is severely compromised in medial prefrontal cortex (mPFC) of α5 KO mice, a brain region known to regulate drug self-administration behavior [124]. Finally, using functional magnetic resonance imaging (fMRI), Stein and co-workers have shown that humans carrying the D398N risk allele had decreased functional connectivity between the anterior cingulate cortex (ACC) with the NAc and extended amygdala [128]. The same group has previously shown that weakened functional connectivity in this circuit predisposes individuals to smoking and predicts addiction severity in those who smoke [128,129], perhaps by diminishing executive control over tobacco smoking behaviors. These findings raise the possibility that α5* nAChRs located in VTA, mPFC, ACC and perhaps in other cortical areas and the hippocampus, may regulate nicotine intake similar to α5* nAChRs located in the MHb–IPN tract.

1.3. α3* nAChRs in nicotine self-administration

Although the α3 nAChR subunit was the first mammalian subunit cloned [130], relatively little is known regarding its involvement in brain function. Neuronal expression of α3 subunit mRNA is most predominantly found in the MHb, IPN, hippocampus, and VTA [61,112,131], and α3β4*and α3β3β4* nAChRs are known to regulate acetylcholine release in the habenulo-interpeduncular tract [26]. Novel compounds with selectivity for α3* nAChRs remain in the early stages of development and/or exhibit off-target actions at other classes of nAChR subtypes, such as α6*nAChRs [132–136]. For instance, the nicotinic antagonist bPiDDB is thought to antagonize α3* nAChRs, but may have an even greater action at α6β2* nAChRs [137–139]. Nevertheless, α3* nAChRs are thought to play a major role in regulating the stimulatory effects of nicotine on dopamine transmission in the NAc and striatum [140,141], suggesting that these nAChRs are likely to play a key role in regulating nicotine self-administration behavior. Indeed, bPiDDB dose-dependently decreased nicotine self-administration and nicotine-induced hyperactivity [138]. Unfortunately, null mutation of the α3 nAChR subunit gene leads to autonomic dysfunction and results in postnatal lethality in mice on a C575BL6 background [142], so examination of α3 knockout mice for nicotine self-administration has been greatly hampered. Interestingly, however, a genetically modified mouse was recently created with pharmacological sensitivity to α-bungaratoxin (α-Bgt) [143]. Specifically, chimeric α3 nAChR subunits were generated by substituting five amino acids in the α3 subunit with the corresponding residues from the muscle α1 subunit from *Torpedo californica*, rendering α3* nAChRs in these mice sensitive to blockade by α-Bgt [143]. It will be interested to assess the effects of α-Bgt on nicotine self-administration in these knock-in mice on a wildtype background and also on an α7nAChR subunit KO background since α7 nAChRs are sensitive to α-Bgt blockade.

1.4. α6* nAChRs in nicotine self-administration

The α6*nAChR subtype is considered a major class of nAChRs involved in regulating the reinforcing properties of nicotine. Recent evidence for genome-wide association studies have shown that genetic variation in the *CHRNA6–CHRNB3* gene cluster, encoding the α6 and β3 nAChR subunits respectively, increase vulnerability to tobacco smoking [144–146]. There is dense expression of α6 subunit mRNA in the VTA, SN, NAc, MHb, IPN, and locus coeruleus [147–150]. In the VTA, α6* nAChRs appear to regulate GABA release onto dopamine neurons [151], and following nicotine self-administration, α6 mRNA expression is markedly upregulated [152]. In the striatum, dopaminergic terminals express α6β2β3* and α4α6β2β3* nAChR subtypes [153–155], with considerable evidence suggesting that these α6* nAChRs regulate the stimulatory effects of nicotine on dopamine release in this region [154]. Intriguingly, the α4α6β2β3* nAChR subtype is enriched in the NAc, and the striatum has the highest sensitivity to nicotine of any native nAChR so far identified [156]. Hence, it is an interesting possibility that the shape of the D–R curve for nicotine self-administration may reflect activation of mesoaccumbens α4α6β2β3* nAChR at lower doses of nicotine, supporting increased responding for nicotine intake (ascending limb of D–R curve). However, as the amounts of nicotine consumed continue to increase, then α5* nAChRs in the MHb–IPN tract may be activated, which theoretically serves to limit nicotine intake and decrease responding (descending limb of D–R curve).

As noted above, the effects of bPiDDB may be due to actions on α6β2* nAChRs, leading to a reduction in nicotine intake in rats [138]. Recently, α-conotoxin MII (αCTX MII), has been identified as a selective antagonist of α6β2* nAChRs [149,157]. In the mouse NAc *in vitro*, αCTX MII attenuates dopamine release induced by single and low-frequency neuronal firing, while enhancing dopamine release with high-frequency firing [158]. Infusions of αCTX MII into the shell compartment of the NAc decreases the

motivation to self-administer nicotine in rats [159]. Further, administration of αCTX MII into the VTA decreases nicotine self-administration behavior and also attenuates nicotine-induced dopamine release in the NAc [160]. Striatal dopamine release can be similarly inhibited with αCTX MII and a novel compound, bPiDI, an analog of bPiDDB [161]. Systemic administration of bPiDI also decreases nicotine self-administration in rats [161]. In mice, knockdown of α6 subunit mRNA with antisense oligonucleotides attenuates the stimulatory effects of nicotine on locomotion [162]. Furthermore, Pons et al. have found that α6 KO mice do not acquire nicotine self-administration behavior [91]. However, lentiviral-mediated re-expression of α6 subunits in the VTA of the α6 KO mice re-established sensitivity to nicotine, and the KO mice responded for nicotine infusions at the same rate as their wildtype counterparts [91]. These findings support a key role for α6* nAChRs in VTA-NAc in regulating nicotine self-administration behavior.

1.5. α7* nAChRs in nicotine self-administration

Similar to the α4 and β2 nAChR subunits, the α7 subunit exhibits widespread expression throughout the brain. The greatest density of α7 subunit mRNA expression is found in the amygdala, hypothalamus and hippocampus [163]. Unlike most other nAChR subunits, the α7 subunit forms functional homopentameric receptors in CNS [164]. In the VTA, approximately 40% of dopaminergic and GABAergic neurons express α7 subunit mRNA [60], and α7 nAChRs regulate presynaptic glutamate release onto dopamine neurons [165–167]. Administration of the α7 nAChR antagonist methyllycaconitine (MLA) into the VTA attenuates nicotine-induced conditioned rewarding effects and nicotine-induced lowering of ICSS thresholds in rats [168,169]. This suggests that α7 nAChRs regulate the reward-enhancing properties of nicotine that may support nicotine self-administration behavior. However, the precise role for α7* nAChRs in regulating nicotine intake remains unclear. Markou and Patterson found that systemically administered MLA decreased nicotine self-administration in rats [170]. In contrast, Grottick et al. found that MLA had no effect on nicotine self-administration or nicotine-stimulated locomotion in rats [171]. Interestingly, prior nicotine exposure alters the ability of MLA to enter the brain [172], an effect that may have contributed to differences found between the two studies. Furthermore, MLA may also antagonize non-α7* nAChRs [173], making it difficult to attribute any action of MLA specifically to an action at α7* nAChRs in the reward-related actions of nicotine. It was found that α7 subunit KO mice had no difference in nicotine self-administration behavior or nicotine-induced conditioned place preference compared with wildtype mice [90,91]. Taken together, there is some evidence supporting a role for α7* nAChRs in regulating nicotine intake, but much work still needs to be done to properly define the precise contribution of this subtype of nAChRs to nicotine reinforcement.

Overall, the above data suggest a role for the α4*, α6* and β2* nAChRs in the positive reinforcing effects of nicotine, and α5* nAChRs in the aversive processing of nicotine. The balance among the respective contribution of certain nAChR subtypes likely contributes to the subjective nature of nicotine's reinforcing qualities that thereby determine the quantity of nicotine consumed by an individual. Much less is known about the roles of α2, α3, β3 and β4 nAChR subunits in nicotine reinforcement. In addition, research efforts should be directed at identifying the specific receptor combinations of subunits within brain regions that may differentially modify neuronal responses to nicotine. With further investigation of the nAChR subunits involved in nicotine reinforcement, novel pharmaceuticals may be developed to selectively act discretely on select nAChR subtypes with the goal of developing novel, highly efficacious treatment options for smoking cessation.

1.6. nAChRs in psychomotor stimulant self-administration

Tobacco smoking behavior is often associated with the abuse of other classes of addictive drugs including psychomotor stimulants and opiates [174]. This suggests that, in addition to regulating nicotine self-administration behavior, endogenous cholinergic transmission at nAChRs also plays a key role in influencing the reinforcing properties of other classes of addictive drugs [176–180]. Although not considered in detail here, it is important to note that illicit drugs may also impact nAChR function and thereby influence tobacco use [175,181]. Epidemiological studies have shown that there is a higher prevalence of cigarette smoking among cocaine-dependent individuals [182]. Human genome-wide association studies have also shown that the same risk alleles in the *CHRNA5* gene, which encodes the α5 nAChR subunit, may be protective against cocaine dependence [104]. Decreased cholinergic activity has been detected in the brains of methamphetamine users, reflected as decreased expression of choline acetyltransferase and elevated vesicular acetylcholine transporter expression [183]. Interestingly, the nAChR antagonist mecamylamine reduces cravings for cocaine in human users [184]. These findings suggest that similar brain circuitries, and nAChRs within these circuits, regulate the reinforcing properties of cocaine and nicotine.

In rats, nAChR antagonists attenuate amphetamine-induced behavioral effects including locomotor sensitization [176,185] and the discriminative effects of the drug [186]. Conversely, nicotine facilitates the development of sensitized locomotor activity in response to amphetamines [187–191]. This effect of nicotine appears to be dependent on β2*, but not α7*nAChRs, as DHβE but not MLA blocked amphetamine-stimulated locomotion [192]. Nicotine increases cocaine self-administration behavior [193]. Conversely, mecamylamine reduces cocaine self-administration behavior [194,195] and prevents the development of escalated cocaine self-administration behavior in rats with extended daily access to cocaine [196]. Intra-NAc infusion of mecamylamine or co-infusion of DHβE and MLA blocks the stimulatory effects of cocaine on NAc dopamine release [178]. Further, mecamylamine blocks the rewarding properties of cocaine as measured in a preference conditioning procedure [197]. The putative α3β4* nAChR antagonist 18-MC decreases cocaine and methamphetamine self-administration in rats [198–201]. nAChRs are also believed to play a contributory role in relapse-like behaviors to psychostimulant seeking in rats. Indeed, nicotine and the acetylcholinesterase inhibitor donepezil attenuate reinstatement of previously extinguished methamphetamine seeking in abstinent rats [177,202].

More recently, Deisseroth and co-workers have used a novel optogenetics approach to modulate the activity of cholinergic interneurons in the NAc of mice [203]. Using this approach they have shown that cholinergic transmission at nAChRs in NAc regulates the activity of medium spiny neurons in this brain site [203]. Moreover, silencing of cholinergic interneurons in NAc prevented the establishment of a cocaine-induced conditioned place preference [203], supporting a key role for cholinergic transmission at nAChRs in the rewarding properties of cocaine. Consistent with this notion, mecamylamine disrupts the development of a place preference to a low (5 mg kg^{-1}) cocaine dose [197]. Moreover, β2 nAChR subunit KO mice show decreased place preference to cocaine [197]. These findings suggest that β2* and perhaps also α3β4* nAChRs play a key role in regulating cocaine reward. Cocaine self-administration behavior in mice with genetic manipulation of individual nAChRs has not yet been assessed. It will therefore be important to more directly assess the role for discrete nAChR subunits in cocaine reinforcement by assessing cocaine self-administration behavior in nAChR subunit KO mice.

1.7. nAChRs in ethanol self-administration

There is a strong link between alcohol consumption and tobacco smoking in humans. Epidemiological studies suggest that approximately 80–90% of alcoholics are also tobacco smokers [204–208]. Conversely, tobacco smokers are reported to consume twice the amount of alcohol as non-smokers [209]. Further, the incidence of alcohol abuse is estimated to be between 10 and 14 times higher in tobacco smokers than in non-smokers [210]. In rats, nicotine enhances ethanol consumption and reinstates previously extinguished alcohol seeking behaviors [211]. Offspring from ethanol-preferring rats display higher susceptibility to nicotine self-administration and relapse [212], suggesting that genetic and epigenetic factors that influence vulnerability to alcoholism may also influence vulnerability to smoking. Consistent with this notion, humans carrying risk alleles in *CHRNA5–CHRNA3–CHRNB4* gene cluster and the *CHRNA6–CHRNB3* gene cluster appear to have increased vulnerability to develop both tobacco smoking and alcohol abuse [213–216]. Genetic variation in the genes encoding the α5 and β4 nAChR subunits also influences alcohol preference in mice [217]. More directly, mecamylamine decreases the desire to consume alcohol in healthy volunteers [218] and attenuates the self-reported euphoric effects of alcohol consumption [219]. This has led to the idea that nAChRs may be viable targets for the development of novel therapeutics for alcoholism.

Similar to nicotine and psychomotor stimulants, the reinforcing properties of alcohol are believed to involve dopaminergic transmission in the mesoaccumbens system. Ethanol increases dopamine release in NAc [220]. Peripheral or intra-VTA administration of mecamylamine of nAChRs attenuates the stimulatory effects of ethanol on NAc dopamine release [221–224]. Further, in rats mecamylamine and 18-MC also reduce preference for alcohol [221] and volitional intake [221,222,225,226].

New studies are beginning to identify the nAChR subtypes likely to be involved in the reinforcing properties of ethanol. Similar to nicotine and psychomotor stimulant reinforcement, β2* nAChRs are likely to regulate ethanol consumption, but may be less important in regulating alcohol intake compared with other drugs of abuse. Using [^{123}I]-5-IA-85380 as an imaging agent for β2 nAChRs in the brain, it was reported that chronic oral consumption of alcohol resulted in decreased β2* nAChR availability throughout the cortex and thalamus of non-human primates [227]. In rats, the β2* nAChRs were also reported to play a role in ethanol-dependent locomotor activity [228] and ethanol-induced ataxia [229]. However, Picciotto and co-workers found that β2 KO mice consumed a similar amount of ethanol as wildtype mice [230]. In contrast, α7 KO mice drank significantly less ethanol than wildtype mice, but consumed comparable amounts of water, saccharin, and quinine [230]. In wildtype mice, varenicline dose-dependently decreased ethanol intake [230] similarly in the β2 and α7 KO mice [230], consistent with previously reported inhibitory effects of varenicline on alcohol drinking results in rats [231]. This suggests that β2* and α7* nAChRs are not involved in regulating the inhibitory effects of varenicline on alcohol intake, and perhaps are not predominantly involved in alcohol reinforcement. Instead, perhaps the α3β4* nAChRs regulate the inhibitory effects of varenicline on alcohol consumption, as the α3β4* nAChR partial agonists CP-601932 and PF-4575180 decrease volitional ethanol intake in rats [232]. In addition to α3β4* nAChR, there is some evidence that α4* nAChRs may also regulate the inhibitory effects of varenicline on ethanol intake. Indeed, α4 subunit knock-in mice expressing hyper-responsive α4* nAChRs were dramatically more sensitive to the inhibitory effects of varenicline on ethanol consumption compared with wildtype littermates [233]. Furthermore, varenicline-induced reductions in ethanol consumption were attenuated in α4 KO mice compared with wildtype mice [233]. Taken together, these findings suggest that α4*, α3β4* and to a far lesser extent, α7* and β2* nAChRs regulate alcohol consumption. However, the role for other nAChRs in ethanol consumption, particularly the α5*, α6* and β3* nAChRs thought to play an important role in regulating nicotine intake, remains poorly understood.

1.8. nAChRs in cannabinoid self-administration

Nicotinic receptors, particularly α7* nAChRs, appear to play an important role in the reinforcing properties of cannabinoids. The relatively selective α7* nAChR antagonist MLA (see above for evidence of action at other nAChR subtypes) attenuates increases in dopamine overflow in the NAc in response to the cannabinoid receptor agonist Δ9-tetrahydrocannabinol (THC), the major psychoactive ingredient in cannabis [234]. MLA also reduces the discriminative effects of THC, and decreases self-administration of the cannabinoid-1 (CB1) receptor agonist WIN55, 212-2 [234]. This suggests that α7* nAChR play an important role in modulating the reinforcing effects of cannabinoids. Interestingly, pharmacological blockade of CB1 receptors can attenuate the reinforcing properties of nicotine. Indeed, the CB1 receptor antagonist SR141716 (rimonabant; *Acomplia*) decreases cigarette consumption in smokers [235–237]. Based on concerns related to suicidal ideation in small numbers of these treated with rimonabant [238], the use of this agent has been suspended in Europe and has not been approved for use in the United States. Rimonabant also abolishes nicotine-induced place conditioning in mice [239], and CB1 receptor KO mice fail to develop a nicotine-induced place preference [240]. Rimonabant also decreased nicotine self-administration in rats [241]. These findings support an important interaction between nAChRs and cannabinoid receptors in regulating drug reward. However, the precise nAChR subtypes that may regulate these interactions remain unclear.

1.9. nAChRs in opiate self-administration

There is considerable evidence suggesting that opioid and nicotinic receptor systems may interact to regulate opioid and nicotine intake. Similar to its role in vulnerability to tobacco and alcohol dependence, genetic variation in the *CHRNA5–CHRNA3–CHRNB4* gene cluster increases vulnerability to opioid dependence [242]. Furthermore, genetic deletion of the preprodynorphin gene (dynorphin is an agonist primarily at κ-opioid receptors) increases nicotine self-administration behavior in mice [42]. Conversely, genetic disruption of the μ-opioid receptor signaling decreases the rewarding and reinforcing properties of nicotine [243,244], although it is thought that μ-opioid receptors may play a more important role in nicotine-seeking rather than nicotine-taking behaviors [245,246].

Physostigmine, an acetylcholinesterase inhibitor, reduces heroin acquisition and self-administration in rats [247]. Physostigmine administered directly into the NAc also inhibits morphine-induced locomotor sensitization and place conditioning [248], as well as cue-induced reinstatement of heroin seeking [247]. These findings support a role for cholinergic transmission in regulating opiate reinforcement. However, the effects of physostigmine on heroin self-administration and reinstatement are most likely related to muscarinic actions of the drug, as scopolamine but not mecamylamine reversed these effects [247]. Nevertheless, 18-MC (putative α3β4* nAChR antagonist), particularly after direct administration into the MHb or IPN, decreases morphine self-administration in rats [201,249,250]. Indeed, dextromethorphan (DM), a structural analog of morphine and a popular cough suppressant, has also been shown to attenuate opiate tolerance in rats [251]. Similar to 18-MC, DM may also antagonize α3β4* nAChRs [252]. More recently, disruption of α4β2* or α7* nAChR

signaling through DHβE or MLA administration, respectively, blocked the morphine-induced place conditioning [253].

The contribution of precise nAChR subtypes involved in opiate reinforcement remains largely unknown. Hence, it will be important to assess opiate self-administration behavior in mice with null mutation in different nAChR subunits to provide a deeper understanding of the relationship between nicotinic receptors and opiate reinforcement.

2. Conclusions

The use of genetically modified mice is beginning to reveal which nAChRs subunits play a role in nicotine reinforcement. Intriguingly, the use of subunit knockout mice is revealing that different subunits play dissociable roles in different aspects of nicotine self-administration behavior. For example, α4* and β2* nAChRs appear to play a central role in regulating the stimulatory effects of nicotine on brain reward systems and the positive reinforcing effects of nicotine. Conversely, α5* nAChRs appear to regulate the inhibitory effects of nicotine on brain reward systems. These studies are therefore revealing fundamental insights into the mechanisms of nicotine reinforcement that may be of considerable clinical utility for the development of novel smoking cessation therapeutics. Emerging evidence suggests that endogenous cholinergic transmission at nAChRs may also play a key role in regulating the reinforcing properties of other classes of addictive drugs including psychomotor stimulants, opiates, alcohol and cannabinoids. Hence, increased understanding of the roles for nAChRs in drug reward may prove valuable for therapeutic interventions for all forms of substance abuse disorders. These studies also highlight current technical limitations in understating which populations of neurons in the brain express particular nAChR subtypes that contribute to drug-taking behaviors. As such, it will be important to develop conditional knockout mice, in which the expression of individual nAChR subunits can be altered in discrete cell populations, to address this critical issue.

Acknowledgements

Supported by the National Institute on Drug Abuse (DA020686 to PJK;DA026693 to CDF; DA032225 to LMT). This is manuscript #21235 from Scripps Florida.

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