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The Roles of α5-Containing nAChRs in the Brain

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Abstract

Neuronal nicotinic acetylcholine receptors (nAChRs) are in the superfamily of the ligand-gated ion channels with an assembly of five subunits (α, βsubunit). nAChRs, such as α4β–αvδ α7-nAChRs play crucial roles in nicotine reward, dependence and withdrawal. Recently, functional profiles of the α5 nAChRs have been studied using the α5 knockout (KO) and the overexpression mice. α5-nAChRs in the brain participate in neuronal activities associate with nicotine dependence, withdrawal, aversion, as well as alcohol use disorders. The main focus of this review is to understand α5-containing nAChR's properties, function, and related disorders recently discovered.

Keywords: nAChRs; Alpha 5 subunits; Nicotine; Alcohol

Introduction

Nicotine binds to nicotinic acetylcholine receptors (nAChRs), which are transmembrane proteins that form the pentameric ligand-gated ion channels with an assembly of five subunits. Neuronal nAChRs can either be heteromeric, consisting of a combination of α(α2–α6)6) and β subunits β2–β4), or homomeric, which consists of only α subunits (α7–α10) [1]. Each nAChR subunit consists of an extracellular N-terminus, four transmembrane segments (designated M1-M4), a variable intracellular loop between M3 and M4, and an extracellular C-terminus [2]. All five subunits form the conducting channel pore serve as the ACh-binding site in the N-terminus [2,3]. When the activation by an agonist, nAChRs open the ion channels that desensitize and are potentiated by calcium ions [4]. The combination of various nAChR subunits determines the distinct pharmacological function and kinetic properties of each specific nAChR subtype [1]. nAChRs are identified throughout the central (CNS) and peripheral nervous systems (PNS), as well as at skeletal neuromuscular junctions. Nicotinic receptors containing α4 and α2 subunits (denoted as α4β2nAChRs) are the predominant subtypes in the CNS, and account for most of the high affinity nicotine binding sites [5]. Animal studies show that this type of nAChRs plays critical roles in nicotine reward, dependence and withdrawal [6-8]. However, different from the α4β2*nAChRs, the homomeric α7 nAChRs have a lower affinity to nicotine and can rapidly recover from desensitization, thus appear mainly to be involved in the later stages of nicotine dependence [9]. Studies of the involvement of α6 nAChR subunit in nicotine dependence have only recently emerged [9,10]. Furthermore, the α5-containing nAChRs have shown to be crucially important in the regulation of the medial habenula of the aversion and intakes of nicotine [11,12]. This review will summarize the function and the properties of α5 nAChRs in the brain, and graduate our understanding for neurobiology of nicotine and ethanol addiction.

4α5 Distribution and Function

α5 is an accessory subunit that cannot form functional receptors without joining with the other essential subunits, and they do not contribute to the formation of the ACh binding sites. However, α5 subunit can be incorporated in the pentamer as accessory subunits [13-15], which can have dramatic effects on the conductance and desensitization of the receptors [13,14,16,17]. The accessory subunits may also involve in forming binding sites for positive allosteric modulators [18,19]. Among the CNS, α5 subunit is associated with 37% of the nAChRs in hippocampus, 24% of the nAChRs in striatum, and 11–16% of the receptors in cerebral cortex, thalamus, superior colliculus, VTA and other regions [20, 21].

The mesocorticolimbic dopamine (DA) system has received the most attention for its role in reinforcing rewarding behaviors [22]. Therefore the expression of α5-containing nAChRs in this system is expected to play an important role in the regulation of drug addiction. The α4α5αβ2 subtype is present at high density in the midbrain dopaminergic reward pathway [23-26]. α5 subunit significantly increases α4 subunit expression on the cell surface, strengthens baseline nAChRs currents and blunts the desensitization of nAChRs following nicotine exposure in the VTA. But α5 subunit does not alter the amount of ethanol potentiation in the VTA DA neurons. This suggests that α5 subunit is critical for controlling expression and function of a population of α4-contatining nAChRs in VTA [26]. Furthermore, α4α5β2 nAChRs also involve in regulation of DA transmission in dorsal caudatoputamen (CPu) where it affects instrumental and habitual behaviors, but not in nucleus accumbens core (NAc), a region where generates pavlovian association [27]. Prefrontal cortex (PFC) is involved in higher order processes such as attention, impulse control, working memory, as well as drug addiction [28]. Exposure to nicotine can increase nAChRs expression, change GABAergic synaptic transmission, and decrease mGluR protein expression, thus causes altered synaptic function, and learning and attention behaviors [29-31]. α5 subunit is preferentially expressed by neurons in deep layers such as layer VI [32]. α5 subunits on layer VI pyramidal neurons are incorporated into the α4β2-containing nAChRs, and greatly enhance channel conductance [14] and inward currents [33]. Its presence also protects α4β2-nAChRs from complete desensitization [34,35]. In experiments, the presence of α5 subunit makes wild-type mice more sensitive to nicotine exposure, however, its loss results in attention deficiency [34]. Besides in the deep layers, α5 subunit is also expressed at a much lower levels by the GABAergic interneurons in the superficial layers [32], which only constitute a small number of cells modulated by

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β2–containing nAChRs [29].

The medial habenular-interpeduncular pathway (MHb-IPN) is involved in regulation of negative reward or the absence of anticipated positive reward [36-38], nicotine withdrawal [39], nicotine self-administration [40], and aversion to nicotine [11]. α5 sub-unit is expressed at high levels in the MHb-IPN pathway, which can co-assemble with α2β4- [39,41], or α3β4 [41-43], or α3β4 containing nAChRs [44]. Recent reports have provided solid evidence that support the critical roles of MHb-IPN α5 assembly in nicotine abuse and dependence [45,46].

α5 subunit is also highly expressed in the periphery, where it co-assembles with α3 αvδ β4 subunits to form functional receptors in the autonomic ganglion cells [47,48]. In the α3 β4 α5 combination, the α5 (Asn398) variant can involve in the regulation of autonomic responses, such as control of cardiac rate, blood pressure, and perfusion, which can affect nicotine intakes in humans. In addition, α3, α4, and α5 subunits are expressed in a number of non-neural cells, including bronchial and epithelial cells and lung cancer cell lines, where, the activation of nicotinic receptors plays a role in tumor initiation and growth [49,50].

α5 Associated Disorders

Alcohol use disorders

Alcohol use disorders (AUDs) are a world-wide problem with few effective treatments. In the United States, about 18 million people have AUDs, classified as either alcohol dependence or alcohol abuse. There remains a need for improved treatment methods and treatment options to help individuals with AUDs. Alcohol has been shown to interact with nAChRs in the brain [51-53], therefore, nAChRs can serve as a therapeutic target for the treatment of AUDs [54]. Evidence suggests that as many as 80% of alcoholics are also smokers. The high incidence of smoking and alcoholism co-abuse indicates that nAChRs play important roles in alcohol consumption and relapse-like behavior [55]. Furthermore, there is evidence showing that genetic factors are predictors of both long-term alcohol and tobacco consumptions [56]. Overall, this correlation provides a potential opportunity in which it makes nAChR as an attractive target for the treatment of both AUDs and nicotine dependence [54].

Recent human genetic studies show that single nucleotide polymorphisms (SNPs) implication in the CHRNA5 gene, which encodes for α5 nAChR subunit, has strongly association with higher risk of developing alcohol dependence [56,57]. The genome-wide association (GWA) study also has shown that the CHRNA5/A3/B4 gene cluster, coding for α5, α3, and β4 nAChR subunits, respectively, not only implicates in alcohol dependence, but also multiple substances of abuse [58]. Without any change in acute alcohol response such as preference for a sweet or bitter solution, the TgCHRNA5/A3/B4 mice overexpress the human nicotinic CHRNA5/A3/B4 gene cluster have shown a reduced interest of alcohol intakes [59]. While α5 gene deletion enhances acute behaviors, such as alcohol-induced hypothermia, hypnosis recovery time, and the anxiolytic-like response in mice. α5 gene deletion results in decreased alcohol conditioned place preference test (CPP) score, but has no effect on alcohol consumption in drinking behavior tested under normal conditions. However, under the conditions of stress, by multiple daily injections of either saline or nicotine, Drinking-in-the-Dark intake actually reduces in α5 null mutant mice [60]. α5 KO mice show slower recovery from alcohol-induced sleep, as measured by loss of righting reflex. Additionally, the α5 KO mice show enhanced impairment to alcohol-induced ataxia [61]. These results suggest that the absence of α5 subunits leads to an increase in alcohol-induced sedation and slower recovery, the over expression of α5 leads to a reduction in sedation and a quicker recovery from alcohol-induced sleep, and hence higher tolerance. Moreover, recent studies have shown that varenicline, a smoking cessation aid, efficiently reduces alcohol intake in humans [62].

Nicotine aversion and withdrawal: MHb-IPN pathway

Habenula is a diencephalic structure located on dorsomedial surface of caudal thalamus that is divided into MHb and two divisions of lateral nucleus (LHb). Hebanula receives massive afferents from mPFC, NAc, olfactory bulb, septum, and striatum via stria medullaris thalami, and sends projections to IPN, VTA, SNc, medial raphe complex, locus coeruleus, and periaqueductal gray [63-69]. Whereas MHb receives inputs primarily from the limbic system, and sends outputs mainly to IPN; LHb receives inputs primarily from basal ganglia and sends outputs mainly to dopaminergic and serotonergic neurons [22,70]. MHb is involved in the regulation of fear, anxiety, depression and stress by processing aversive and negative sensory inputs.

MHb contains some of the highest densities of nAChRs, especially α5, α3, and β4 subunits [39]. Approximately 20% of functional nAChRs in rat MHb neurons project to IPN contain α5 subunit [41]. α5-containing nAChRs in MHb and IPN have recently been implicated in nicotine self-administration and reward. Allelic variation in the α5/α3/β4 nAChRs subunit gene cluster increases the risk of tobacco addiction [71]. In experiments, the α5 nAChR KO mice show an increase in nicotine intakes, and intravenously self-administer a lot more nicotine than their wild-type littermates [12]. This phenomenon is restored by re-expressing α5 subunit in MHb in the α5 KO mice, and repeated by α5 knockdown in rat's MHb [12]. The α5 nAChR KO mice are less sensitive to the acute behavioral effects of nicotine, but maintain the expression of CPP at higher doses of nicotine that are aversive in wild-type littermates [72]. This effect is independent from α3β4-nAChR subunit [12,72]. Nicotine-induced activation of MHb-IPN pathway results in a negative motivational signal that serves to limit further nicotine intake. Hence, disruption of α5 nAChR signaling diminishes the stimulatory effects of nicotine on MHb-IPN activity, and thereby permits greater quantities of consumption for nicotine, and facilitates brain reward activity, which may help explain the increased tobacco addiction vulnerability associated with CHRNA5 risk alleles [45,73].

In humans, cessation of tobacco intake precipitates both somatic and affective symptoms of withdrawal, which may include symptoms like severe craving for nicotine, irritability, anxiety and so on. In experiments, mice null for α5 nAChRs subunits abolish nicotine withdrawal somatic signs when withdrawal precipitated by injecting nicotinic antagonist mecamylamine [74]. Moreover, direct infusion of mecamylamine into the IPN, but not to the VTA, of nicotine-dependent wild-type mice precipitates the expression of somatic withdrawal signs [74]. This suggests that α5 nAChRs in the MHb-IPN pathway regulate the expression of somatic signs of nicotine withdrawal.

Anxiety and impulsive-like behaviors

Nicotine is known to play an important role in modulating behaviors in different types of animal model for anxiety [75], and different nAChR subtypes are likely to contribute to these effects. Female α5 KO mice show reduced anxiety-like behavior, and this could be related to progesterone effect on α5 subunit expression [76]. β4 KO, not β2 KO mice also manifestly reduce anxiety-related behaviors [76,77]. These data suggest that the stimulation of α5- and β4- containing nAChRs is

important for the anxiogenic effects of nicotine.

Recent studies have revealed a direct relationship between impulsivity and vulnerability to develop the addiction-like behavior in rodents [78]. Studies on CHRNA3/A5/B4 gene cluster show its association with nicotine dependence [79] and lung cancer [80,81], suggesting that these genes are involved in nicotine dependence vulnerability. Over-expression of the α3α5β4 nAChR combination/subtype exhibits less impulsive-like behavior than wild-type controls, and this behavioral phenotype is related to the numbers of copy of this transgene. Furthermore, this gene cluster over-expression also reduces spontaneous alternation behavior deficits in working memory [82]. The decreased impulsivity suggests the involvement of α3α5β4 nAChRs subtype in the personality trait directly relates to drug addiction vulnerability [82].

Conclusions

Both animal and human genetic studies show that α5 nAChR subunit, especially in MHb-IPN pathway, has been implicated in modulation of nicotine aversion that controls the quantities of drug consumed, and in the development of tobacco dependence. Moreover, α5 nAChRs are also involved in the alcohol use disorders, which provides new target to treat nicotine and alcohol co-dependence. In the next step of research, development of new specific pharmacological ligands for α5 subunit will help to understand the underlying mechanisms of nicotine and/or alcohol addiction and withdrawal.

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