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Review

Cellular events in nicotine addiction

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ABSTRACT

In the 25 years since the observation that chronic exposure to nicotine could regulate the number and function of high affinity nicotine binding sites in the brain there has been a major effort to link alterations in nicotinic acetylcholine receptors (nAChRs) to nicotine-induced behaviors that drive the addiction to tobacco products. Here we review the proposed roles of various nAChR subtypes in the addiction process, with emphasis on how they are regulated by nicotine and the implications for understanding the cellular neurobiology of addiction to this drug.

Contents

1. Introduction

The tobacco plant alkaloid, nicotine, is generally agreed to be the major, if not sole, compound responsible for driving the addiction of more than one billion people (≈20% world population), which, in turn, results in five million deaths worldwide each year [1]. The unaided quitting rate for smokers is 3–5% [2,3] and, despite the availability of several nicotine replacement therapies [4], only about one third of people that would like to stop using tobacco products are permanently successful by the age of 60, usually after multiple failed attempts (reviewed in [5]). After nicotine enters the body, it binds to nicotinic acetylcholine receptors (nAChRs) of the central nervous system (CNS), specifically those in the brain, and initiates drug addiction [6,7]. The persistent interaction between nicotine and nAChRs must ultimately lead to downstream plasticity at the molecular, cellular and circuit levels that then results in the behavioral desire to continue to intake nicotine.

Abbreviations: nAChRs, nicotinic acetylcholine receptors; CNS, central nervous system; PNS, peripheral nervous system; NMJ, neuromuscular junction; ACh, acetylcholine; IPN, interpeduncular nucleus; VTA, ventral tegmental area; αBTX, α-bungarotoxin; MLA, methyllycaconitine; MHb, medial habenula; DHβE, dihydro-β-erythroidine; GFP, green fluorescent protein.

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Transmembrane nAChRs are fast-activating ligand-gated ion channels that produce membrane depolarization and cellular excitation [8]. While much is known about the physiological role of nAChRs in the peripheral nervous system (PNS), the relevance of these receptors in CNS signaling has been somewhat obscure (for a concise historical perspective see [9]). In the PNS, it is now firmly established that the major role of nAChRs present postsynaptically at both the neuromuscular junction (NMJ) and within the autonomic ganglia, is to faithfully detect the presence of the chemical neurotransmitter, acetylcholine (ACh), thereby enabling efficient synaptic signaling. The synapses at the NMJ are designed never to fail and vertebrates would no doubt not have survived long if they were less than 100% reliable (see discussion in [10,11]). Exceptions to this generalization occur during development and with disease, e.g. myasthenia gravis, and usually result in significant changes in postsynaptic nAChR number [12,13]. Autonomic ganglion synapses may be more pliable than the NMJ, as indicated by their ability to support activity dependent long-term changes in synaptic transmission [14]. Mechanisms underlying the plasticity of nAChRs in the periphery may provide useful clues for understanding the changes in CNS receptors following chronic exposure to nicotine, particularly those in the autonomic ganglia, which share an overlapping neuronal subtype.

In the CNS the situation is more elusive, with only a few clear examples of fast synaptic transmission involving nAChRs, despite the widespread expression of these receptors and innervation by cholinergic fibers [9,15,16]. Coupled with a lack of anatomically defined cholinergic synapses, this has led to the postulation that nAChRs may function in part through more diffuse signaling, perhaps contributing to "volume" transmission – with receptors detecting ambient levels of ACh [17–19]. Although there is a somewhat limited knowledge of the operation of nicotinic synapses in the CNS, it is well established that nAChRs can contribute to long-lasting neuronal plasticity – including changes induced by the exogenous drug nicotine. Importantly, such plasticity likely helps condition the brain to secondary drug-related cues and/or context that make successful withdrawal from drugs like nicotine extremely difficult [20,21], lending support to the idea that chemical addiction is a form of associative learning [22]. Indeed, it is now appreciated that changes in synaptic efficacy as well as downstream gene regulation may provide a common molecular and cellular basis for both normal learning and addiction [23]. The effects of nicotine on synaptic transmission and plasticity have been discussed elsewhere [24–26] and here we will focus on the mechanisms that lead to nicotine-induced alterations in nAChR number and function, changes in other classes of proteins, and their relationships to long-lasting nicotine dependence.

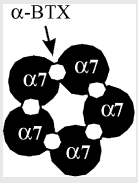
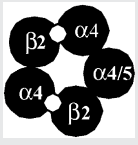
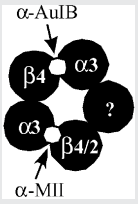
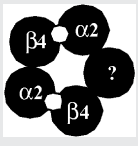
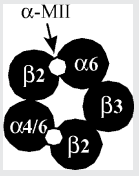
2. nAChRs in the brain

The diversity of nAChR subtypes, both in terms of their regional and subcellular distribution, implies that specific receptors may be localized to control cellular events that ultimately underlie a variety of discrete behaviors [16,27–29]. Thus, in order to understand how nicotine-induced plasticity contributes to the long-term disruptions of neuronal activity in the CNS that underlie the behavioral adaptations acquired during nicotine exposure and withdrawal, it is necessary to know how these receptors operate and what specific properties, based on their subunit composition, allow them to interact with the low concentrations of nicotine in the cerebrospinal fluid (CSF) that are associated with the use of tobacco products.

2.1. Composition of nAChRs in the CNS

Unlike muscle type nAChRs whose subunit composition is known and fixed, except during development [30], the molecular composition of neuronal nAChRs expressed in the nervous system is not completely defined [28,31–35]. Indeed, even armed with the knowledge that only certain subunits can co-assemble, the question of just how many different native nAChR subtypes exist is difficult to answer. The mere presence of a large number of subunits (and possibly more based on sequence homology in other species, e.g. *Caenorhabditis elegans*; [36]) has led some to conclude that diversity is the general rule rather than the exception [27,28]. Based to some extent on the non-overlapping cellular distributions of nAChR subunit mRNAs in the CNS (e.g. [37]), it is likely that the number of native nAChR subtypes will be restricted by specific patterns of subunit expression. Conversely, because many central neurons express multiple genes, their potential promiscuous assembly may not always limit the number of nAChRs subtypes found on single cells – and hinder determination of receptor composition [38]. However, despite the enormity of the task, the wide range of

Table 1
Functional nAChR subtypes in the CNS.

Subtype[a]	α7* (type 1)[b]	α4β2* (type 2)	α3β4* (type 3)	α2β4* (type 4)	α6β2β3*
Selective toxins[c]					
Other subunits	[α5, β2]	[None]	[α4-6, β3]	[α3-6, β3]	[None]
Potent agonists	Choline	Nicotine (high affinity)	Cytisine	DMPP (relative to nicotine)	
Selective antagonists	MLA	DHβE			MLA
Distribution [d]	Hippocampus and cortex	Thalamus and cortex	MHb	IPN	VTA/SN
Generalized role in nicotine addiction	Cognitive, withdrawal, homeostatic balance with β2* nAChRs	Critical for drug-seeking behavior	Withdrawal, secondary reward axis	Secondary reward axis	Regulation of dopamine release

Abbreviations: α-BTX, α-bungarotoxin; α-AuIB, α-conotoxin-AuIB; α-MII, α-conotoxin-MII; MLA, methyllycaconitine; DHβE, dihydro-β-erythroidine; MHb, medial habenula; IPN, interpeduncular nucleus; VTA, ventral tegmental area; and SN, substantia nigra.

[a] α9/α10 subunit-containing receptors constitute another nAChR subtype, but are not included due to their unique distribution [131,132]. α8 Subunits are not present in mammals.

[b] Numbers in parenthesis refer to the original classification [79,105].

[c] Filled circles represent individual subunits within a pentameric nAChR. The open circles represent the agonist-binding interface.

[d] Based in part on previously reviewed data [35].