Biochemical Pharmacology 82 (2011) 800–807

Contents lists available at ScienceDirect

Biochemical Pharmacology

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

Review

Naturally-expressed nicotinic acetylcholine receptor subtypes

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ARTICLE INFO

Article history:
Received 25 April 2011
Accepted 5 July 2011
Available online 20 July 2011

Keywords:
Nicotine
Nicotinic receptor
Acetylcholine
Alzheimer's disease
Drug dependence

ABSTRACT

Nicotinic acetylcholine receptors (nAChRs) warrant attention, as they play many critical roles in brain and body function and have been implicated in a number of neurological and psychiatric disorders, including nicotine dependence. nAChRs are composed as diverse subtypes containing specific combinations of genetically-distinct subunits and that have different functional properties, distributions, and pharmacological profiles. There had been confidence that the rules that define ranges of assembly partners for specific subunits were well-established, especially for the more prominent nAChR subtypes. However, we review here some newer findings indicating that nAChRs having largely the same, major subunits exist as isoforms with unexpectedly different properties. Moreover, we also summarize our own studies indicating that novel nAChR subtypes exist and/or have distributions not heretofore described. Importantly, the nAChRs that exist as new isoforms or subtypes or have interesting distributions require alteration in thinking about their roles in health and disease.

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Contents

1. Introduction

nAChRs are prototypical members of the ligand-gated ion channel superfamily of neurotransmitter receptors. nAChRs represent both classic and contemporary models for the establishment of concepts pertaining to mechanisms of drug action, synaptic transmission, and structural/functional diversity of transmembrane signaling molecules (see reviews [1–7]). nAChRs are found throughout the nervous system (e.g., in muscle, autonomic and sensory ganglia, and the CNS). They are very important, because they play many critical roles in brain and body function, making it logical that nAChRs also are implicated in a number of neurological and psychiatric disorders, as they are in nicotine dependence. nAChRs exist as multiple, diverse subtypes composed as pentamers of unique combinations from a family of at least seventeen (α1–α10, β1–β4, γ, δ, ε) similar, but genetically-distinct, subunits. nAChR subtypes are named according to their known subunit composition (using an "*" to indicate possible additional assembly partners; [6]). Each subunit gene has a unique promoter, even though some are collected in a cluster, suggesting a means for cell-specific expression. There also are unique protein sequence elements for each, especially in the large, cytoplasmic loop, suggesting means for differential post-translational control of subunit trafficking. There is evidence for specificity of targeting of nAChR subunit proteins and the relevant nAChR assemblies to sub- or peri-synaptic destinations in somatodendritic domains, but also down axons to pre-terminal or synaptic terminal locations.

Abbreviations: nAChR(s), nicotinic acetylcholine receptor(s); VTA, ventral tegmental area; DAergic, dopaminergic; DA, dopamine; SN, substantia nigra; ACh, acetylcholine; IPSC(s), inhibitory post synaptic current(s); Bgt, α-bungarotoxin; αCtx, α-conotoxin.

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doi:10.1016/j.bcp.2011.07.067

Although many nAChR subtypes are possible in theory, there seem to be some rules that define and limit the number of viable subunit combinations. Most of these nAChR subtypes appear to exist as heteropentamers containing two or more different kinds of subunit. For example, heterologous expression studies suggest that α2, α3, α4, or α6 subunits can combine in binary fashion with β2 or β4 subunits to form ligand-binding and/or functional nAChRs (e.g., α4β2-nAChRs). β3 and α5 subunits are "wild-cards" not able to form nAChRs alone or with any other single type of subunit. However, they are capable of integrating into complexes with two other subunit types found in binary complexes to form distinctive, trinary complexes (such as α4β2α5- or α3β4α5-nAChRs (found naturally expressed). They also can contribute to formation of quaternary complexes that contain more than one of the α2–4 or α6 subunits or that contain both β2 or β4 subunits (for example, α4α6β2β3- or α3β2β4α5-nAChRs). In addition, mammalian muscle-type nAChRs are quaternary complexes composed of α1, β1, δ and either γ (fetal) or ε (adult) subunits. By contrast, phylogentically ancient nAChR α7 subunits are able to form functional homopentamers, the simplest possible prototype for a ligand-gated ion channel. Although nAChR α9 subunits also are able to form functional homomers with modest channel activity, function is markedly enhanced when they and α10 subunits co-assemble to form a novel binary complex [8] (note that these subunits and the unusual nAChRs they constitute are not substantially expressed in the brain). nAChRs containing α7 subunits (α7-nAChRs) are the most abundant curaremimetic neurotoxin-binding nAChRs in the brain. nAChRs containing α4 and β2 subunits (α4β2*-nAChRs) are the most abundant high affinity nicotine-binding nAChRs in the brain. However, other, less abundant nAChRs (e.g., α3*-nAChRs, α6*-nAChRs) must exist and may play important physiological roles.

Nevertheless, the field has been somewhat altered by realization that the lack of two-fold symmetry in pentameric assemblies allows for more diversity across nAChR subtypes than heretofore realized. More recent work has indicated that even for α4β2*-nAChR, having two α4β2 subunit cassettes thought to provide an α4:β2 subunit interface where nicotinic agonists bind to gate channel opening, there exist unique isoforms that have different subunits occupying the "fifth" or "accessory" position in the pentamer [9–12]. Remarkably, the pharmacological properties of these isoforms can be quite different. For example, α4β2*-nAChR having 2 α4 subunits and 3 β2 subunits [$(\alpha4)_2(\beta2)_3$-nAChR; i.e., having a β2 subunit in the "fifth" or "accessory" position] have higher sensitivity for many nicotinic agonists than "low sensitivity" $(\alpha4)_3(\beta2)_2$-nAChR having an α4 subunit in the accessory position. Moreover, wild-card subunits α5 or β3 can occupy the fifth position, creating $(\alpha4)_2(\beta2)_2\alpha5$- or $(\alpha4)_2(\beta2)_2\beta3$-nAChR having yet again distinctive pharmacological character. It is likely that further diversity exists in other complexes that contain, for example, α4 and α6 subunits. The characterization of these isoforms presents new and larger challenges than before. Although the physiological implications of this unexpectedly broader diversity are currently poorly understood, they are bound to influence our understanding of phenomena such as nicotine dependence as well as strategies for translation of nAChR drug discovery to treatment of neuropsychiatric disorders.

Functionally, nAChRs in the brain play roles not only in the mediation of classical, excitatory, cholinergic neurotransmission at selected loci, but also and perhaps more globally in the modulation of neurotransmission by other chemical messengers, including glutamate, GABA, the monoamines dopamine, norepinephrine and serotonin, and acetylcholine (ACh) itself [2–5,13–17]. This means that some nAChR subtypes have postsynaptic (or peri-synaptic), somatodendritic localizations, whereas others have pre-synaptic dispositions (i.e., on neuronal terminals). However, care should be exercised in calling some nAChRs according to their disposition in synaptic space. Indeed, so called "pre-synaptic" nAChRs that reside on nerve terminals and that perhaps locally modulate neurotransmitter release might actually be called "post-synaptic" if they lie under cholinergic nerve endings. It probably is wise to speak of nAChRs with respect to their location on soma, dendrites, nerve terminals, or even processes slightly distal to nerve terminals. Moreover, some nAChRs have been implicated in processes such as the structuring and maintenance of neurites and synapses [18–20] and even in modulation of neuronal viability/death [21–24]. Thus, nAChR subtypes in the brain play complex and interesting roles in modulation of the chemical milieu of the brain, in completion of neuronal circuits, and perhaps in development and architecture of synapses. In this review, we summarize some of the recent progress in studies of naturally-expressed nAChR subtypes in the brain and their function, and we highlight just some of the possible roles for nAChRs in diseases.

2. Discussion

2.1. α4*-nAChRs in the brain

nAChRs that bind radiolabeled nicotine with the highest affinity contain α4 subunits (α4*-nAChR; see reviews and/or tables by [1–7]. Immunoassays have shown that the predominant, naturally expressed form of α4*-nAChRs in the vertebrate brain contains α4 and β2 subunits (α4β2-nAChRs) [25,26]. α4β2-nAChRs have been implicated in nicotine self-administration, reward, and dependence, and in diseases such as Alzheimer's and epilepsy [1–5,27–33]. α4 subunits can also assemble with β4 subunits to form α4β4-nAChRs that have comparably high nicotine affinity [34–36]. β4 subunit mRNA colocalizes with α4 subunit mRNA in many brain regions [37,38] that could be involved in complex behaviors including nicotine dependence. Moreover, in addition to existence in "binary" nAChR complexes containing two types of subunits, α4 subunits can have more than one type of assembly partner [39–56]. For example, nAChRs containing α4, β2, and α5 subunits are expressed naturally, and heterologously-expressed α4β2α5-nAChRs have interesting properties distinct from those of simpler α4β2-nAChR. To the first approximation, properties of heterologously expressed α4*-nAChRs and naturally-expressed α4*-nAChRs of the same composition (as best can be ascertained) are very similar (op. cit.). However, given their evident physiological importance and their potential to form as diverse combinations of subunits, including α4β2α5- or α4β2β3-nAChR isoforms containing the indicated subunits in the accessory position, more work on heterologously expressed α4*-nAChRs is warranted, as are careful comparisons of properties of these α4*-nAChRs of defined subunit composition(s) with properties of naturally expressed α4*-nAChRs in vertebrate brain neurons.

Considerable attention has been given to effects of chronic nicotine exposure on nAChRs because of relevance to habitual use of tobacco products [57] but information about these effects remains incomplete. Chronic nicotine exposure for periods of days induces increases in numbers of nAChR-like radioligand binding sites (or, in some studies, subunit polypeptides) in human or non-human animal brain or in cells from a variety of primary or continuous culture systems [2–5,26,58–62]. Although these binding sites can be in intracellular pools of possible assembly intermediates and not always on functional, cell surface nAChRs, the magnitude of their upregulation varies considerably across experiments and experimental systems, and concentration-response studies show that nAChR subtypes most sensitive to nicotine-induced upregulation include α4 subunits [26,61,63,64]. Upregulation seems to reflect nicotine-mediated, "chaperone-like" facilitation of α4 and β2 subunit assembly that is manifest as

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