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Nicotinic acetylcholine receptors (nACh) in GtoPdb v.2021.3

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Abstract

Nicotinic acetylcholine (ACh) receptors are members of the Cys-loop family of transmitter-gated ion channels that includes the $GABA_A$, strychnine-sensitive glycine and $5\text{-}HT_3$ receptors [215, 3, 159, 225, 259]. All nicotinic receptors are pentamers in which each of the five subunits contains 4 TM domains. Genes encoding a total of 17 subunits (α1-10, β1-4, γ, δ and ε) have been identified [120]. All subunits with the exception of α8 (present in avian species) have been identified in mammals. All α subunits possess two tandem cysteine residues near to the site involved in acetylcholine binding, and subunits not named α lack these residues [159]. The orthosteric ligand binding site is formed by residues within at least three peptide domains on the α subunit (principal component), and three on the adjacent subunit (complementary component). Nicotinic ACh receptors contain several allosteric modulatory sites. One such site, for positive allosteric modulators (PAMs) and allosteric agonists, has been proposed to reside within an intrasubunit cavity between the 4 TM domains [264, 87]; see also [106]). The high resolution crystal structure of the molluscan ACh binding protein, a structural homologue of the extracellular binding domain of a nicotinic receptor pentamer, in complex with several nicotinic receptor ligands (*e.g.*[35]) and the crystal structure of the extracellular domain of the α1 subunit bound to α-bungarotoxin at 1.94Â resolution [55], has revealed the orthosteric binding site in detail (reviewed in [215, 120, 39, 198]). Nicotinic receptors at the somatic neuromuscular junction of adult animals have the stoichiometry $(\alpha1)_2\beta1\delta\varepsilon$, whereas an extrajunctional $(\alpha1)_2\beta1\gamma\delta$ receptor predominates in embryonic and denervated skeletal muscle and other pathological states. Other nicotinic receptors are assembled as combinations of α(2-6) and β(2-4) subunits. For α2, α3, α4 and β2 and β4 subunits, pairwise combinations of α and β (*e.g.* α3β4 and α4β2) are sufficient to form a functional receptor *in vitro*, but far more complex isoforms may exist *in vivo* (reviewed in [96, 93, 159]). There is strong evidence that the pairwise assembly of some α and β subunits can occur with variable stoichiometry [*e.g.* $(\alpha4)_2(\beta2)_2$ or $(\alpha4)_3(\beta2)_2$] which influences the biophysical and pharmacological properties of the receptor [159]. α5 and β3 subunits lack function when expressed alone, or pairwise, but participate in the formation of functional hetero-oligomeric receptors when expressed as a third subunit with another α and β pair [e.g. α4α5αβ2, α4αβ2β3, α5α6β2, see [159] for further examples]. The α6 subunit can form a functional receptor when co-expressed with β4 *in vitro*, but more efficient expression ensues from incorporation of a third partner, such as β3 [263]. The α7, α8, and α9 subunits form functional homo-oligomers, but can also combine with a second subunit to constitute a hetero-oligomeric assembly (*e.g.* α7β2 and α9α10). For functional expression of the α10 subunit, co-assembly with α9 is necessary. The latter, along with the α10 subunit, appears to be largely confined to cochlear and vestibular hair cells. Comprehensive listings of nicotinic receptor subunit combinations identified from recombinant expression systems, or *in vivo*, are given in [159]. In addition, numerous proteins interact with nicotinic ACh receptors modifying their assembly, trafficking to and from the cell surface, and activation by ACh (reviewed by [158, 9, 118]).

The nicotinic receptor Subcommittee of **NC-IUPHAR** has recommended a nomenclature and classification scheme for nicotinic acetylcholine (nACh) receptors based on the subunit composition of known, naturally- and/or heterologously-expressed nACh receptor subtypes [143]. Headings for this table reflect abbreviations designating nACh receptor subtypes based on the predominant α subunit contained in that receptor subtype. An asterisk following the indicated α subunit denotes that other subunits are known to, or may, assemble with the indicated α subunit to form the designated nACh receptor subtype(s). Where subunit stoichiometries within a specific nACh receptor subtype are known, numbers of a particular subunit larger than 1 are indicated by a subscript following the subunit (enclosed in parentheses- see also [46]).

Contents

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