

Acetylcholine Receptors (Nicotinic)

Key References

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Overview

Nicotinic acetylcholine receptors (nAChRs) constitute a family of ligand-gated channels, originally classified on the basis of their activation by the alkaloid nicotine, with acetylcholine (ACh) being the endogenous ligand. nAChRs are pentameric transmembrane proteins that form cationic channels permeable to Na^+ , K^+ , and Ca^{2+} . nAChRs consist of five homologous subunits, from a portfolio of ten α ($\alpha 1$ - $\alpha 10$) and four β ($\beta 1$ - $\beta 4$) subunits cloned from mammalian and avian sources. Each nAChR subunit comprises four transmembrane spanning domains, M1-M4, of which M2 lines the channel. The structure of the muscle-type (from Torpedo electric organs) nAChR has been resolved to 4 Å by electron microscopy, whereas insight into the extracellular domain and agonist binding site of nAChRs has come from the X-ray crystal structure (resolution down to 2.7 Å) of a molluscan ACh binding protein. The latter has provided a template for modelling the binding site of neuronal nAChRs.

$\alpha 1$, $\beta 1$, γ , δ and ϵ subunits are only expressed in skeletal muscle, whereas the other subunits are found mainly in neurons (hence "neuronal nicotinic receptors") but also in other cell types. For example, it has been reported that the $\alpha 7$ subunit is transiently expressed in skeletal muscle during development and in activated macrophages, whereas other subunits are also expressed by various epithelial and endothelial cell types.

The predominant forms of nAChRs found in the brain are $\alpha 4\beta 2^*$ and putative homomeric $\alpha 7$ nAChRs, where * denotes the possible presence of additional subunits. In dopaminergic neurons for example, there is evidence for multiple nAChR subtypes: $\alpha 4\beta 2$, $\alpha 4\alpha 5\beta 2$, $\alpha 6\beta 2\beta 3$, $\alpha 4\alpha 6\beta 2\beta 3$ on terminals; $\alpha 7$ nAChR and some of the heteromeric forms on

somatodendritic regions. In autonomic ganglia, $\alpha 3\alpha 5\beta 4$ and $\alpha 3\alpha 5\beta 2\beta 4$ combinations exist, in addition to $\alpha 7$ homomers. The $\alpha 9$ and $\alpha 10$ subunits have a restricted distribution, limited to sensory tissues (principally cochlear hair cells). The $\alpha 10$ subunit is only functional as a heteromer with $\alpha 9$, whereas $\alpha 9$ can form homomeric nAChR. These are the most divergent of the nAChR family and show mixed nicotinic/muscarinic pharmacology, and sensitivity to other drugs including strychnine and 5HT_3 ligands.

The ACh binding site resides at the interface between an α subunit (except $\alpha 5$) and the neighboring subunit; thus nAChR heteromers typically have two binding sites for agonists and competitive antagonists, while $\alpha 7$ homomers could have up to five putative binding sites. Most of the potent and selective ligands for nAChRs are natural products, like nicotine. They have provided a basis for rational drug design, stimulated by the perception of neuronal nAChRs as therapeutic targets.

The frog alkaloid epibatidine is one of the most potent nicotinic agonists ($K_i \sim 50$ pM for binding to $\alpha 4\beta 2$ nAChR) and is 100-fold more potent than morphine as an analgesic. However its interactions with ganglionic and neuromuscular nAChRs result in toxicity at doses close to the analgesic ones. Most synthetic chemistry efforts have focussed on $\alpha 4\beta 2$ or $\alpha 7$ nAChRs. ABT-418, an isoxazole isostere of nicotine, exhibits cognition-enhancing activities and shows activity in adults with attention deficit hyperactivity disorder; ABT-594, an azetidine analog of epibatidine, is a potent analgesic with reduced side effects in animal models, compared to epibatidine; SIB-1508Y is an $\alpha 4\beta 2$ -preferring nicotine analog that shows activity in animal models of Parkinson's disease. The 3-pyridyl ether A-85380 was designed to discriminate central and peripheral nAChRs, and can also

distinguish subpopulations of [^3H]-epibatidine binding sites in brain membranes. The 5-iodo analog (5-I-A-85380) was developed for SPECT imaging and shows improved potency and selectivity compared with the parent compound. GTS-21 is a partial agonist at $\alpha 7$ nAChR, with reported cognition enhancing activity, while AR-R 17779 is a full agonist at $\alpha 7$ nAChRs. SIB-1553A is an $\alpha 3\beta 4$ -preferring agent that showed some cognitive enhancing activity in animal models. Various α -conotoxins isolated from the venoms of Conus snail species provide subtype-selective nAChR antagonists and represent important research tools (although their exquisite specificity can result in differences in recognition of homologous nAChR from different species). Certain α -conotoxins have also been mooted as potential analgesics.

In addition to the ACh binding site, nAChRs contain modulatory sites, e.g. for neurosteroids, calcium and certain acetylcholinesterase inhibitors (physostigmine, galantamine). Other binding sites are located within the ion channel, e.g. for anesthetics (such as lidocaine), phencyclidine and MK-801. The anthelmintic, ivermectin, and 5-hydroxy-indole potentiates $\alpha 7$ nAChR (the latter also potentiates 5-HT_3 receptors), whereas 17- β -estradiol selectively potentiates $\alpha 4\beta 2$ nAChR. The neurotoxic peptide, A β 1-42, is reported to interact with the $\alpha 7$ nAChR and an association of α -synuclein with $\alpha 7$ subunits has also been proposed. The $\alpha 7$ nAChR plays a role in hippocampal paired pulse inhibition, and defects in this mechanism, in addition to genetic data, have implicated $\alpha 7$ nAChR in the pathophysiology of schizophrenia. Transgenic mice lacking particular subunits or over-expressing mutated subunits, support a role for both $\alpha 4$ and $\beta 2$ subunits in nicotine dependence and in nociception. Human mutations in either $\alpha 4$ or $\beta 2$ subunits underlie rare epileptic diseases such as ADNFLE (autosomal dominant nocturnal frontal lobe epilepsy).

Acetylcholine Receptors (Nicotinic)

CURRENTLY USED NAME	Neuronal (CNS) (α -Bungarotoxin insensitive)	Neuronal (ANS) (α -Bungarotoxin insensitive)	Neuronal (CNS & ANS) (α -Bungarotoxin sensitive)	Neuromuscular junction
SUBUNITS (ARRANGED AS PENTAMERS)	$\alpha 4\beta 2^*$ (predominant) $\alpha 3\beta 4^*$ $\alpha 6\beta 2\beta 3^*$ $\alpha 2^*$	$\alpha 3\alpha 5\beta 4$ $\alpha 3\alpha 5\beta 2\beta 4$	$\alpha 7$ homomers (predominant) $\alpha 8$ homomers? (avian only) $\alpha 7\alpha 8$ (avian only) $\alpha 9$ homomers? $\alpha 9\alpha 10$	($\alpha 1$) ₂ $\beta 1\delta\gamma$ (developmental/extrasynaptic) ($\alpha 1$) ₂ $\beta 1\delta\epsilon$ (endplates)
RECEPTOR SELECTIVE AGONISTS	($\beta 2 > \beta 4 > \alpha 7$), (-)-Nicotine, Cytisine ^a (C2899), (+)-Anatoxin-a (A224), Epibatidine (E1145), RJR-2403 (R130), ABT-418 (A6476), A-85380 (A251), 5-Iodo-A-85380	(-)-Nicotine (N3876), Epibatidine (E1145), SIB-1553A, DMPP (D5891)	$\alpha 7$: DMAC, GTS-21, ^a AR-R17779, Choline $\alpha 9$, $\alpha 10$: Carbachol, DMPP, Oxotremorine (O100)	Epibatidine (E1145), Anatoxin-a (A224), TMA (T3411)
RECEPTOR SELECTIVE ANTAGONISTS	Mecamylamine ($\beta 2$, $\beta 4 > \alpha 7$) (M9020), Dihydro- β -erythroidine ($\beta 2 > \beta 4$) (D149), α -Conotoxin AulB ($\alpha 3\beta 4^*$), α -Conotoxin MII ($\alpha 3/\alpha 6\beta 2^*$), α -Conotoxin PIA ($\alpha 6\beta 2$), Chlorisondamine (C5366)	Mecamylamine ($\beta 2$, $\beta 4 > \alpha 7$) (M9020), Hexamethonium (H0879), Neuronal-Bungarotoxin, α -Conotoxin AulB ($\alpha 3\beta 4^*$), Chlorisondamine (C5366)	$\alpha 7$: α -Bungarotoxin (T3019), Methyllycaconitine ($\alpha 7 > \alpha 6 > \alpha 3 > \alpha 4 = \alpha 1$) (M168), α -Conotoxin IMI (C2461), $\alpha 9$, $\alpha 10$: α -Bungarotoxin, d-Tubocurarine (T3019), Nicotine (N3876), Atropine (A0132), Muscarine (M6532), Strychnine (S0532), Bicuculine (B9130), Tropisetron (T104)	α -Bungarotoxin (T3019) d-Tubocurarine α -Conotoxin GI α -Conotoxin MI α -Conotoxin SI
SIGNAL TRANSDUCTION MECHANISMS	Na ⁺ /K ⁺ /Ca ²⁺ fluxes	Na ⁺ /K ⁺ /Ca ²⁺ fluxes	Na ⁺ /K ⁺ /Ca ²⁺ fluxes	Na ⁺ /K ⁺ /Ca ²⁺ fluxes
RADIOLIGANDS OF CHOICE	[³ H]-Nicotine ($\alpha 4\beta 2^*$) [³ H]-Cytisine ($\alpha 4\beta 2^*$) [³ H]-Epibatidine ($\beta 2 > \beta 4$) [¹²⁵ I]- α -Conotoxin MII ($\alpha 6/\alpha 3\beta 2$)	[³ H]-Epibatidine	[¹²⁵ I]- α -Bungarotoxin [³ H]-Methyllycaconitine	[¹²⁵ I]- α -Bungarotoxin
TISSUE EXPRESSION	$\alpha 4, \beta 2$: throughout CNS, especially high in thalamus $\alpha 2$: interpeduncular nucleus, reticular formation, inferior colliculus, septum (medial nucleus) $\alpha 3$: thalamus, locus coeruleus, medial habenula, retina $\alpha 5$: hippocampus, substantia nigra, ventral tegmentum, some brainstem nuclei $\alpha 6$: substantia nigra, ventral tegmentum, locus coeruleus $\beta 3$: substantia nigra, ventral tegmentum, locus coeruleus, retina $\beta 4$: medial habenula, interpeduncular nucleus, retina, also weaker expression in cortex, hippocampus	Sympathetic ganglia, sensory ganglia, chromaffin cells, fibroblasts, keratinocytes	$\alpha 7$: widespread in CNS, especially cortex, hippocampus, hypothalamus, amygdala, some brainstem nuclei, retina autonomic neurons, cardiac ganglia also reported in macrophages, glia, $\alpha 9$: outer hair cells of the cochlea also transcribed in hypophyseal gland and sensory neurons, sternohyoid and tongue muscle, bone marrow cells, embryonic blood cells $\alpha 10$: outer hair cells of the cochlea	Skeletal muscle

FOOTNOTES

Acetylcholine Receptors (Nicotinic)

PHYSIOLOGICAL FUNCTION	Postsynaptic receptors: synaptic transmission (rare), Presynaptic receptors extrasynaptic receptors: modulation of synaptic transmission	Synaptic transmission (sympathetic ganglia), Presynaptic modulation of transmitter release	$\alpha 7$: Postsynaptic receptors: synaptic transmission (rare: e.g. hippocampus) Presynaptic receptors: modulation of glutamate, GABA release; Ca^{2+} signaling; synaptic plasticity; extrasynaptic receptors: gene regulation $\alpha 9, \alpha 10$: ACh-gated depolarization leading to activation of K^+ channels and hyperpolarization of outer hair cells	Neuromuscular transmission
DISEASE RELEVANCE	Alzheimer's disease, pain, autism, ADNFLE ($\alpha 4, \beta 2$ point mutations), nicotine addiction, Parkinson's disease	Megacystis-microcolon-intestinal hypoperistalsis syndrome, ulcerative colitis	$\alpha 7$: Alzheimer's disease, inflammation?, schizophrenia	Myasthenia gravis

Abbreviations

A-85380: 3-(2[S]-Azetidylmethoxy)pyridine

ABT-418: (S)-3-Methyl-5-(1-methyl-2-pyrrolidinyl)isoxazole

ADNFLE: Autosomal dominant nocturnal frontal lobe epilepsy

AR-R 17779: (-)-spiro[1-Azabicyclo[2.2.2]octane-3,5'-oxazolidin-2'-one (4a)

DMAC: 3-(4)-Dimethylaminocinnamylidene anabaseine

DMPP: N,N-Dimethyl-N'-phenyl-piperazinium iodide

GTS-21: [3-(2,4-Dimethoxybenzylidene)-anabaseine

RJR-2403: N-Methyl-4-(3-pyridinyl)-3-buten-1-amine

SIB-1553A: 4-[[2-(1-Methyl-2-pyrrolidinyl)ethyl]thio]phenyl hydrochloride

TMA: Tetramethylammonium