

Acetylcholine Receptors (Muscarinic)

Key References

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Overview

Muscarinic acetylcholine receptors are members of the superfamily of G protein-coupled receptors (GPCRs). They are relatively abundant and mediate many of the diverse actions of acetylcholine in the CNS, as well as throughout non-nervous tissues innervated by the parasympathetic nervous system. Five genes (m1-m5) encode muscarinic receptor proteins that contain the rhodopsin-like structural motif of seven transmembrane domains. They show strong sequence homology with each other and with related GPCRs within the transmembrane spanning domains, but each receptor also has unique amino acid sequences located at the amino end (extracellular), and in the third intracellular loop (I3). As with other biogenic amine receptors, much of the effector coupling specificity of these receptors resides in their intracellular domains, in particular the I3 loop.

The five muscarinic receptor subtypes are referred to as M₁-M₅. The odd-numbered receptors (M₁, M₃, M₅) couple efficiently, through G_{q/11}, to activation of phospholipase C, that initiates the phosphatidylinositol turnover response. This leads to inositol trisphosphate-mediated release of calcium from the endoplasmic reticulum and to diacylglycerol-mediated activation of protein kinase C. As a consequence, depending on cell type, other cellular effectors may become activated subsequent to the stimulation of phosphatidylinositol turnover. In smooth muscle, muscarinic receptor (M₃) activation of the phosphatidylinositol turnover response leads to elevation in cellular calcium and contraction. In glandular tissue, M₃ receptor-mediated phosphatidylinositol turnover leads to hormone secretion. In brain, activation of post-synaptic M₁ or M₃ receptors often mediates "slow" neuronal excitability. One

mechanism for this involves inhibition of calcium-regulated potassium channels, and this leads to an inhibition of the after-hyperpolarization phase of the neuronal action potential. Stimulation of post-synaptic muscarinic receptors themselves may not directly lead to action potentials, but commonly the activation of these muscarinic receptors enhances the neuron's response to excitatory input (this is sometimes called "neuromodulation"). Cortical and hippocampal muscarinic receptors transduce cholinergic input from the basal forebrain, in circuits believed to be important in the attentional aspects of cognition. In these brain areas, the predominant receptor subtypes are M₁, M₃ and M₄. The striatum also expresses a mixture of muscarinic receptor subtypes, but the M₄ subtype predominates. The M₂ subtype is expressed at low levels in the telencephalon, most notably in the basal forebrain, and at relatively higher levels in the brainstem. The M₅ subtype is expressed in brain at very low levels with a limited distribution.

The even-numbered muscarinic receptors (M₂, M₄) inhibit adenylyl cyclase activity via activation of the G_i class of G proteins. The M₂ and M₄ muscarinic receptors also activate G protein-coupled potassium channels, which leads to hyperpolarization of the plasma membrane of excitable cells. In nervous tissue, M₂ and M₄ receptors appear to frequently inhibit neuronal firing, and one or both of these subtypes are found on axon terminals where they inhibit neurotransmitter release (autoreceptors or heteroreceptors). The M₂ muscarinic receptor inhibits adenylyl cyclase in smooth muscle and, as a consequence, opposes the effects of adrenergic innervation. In cardiac tissue, M₂ muscarinic receptors activate G protein-coupled potassium channels to

hyperpolarize the muscle, contributing to the slowing of the heart rate.

Besides their coupling to the well-established phosphatidylinositol and cyclic AMP effector systems, it is becoming increasingly clear that muscarinic receptors also couple to, or intersect with, signaling pathways which involve sequential activation of serine/threonine protein kinases, from which modulation of gene expression can result. For example, muscarinic receptors can activate certain MAP kinase pathways. Some components of the phosphokinase pathways that could conceivably be modulated by muscarinic receptors *in vivo* have the potential to enhance cell survival by upregulation of certain protection systems and/or blockade of apoptosis, or modulation of learning and memory.

Recent developments in muscarinic receptor biology include advances in the study of allosterism, including molecular work establishing where on the M₁ receptor the novel agonist AC-42 binds. Other recent interesting discoveries include findings that muscarinic receptors regulate the proliferation of neural stem/progenitor cells and certain neurotransmitter uptake processes (e.g., GABA and norepinephrine transporters). Another recent study shows possible linkage between certain M₂ receptor gene polymorphisms and alcohol dependence and depression. Thus, the therapeutic potential of muscarinic agonists seems to be expanding beyond the "replacement" for decreased acetylcholine in neurodegenerative disorders. Muscarinic receptor antagonists continue to be widely used in alleviating various symptoms of cholinergic hyperactivity.

Acetylcholine Receptors (Muscarinic)

CURRENTLY ACCEPTED NAME	M ₁ (M194)	M ₂ (M4560)	M ₃ (M176)	M ₄ (M4810)	M ₅ (M179)
MOLECULAR BIOLOGY CLASSIFICATION	m1	m2	m3	m4	m5
STRUCTURAL INFORMATION	460 aa (human)	466 aa (human)	590 aa (human)	479 aa (human)	532 aa (human)
SUBTYPE SELECTIVE AGONISTS ^a	McN-A-343 (C7041) (ganglion), Pilocarpine (P6503), (relative to M3 and M5) L-689,660, Xanomeline, CDD-0097 (C258), AC-42	Bethanechol (C5259) (relative to M ₄)	L-689,660 Xanomeline	McN-A-343 (C7041) (relative to M ₂),	Not known
SUBTYPE SELECTIVE ANTAGONISTS ^a	Pirenzepine (P7412), Telenzepine (T122)	Methoctramine (M105), AF-DX 116, AF-DX 384, Gallamine (G8134), (allosteric) Himbacine (H4904), Triptamine	Hexahydro-sila-difenidol, p-Fluorohexahydro-sila-difenidol (H127), 4-DAMP (D104)	Tropicamide (T9778), Not known, AF-DX 384	Himbacine (H4904)
RECEPTOR SELECTIVE AGONISTS	Bethanechol (C5259), Metoclopramide (M0763), Muscarine (M6532), Pilocarpine (P6503), Oxotremorine M (O100)	Bethanechol (C5259), Metoclopramide (M0763), Muscarine (M6532), Pilocarpine (P6503), Oxotremorine M (O100)	Bethanechol (C5259), Metoclopramide (M0763), Muscarine (M6532), Pilocarpine (P6503), Oxotremorine M (O100)	Bethanechol (C5259), Metoclopramide (M0763), Muscarine (M6532), Pilocarpine (P6503), Oxotremorine M (O100)	Bethanechol (C5259), Metoclopramide (M0763), Muscarine (M6532), Pilocarpine (P6503), Oxotremorine M (O100)
RECEPTOR SELECTIVE ANTAGONISTS	Scopolamine (S1875), QNB, (±)- (C002), QNB, R(-)- (C003), Atropine (A0257)	Scopolamine (S1875), QNB, (±)- (C002), QNB, R(-)- (C003), Atropine (A0257)	Scopolamine (S1875), QNB, (±)- (C002), QNB, R(-)- (C003), Atropine (A0257)	Scopolamine (S1875), QNB, (±)- (C002), QNB, R(-)- (C003), Atropine (A0257)	Scopolamine (S1875), QNB, (±)- (C002), QNB, R(-)- (C003), Atropine (A0257)
SIGNAL TRANSDUCTION MECHANISMS	G _{q/11} (increase IP ₃ /DAG) NO	G _i (cAMP modulation) ↑K ⁺ (G)	G _{q/11} (increase IP ₃ /DAG) NO	G _i (cAMP modulation) ↑K ⁺ (G)	G _{q/11} (increase IP ₃ /DAG) NO
RADIOLIGANDS OF CHOICE	[³ H]-Pirenzepine [³ H]-Telenzepine [³ H]-QNB	[³ H]-AF-DX 384 [³ H]-QNB	[³ H]-4-DAMP [³ H]-QNB	[³ H]-AF-DX 384 [³ H]-QNB	[³ H]-QNB [³ H]-NMS
TISSUE EXPRESSION	Brain	Heart, smooth muscle	Glands	Brain	Brain
PHYSIOLOGICAL FUNCTION	Neuromodulation	Bradycardia, contraction	Secretion	Autoreceptors	Heteroreceptors
DISEASE RELEVANCE	Alzheimer's disease	Heart disease, drug side effects	Drug side-effects	Alzheimer's disease	Parkinson's disease

Abbreviations

AC-42: 4-n-butyl-1-[4-(2-Methylphenyl)-4-oxo-1-butyl]-piperidine hydrogen chloride
AF-DX 116: 11-[[2-[(Diethylamino)methyl]-1-piperidinyl]acetyl]-5,11-dihydro-6-pyrido[2,3-b][1,4]benzodiazepin-6-one
AF-DX 384: 5,11-Dihydro-11-[2-[2-[(N,N-dipropylaminomethyl)piperidin-1-yl]ethylamino]-carbonyl]6H-pyrido[2,3-b][1,4]benzodiazepin-6-one
CDD-0097: 5-Propargyloxycarbonyl-1,4,5,6-tetrahydropyrimidine

4-DAMP: 4-Diphenylacetoxy-N-methylpiperidine methiodide
L-689,660: 1-Azabicyclo[2,2,2]octane, 3-(6-chloropyrazinyl)maleate
McN-A-343: 4-(N-[3-Chlorophenyl]carbamoyloxy)-2-butylyltrimethylammonium chloride
NMS: N-Methylscopolamine
QNB: Quinuclidinyl- α -hydroxydiphenylacetate; Quinuclidinylbenzylate

FOOTNOTES

^a Absolute selectivity for any muscarinic agent has so far not been achieved. The compounds listed are relatively, but not absolutely selective. Variations in their potencies/affinities may occur as a result of numerous factors, including tissue/species differences, variations in receptor densities and differences in the receptor/effector coupling efficiency. The reader is directed to the literature for detailed information concerning the pharmacological specificity of these compounds.