The muscarinic acetylcholine receptor

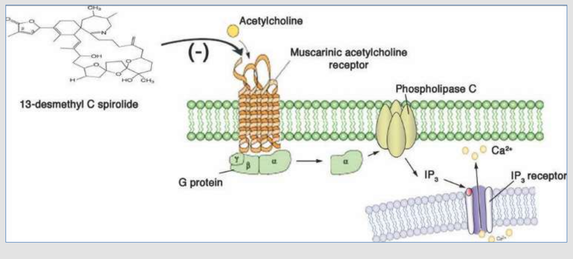
An-Najah National University

Summary

The muscarinic acetylcholine receptor is a vital component of the cholinergic signaling system found in both the central and peripheral nervous systems. Structurally, it is a transmembrane protein that spans the cell membrane, consisting of five subtypes (M1-M5) with distinct patterns of distribution. These receptors are widely expressed in various tissues and organs, including the brain, heart, lungs, gastrointestinal tract, and eyes. They are activated by acetylcholine, serving as an agonist, while antagonists such as atropine block their function. Signal transduction occurs through G proteins, leading to the modulation of numerous physiological processes, including neuronal excitability, cardiovascular function, smooth muscle contraction, and glandular secretion. Dysregulation of muscarinic acetylcholine receptors has been associated with various human diseases, such as Alzheimer's disease, Parkinson's disease, asthma, and cardiovascular disorders. Understanding the structure, distribution, and signaling mechanisms of these receptors provides insights into their biological roles and potential implications for therapeutic interventions.

structure and cellular localization

The GPCR family of receptors, which includes the distinct sub-types of receptors M1, M3, and M5, includes five muscarinic acetylcholine receptors that may be activated by the neurotransmitter acetylcholine. It preferentially communicates via G proteins that are active phospholipases of the Gaq/11 subfamily. In contrast, the other subtypes, M2, and M4, signal through the G(i/o) of G proteins and inhibit the activity of the enzyme adenylyl cyclase. This process is initiated by a chain of phosphatidylinositol trisphosphate cascade, which allows calcium ions (Ca+2) to enter cells and activate a protein kinase C (which participates in controlling the function of proteins by phosphorylating hydroxyl (converts ATP to cAMP) in which Acetylcholine receptors are found on the surface of muscle cells, concentrated in the synapse between nerve cells and muscle cells.



Tissue distribution

The muscarinic acetylcholine receptor exhibits a widespread distribution in various organs and tissues throughout the body. In the central nervous system, these receptors are found in regions such as the cerebral cortex, hippocampus, and basal ganglia, where they play critical roles in regulating cognitive functions and motor control. Peripheral tissues, including the heart, lungs, smooth muscles, and gastrointestinal tract, also express muscarinic acetylcholine receptors, where they modulate autonomic functions and smooth muscle contractions. Furthermore, these receptors are present in the eye, specifically in the iris sphincter and ciliary muscle, governing pupil size and accommodation. The tissue-specific expression patterns and functional roles of muscarinic acetylcholine receptors highlight their importance in mediating a wide range of physiological processes.

Agonist & Antagonist

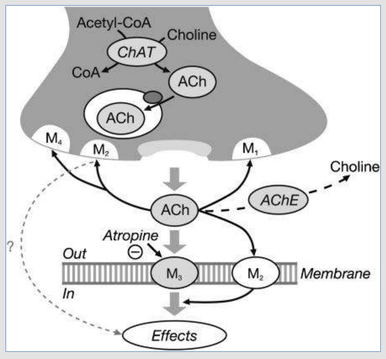
Muscarinic Cholinergic agonists are drugs that mimic the action of the neurotransmitter acetylcholine, examples: 1- bethanechol is a synthetic ester hygroscopic crystalline powder, is used for M3, M4 , M5 receptors . 2- Cevimeline is a white to off white crystalline powder, Inactive ingredients include lactose monohydrate, hydroxypropyl cellulose, and magnesium stearate used for M1 receptor. 3-pialocarpine a slowly hydrolyzed muscarinic agonist with no nicotinic effects.

Muscarinic Cholinergic antagonist: are drugs that do the opposite action of ACh. Examples: 1- atropine, another name is daturin, it occurs naturally in several plants of the nightshade family including deadly nightshade. 2- scopolamine also known as hyoscine, or Devil's Breath, is a natural or synthetically produced tropane alkaloid and anticholinergic drug. 3- glycopyrrolate: It is a synthetic quaternary ammonium compound. 4-ipratropium bromide: is a quaternary ammonium compound, is used to help control the symptoms of lung diseases.

Receptor signal transduction

This figure shows the functional role of the M3 receptor in detrusor contraction. In presynaptic terminal Acetylcholine is produced and this is done by the action of choline acetyl transferase on choline and acetyl coenzyme A, then it is released by exocytosis. Acetylcholine is metabolized by acetyl cholinesterase to release choline. Acetylcholine binds to muscarinic M3 receptor at postjunctional membrane leading to the activation of the contractile proteins within the detrusor muscle resulting in detrusor contraction.

The M2 and M4 receptors work as inhibitors, whereas prejunctional M1 receptors mediate the release of Acetylcholine. Also, the M2 receptors have an indirect role in detrusor contractility. It is possible to be a minor direct effect, but the mechanism is still unclear. Inhibition of contraction by Atropine that blocks muscarinic receptors.



Biologic Role

The muscarinic acetylcholine receptor is a type of G protein-coupled receptor found in the central and peripheral nervous system, as well as other tissues. It is activated by the neurotransmitter acetylcholine and regulates various physiological functions. The receptor has five subtypes and is located in organs like the heart, lungs, brain, bladder, and eyes. Ligands for this receptor include acetylcholine, muscarine (found in toxic mushrooms), and various drugs.

Clinically, the receptor is targeted by drugs like atropine and ipratropium for conditions like asthma, while drugs like pilocarpine are used for xerostomia and glaucoma. Ongoing research aims to develop new drugs for disorders such as Alzheimer's disease and overactive bladder.

Muscarinic receptor &human disease:

The involvement of the cholinergic system in bipolar disorder was first indicated in a study that demonstrated an increase in depressive symptoms upon the administration of cholinesterase inhibitors. Conversely, these inhibitors were found to generally improve manic symptoms in individuals with bipolar disorder. Subsequent research supported these initial findings, showing that the cholinesterase inhibitor physostigmine reduced mania in bipolar patients. However, it should be noted that in some cases, physostigmine exacerbates depression. These observations led to the development of the cholinergic-adrenergic hypothesis of mania and depression, which suggests that the cholinergic system is less active during manic episodes, while the adrenergic system is overly active. It is worth mentioning that this hypothesis consolidates the findings from various studies on affective disorders and proposes that the cholinergic system is overactive in patients with depression, whereas the adrenergic system exhibits heightened activity during episodes of mania.

References

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1751864/

https://pubmed.ncbi.nlm.nih.gov/8248499/

https://pubmed.ncbi.nlm.nih.gov/8412508/

https://pubmed.ncbi.nlm.nih.gov/8249149/

https://pubmed.ncbi.nlm.nih.gov/9009703/

https://pubmed.ncbi.nlm.nih.gov/34212451/

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6493542/

https://pubmed.ncbi.nlm.nih.gov/31073061/