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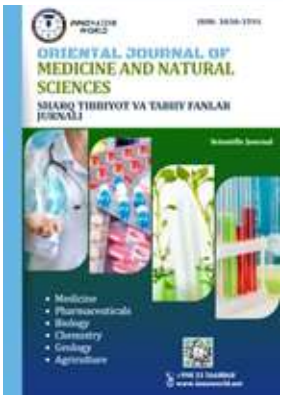

Acetylcholine and related diseases.

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Abstract: Transmission of signals is conducted by release of neurotransmitters from presynaptic neurons and uptake by postsynaptic neurons. One of the most important and abundant neurotransmitters in human body is Acetylcholine. This article discusses transmission and importance of acetylcholine and related diseases.

Keywords: Acetylcholine-ACh, peripheral nervous system-PNS, acetylcholinesterase-ChAT, choline transporters-ChT, Choline acetyltransferaseChA, vesicular acetylcholine transporter-VAChT, voltage-gated calcium channels-VGCC, Acetylcholine esterase-AChE, Lambert-Eaton Myasthenic Syndrome-LEMS, **black widow spider venom-BWSV,** electrical endplate potential-EPP, GPCR-G protein coupled receptor, Alzheimer's disease -AD,

What is Acetylcholine?

Acetylcholine, the first neurotransmitter discovered, was originally described as "vagus stuff" by a German-born pharmacologist Otto Loewi because of its ability to mimic the electrical stimulation of the vagus nerve. **Acetylcholine (ACh)** is now a major neurotransmitter, derived from acetyl CoA and choline ($[(CH_3)_3NCH_2CH_2OH]^+$), in the peripheral nervous system (PNS), at the neuromuscular junction, and at many synapses in the CNS.

Synthesis of Ach. Acetylcholine is synthesized from two major compounds, choline and Acetyl-CoA. Much of the **choline** used for ACh synthesis comes from the recycling of choline from metabolized ACh. Another source is the breakdown of the phospholipid, **phosphatidylcholine**. Although humans synthesize choline in the liver, the amount produced naturally is insufficient to meet cellular functions, requiring that some choline be obtained from foods or dietary supplements. One of the strategies to increase ACh neurotransmission is the administration of choline in the diet. Food rich in choline include eggs, poultry, meats and other animal-based products, whole grains, beans, and nuts. However, this has not been effective, probably because the administration of choline may not increase the availability of choline in the CNS. The rate-limiting steps in ACh synthesis are the availability of choline and **acetyl-CoA**. During increased neuronal activity the availability of acetyl-CoA from the mitochondria is upregulated as is the uptake of choline into the nerve ending from the synaptic cleft. Ca^{2+} appears to be involved in both of these regulatory mechanisms. **Acetyl-CoA** is a metabolic intermediate that is involved in many metabolic pathways in an organism. Acetyl-CoA is produced

mainly in the mitochondria of the neuron. It comes from the oxidation of pyruvate, which is formed during glucose metabolism (glycolysis). This is found as a result of the experiment that was conducted in 1936 when scientists incubated animal brain cells in various medium and found that glucose, pyruvate and lactate all equally resulted in an increase in ACh production in the presence of oxygen. They stated, "We know now, of course, that acetylCoA (AcCoA) is required for ACh biosynthesis and that it must be the substance produced during the combustion of glucose, lactate or pyruvate in the brain that gives rise to ACh." Ach is synthesized by a single step reaction catalyzed by the enzyme choline acetyltransferase (**ChAT**). As in case of all nerve terminal proteins, Chat is synthesized in the cholinergic cell bodies of neurons and transported down to the nerve terminals. Both ChAT and ACh may be found throughout the neuron, but their highest concentration is in axon terminals. The presence of ChAT is the "marker" that a neuron is cholinergic, only cholinergic neurons contain ChAT. On the cell membrane of axon terminal, there is high affinity **choline transporters** (**ChT**) that take choline from the extracellular space and transport them into the cytoplasm of the neuron. **Choline acetyltransferase** (**ChAT**) is a transferase enzyme responsible for the synthesis of the neurotransmitter acetylcholine. ChAT catalyzes the transfer of an acetyl group from the coenzyme acetyle-CoA to choline. As with most nerve terminal proteins, ChAT is produced in the body of the neuron and is transported to the nerve terminal, where its concentration is highest. Presence of ChAT in a nerve cell classifies this cell as a "cholinergic" neuron.

Many neurons release acetylcholine including both pre-ganglionic and postganglionic sympathetic neurons, and all somatic motor neurons. Moreover, neurons in the basal forebrain, diencephalon, and hippocampus release Ach as well.

Storage of Ach. Even though small amount of Ach is free in cytosol of the neuron, the majority of the neurotransmitter is stored in 100 um vesicles. Vesicle-stored ACh is away from degradation by **acetylcholinesterase**. Storage of ACh into vesicle occurs through ATP dependent storage of H^+ ions into vesicles which acidifies the vesicle. Acetylcholine is transported from the cytosol into a vesicle by a carrier protein **vesicular acetylcholine transporter** (**VAChT**). VACHT then uses the stored protons to exchange ACh. This protects them from direct exposure with acetylcholinesterase. The gene for VAChT is contained on the first intron of the **choline acetyltransferase** gene. This proximity implies the two important cholinergic proteins are probably regulated coordinately.

Release of Ach. The release of ACh occurs through Ca^{2+} stimulated docking, fusion, and fission of the vesicle with the nerve terminal membrane. Once action potential spreads over to axon terminal, it causes **voltage-gated Ca2+ channels** to open. Opening of these channels results in increased concentration of Ca^{2+} ions in the cytoplasm of axon terminal, which in turn, leads to the fusion of, ACh filled, vesicles with the pre-synaptic membrane via the **SNARE** proteins. Many toxins are known that interfere with these processes and are effective in

preventing ACh secretion including **botulinum toxin** inhibition and **black widow spider venom (BWSV)** stimulation of ACh release.

Cholinergic Receptors: The receptors that respond to Ach is generally called "cholinergic". There are two types of cholinergic receptors, and they are distinguished by their responsiveness to two different chemicals, nicotin and muscurine.

Nicotinic	Muscurinic
Bind nicotine	Bind muscarine
Blocked by curare	Blocked by atropine
Ligand gated ion channel	Metabotropic and couple with G proteins
On post-ganglionic neurons in the autonomic ganglia, at the neuromuscular junctions of skeletal muscle and on some CNS neurons.	On smooth muscle, cardiac muscle, gland cells, some CNS neurons,
Only postsynaptic	Both postsynaptic and presynaptic

Nicotinic receptors. Although a receptor is considered specific for a given ligand, such as ACh, most receptors will recognize natural or synthetic compounds that exhibit some degree of chemical similarity to that ligand. Some Ach receptors respond not only to acetylcholine but to the compound nicotine and have therefore come to be known as nicotinic receptors. Nicotine is a plant alkaloid compound that constitutes 1% to 2% of tobacco products. It is also contained in treatments for smoking cessation, such as nasal sprays, chewing gums, and transdermal patches. Nicotine's hydrophobic structure allows rapid absorption through lung capillaries, mucous membranes, skin, and the blood–brain barrier. These receptors are located on skeletal muscles, post-ganglionic neuronal cell bodies and adrenal medulla (chromaffin cells).

The Nicotinic Receptor is an Ion Channel. The nicotinic acetylcholine receptor is an excellent example of a receptor that contains an ion channel. In this case, the channel is permeable to both sodium and potassium ions, but because Na+ has the larger electrochemical driving force, the net effect of opening these channels is depolarization due to Na+ influx. The nicotinic acetylcholine receptor at the neuromuscular junction (NMJ) is a pentameric ligand-gated ion channel (specifically $\alpha_2\beta\gamma\delta$ or $\alpha_2\beta\epsilon\delta$) on the postsynaptic muscle membrane that transduces motor nerve acetylcholine release into an electrical endplate potential (EPP). It acts as a rapid, on-off molecular switch for muscle contraction. A funnel-shaped internal ion channel is surrounded by the five subunits. The binding surface of the receptor appears to be primarily on the α subunits, near the outer surface of the molecule. The subunits contain recognition sites for agonists, reversible antagonists, and **α-toxins** (cobra α-toxin and α-bungarotoxin). Whereas the NMJ nicotinic receptor is composed of four different species of subunit ($\alpha_2\beta\gamma\delta$), the neuronal nicotinic receptor also is composed of only two subunit types (2α and 3β).

Muscarinic receptors: The other general type of cholinergic receptor is stimulated not only by acetylcholine but by muscarine, a poison contained in some mushrooms; therefore, these are called **muscarinic receptors.** These receptors are metabotropic and couple with G proteins (**GPCR**), which then alter the activity of

a number of different **enzymes** and **ion channels**. They are prevalent at some **cholinergic synapses in the brain** and at junctions where a major division of the **PNS** innervates **peripheral glands, tissues**, and organs, like **salivary glands**, **smooth muscle cells**, and the **heart**. These receptors are located in CNS(M1), heart(M2), GI, respiratory, smooth muscle, glands, pupil, lacrimal gland, sweat glands and blood vessels.

Muscurinic receptors-GPCR. Muscurinic receptors are single polypeptide proteins that that span the plasma membrane with seven transmembrane α-helices. Seven regions of the polypeptide are made up of 20-25 amino acids. Because each of these regions of the protein is markedly hydrophobic, they span the cell membrane seven times. The site of agonist binding is a circular pocket formed by the upper portions of the seven membrane-spanning regions.

The binding of ACh into the α subunit of the muscarinic receptor leads to the altered conformation of an associated GTP-binding protein (**G protein**). G protein is made up of the the three subunits α, β and γ. In response to the altered conformation of the muscarinic receptor, the α subunit of the G protein releases bound **guanosine diphosphate (GDP)** and simultaneously binds **guanosine triphosphate (GTP)**. The binding of GTP activates the G protein, allowing dissociation of the α subunit from the protein complex and for it to interact with effector systems to mediate specific responses. An inherent **GTPase** catalytic activity of the G protein hydrolyzes the GTP back to GDP. This hydrolysis terminates the action of the G protein. The rate of hydrolysis of the GTP thus dictates the length of time the G protein remains activated.

Inacticvation: After acetylcholine performs its nerve signal transmitter function, it is inactivated by **Acetylcholineesterase** (**AChE**). This enzyme has a very high catalytic activity, one of the highest known in biology. It is bound adjacent to cholinergic receptors, and it is the primary enzyme, in the body, that catalyzes the breakdown of acetylcholine and some other choline esters that function as neurotransmitters: acetylcholine + H_2O = choline + acetate

It is found at mainly neuromuscular junctions and in chemical synapses of the cholinergic type, where its activity serves to terminate cholinergic synaptic transmission.

Acetylcholinesterase inhibitors. Acetylcholinesterase inhibitors (AChEIs) are compounds that block the enzyme responsible for breaking down acetylcholine, increasing its concentration and duration of action at neurotransmitter receptor sites. AChE inhibitors are classified into two types based on their method of action: irreversible and reversible. The mechanism of action of **irreversible inhibitors of AChE** is that they carbamylate the AChE, rendering it inactive. The carbamylation inactivates both the acetyl and choline binding domains. Irreversible **AChE inhibitors** include Diisopropyl Fluorophosphate, Trichlorfon, Tabun, Echothiophate, Diazinon.

In contrast to the irreversible inhibitors, the **reversible AChE inhibitors** are effective in transiently increasing the ACh level and are effective in diseases and conditions where an increased ACh level is desired. These include Rivastigmine, Galantamine, Huperzine A, 7-methoxytacrine, Pyridostigmine and others.

Related diseases:

Alzheimer's disease. Alzheimer's disease is a progressive neurodegenerative disorder marked by decline in memory, cognition, and behavior. A major feature of AD is degeneration of the cholinergic system, particularly neurons in the nucleus basalis of Meynert, forming the basis of the **cholinergic hypothesis**. Increased acetylcholinesterase (AChE) activity lowers acetylcholine levels, worsening cognitive impairment. Therefore, acetylcholinesterase inhibitors are widely used for symptomatic treatment, although they do not halt disease progression. Donepezil, galantamine, and rivastigmine are used to treat symptoms of mild-to-moderate, and sometimes severe, Alzheimer's

Lamber-Eaton myasthenic Syndrome-is a rare autoimmune disorder characterized by muscle weakness of the limbs. **In Lambert-Eaton Myasthenic Syndrome (LEMS)**, antibodies against voltage-gated calcium channels (**VGCC**), particularly the P/Q-type, decrease the amount of calcium that can enter the nerve ending. As a result, the release of acetylcholine at the neuromuscular junction is reduced significantly, leading to impaired nerve signal transmission between nerves and muscles. **The weakness from Lambert-Eaton Myasthenic Syndrome** typically involves the muscles of the proximal arms and legs — that is, the muscles closer to the trunk. In contrast to myasthenia gravis, the weakness affects the legs more than the arms. This leads to difficulties climbing stairs and rising from a sitting position. Interestingly, weakness is often relieved temporarily after exertion or physical exercise.

Myasthenia Gravis is an autoimmune disease that result from antibodies that block or destroy nicotinic acetylcholine receptors (AChR) on post-synaptic neurons at neuromuscular junctions. This prevents the transmission of signals from pre-synaptic to post-synaptic neurons. IgG1 and IgG3 are the main anti-bodies that attach AChR in the post-synaptic membrane. **Myasthenia gravis** generally starts with ocular (eye) weakness and may later progress to a more severe, generalized form. This advanced stage is characterized by weakness in the extremities or in muscles that control essential life functions such as breathing and swallowing. Acetylcholine esterase inhibitors, such as neostigmine and pyridostigmine can be used in mild forms of myasthenia gravis. When acetylcholine esterase inhibitors are insufficient, immunosuppressants, such as prednisone and azathioprine are required to treat.

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