Volume 2, Issue 01, January 2024 ISSN (E): 2938-3765

AGENTS ACTING ON CHOLINERGIC SYNAPSES

(LITERATURE REVIEW)

Mustanov T. B.
Alfraganus University, Tashkent, Uzbekistan

Djanaev G. Yu.
Tashkent Medical Academy, Tashkent, Uzbekistan

Mamadaliev Sh. I.
Andijan State Medical Institute, Andijan City, Uzbekistan

Abstract

The autonomic nervous system (ANS) controls and regulates the whole system of bodily functions. It works silently, that is, acts unconsciously to maintain the rhythm of a large number of signal inputs and outputs and maintain a simple way of life. Most prominently, ANS is separated in two divisions—thoracolumbar outflow (sympathetic) and craniosacral outflow (parasympathetic)—which act on heart rate, digestion, respiratory rate, the sensory organs, major glands, urination, and sexual responses. By maintaining chemical–receptor (muscarinic and nicotinic receptors) interactions, this autonomic system generates smooth work output and maintains a balance between body and environment.

Cholinergic agonists basically act on both muscarinic and nicotinic receptors and are clinically beneficial for urinary retentions, topically usable mitotic effects, and the promotion of saliva. To inhibit the hydrolysis of acetylcholine to cholinesterase, anti-acetylcholinesterase drugs, which show cholinergic effects, are used. Ganglia can be stimulated by anticholinesterase drugs through muscarinic receptors. Simultaneously, they can also cause bradycardia, hypotension, ganglionic stimulation, increase in heart rate, blood pressure, smooth muscles, glands, gastrointestinal movement, respiratory rate, urinary tracts, and eye. Chemical agents like atropine have the ability to block the muscarinic receptor, and certain synthetic chemical agents have significant properties to block (competitive antagonists) the nicotinic receptors. By blocking the muscarinic receptor, anticholinergic drugs cause tachycardia, block vasodepressor action, mydriasis and miotics, bronchodilation, relax the urinary bladder, urinary retention, decrease the sweat, saliva, tracheobronchial and lacrimal secretion, and increase the body temperature. This chapter provides a brief overview of cholinergic agonists, antagonists, and anticholinesterase drugs, their mechanisms, and their applications.

Keywords: M- and n-cholinomimetics, Acetylcholine, Carbacholin, Cyclodol, Anticholinesterase agents Physostigmine salicylate, Prozerin, Galantamine hydrobromide, Armin.

Introduction

Cholinergic agents are compounds which mimic the action of acetylcholine and/or butyrylcholine.[1] In general, the word "choline" describes the various quaternary ammonium salts containing the *N*,*N*,*N*-trimethylethanolammonium cation. Found in most animal tissues, choline is a primary component of

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

the neurotransmitter acetylcholine and functions with inositol as a basic constituent of lecithin. Choline also prevents fat deposits in the liver and facilitates the movement of fats into cells.

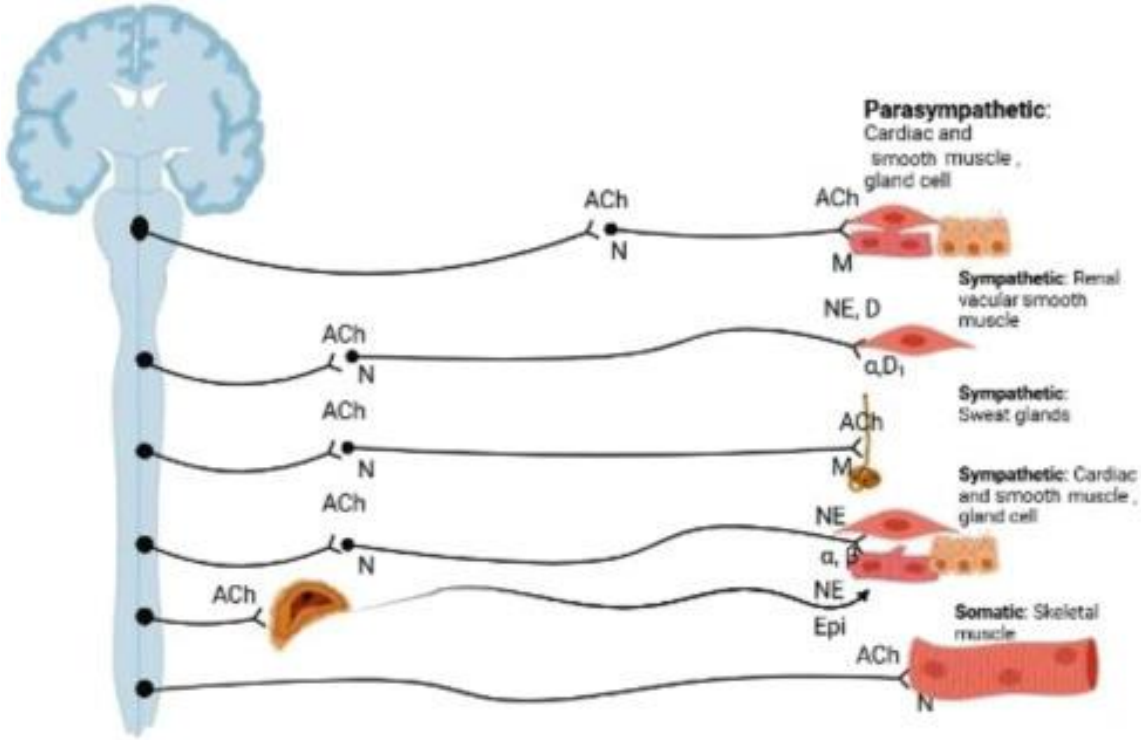
The parasympathetic nervous system, which uses acetylcholine almost exclusively to send its messages, is said to be almost entirely cholinergic. Neuromuscular junctions, preganglionic neurons of the sympathetic nervous system, the basal forebrain, and brain stem complexes are also cholinergic, as are the receptor for the merocrine sweat glands.

In neuroscience and related fields, the term cholinergic is used in these related contexts:

- A substance (or ligand) is cholinergic if it is capable of producing, altering, or releasing acetylcholine, or butyrylcholine ("indirect-acting"), or mimicking their behaviours at one or more of the body's acetylcholine receptor ("direct-acting") or butyrylcholine receptor types ("direct-acting"). Such mimics are called parasympathomimetic drugs or cholinomimetic drugs.

Efferent innervation consists of autonomic nerves (controlling internal organs, blood vessels, and glands) and motor nerves innervating skeletal muscles.

Vegetative control is divided into cholenergic or parasympathetic (mediator - acetylcholine) and adrenergic or sympathetic (mediator - noradrenaline) nerve fibers, depending on the mediators released in neuroeffector synapses.

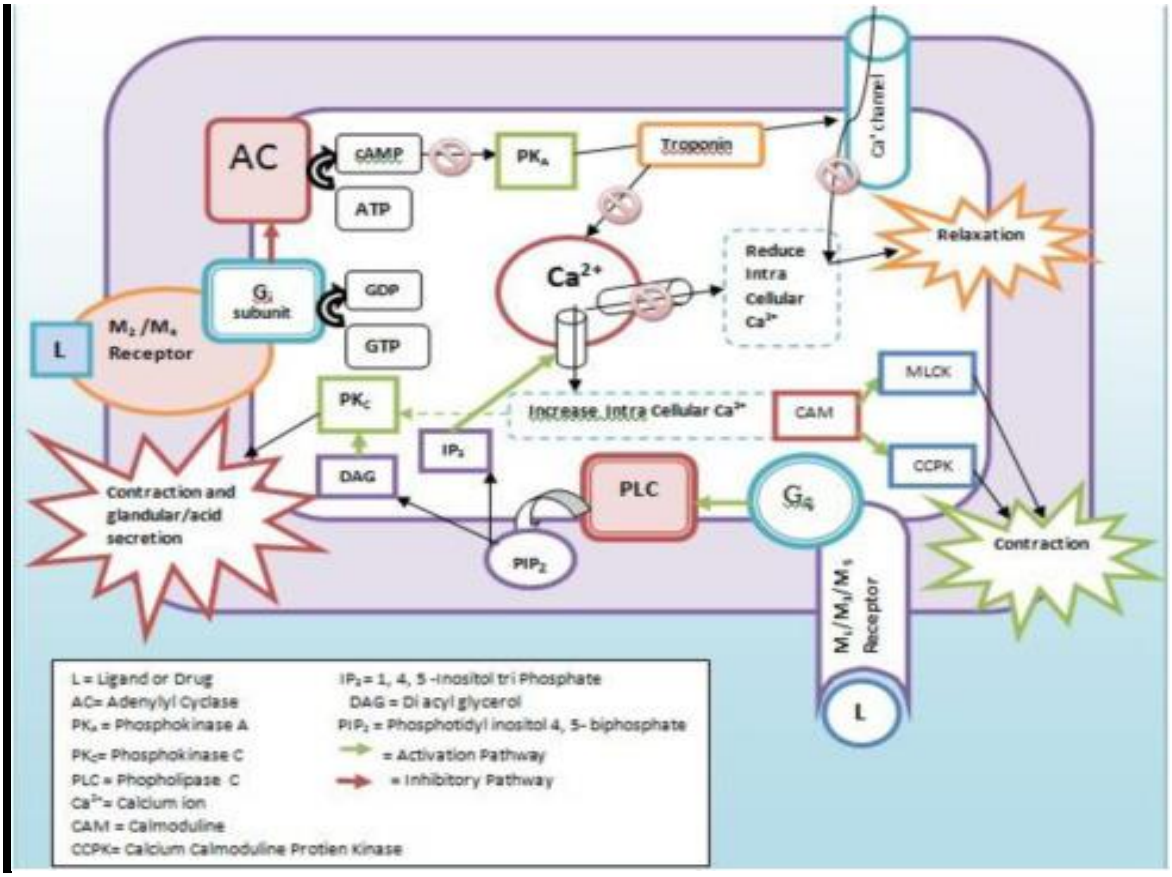


The efferent path of vegetative nerve fibers consists of 2 neurons: preganglionic and postganglionic. In cholinergic innervation, the trunks of preganglionic neurons are located cranio-sacral (Fig. 3.1). Cranial nuclei are located in the midbrain and medulla oblongata. In this case, cholinergic nerve fibers are separated from 12 pairs of nerve fibers of the brain in the following pairs: III (n. oculomotorius), VII (n. facialis), IX (n. glossopharyngeus) and X (n. vagus). In the sacral part, preganglionic neurons originate from the lateral branches of the gray matter of the spinal cord.

In adrenergic control, preganglionic neurons are located in the lateral branches of the thoracolumbar division of the spinal cord (C8, Th1-L3).

At the parasympathetic nerve endings, in the presynaptic membrane, acetylcholine is produced as a mediator, and at the sympathetic nerve endings, noradrenaline is produced.

In cholinergic and adrenergic control, axons of nerve fibers of preganglionic neurons terminate in autonomic ganglia, where they form synaptic connections with ganglionic neurons. Sympathetic ganglia are located away from organs near the exit from the spinal cord, while parasympathetic ganglia are located near or within organs. Acetylcholine acts as a mediator in both ganglia. In parasympathetic nerve fibers, the preganglionic fiber is long and the postganglionic fiber is short, and in the sympathetic nerve fibers, the preganglionic fiber is short and the postganglionic fiber is long.



As mentioned, autonomic cholinergic and adrenergic control consists of 2 neurons. The only exception is the efferent nerves in the medulla, which are formed from chromaffin cells of the adrenal glands. Chormmaffin cells are embryogenetically similar to neurons of sympathetic ganglia. Therefore, only pre-ganglionic (cholinergic) neurons participate in the control of the medulla of the adrenal glands, and acetylcholine acts as a mediator. Thus, in this case, a single-neuron pathway will do the job. When these neurons are excited, adrenaline is released from the chromaffin cells of the adrenal glands. The resulting adrenaline stimulates postsynaptic α2-adrenoceptors located in the intima of blood vessels, which are not controlled by nerves, and causes vasoconstriction.

Examples of direct-acting cholinergic agents include choline esters (acetylcholine, methacholine, carbachol, bethanechol) and alkaloids (muscarine, pilocarpine, cevimeline). Indirect-acting cholinergic agents increase the availability of acetylcholine at the cholinergic receptors.

It has been determined that the p u r i n e r g i c t i z i m is involved in the management of internal organs. It is known that ATF (adenosine triphosphate), which acts as a mediator (or comedian), is

stored in the vesicles of cholinergic and adrenergic nerve endings. Peripheral nerve endings (in varicose veins) release ATF and its breakdown products (including adenosine), which has a relaxing effect on intestinal smooth muscles, and also relaxes bronchial smooth muscles, causing bladder contraction and vasodilation. . In addition, the existence of special p u r i n e r g i c (postganglionic) fibers is also possible. It is believed that there are 2 types of purine receptors: R1 (more sensitive to adenosine than ATF) and R2 (more sensitive to ATF than adeno-zine). In turn, R1 receptors are divided into A1 (blocks adenyl cyclase) and A2 (activates adenyl cyclase)1 receptors of adenosine. Adenosine affects the presynaptic membrane and reduces the release of mediators. Adenosine has also been shown to stimulate nociceptors in afferent nerve endings.

Nerve fibers controlling skeletal muscles belong to cholinergic fibers (neuromuscular transmission is carried out by means of acetylcholine). Their nuclei come from the anterior branches of the gray matter of the spinal cord and from the nuclei of certain brain nerves, and their axons go directly to skeletal muscles and form neuromuscular synapses without forming ganglia. In them, the mediator is acetylcholine, and the receptor is n-cholinergic receptors.

Chemical compounds can affect different stages of synaptic transmission (see Chapters 3 and 4). However, it is necessary to take into account that different binding sites of the receptor with the effector can also be "targets" for the action of substances. It is known that the enzymes of the cell membrane are connected to the receptors by means of special control proteins. For example, the activity of adenylate cyclase under the action of agonists on the corresponding receptors is controlled by G-proteins (guanine nucleotide binding proteins2), which are activated when the receptor is stimulated. Adenylate cyclase-activating (Gs) and inhibitory (Gi) G-proteins are known (Fig. 3.2). Cholera vibrio toxin binds to Gs-protein, and pertussis toxin binds to Gi-protein. Thus, there is a possibility that G-proteins can be directly affected by chemicals. However, there are currently no drugs with such an effect.

In addition, it is possible to directly affect the enzymes that control the biosynthesis and biotransformation of some secondary transmitters. For example, a substance known to directly stimulate adenylate cyclase (bypassing G-protein) is forskolin3, a diterpene substance obtained from plants (used in experimental studies). Also known are substances that inhibit the phosphodiesterase enzyme that converts tsAMF to 5'-AMF. Both forskolin and methylxanthines increase cellular levels of tsAMF: forskolin acts by increasing tsAMF formation, while methylxanthines act by inhibiting its hydrolysis.In this section, drugs affecting efferent innervation Systematization is mainly based on the direction of action on synapses through the transmission of nerve impulses with acetylcholine or noradrenaline. There are 2 groups of substances: 1) agents affecting cholinergic synapses; 2) agents affecting adrenergic synapses. These groups have been studied in some detail and are widely used in medical practice.Excitations in cholinergic synapses are carried out using acetylcholine.

Acetylcholine interacts with the α-subunit of the cholinergic receptor, leading to the opening of the ion channel and the depolarization, (depolarization) of the postsynaptic membrane, ultimately opening it.

Cholinergic receptors with different locations differ from each other in their sensitivity to pharmacological substances. Therefore, they are divided into muscarinic (m-) and nicotine (n-) sensitive cholinergic receptors1. M-cholinoreceptors are located in the postsynaptic membrane at the end of the postganglionic fiber of the parasympathetic nerve fibers of the effector organ. In addition, they are also present in the neurons of the autonomic ganglia located outside the synapse and in the MNS. Since m-cholinoreceptors with different localization also differ in their sensitivity

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

to various pharmacological agents, they are divided into m1-, m2-, m3-, m4- and m5-cholinoreceptors. M1-cholinoreceptors are located mainly in vegetative ganglia and MNS, m2-cholinoreceptors in the heart2, m3-cholinoreceptors in smooth muscles and most exocrine glands, m4-cholinoreceptors in the heart, walls of lung alveoli and MNS, and m5-cholinoreceptors in the MNS, salivary glands, blood mononuclear cells determined. The main effects of most agents acting on M-cholinoreceptors are due to interaction with postsynaptic m2- and m3-cholinoreceptors. Therefore, in this topic, without paying special attention to the subtypes of m-cholinoreceptors, only a general understanding of m-cholinotrope drugs is given.

1Muscarine (an alkaloid obtained from some poisonous fungi such as mushrooms) and nicotine (an alkaloid obtained from tobacco leaves) have a selective effect on the corresponding cholinergic receptors.

2 M-cholinoreceptors of autonomic ganglion neurons are located outside the synapse.

N-cholinoceptors are located in the postsynaptic membranes of all sympathetic and parasympathetic ganglia, chromaffin cells of the adrenal medulla, sinocarotid zone, end plates of skeletal muscles and MNS (neurogypophysis, Renshaw cells, etc.). The sensitivity of different N-cholinergic receptors to substances is different. For example, n-cholinoreceptors of autonomic ganglia (neuronal type n-cholinoreceptors) differ from n-cholinoreceptors of skeletal muscles (muscular type n-cholinoreceptors) are dramatically different. This can explain the selective effect of ganglioblockers and muscle relaxants.

Presynaptic cholino- and adrenoreceptors participate in the control of acetylcholine release in neuroeffector synapses. Their stimulation slows down the release of acetylcholine.

Acetylcholine increases the permeability of the postsynaptic membrane by interacting with N-cholinerceptors, changing their conformation. Under the excitatory effect of acetylcholine, sodium ions enter the cell and cause depolarization of the postsynaptic membrane. Initially, it is manifested by the local synaptic potential, which has a certain value and gives rise to the action potential. Then the local excitation, confined to the synaptic area, propagates across the cell membrane. G-proteins and secondary conductors (cyclic adenosine monophosphate - tsAMF; 1,2-diacylglycerol; inositol (1,4,5) triphosphate) play an important role in the transmission of nerve impulses through M-cholinoreceptors.

The duration of action of acetylcholine is very short, because it is quickly broken down by the enzyme acetylcholinesterase in neuromuscular synapses or removed from the synaptic gap in autonomic ganglia. Most of the choline produced by the hydrolysis of acetylcholine (about 50 percent) is recaptured by the presynaptic membrane and re-directed to the cytoplasm for the synthesis of new acetylcholine.

The stages of cholinergic transmission at neuromuscular synapses are shown

Substances can affect various processes related to synaptic transmission: 1) acetylcholine synthesis; 2) mediator release; 3) interaction of acetylcholine with cholinergic receptors; 4)

to the breakdown of acetylcholine using acetylcholinesterase; 5) re-introduction of choline formed from the breakdown of acetylcholine through the presynaptic membrane (Table 3.1). Agents that act on cholinergic receptors and acetylcholinesterase are widely used as drugs.

For example, carbacholin, which enhances the release of acetylcholine, as well as botulinum toxin, which prevents the release of the mediator, acts on the presynaptic endings. Hemicholine inhibits the reuptake of choline through the presynaptic membrane (neuronal uptake), which is used to analyze the mechanism of action of substances in experiments. Cholinomimetic substances (acetylcholine, pilocarpine, cytisine) and cholinoblocker (m- cholinergic blockers,

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

ganglioblockers, curare-like agents) have a direct effect on cholinergic receptors. Anticholinesterase drugs (proserin, etc.) can be used to reduce the enzyme acetylcholinesterase. Drugs that act on cholinergic receptors and acetylcholinesterase are of more interest as drugs.

1. Agents affecting M- and n-cholinerceptors

M- and n-cholinomimetics

Acetylcholine, Carbacholin

M- and n-cholinoblockers Cyclodol

2. Anticholinesterase agents:

Physostigmine salicylate, Prozerin, Galantamine hydrobromide, Armin

3. Agents affecting M-cholinergic receptors:

M-cholinomimetics (muscarinomimetics)

Pilocarpine hydrochloride, Aceclidine

M-cholinoblockers (atropine-like agents:)

Atropine sulfate, Metacin, Platyphyllin hydrotartrate, Ipratropium bromide, Scopolamine hydrobromide

4. Means affecting N-cholinerceptors

N-cholinomimetics (nicotinomimetic agents) Tsititon, Lobelin hydrochloride,

N-cholinergic receptors or ion channels connected with them-

n ing blockers

Ganglioblockers

Benzohexonium, Pentamine, Hygronium, Pyrylene, Arfonad

Curare-like agents (peripherally acting laxatives)

Tubocurarine chloride, Pancuronium bromide, Pipecuronium bromide, Anatruxonium, Ditilin, Mellictin

Under the direct influence of m- and n-cholinomimetics, n-cholinoreceptors in the ganglia of the autonomic nervous system and the oxi- of the parasympathetic nervous system

m-cholinergic receptors located in the brain are stimulated. It is dominated by the changes caused by the stimulation of m-cholinerceptors, that is, the pupil narrows, the intraocular pressure decreases, spasm of accommodation is observed, etc.

The excitatory effect of acetylcholine on n-cholinoreceptors of autonomic ganglia is masked by its m-cholinomimetic effect. When m-cholinoreceptors are blocked (for example, with the m-cholinoblocker atropine), the n-cholinomimetic effect occurs quickly. Against this background, acetylcholine in large doses, instead of lowering arterial pressure, causes a pressor effect due to the stimulation of n-choline receptors of the sympathetic ganglia and the hormones of the medulla of the adrenal glands.

Acetylcholine has a stimulating effect on N-cholinergic receptors in skeletal muscles. The MNS also contains acetylcholine-sensitive cholinergic receptors. It should be borne in mind that acetylcholine at high (non-physiological) concentrations can weaken cholinergic conductance.

In medical practice, carbacholin, an analogue of acetylcholine, is used in glaucoma (see structure: R=NH2, G=Cl). Carbacholin differs from acetylcholine in its stability and duration of action. It is not hydrolyzed by acetylcholinesterase, so it has a long-lasting effect (1-1.5 hours). Carbacholin not only has a cholinomimetic effect, but also stimulates the release of acetylcholine from presynaptic fibers. The pharmacological action of carbacholin is similar to that of acetylcholine. It is determined by its effect on M and N-cholinergic receptors

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

Acetylcholinesterase agents inhibit the hydrolysis of acetylcholine and prolong its muscarinic and n-nicotinic effects. M-cholinomimetic effect is manifested by increasing the tone and contraction activity of a number of smooth muscles (circular and ciliary muscles of the eye, bronchi, gastrointestinal tract, bile ducts and other muscles). Anticholinesterase agents in therapeutic doses usually cause bradycardia, reduce heart work, slow down impulse transmission along the conduction pathways of the heart. Arterial pressure decreases. In high doses, it can cause tachycardia (its effect on the frequency of heart contractions is not only related to the excitation of M-cholinergic receptors, but also related to the stimulation of cholinergic receptors of sympathetic ganglia, adrenal medulla, and medulla oblongata).

Anticholinesterase agents increase the secretion of glands with cholinergic innervation (bronchi, digestive tract, sweat glands, etc.).

The nicotinic effects of anticholinesterase agents are manifested through neuromuscular transmission in autonomic ganglia.

In small doses, anticholinesterase agents facilitate the transmission of impulses in skeletal muscles and autonomic ganglia, and in large doses have a depressant effect.

Anticholinesterase agents stimulate the MNS in small doses (desynchronization of the electroencephalogram occurs, the time of a series of reflex reactions decreases). In large doses, especially toxic doses, these substances weaken the MNS.

Effects of anticholinesterase agents on certain eye functions, MIT and bladder tone and motility, neuromuscular conduction and MNS are of great importance in medical practice.

Anticholinesterase agents affect the eye as follows (Fig. 3.7):

a) narrows the pupil (myosis1), which is associated with the stimulation of M-cholinoreceptors in the circular muscles of the eye (m. sphincter pupillae) located on the colored membrane and the contraction of these muscles;

b) lowers intraocular pressure. This is the result of miosis. The colored membrane becomes thinner, the corners of the anterior chamber of the eye are opened to a greater extent, and in this regard, the outflow of intraocular fluid through the corner space of the colored membrane-corneal membrane (fonta-nuva space) into the venous sinus of the sclera (Schlemmov's canal) is improved. In this case, the circle is also important with an increase in muscle tone;

c) causes spasm of accommodation. In this case, the substance directly stimulates M-cholinergic receptors of circular muscles (m. ciliaris) that have cholinergic innervation. Contraction of the circular muscles of the eye relaxes the muscle ligament (ligament of the tsinn), which increases the convexity of the eyeball. The eye adapts to near vision;

Intraocular pressure lowering by anticholinesterase agents is sometimes used to treat glaucoma.

Anticholinesterase substances have a stimulating effect on the motility of the gastrointestinal tract through m- and n-cholinergic innervation and intermuscular tangle (Auerbachov, plexus myentericus). Bladder muscle tone and contractile activity also increase. These effects are used to relieve bowel or bladder atony

When choosing drugs, attention is paid to their activity, toxicity, dose, duration of action, ability to pass through various barriers. In the treatment of glaucoma, proserin (neostigmine methylsulfate), phisostigmine, armine are used (their solution is dripped into the conjunctival space). Galantamine is not used for this purpose because it has a tickling effect on the conjunctiva and causes swelling of the conjunctiva.

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

For the resorptive effect (as an antagonist of antidepolarizing curare-like drugs in myasthenia, intestinal and bladder atony, polymyelitis), usually less toxic representatives of drugs are chosen - proserin and galantamine, sometimes - physostigmine.

Gallamine (nivalin) and physostigmine (tertiary amines) cross the blood-brain barrier. Therefore, when it is necessary to activate cholinergic transmission not only in the periphery, but also in the MNS, galantamine is mainly used in the treatment of residual complications of transferred polymyelitis.

According to available data, physostigmine improves memory in adults and the elderly in the early stages of developing dementia (Alzheimer's disease). Galantamine1 can also be used for this purpose.

Physostigmine is also used in poisoning with m-cholinoblockers and centrally acting substances (for example, some psychotropic drugs), which have a pronounced m-cholinoblocking component in the spectrum of action.

Pyridoxine bromide (mestinon) and

ox s a zil (ambenonium chloride) can be used. These have a longer-lasting effect than prozerin.

Edrophonic (tensilon) has a very short duration of action and is used as an antagonist of antidepolarizing muscle relaxants.

Poisoning with anticholinesterase drugs is possible. This is mainly due to the accumulation of acetylcholine in large concentrations in the body, as well as the direct stimulation of cholinergic receptors. In most cases, poisoning can be observed when using FOB2 (organic phosphorus compounds), which have a high level of lipophilic properties, therefore, regardless of the route of administration (including when applied to the skin), are very quickly absorbed in the body and inhibit acetylcholinesterase for a long time. Acute poisoning with FOB requires immediate medical attention. The work to be done is to first remove the FOB from the landing site. If it is on the surface of the skin or mucous membranes, they should be washed clean with 3-5% sodium bicarbonate solution. If the substance has entered the MIT, the stomach is washed, adsorbing and pushing agents are given, and a siphon enema is prescribed. These actions are repeated several times until the symptoms of intoxication disappear. If FOB has been absorbed into the blood, it is necessary to accelerate its excretion through urine (with the help of enhanced diuresis). Hemosorption, hemodialysis, peritoneal dialysis are among the effective methods of blood purification from FOB[1,2,3,4,5,6,7,8,9,10,11,12].

Conclusion

This chapter presents an overview of some chemical agents or drugs that act on a specific receptor and regulate the normal physiological and biochemical balance, which in turn regulates the autonomic system of the body and maintains the balance with CNS and other biochemical pathways. Some scientific studies have already proved that neurotransmitters play a vital role in cardiovascular, smooth muscles, glands, CNS, blood vessels, and ganglia. Sometimes neurotransmitter-blocking agents also exhibit vital pharmacological effects, and the enzyme that converts the neurotransmitter into an inactive form also has pharmacological effects.

References

1. Katzung BG, Masters SB Trevor, AJ, eds. (2004). *Basic & Clinical Pharmacology*.
2. Харкевич Д. А. Фармакология с общей рецептурой. – 2017.

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5

3. Whittaker V. P. (ed.). The cholinergic synapse. – Springer Science & Business Media, 2012. – T. 86.
4. Dashniani M. G. et al. Modulation of spatial memory and expression of hippocampal neurotransmitter receptors by selective lesion of medial septal cholinergic and GABAergic neurons //Experimental Brain Research. – 2020. – T. 238. – №. 10. – C. 2385-2397.
5. Deutsch J. A. The cholinergic synapse and the site of memory //Science. – 1971. – T. 174. – №. 4011. – C. 788-794.
6. https://en.wikipedia.org/wiki/Cholinergic
7. Krnjević K. Central cholinergic mechanisms and function //Progress in brain research. – 1993. – T. 98. – C. 285-292.
8. Chen C. C. et al. A subset of cholinergic mushroom body neurons blocks long-term memory formation in Drosophila //Cell Reports. – 2023. – T. 42. – №. 8.
9. Jerusalinsky D., Kornisiuk E., Izquierdo I. Cholinergic neurotransmission and synaptic plasticity concerning memory processing //Neurochemical research. – 1997. – T. 22. – C. 507-515.
10. Fayziyeva U. et al. XOLINERGIK RETSEPTORLAR SISTEMASI DORILARI //Евразийский журнал медицинских и естественных наук. – 2023. – Т. 3. – №. 8. – С. 68-70.
11. Reza K. H. et al. Mechanism of action of cholinergic drugs //How Synthetic Drugs Work. – Academic Press, 2023. – C. 27-46.

Web of Medicine: Journal of Medicine, Practice and Nursing
webofjournals.com/index.php/5