DRUGS THAT ACT IN THE ANS

The cholinergic drugs

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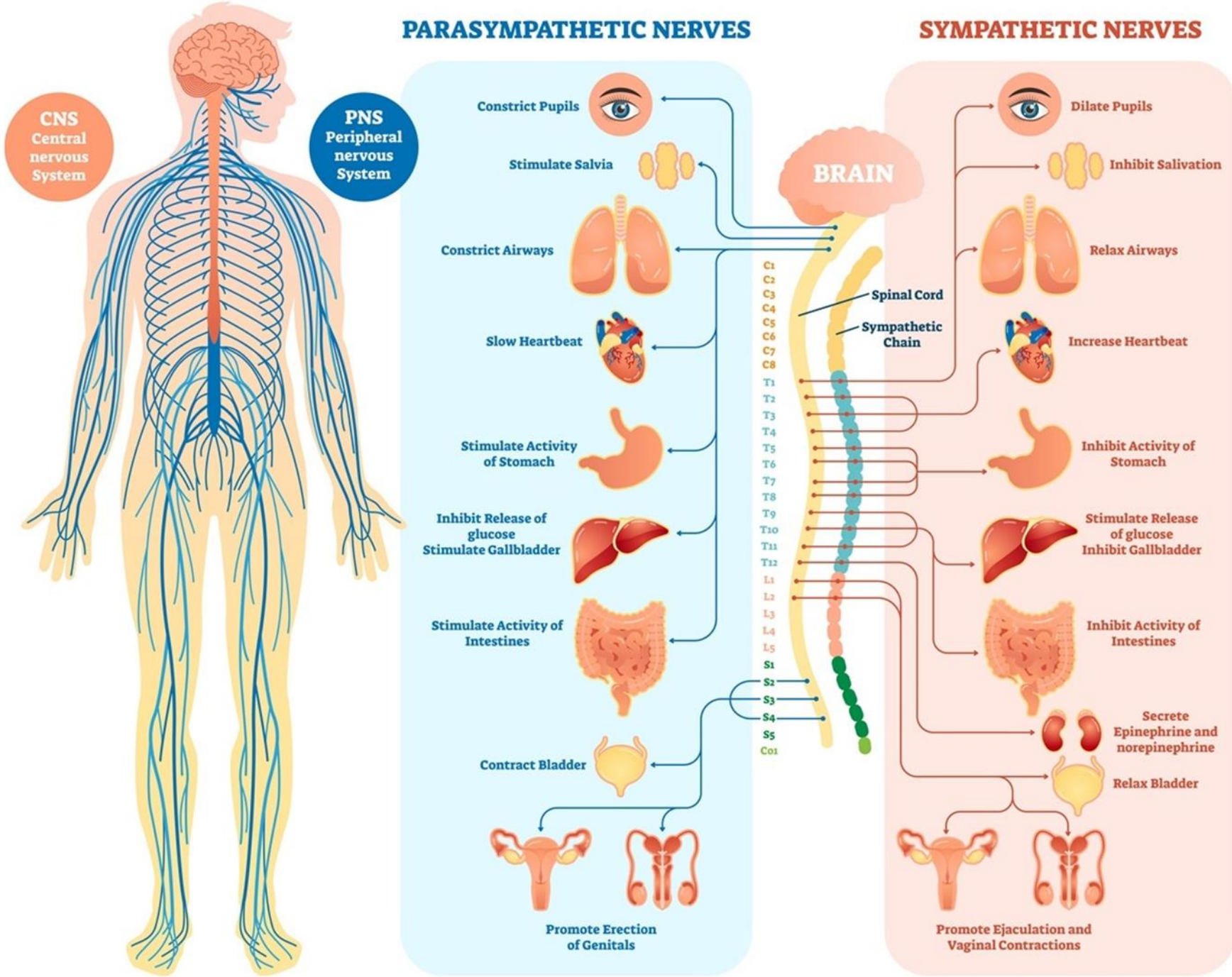
CNS
Central nervous System
PNS
Peripheral nervous System
PARASYMPATHETIC NERVES
SYMPATHETIC NERVES
BRAIN
Spinal Cord
Sympathetic Chain
Constrict Pupils
Stimulate Salvia
Constrict Airways
Slow Heartbeat
Stimulate Activity of Stomach
Inhibit Release of glucose
Stimulate Gallbladder
Stimulate Activity of Intestines
Contract Bladder
Promote Erection of Genitals
Dilate Pupils
Inhibit Salivation
Relax Airways
Increase Heartbeat
Inhibit Activity of Stomach
Stimulate Release of glucose
Inhibit Gallbladder
Inhibit Activity of Intestines
Secrete Epinephrine and norepinephrine
Relax Bladder
Promote Ejaculation and Vaginal Contractions
C1
C2
C3
C4
C5
C6
C7
C8
T1
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Cholinergic Agonists

Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in their mechanism of action.

The cholinergic drugs act on receptors that are activated by acetylcholine (ACh), whereas **the adrenergic drugs** act on receptors stimulated by norepinephrine or epinephrine.

Cholinergic and adrenergic drugs act by either stimulating or blocking receptors of the ANS.

DIRECT ACTING

Acetylcholine MIOCHOL-E
Bethanechol URECHOLINE
Carbachol MIOSTAT, ISOPTO CARBACHOL
Cevimeline EVOXAC
Pilocarpine SALAGEN, ISOPTO CARPINE

INDIRECT ACTING (reversible)

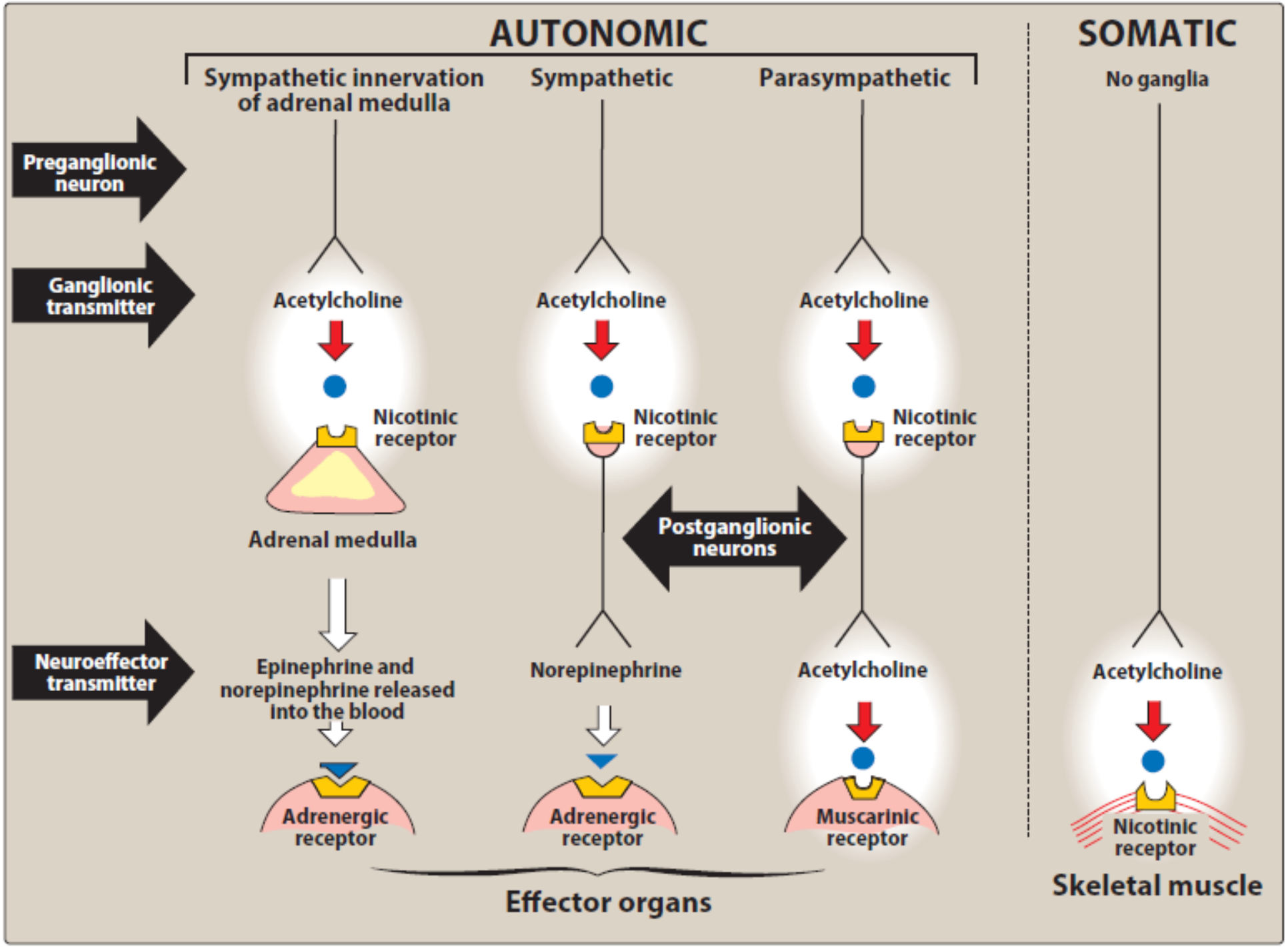
Ambenonium MYTELASE
Donepezil ARICEPT
Galantamine RAZADYNE
Neostigmine PROSTIGMIN
Physostigmine ANTILIRIUM
Pyridostigmine MESTINON
Rivastigmine EXELON
Tacrine COGNEX

INDIRECT ACTING (irreversible)

Echothiophate PHOSPHOLINE IODIDE

REACTIVATION OF ACETYLCHOLINESTERASE

Pralidoxime PROTOPAM



Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems

THE CHOLINERGIC NEURON

The preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia (both parasympathetic and sympathetic), and the postganglionic fibers of the parasympathetic division use ACh as a neurotransmitter.

The postganglionic sympathetic division of **sweat glands** also uses acetylcholine.

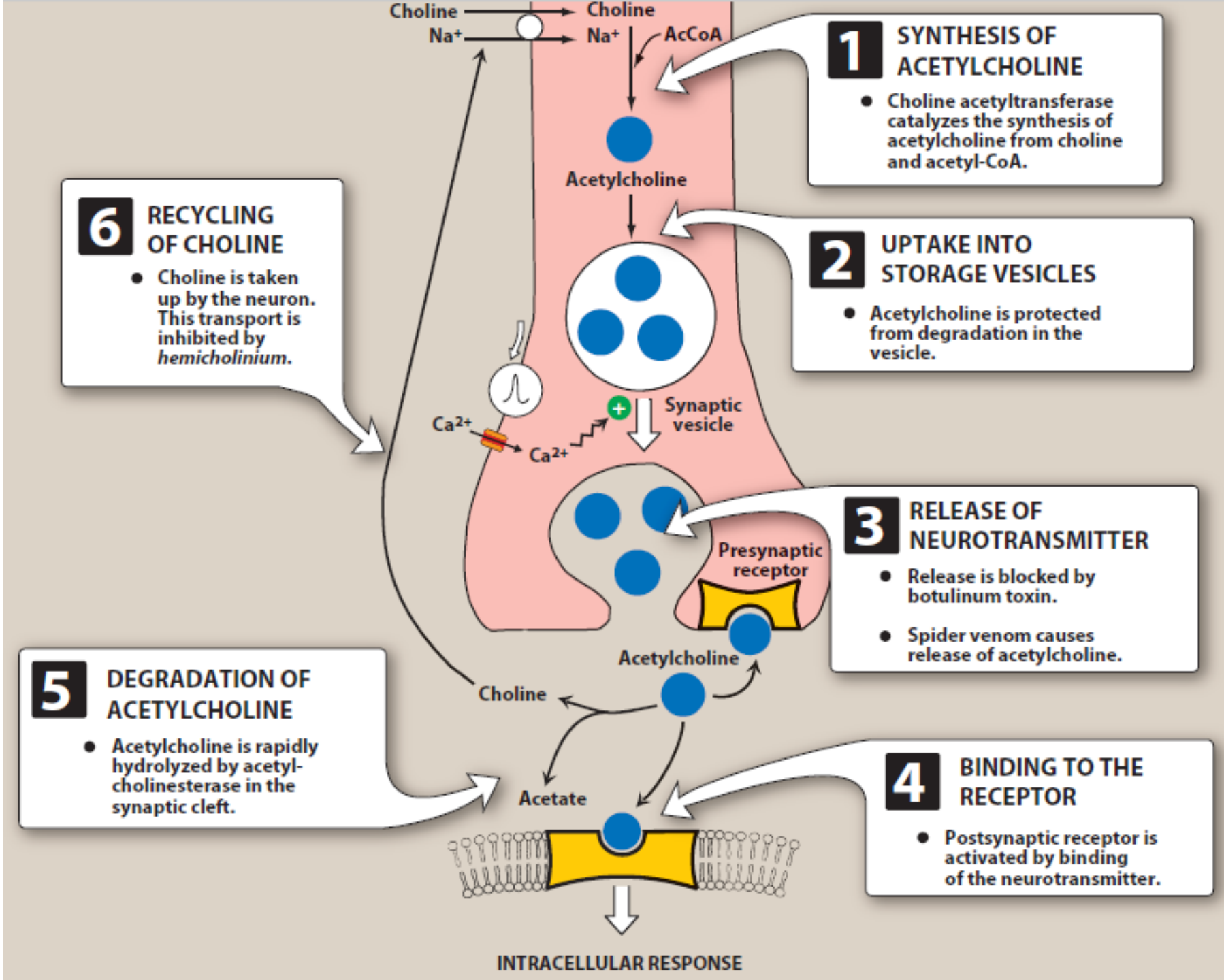
In addition, cholinergic neurons innervate the muscles of the **somatic system** and also play an important role in the central nervous system (CNS).

A. Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves six sequential steps:

1) synthesis,
2) storage,
3) release,
4) binding of ACh to a receptor,
5) degradation of the neurotransmitter in the synaptic cleft (that is, the space between the nerve endings and adjacent receptors located on nerves or effector organs), and
6) recycling of choline and acetate.

A. Neurotransmission at cholinergic nuerons



Synthesis and release of acetylcholine from the cholinergic neuron.
AcCoA = acetyl coenzyme A.

A. Neurotransmission at cholinergic neurons/ 1. Synthesis of acetylcholine:

Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system that cotransports sodium and can be inhibited by the drug **hemicholinium**.

Choline has a quaternary nitrogen and carries a permanent positive charge and, thus, cannot diffuse through the membrane.

The uptake of choline is the rate-limiting step in ACh synthesis.

Choline **acetyltransferase** catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol.

A. Neurotransmission at cholinergic neurons/ 2. Storage of acetylcholine in vesicles:

ACh is packaged and stored into presynaptic vesicles by an active transport process coupled to the efflux of protons.

The mature vesicle contains not only ACh but also adenosine triphosphate and proteoglycan.

Cotransmission from autonomic neurons is the rule rather than the exception.

This means that most synaptic vesicles contain the primary neurotransmitter (here, ACh) as well as a cotransmitter that increases or decreases the effect of the primary neurotransmitter.

A. Neurotransmission at cholinergic neurons/ 3. Release of acetylcholine:

When an action potential propagated by voltage-sensitive sodium channels arrives at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium.

Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of their contents into the synaptic space.

This release can be blocked by **botulinum toxin**.

In contrast, the toxin in black widow spider venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap.

A. Neurotransmission at cholinergic neurons/ 4. Binding to the receptor::

ACh released from the synaptic vesicles diffuses across the synaptic space and binds to postsynaptic receptors on the target cell, to presynaptic receptors on the membrane of the neuron that released the ACh, or to other targeted presynaptic receptors.

The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classes: muscarinic and nicotinic.

Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells, as mediated by second messenger molecules.

A. Neurotransmission at cholinergic neurons/ 5. Degradation of acetylcholine:

The signal at the postjunctional effector site is rapidly terminated, because acetylcholinesterase (AChE) cleaves ACh to choline and acetate in the synaptic cleft.

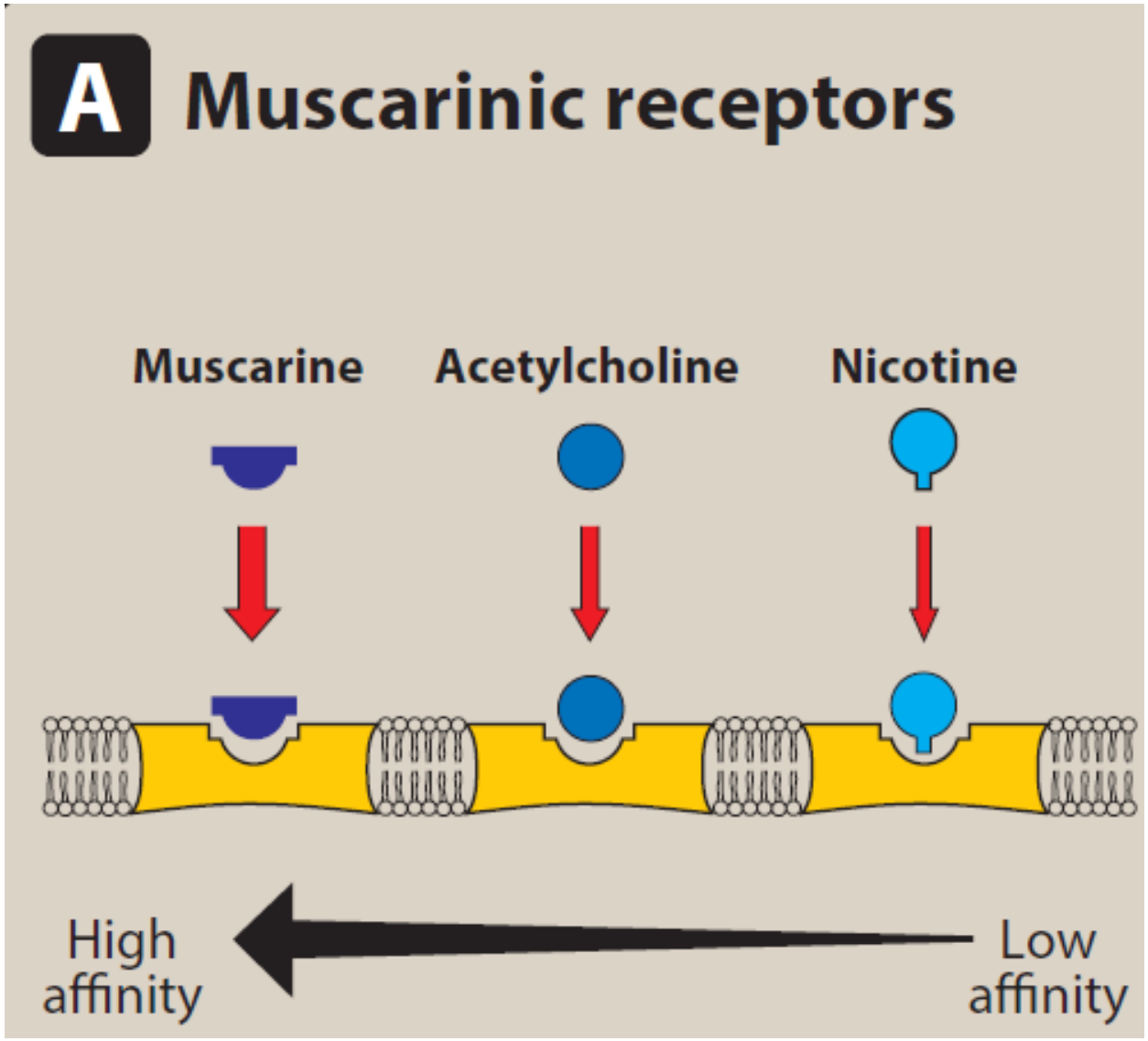
Butyrylcholinesterase, sometimes called **pseudocholinesterase**, is found in the plasma, but does not play a significant role in the termination of the effect of ACh in the synapse.

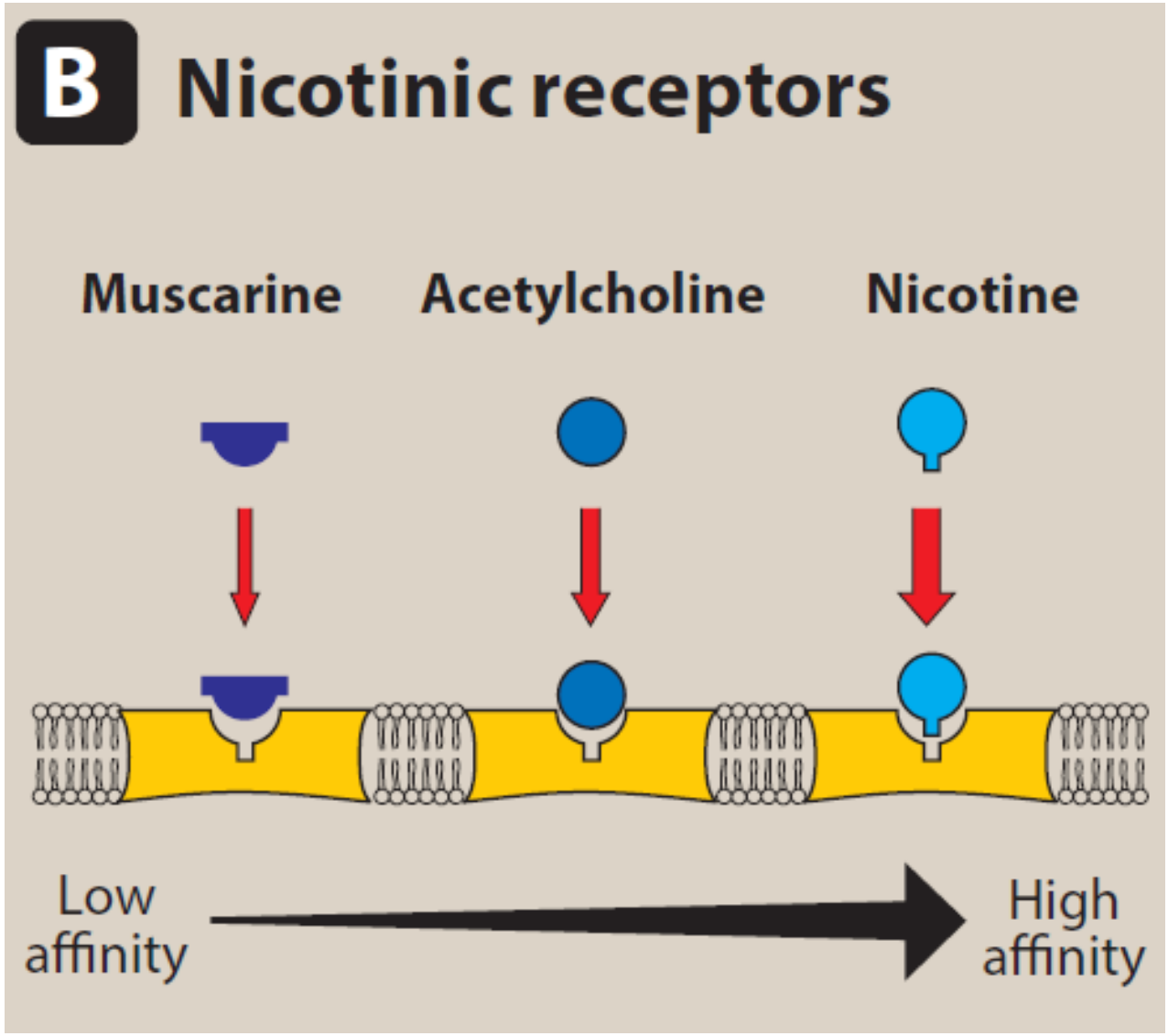
A. Neurotransmission at cholinergic neurons/ 6. Recycling of choline:

Choline may be recaptured by a sodium coupled, high-affinity uptake system that transports the molecule back into the neuron.

There, it is acetylated into ACh that is stored until released by a subsequent action potential.

CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)

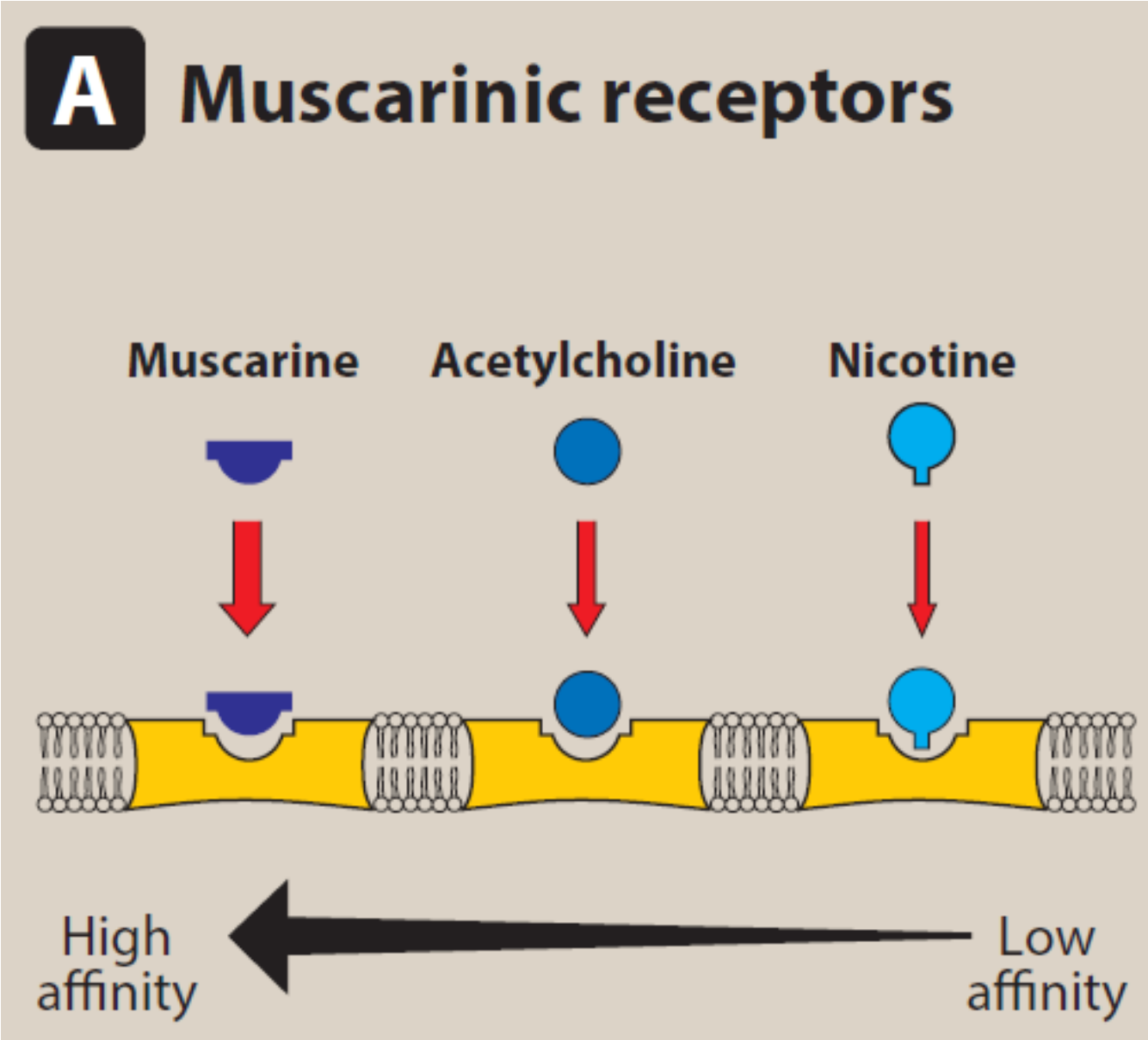




CHOLINERGIC RECEPTORS (CHOLINOCEPTORS)/ A. Muscarinic receptors

Muscarinic receptors belong to the class of G protein–coupled receptors (metabotropic receptors). These receptors, in addition to binding ACh, also recognize **muscarine**, an alkaloid that is present in certain poisonous mushrooms.

There are five subclasses of muscarinic receptors. However, only **M1, M2, and M3** receptors have been functionally characterized.



A. Muscarinic receptors/ 1. Locations of muscarinic receptors:

These receptors are found on ganglia of the peripheral nervous system and on the autonomic effector organs, such as the heart, smooth muscle, brain, and exocrine glands.

Although all five subtypes are found on neurons, M1 receptors are also found on gastric parietal cells, M2 receptors on cardiac cells and smooth muscle, and M3 receptors on the bladder, exocrine glands, and smooth muscle.

Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration, they may show some activity at nicotinic receptors.

A. Muscarinic receptors/ 2. Mechanisms of acetylcholine signal transduction:

When **M1 or M3** receptors are activated, the receptor undergoes a conformational change and interacts with a **G protein**, designated Gq, that in turn activates **phospholipase C**.

This ultimately leads to the production of the second messengers inositol-1,4,5-trisphosphate (**IP3**) and diacylglycerol (**DAG**). IP3 causes an increase in intracellular Ca2+.

Calcium can then interact to stimulate or inhibit enzymes or to cause hyperpolarization, secretion, or contraction.

Diacylglycerol activates protein kinase C, an enzyme that phosphorylates numerous proteins within the cell.

In contrast, activation of the **M2** subtype on the cardiac muscle stimulates a **G protein**, designated **Gi**, that inhibits adenylyl cyclase and increases K+ conductance.

A. Muscarinic receptors/ 3. Muscarinic agonists:

Pilocarpine is an example of a nonselective muscarinic agonist used in clinical practice to treat **xerostomia and glaucoma**. Attempts are currently underway to develop muscarinic agonists and antagonists that are directed against specific receptor subtypes.

M1 receptor agonists are being investigated for the treatment of Alzheimer's disease and M3 receptor antagonists for the treatment of chronic obstructive pulmonary disease.

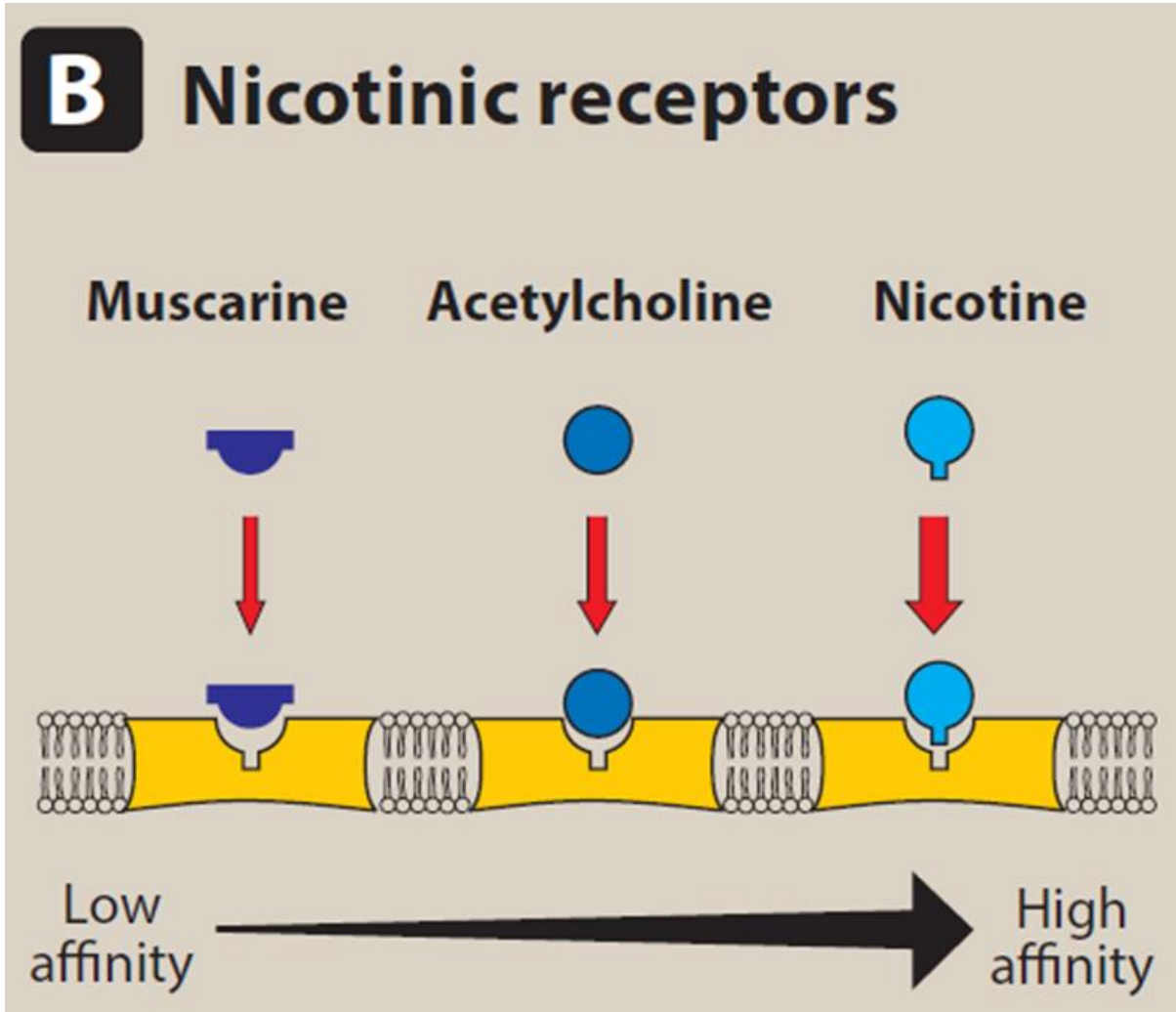
[Note: At present, no clinically important agents interact solely with the M4 and M5 receptors.]

B. Nicotinic receptors

These receptors, in addition to binding ACh, also recognize **nicotine** but show only a weak affinity for muscarine.

The nicotinic receptor is composed of five subunits, and it functions as a ligand-gated ion channel. Binding of two ACh molecules elicits a conformational change that allows the entry of **sodium ions**, resulting in the depolarization of the effector cell.

Nicotine at low concentration stimulates the receptor, whereas nicotine at high concentration blocks the receptor.



B. Nicotinic receptors

Nicotinic receptors are located in the CNS, the adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ) in skeletal muscles.

Those at the NMJ are sometimes designated NM, and the others, NN.

The nicotinic receptors of autonomic ganglia differ from those of the NMJ.

For example, **ganglionic receptors** are selectively blocked by **mecamylamine**, whereas **NMJ** receptors are specifically blocked by **atracurium**.

DIRECT-ACTING CHOLINERGIC AGONISTS

These agents may be broadly classified into two groups:

1) endogenous choline esters, which include Ach and synthetic esters of choline, such as carbachol and bethanechol, and

2) naturally occurring alkaloids, such as nicotine and pilocarpine.

All of the direct-acting cholinergic drugs have a longer duration of action than Ach

The more therapeutically useful drugs (**pilocarpine and bethanechol**) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents.

[Note: Muscarinic receptors are located primarily, but not exclusively, at the neuroeffector junction of the parasympathetic nervous system.]

However, as a group, the direct-acting agonists show little specificity in their actions, which limits their clinical usefulness,

DIRECT-ACTING CHOLINERGIC AGONISTS/ A. Acetylcholine

Acetylcholine is a **quaternary ammonium** compound that cannot penetrate membranes.

Although it is the neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance.

ACh has both muscarinic and nicotinic activity. Its actions include the following:

1. Decrease in heart rate and cardiac output: The actions of ACh on the heart mimic the effects of vagal stimulation. For example, if injected intravenously, ACh produces a brief decrease in cardiac rate (**negative chronotropy**) and stroke volume as a result of a reduction in the rate of firing at the sinoatrial (SA) node.

DIRECT-ACTING CHOLINERGIC AGONISTS/ A. Acetylcholine

2. Decrease in blood pressure: Injection of ACh causes **vasodilation** and lowering of blood pressure by an indirect mechanism of action.

ACh activates **M3** receptors found on endothelial cells lining the smooth muscles of blood vessels.

This results in the production of **nitric oxide** from arginine. Nitric oxide then diffuses to vascular smooth muscle cells to stimulate protein kinase G production, leading to **hyperpolarization** and smooth muscle relaxation via phosphodiesterase-3 inhibition.

In the absence of administered cholinergic agents, the vascular cholinergic receptors have no known function, because ACh is never released into the blood in significant quantities.

Atropine blocks these muscarinic receptors and prevents ACh from producing vasodilation.

DIRECT-ACTING CHOLINERGIC AGONISTS/ A. Acetylcholine

3. Other actions: In the gastrointestinal (**GI) tract**, acetylcholine increases salivary secretion and stimulates intestinal secretions and motility.

It also enhances **bronchiolar** secretions.

In the genitourinary tract, ACh increases the tone of the detrusor muscle, causing **urination**.

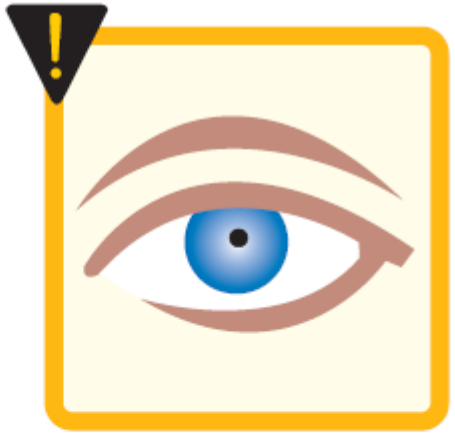
In the eye, ACh is involved in stimulation of ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing **miosis** (marked constriction of the pupil).

ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery.

DIRECT-ACTING CHOLINERGIC AGONISTS/ A. Acetylcholine

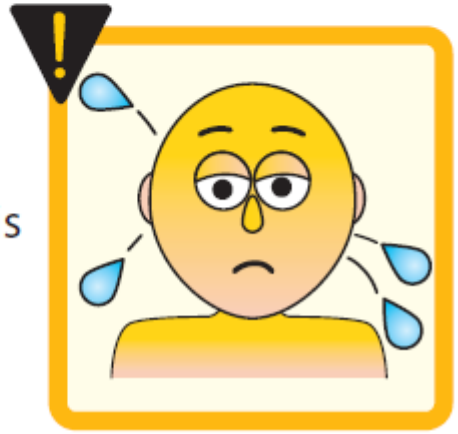
Diarrhea

Miosis



Urinary urgency

Diaphoresis



Nausea

Some adverse effects observed with cholinergic agonists.