Cholinergic Agonists

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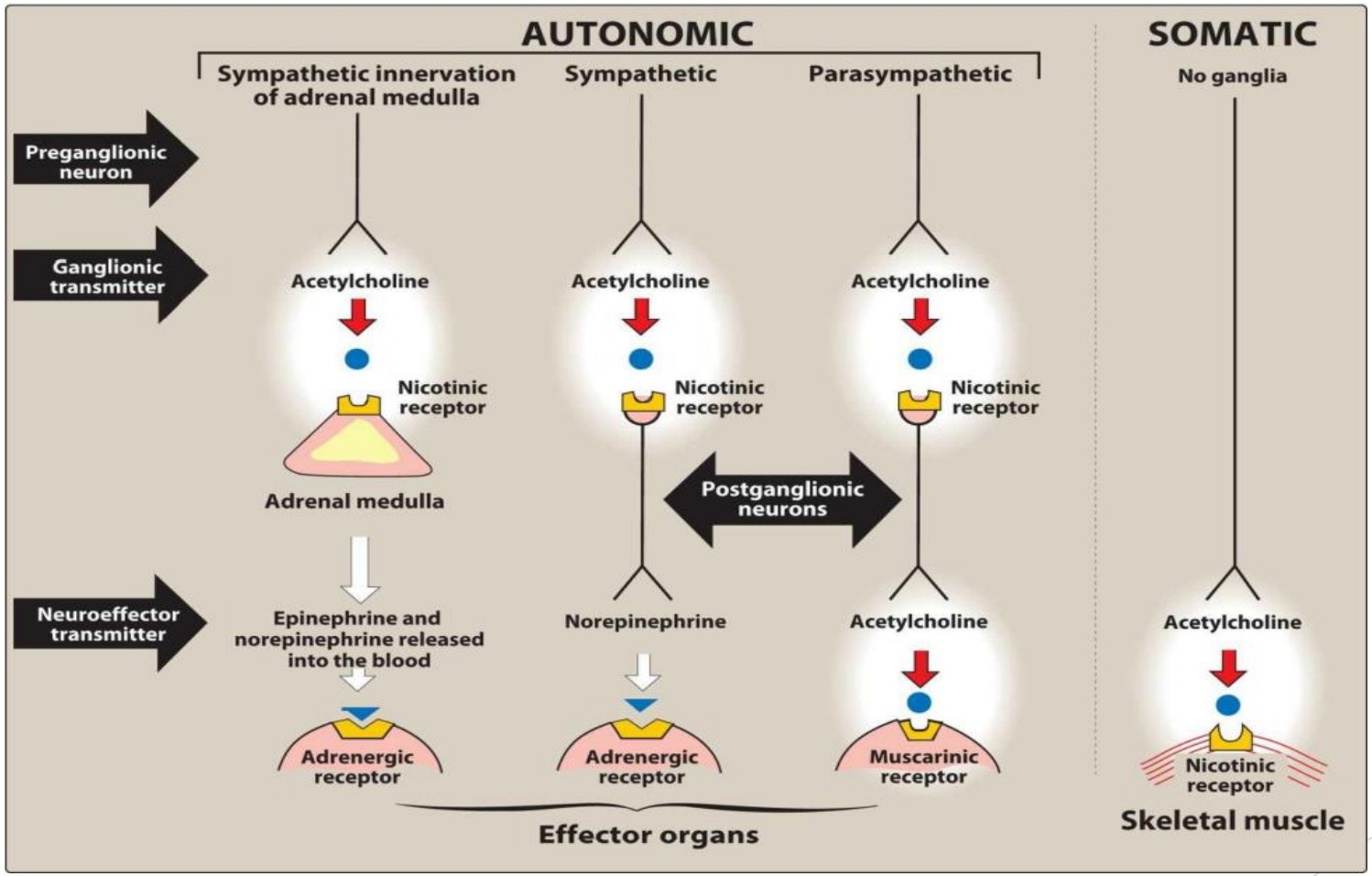
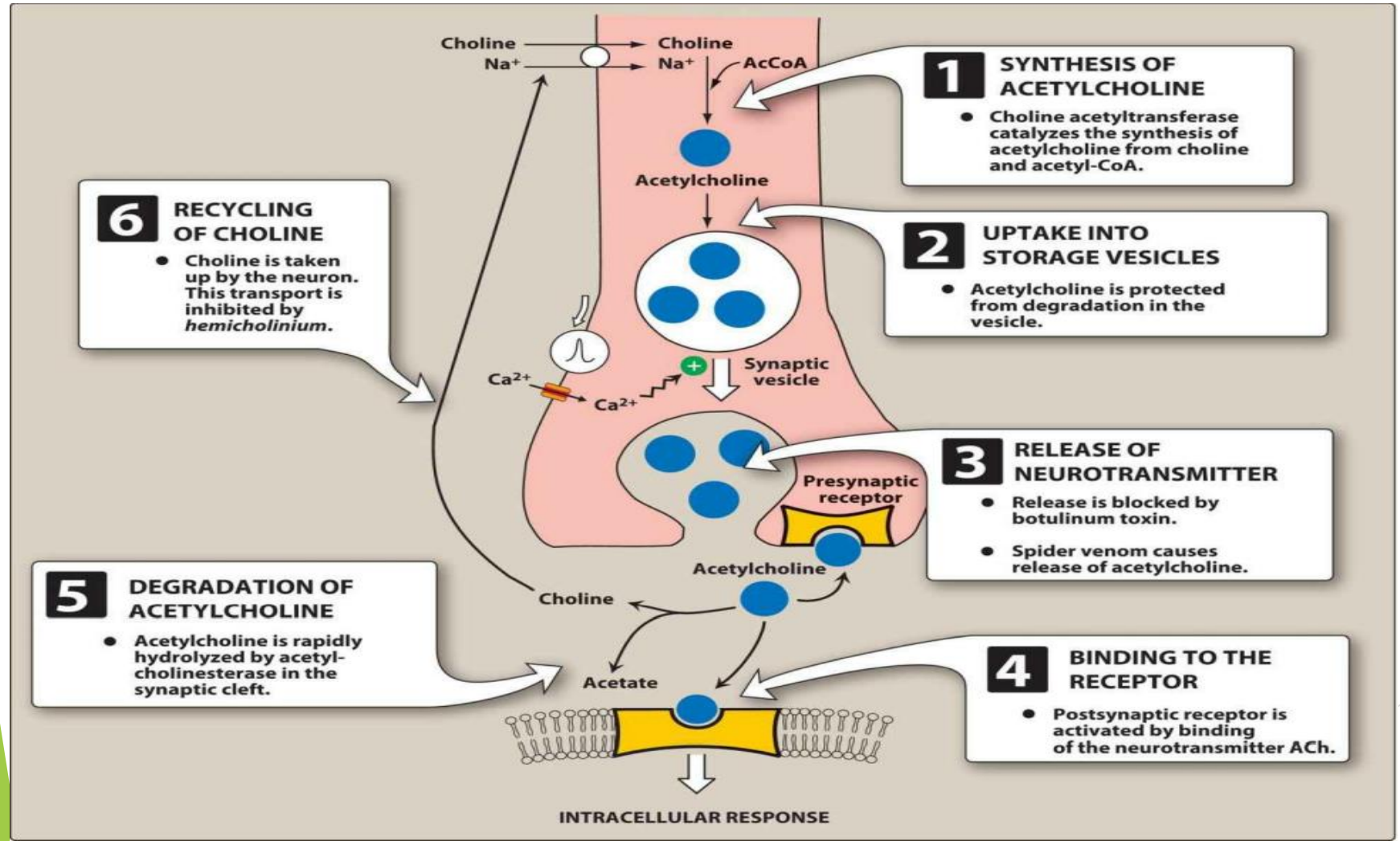
The Cholinergic Neuron

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



A. Neurotransmission at cholinergic neurons

Neurotransmission in cholinergic neurons involves six sequential steps: 1) synthesis of ACh, 2) storage, 3) release, 4) binding of ACh to the receptor, 5) degradation of ACh in the synaptic cleft and 6) recycling of choline



Cholinergic Receptors (Cholinoceptors)

- Two families of cholinoceptors, designated muscarinic and nicotinic receptors, can be distinguished from each other on the basis of their different affinities for agents that mimic the action of Ach

A. Muscarinic receptors : These receptors binding to Ach.

- the muscarinic receptors show only a weak affinity for nicotine.

***** Location of muscarinic receptors

- M1 receptors are also found on gastric parietal cells
- M2 receptors on cardiac cells and smooth muscle
- M3 receptors on the bladder, exocrine glands, and smooth muscle.

B. Nicotinic receptors

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

Direct-Acting Cholinergic Agonists

A. **Acetylcholine** :it lacks therapeutic importance because of its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases.

ACTION :

1. Decrease in heart rate and cardiac output
2. In the gastrointestinal (GI) tract, acetylcholine increases salivary secretion, increases gastric acid secretion, and stimulates intestinal secretions and motility
3. It also enhances bronchiolar secretions and causes bronchoconstriction
4. marked constriction of the pupil
5. ACh increases the tone of the detrusor muscle, causing urination.

DIRECT ACTING	
Acetylcholine	MIOCHOL-E
Bethanechol	URECHOLINE
Carbachol	MIOSTAT, ISOPTO CARBACHOL
Cevimeline	EVOXAC
Methacholine	PROVOCHOLINE
Nicotine	NICORETTE
Pilocarpine	SALAGEN, ISOPTO CARPINE

B. Bethanechol

Therapeutic uses : In urologic treatment, bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention.

Adverse effects :sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, Miosis , and bronchospasm.

***Atropine sulfate may be administered to overcome severe cardiovascular or bronchoconstrictor responses to this agent.

C. Carbachol (carbamylcholine)

THERAPEUTIC USES : carbachol is rarely used. Intraocular use provides miosis for eye surgery and lowers intraocular pressure in the treatment of glaucoma.

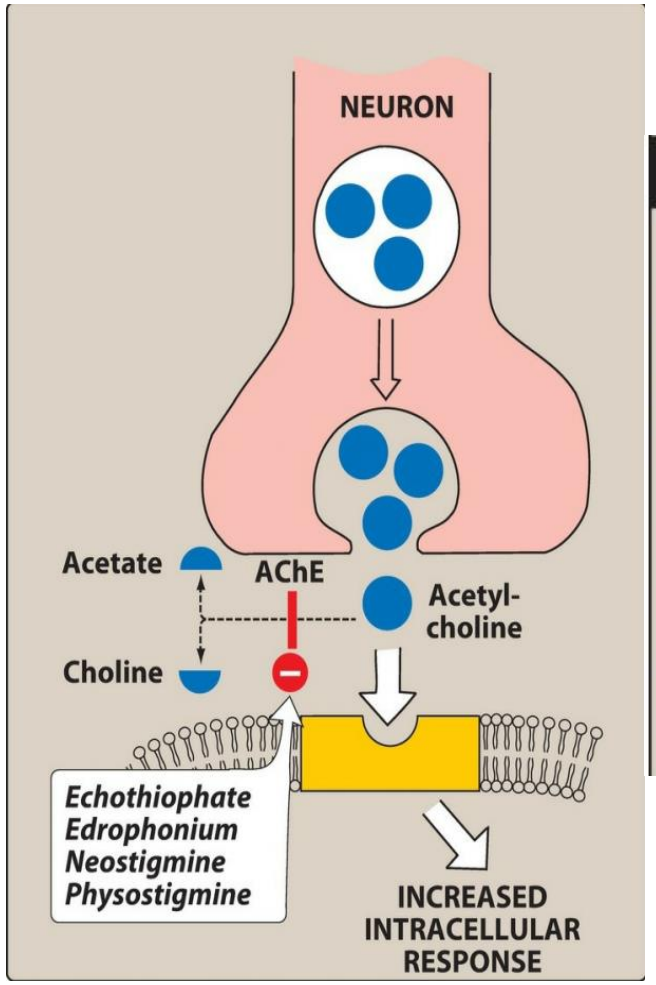
Adverse effects : With ophthalmologic use, few adverse effects occur due to lack of systemic penetration

D. Pilocarpine

* Therapeutic uses Pilocarpine is used to treat glaucoma

* Adverse effects Pilocarpine can cause blurred vision, night blindness,

Indirect-Acting Cholinergic Agonists: Anticholinesterase Agents (Reversible)



INDIRECT ACTING (reversible)

Donepezil ARICEPT
Edrophonium ENLON
Galantamine RAZADYNE
Neostigmine BLOXIVERZ
Physostigmine GENERIC ONLY
Pyridostigmine MESTINON
Rivastigmine EXELON

A. Edrophonium

It is used in the diagnosis of myasthenia gravis, an autoimmune disease

B. Physostigmine

*Therapeutic uses Physostigmine is used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine

*Adverse effects High doses of physostigmine may lead to convulsions. Bradycardia and a fall in cardiac output may also occur. Inhibition of AChE at the NMJ causes the accumulation of ACh and, ultimately through continuous depolarization, results in paralysis of skeletal muscle

C. Neostigmine

* Therapeutic uses It is used to stimulate the bladder and GI tract and e is also used to manage symptoms of myasthenia gravis.

* Adverse effects of neostigmine include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm.

D. Pyridostigmine

*Use in the chronic management of myasthenia gravis.

E. Tacrine, donepezil, rivastigmine, and galantamine

Use to delay the progression of Alzheimer disease

Indirect-Acting Cholinergic Agonists: Anticholinesterase Agents (Irreversible)

- A number of synthetic organophosphate compounds have the ability to bind covalently to AChE. The result is a long-lasting increase in ACh at all sites where it is released
- parathion and malathion, are used as insecticides.
- Echothiophate :Therapeutic uses A topical ophthalmic solution of the drug is available for the treatment of open-angle glaucoma.

INDIRECT ACTING (irreversible)
Echothiophate PHOSPHOLINE IODIDE