Kerbala University
College of Pharmacy
Dep. of Pharmaceutical Chemistry
Organic Pharmaceutical Chemistry II

By:

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Why to study medicinal chemistry?

Medicinal chemistry and/or pharmaceutical chemistry is a discipline of chemistry, especially synthetic organic chemistry, and pharmacology and various other biological specialties, where they are involved with *design, chemical synthesis, and development of pharmaceutical agents*.

Cholinergic Drugs and Related Agents

O V E R V I E W

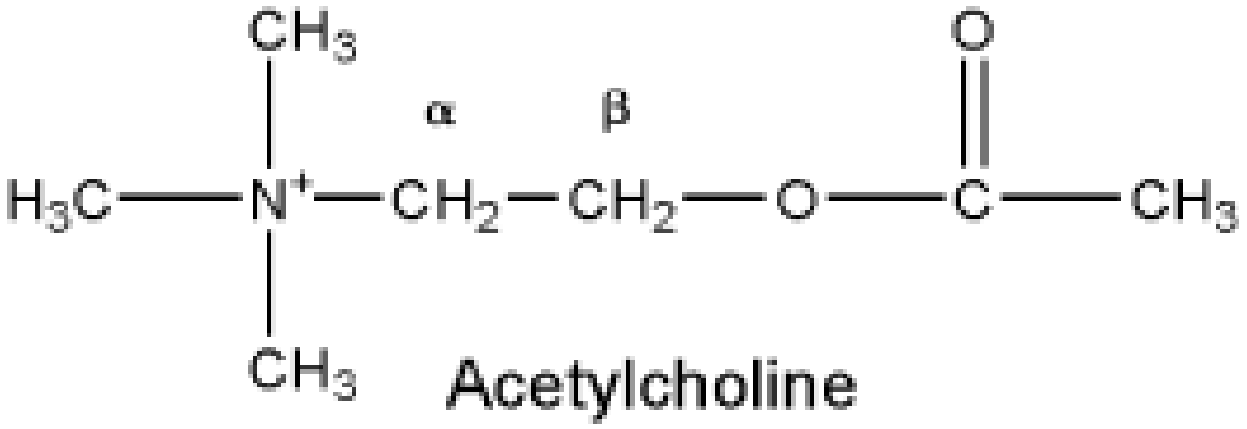
- ACh was first studied in the frog heart in 1921.
- The regularity role of autonomic NS.
- How important is the ACh in the human physiology.
- Trials to create ACh agonists and antagonists.
- Treatment of certain diseases like Alzheimer, Parkinson, and novelty of overactive bladder.
- How to be a “good pharmacist” regarding medicinal chemistry?

Drugs that mimic the action of ACh do so either by:

- Acting directly on the cholinergic receptors in the tissue.
- Inhibiting acetylcholinesterase.

Chemicals that bind or compete with ACh for binding to the receptor MAY block cholinergic neurotransmission.

- What is the difference between the parasympathomimetic and parasympatholytic drugs?



Acetylcholine

CHOLINERGIC RECEPTORS

There are two distinct receptor types for ACh those differ in:

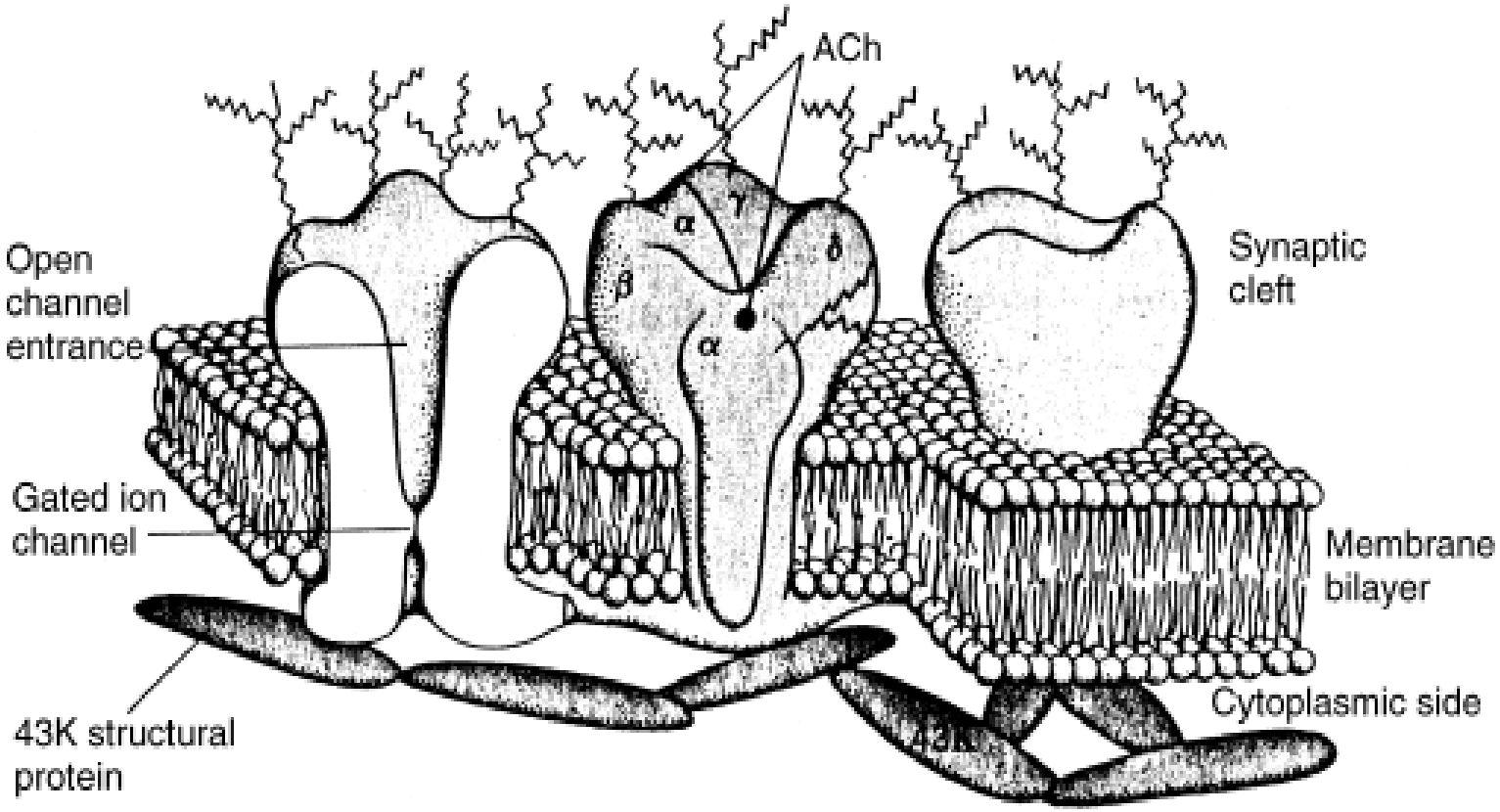
- composition, location, and pharmacological function and have specific agonists and antagonists.

CHOLINERGIC RECEPTORS

- Nicotinic and muscarinic receptors…. Why these names?

❖Nicotinic receptor:

- Is called “gated ion channel” …. Why?

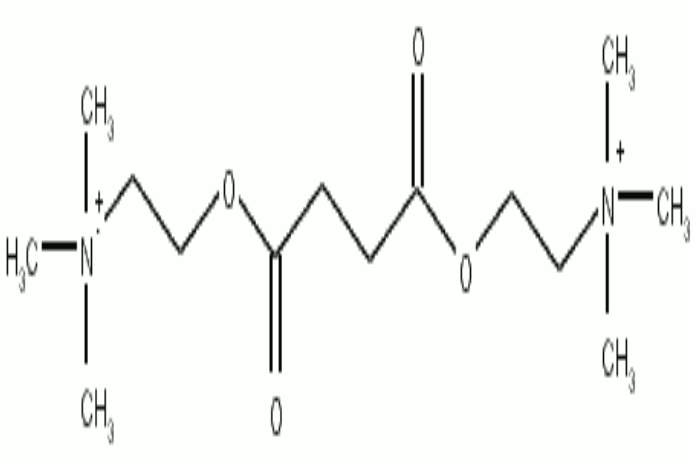

ACh
α
γ
δ
β
α
Open
channel
entrance
Synaptic
cleft
Gated ion
channel
Membrane
bilayer
Cytoplasmic side
43K structural
protein

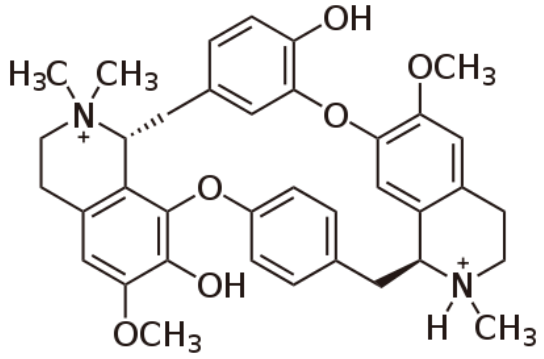
NICOTINIC RECEPTOR SUBTYPES

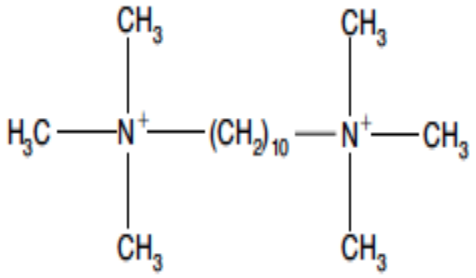
- Nicotinic receptors located in the neuromuscular junction differ from those on neurons, such as those in the CNS and autonomic ganglia, in that they have different ligand criteria.

Nicotinic receptors at the neuromuscular junction (N1)

- Are blocked by succinylcholine, d-tubocurarine, and decamethonium.



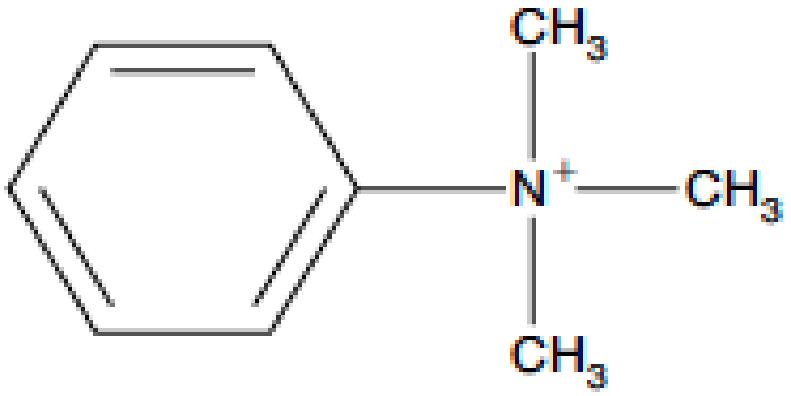




Decamethonium

Nicotinic receptors at the neuromuscular junction (N1)

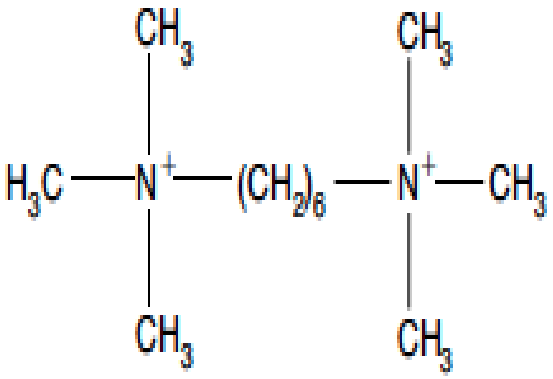
- Are stimulated by phenyltrimethylammonium.



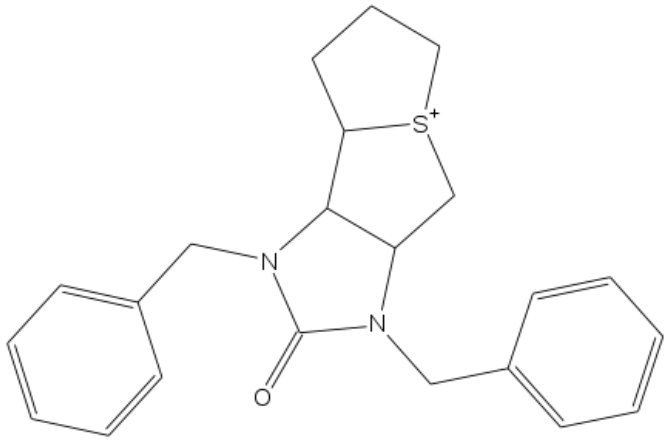
Phenyltrimethylammonium

Nicotinic receptors at the autonomic ganglia (N2).

- blocked by hexamethonium and trimethaphan.

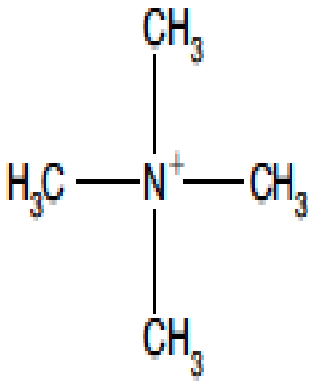


Hexamethonium

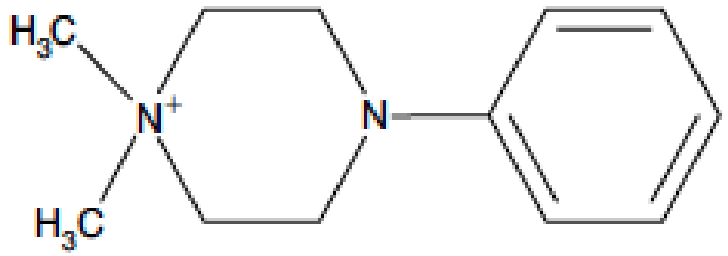


Nicotinic receptors at the autonomic ganglia (N2).

- Stimulated by tetramethylammonium and dimethyl-4-phenylpiperazinium (DMPP).



Tetramethylammonium



DMPP

Muscarinic Receptors

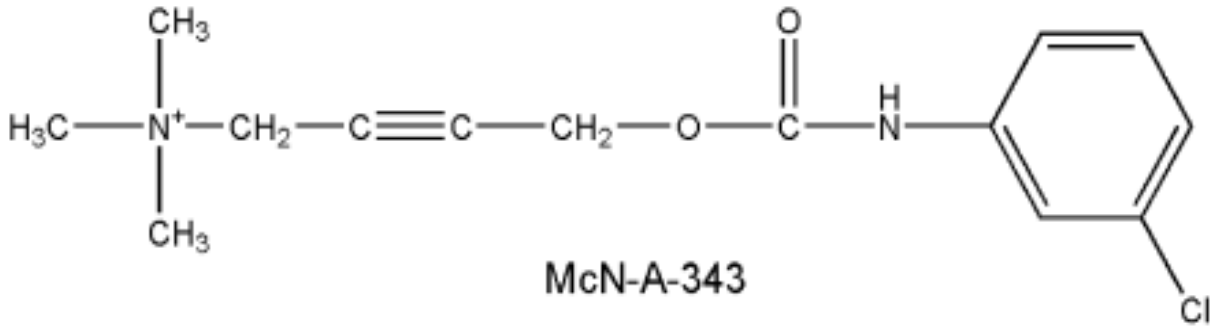
- Effects of ACh on the innervated organs? i.e. lungs, heart, smooth muscles, salivary glands…. Etc.
- Muscarinic receptors may perform their effects via activating (GTP)-binding proteins (G proteins).

MUSCARINIC RECEPTOR SUBTYPES

- According to pharmacological and biochemical studies the muscarinic receptors are assigned M_1 to M_5 and m_1 to m_5 respectively.

M_1 receptors

- E.g. M_1 receptors mediate gastric secretion.
- McN-A343 is a selective agonist (M_1 and M_4).
- Pirenzepine HCl acts as an antagonist and has been used for the treatment of PU disease.



McN-A-343

M_2 receptors

- M_2 receptors mediate a decrease in the strength and rate of cardiac muscle contraction.
- M_2 receptors:

➢ Activate K-channels to cause hyperpolarization of cardiac cells.

➢ Inhibit G-protein and thus reduce cAMP.

➢ Act as “autoreceptors “on presynaptic terminals of postganglionic cholinergic nerves to inhibit ACh release... What about asthmatic patients?

- M_2 receptors are recognized by their high affinity for methoctramine.

M_3 Receptors

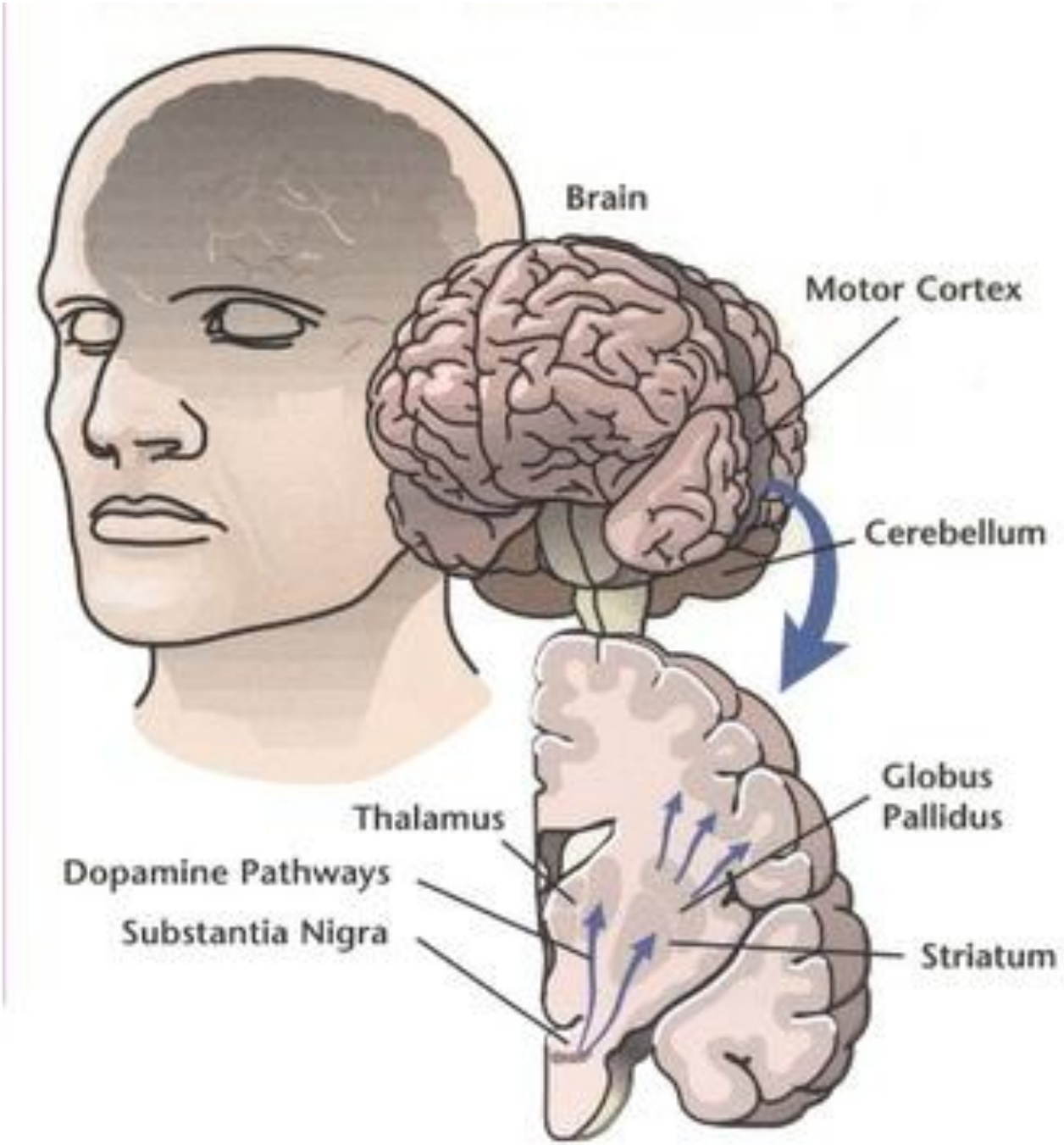
- M_3 receptors, defined as glandular muscarinic receptors, are located in exocrine glands and smooth muscle.
- M_3 effect is mostly stimulatory.
- Glandular secretions from lacrimal, salivary, bronchial, pancreatic, and mucosal cells in the GI tract are characteristic of M_3 receptor activation.
- Contraction of visceral smooth muscle is also a result of M_3 receptor stimulation.

M_4 Receptors

- Similar to M_2 receptors, act through G-protein to inhibit adenylate cyclase.
- When stimulated, M_4 receptors have a regulatory mechanism in the trachea

M_5 Receptors

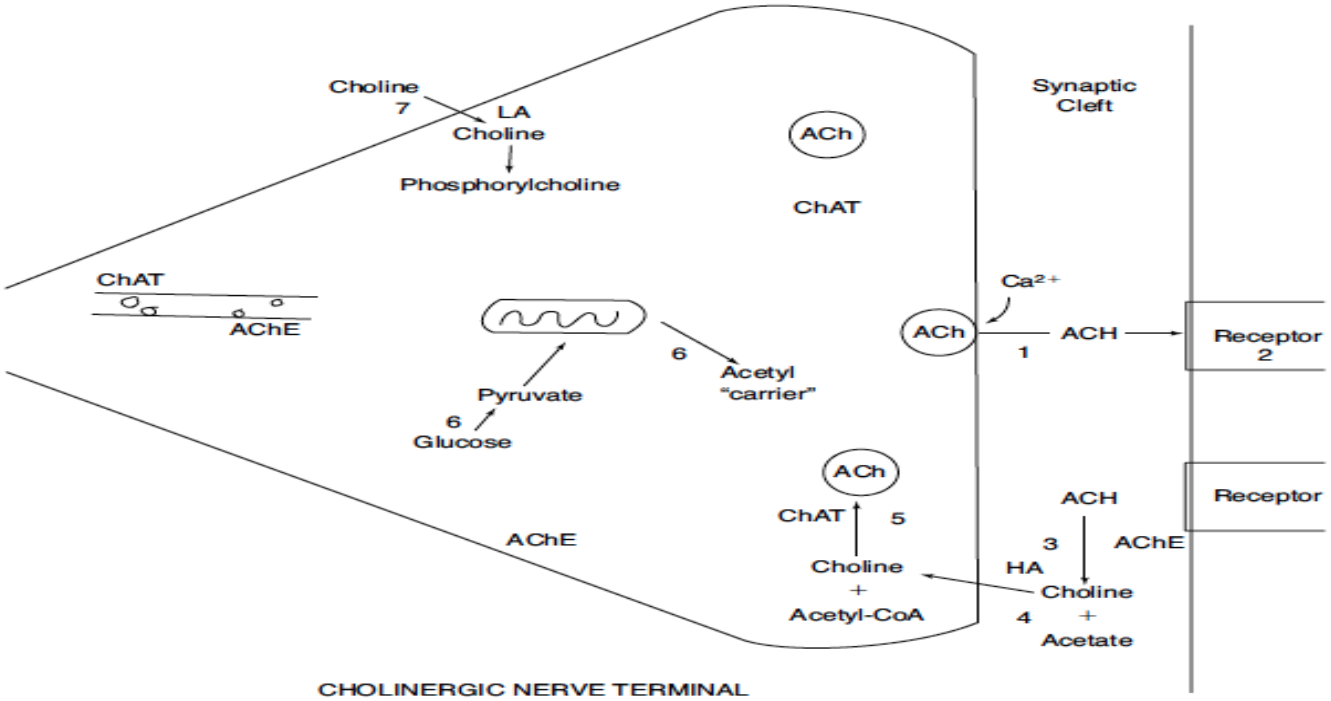
- A great attention to study the M_5 receptor was performed because it has been thought that M_5 receptors may regulate dopamine release at terminals within the striatum.
- This was due to the presence of the (mRNA) in the substantia nigra.


Brain
Motor Cortex
Cerebellum
Globus
Pallidus
Thalamus
Dopamine Pathways
Substantia Nigra
Striatum

CHOLINERGIC NEUROCHEMISTRY

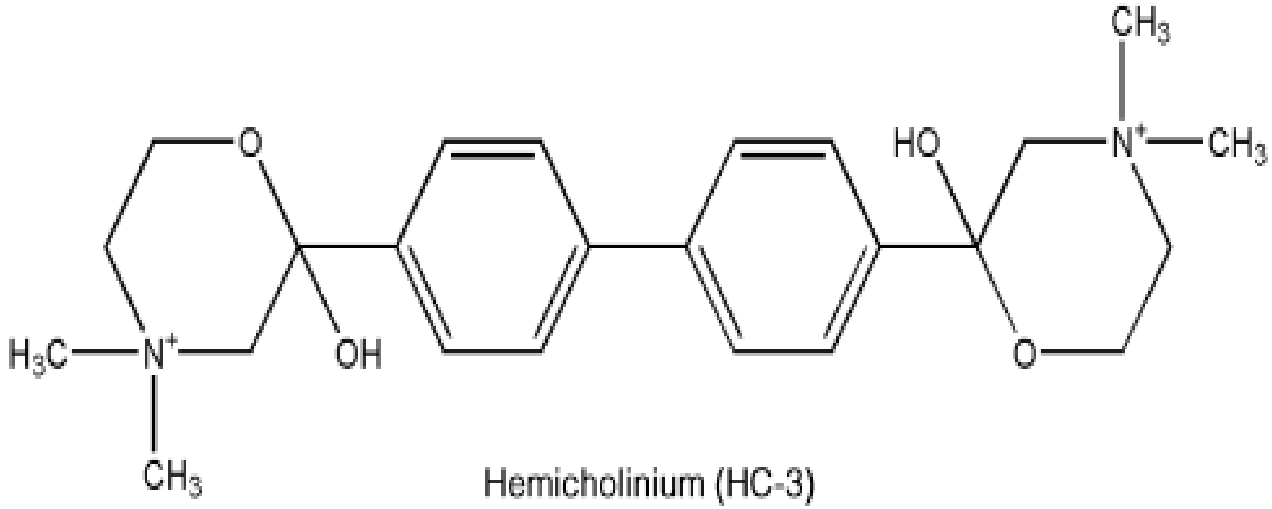
- Cholinergic neurons synthesize, store, and release ACh.
- The neurons also form choline-acetyltransferase (ChAT) and AChE (what is the difference?).

ACh is prepared in the nerve ending by the transfer of an acetyl group from acetyl-coenzyme A (CoA) to choline. The reaction is catalyzed by ChAT. Cell fractionation studies show that much of the ACh is contained in synaptic vesicles in the nerve ending but that some is also free in the cytosol. Choline is the limiting substrate for the synthesis of ACh. Most choline for ACh synthesis comes from the hydrolysis of ACh in the synapse. Choline is recaptured by the presynaptic terminal as part of a high-affinity uptake system under the influence of sodium ions to synthesize ACh.

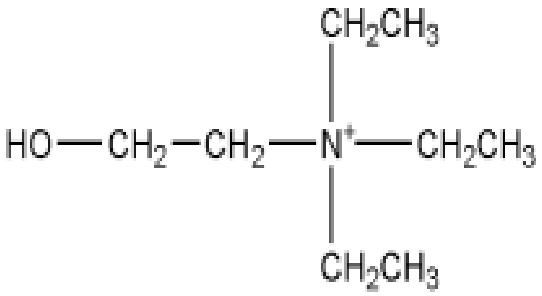


CHOLINERGIC NERVE TERMINAL

Several quaternary ammonium bases act as competitive inhibitors of choline uptake. **Why?** Hemicholinium (HC-3), and the triethyl analog of choline (2-hydroxyethyltriethylammonium) act at the presynaptic membrane to inhibit the high-affinity uptake of choline into the neuron. These compounds cause a delayed paralysis at repetitively activated cholinergic synapses and can produce respiratory paralysis in test animals. The delayed block is caused by the depletion of stored ACh, which may be reversed by choline.

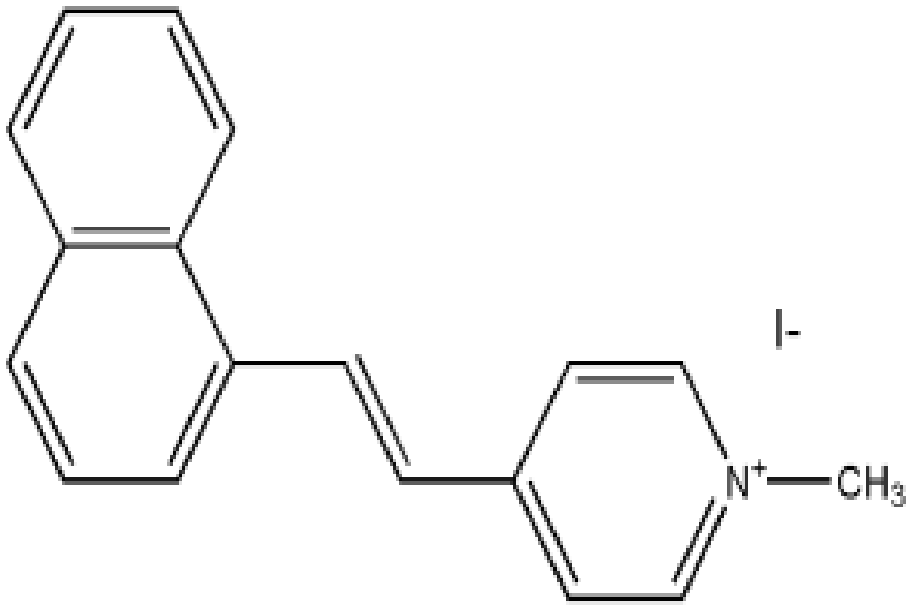


Hemicholinium (HC-3)



2-Hydroxethyltriethylammonium

- The synthesis of ACh from choline and acetyl-CoA is catalyzed by ChAT.
- ChAT is inhibited in vitro by trans-N- methyl-4-(1-naphthylvinyl) pyridinium iodide.



trans-N-Methyl-4-(1-napthylvinyl)pyridinium iodide

Any question?

References:

- Wilson and Gisvold's Textbook of Organic Medicinal And Pharmaceutical Chemistry, 12th Edition.