Organic pharmaceutical chemistry II

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Textbook of Organic medicinal and pharmaceutical chemistry

Wilson and Gisvold's

Nervous system

PNS
includes neurons located out side the brain and spinal cord that is, any nerves that enter or leave the CNS

Efferent portion
whose neurons carry signals away from the brain and spinal cord to the peripheral tissues

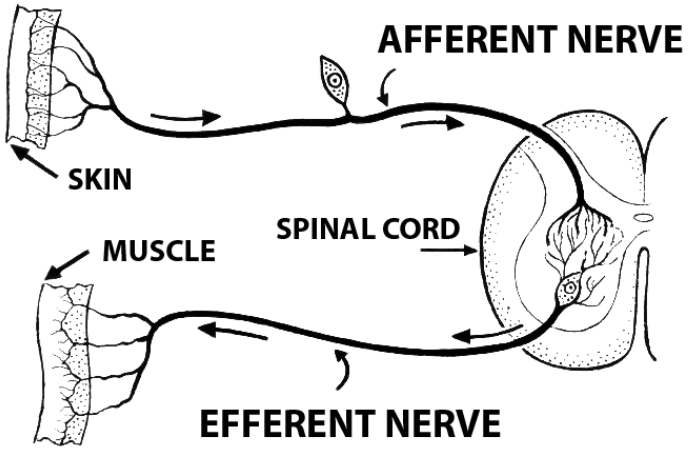
Afferent portion
whose neurons bring information from the peripheral to the CNS

CNS

Brain

Spinal cord

includes the nerves in the brain and spinal cord



(motor nerves)

PNS
Efferent portion

autonomic nervous system (ANS)
This system functions involuntarily to requlate the everyday needs and requirements of the body without the conscious participation of the mind, (regulate the activities of smooth muscle and glandular secretion), such as cotrol of respiration, circulation,digestion, body temperature, metabolism, cardic regulation.

Somatic system
This system functions voluntarily controlled function such as contraction of the skeletal muscles in locomotion

sensory (afferent) nerve

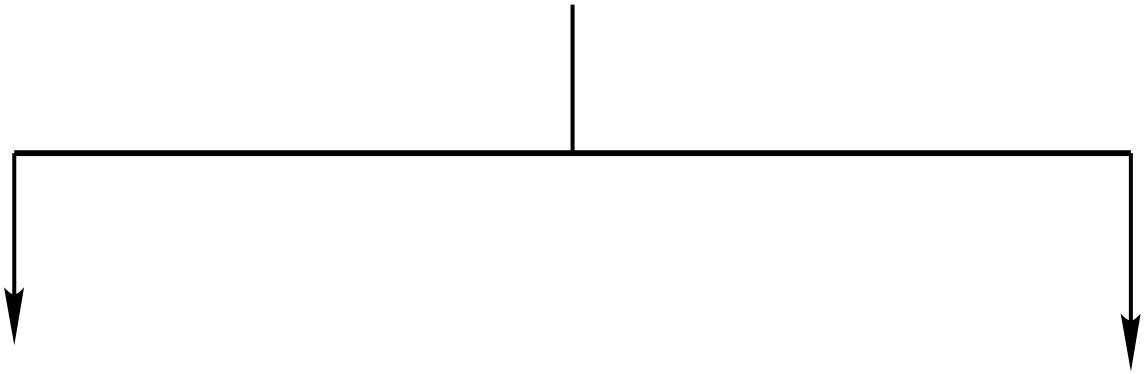
motor (efferent) nerve
The morot nerves arise from the spinal cord and project uninterrupted throughout the body to all skeletal muscle. ACh mediates transmission of impulses from the motor nerve to skeletal muscle (i.e.. neuromuscular junction).

sympathetic neurons
The sympathetic nervous system's primary process is to stimulate the body's fight-or-flight response

Parasympathetic neurons
it is responsible for stimulation of "rest-and-digest" or "feed and breed activities that occur when the body is at rest, especially after eating, including sexual arousal, salivation, lacrimation (tears), urination, digestion and defecation

ACh serves as a neurotransmitter at both sympathetic and parasympathetic preganglionic nerve endings, postganglionic nerve fibers in the parasympathetic division, and some postganglionic fibers (e.g.. salivary and sweat glands) in the sympathetic division of the autonomic nervous system.

Drugs act on the autonomic system



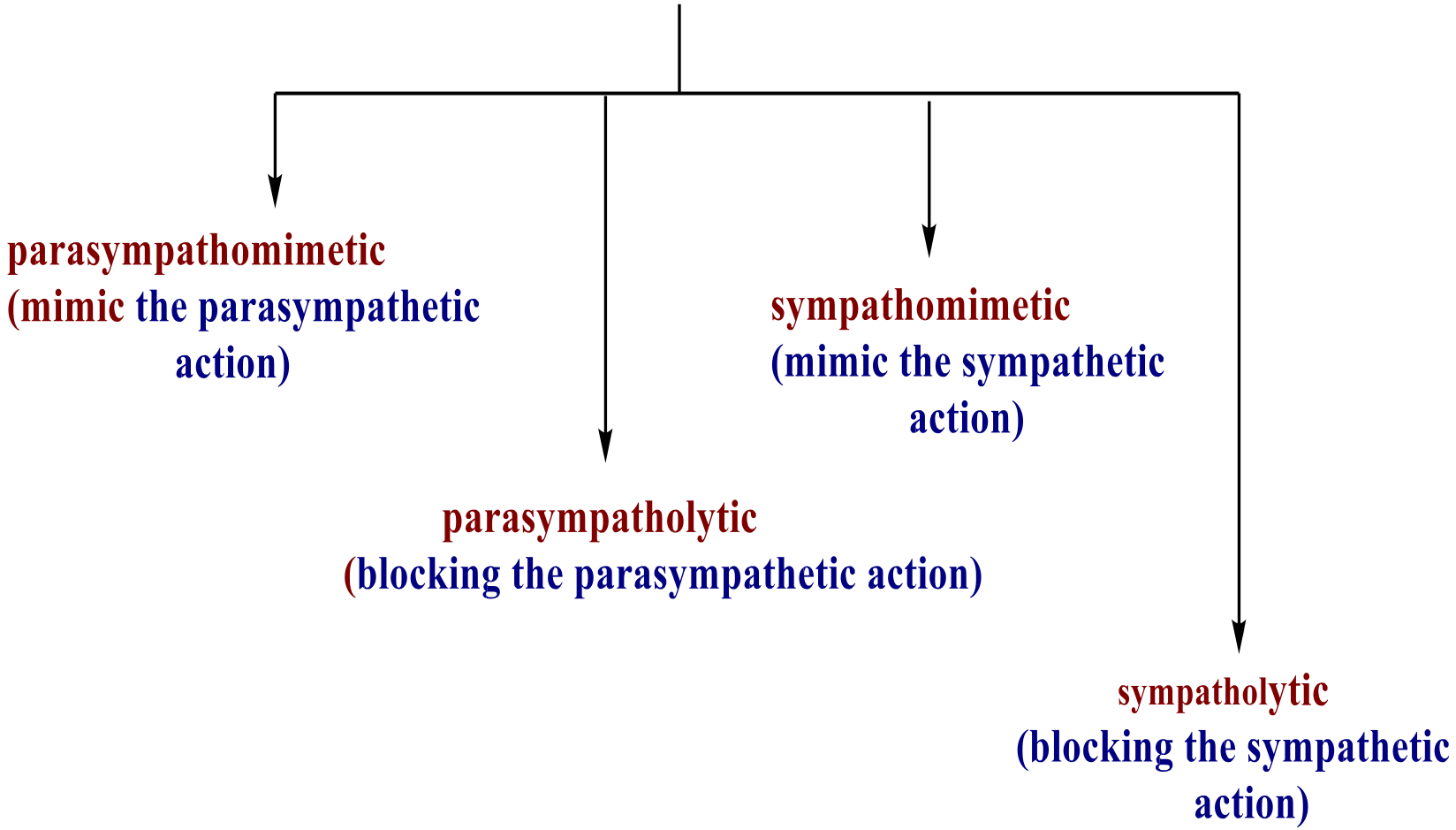
Adrenergic agent

for those postganglionic sympathetic fiber that release of norepinephrine and epinephrine

Cholinergic agent

for the remaining fibers in the autonomic nervous system and the motor fibers of the somatic nerve that release of acetylcholine

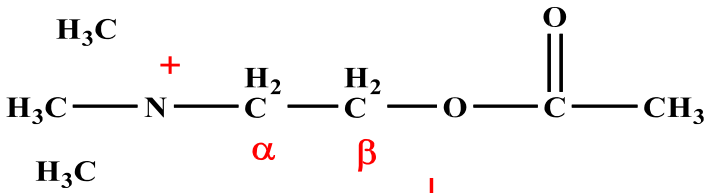
Classifiation of drugs acting on the nervous system



Cholinergic agents: - **are drugs and chemicals that act on cholinergic nerves or the tissues they innervate to either mimic or block the action of ACh.**

Cholinergic agent

Drugs that mimic the action of ACh

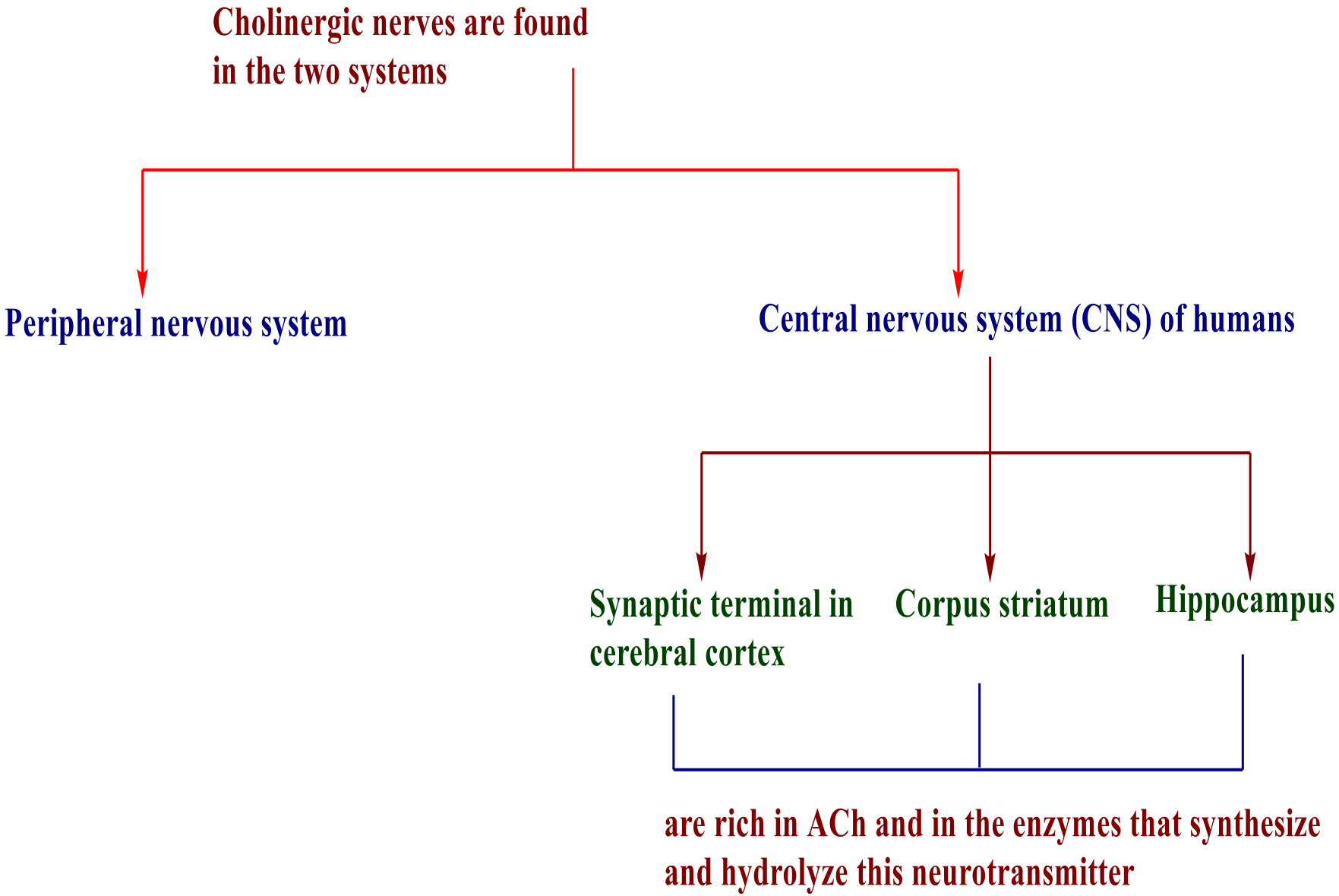


acting directly on the cholinergic receptors in the tissue

acting indirectly inhibiting acetylcholinesterase (AChE), the enzyme that inactivates ACh at the nerve terminal.

Drugs that block the action of Ach

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


Cholinergic nerves are found in the two systems
Peripheral nervous system
Central nervous system (CNS) of humans
Synaptic terminal in cerebral cortex
Corpus striatum
Hippocampus
are rich in ACh and in the enzymes that synthesize and hydrolyze this neurotransmitter

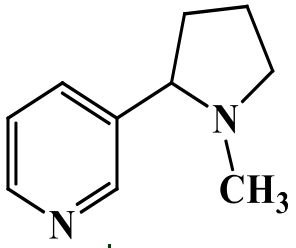
CHOLINERGIC RECEPTORS

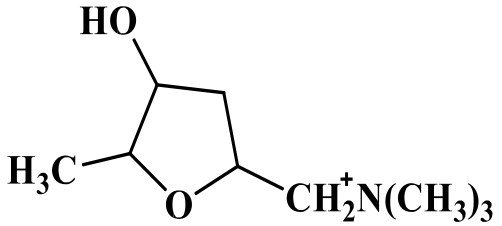
ACh receptors

Two distinct receptor types for ACh

Nicotinic receptor (nAChR) binding to the naturally occurring alkaloids nicotine.

Muscarinic receptor (mAChR) binding to the naturally occurring alkaloids muscarine.





they are differ in

- **composition**
- **location**
- **pharmacological function**
- **have specific agonists and antagonists**

Nicotinic Receptors-: -: (ionotropic receptor, ligande gate ion channel) when stimulated by their neurotransmitter they themselves become an ion channel.

Ion channels are responsible for-:

1-The electrical excitability of nerve and muscle cells.

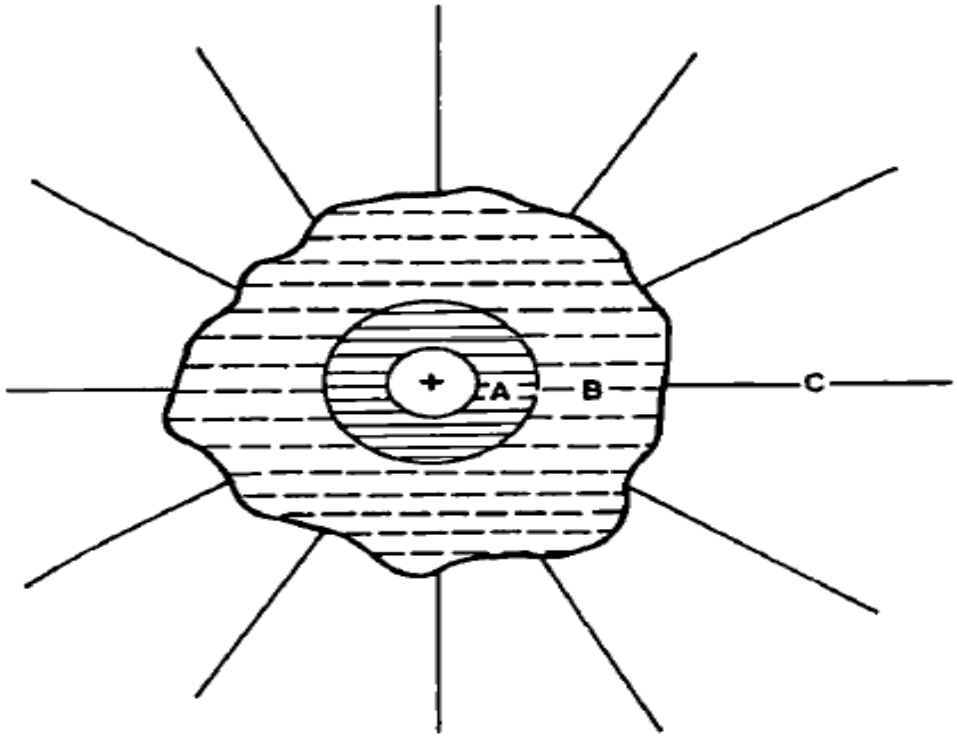
2-The sensitivity of sensory cells.

The channels are pores that open or close on time scales ranging from 0.1 to 10 milliseconds to provide aqueous pathways through the plasma membrane that ions can transverse.

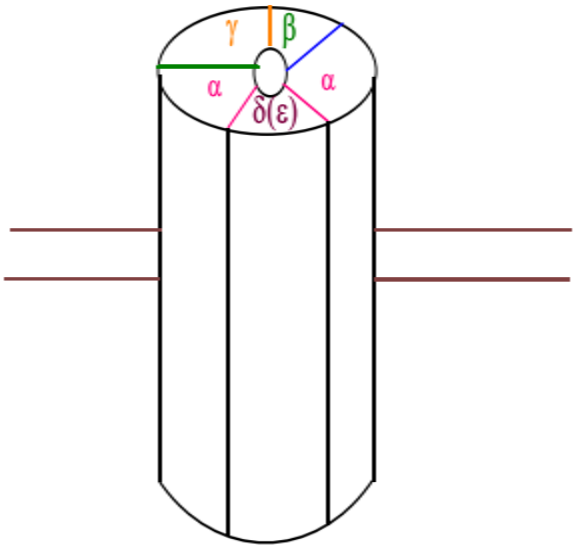
Factors affecting selectivity of ion pores include both-:

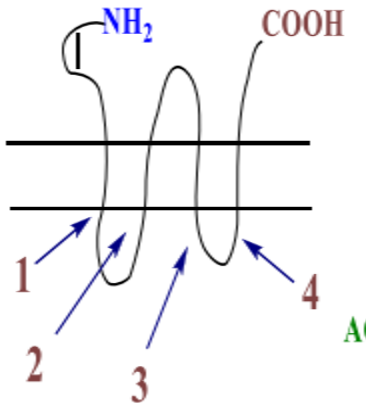
1-The charge of ions.

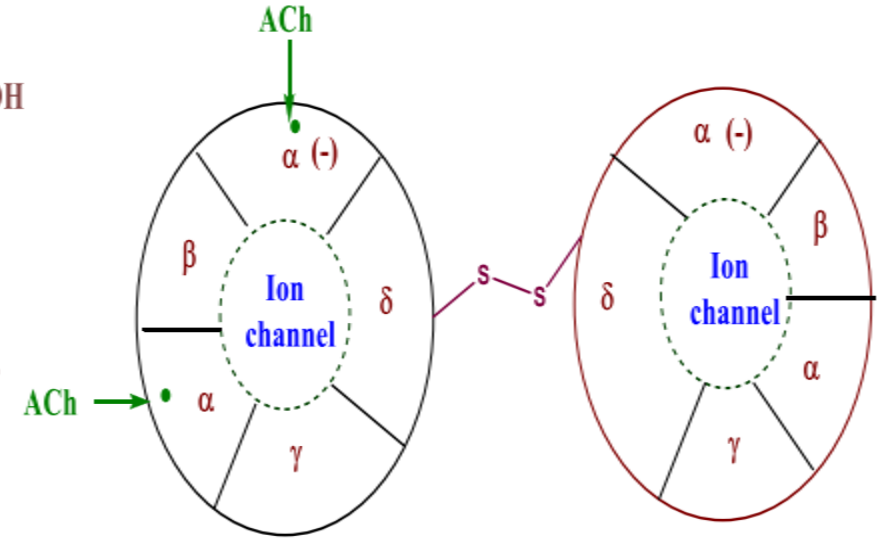
2-The size of ions.



Ions in aqueous solution are hydrated. The water around the ion is characterized by the presence of two distinct water structures: a tightly bound, highly ordered layer immediately surrounding the ion and a second, less structured layer. Ion transport through a channel requires some denuding of the surrounding water shell. The degree of organization of the water structure determines the energy required to remove the hydration shell and is a factor in the selectivity of that ion channel

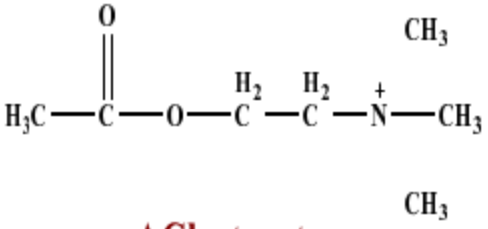




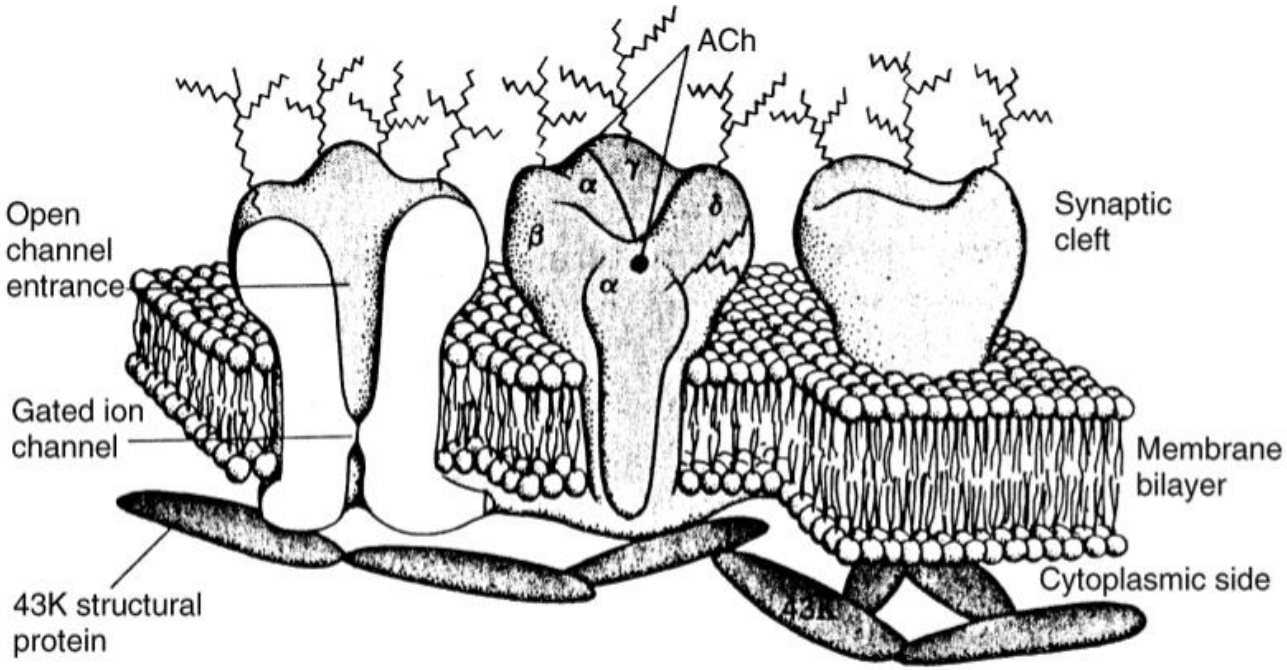


Nicotinic Acetylcholine Receptor
nAChR

The nicotinic ACh receptor was the first neurotransmitter isolated and purified in an active form. It is a **glycoprotein** embedded into the polysynaptic membrane that can be obtained from the electric organs of the marine ray, Torpedo californica and the electric eel, Electrophorus electricus. The receptor is pictured as a cylindrical protein of about 250,000 Da and consists of five-subunit polypeptide chains, of which two appear to be identical. The subunit stoichiometry of the polypeptide units from the Torpedo receptor is α2,β,γ,δ The peptide chains of the receptor are arranged to form an opening in the center, which is the ion channel. **Each chain contains a negatively charged binding site for the quaternary ammonium group of ACh.** The receptor appears to exist as a dimer of the two five-subunit polypeptide chain monomers linked through a disulfide bond between δ chains. A structural protein of molecular weight 43,000 binds the nicotinic receptor to the membrane



ACh structure

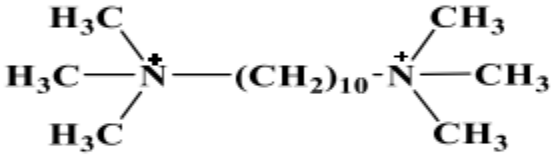


When the neurotransmitter ACh binds to the nicotinic receptor, it causes a change in the permeability of the membrane to allow passage of small cations Ca+2, Na+, and K+. The physiological effect is to temporarily **depolarize** *(**depolarization** is a change within a cell, during which the cell undergoes a shift in electric charge distribution, resulting in less negative charge inside the cell. Depolarization is essential to the function of many cells, communication between cells, and the overall physiology of an organism.)* the end plate. This depolarization results in muscular contraction at a neuromuscular junction or, as occurs in autonomic ganglia, continuation of the nerve impulse. Neuromuscular nicotinic ACh receptors are of interest as targets for autoimmune antibodies in myasthenia gravis and for muscle relaxants used during the course of surgical procedures. Nicotinic receptors in autonomic ganglia, when blocked by drugs, can play a role in the control of hypertension.

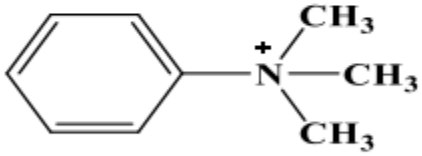
NICOTINIC RECEPTOR SUBTYPES

Nicotinic ACh receptors

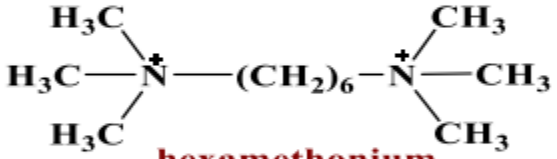
- **Muscle (neuromuscular junction) N1 receptor**
  - **blocked by**
    - succinylcholine
    - d-tubocurarine
    - decamethonium
  - **stimulated by**
    - phenyltrimethylammonium
- **CNS receptor**
- **Ganglionic receptors (found in the autonomic ganglia) (N2 receptor)**
  - **blocked by**
    - hexamethonium
    - trimethaphan
  - **stimulated by**
    - tetramethylammonium
    - dimethyl-4-phenyl piperazinium (DMPP)



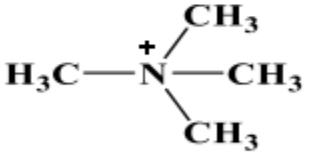
decamethonium



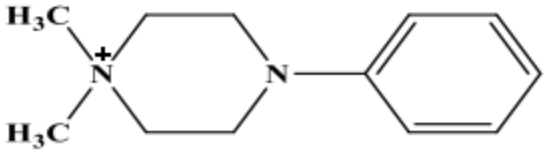
phenyltrimethylammonium



hexamethonium

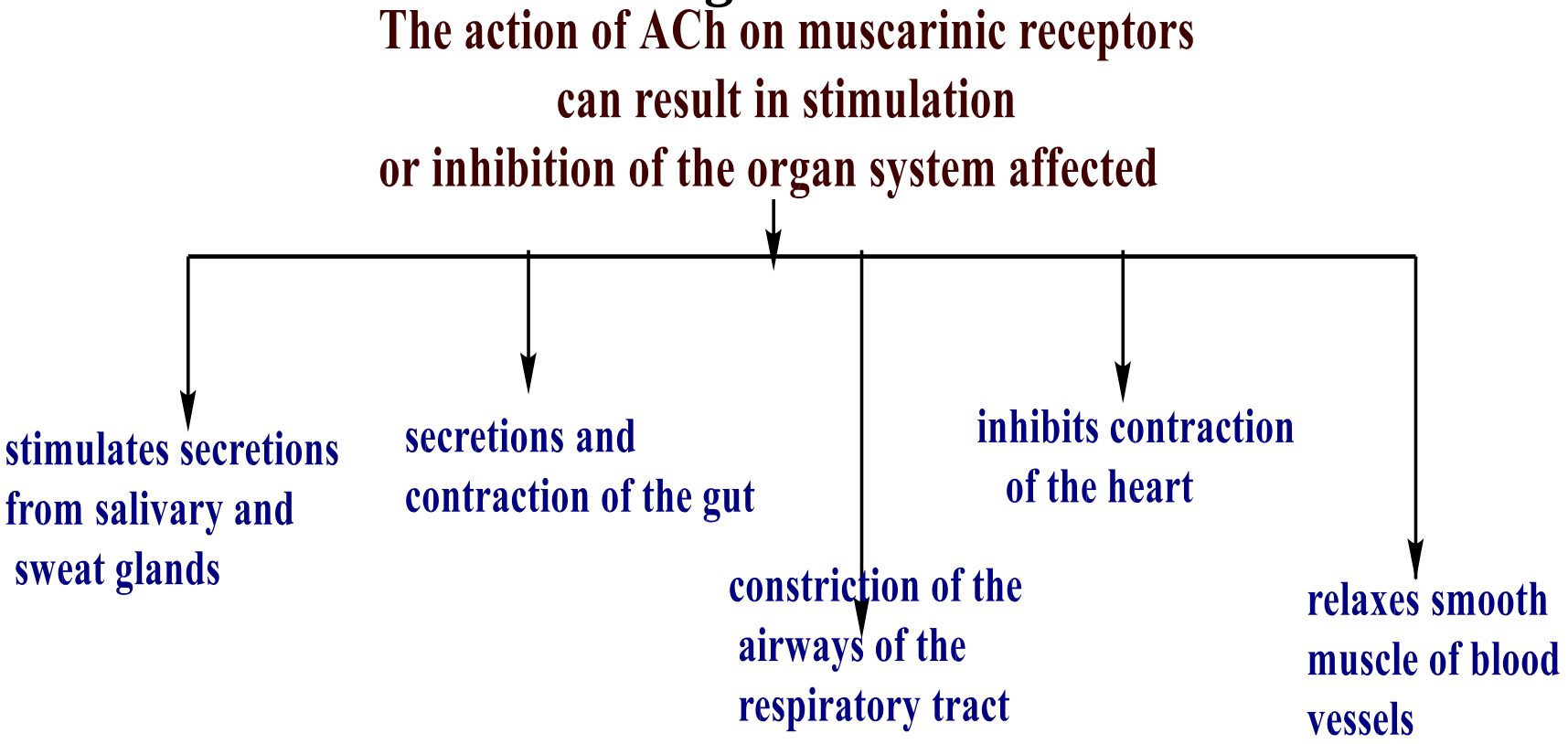


tetramethylammonium



dimethyl-4-phenylpiperazinium (DMPP)

Muscarinic Receptors:- **play an essential role in regulating the functions of organs innervated by the autonomic nervous system to maintain homeostasis of the organism.**



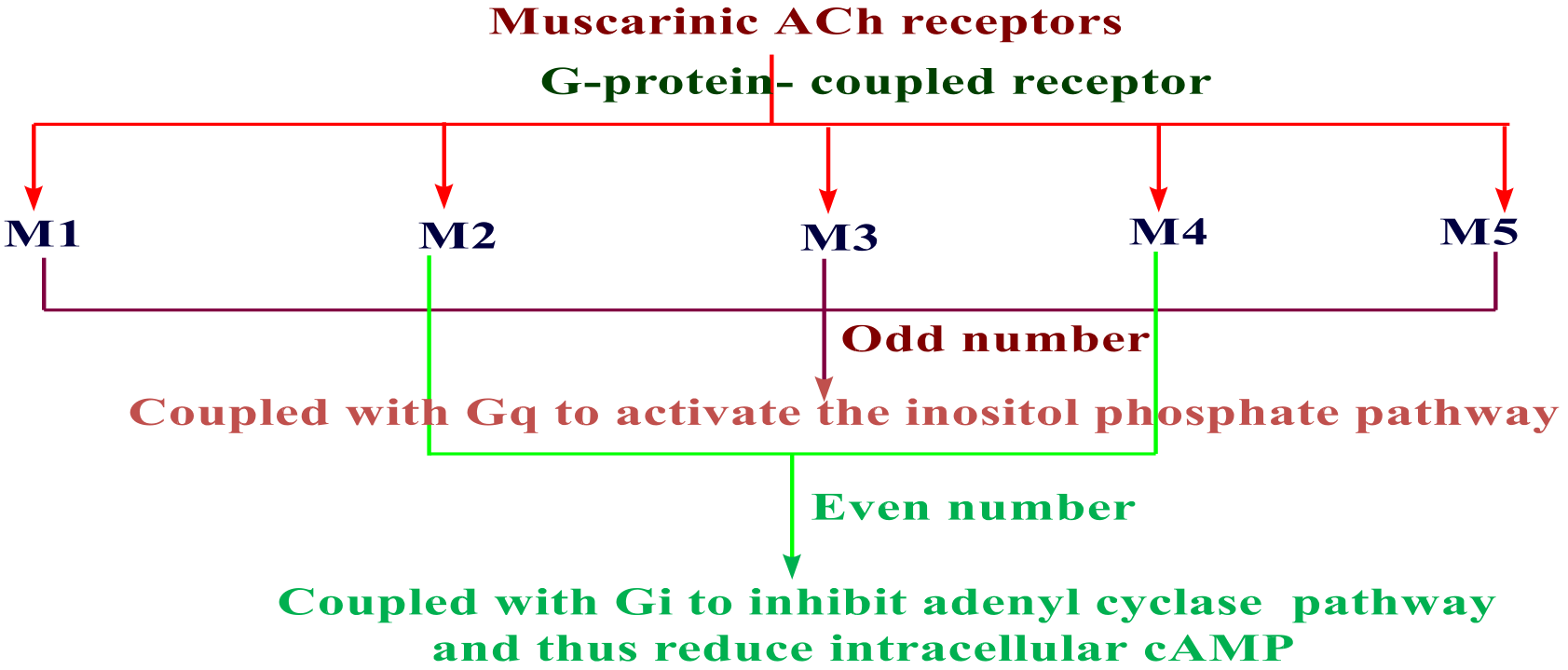
Muscarinic receptors mediate their effects by activating guanosine triphosphate (GTP)-binding proteins) (G-protein). These receptors have seven protein helixes that transcend the plasma membrane, creating four extracellular domains and four intracellular domains. The extracellular domain of the receptor contains the binding site for ACh. The intracellular domain couples with G proteins to initiate biochemical changes that result in pharmacological action from receptor activation.

G_q protein alpha subunit is a family of heterotrimeric G protein alpha subunits. This family is also commonly called the **$G_{q/11}$** (**G_q/G_{11}**) family or **$G_{q/11/14/15}$** family to include closely related family members. G alpha subunits may be referred to as G_q alpha, $G_{\alpha q}$, or $G_q\alpha$. G_q proteins couple to G protein-coupled receptors to activate beta-type phospholipase C (PLC-β) enzymes. PLC-β in turn hydrolyzes phosphatidylinositol 4,5-bisphosphate (PIP_2) to diacyl glycerol (DAG) and inositol trisphosphate (IP_3). IP_3 acts as a second messenger to release stored calcium into the cytoplasm, while DAG acts as a second messenger that activates protein kinase C (PKC).

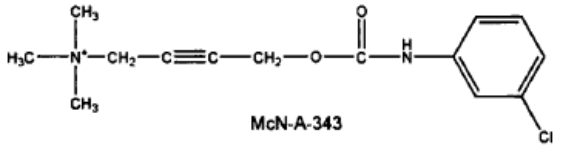
Muscarinic Receptors subtypes

Subtypes of muscarinic receptors are located in the CNS and peripheral nervous system

muscarinic receptor subtypes have been defined on the basis of their affinity for selective agonists and antagonists and the pharmacological effects they cause.



MCN-A-343
is a selective agonist



M1 Receptors
(neural rec)

pirenzepine HCl act as antagonist

Located

CNS mainly
(neural receptor)

exocrine glands
parietal cells in the gastrointestinal
(GI) tract

peripheral neurons
autonomic ganglia
intramural ganglia of the stomach
wall

stimulated, M1 receptors cause

these receptors seem to affect

gastric secretion

arousal
attention

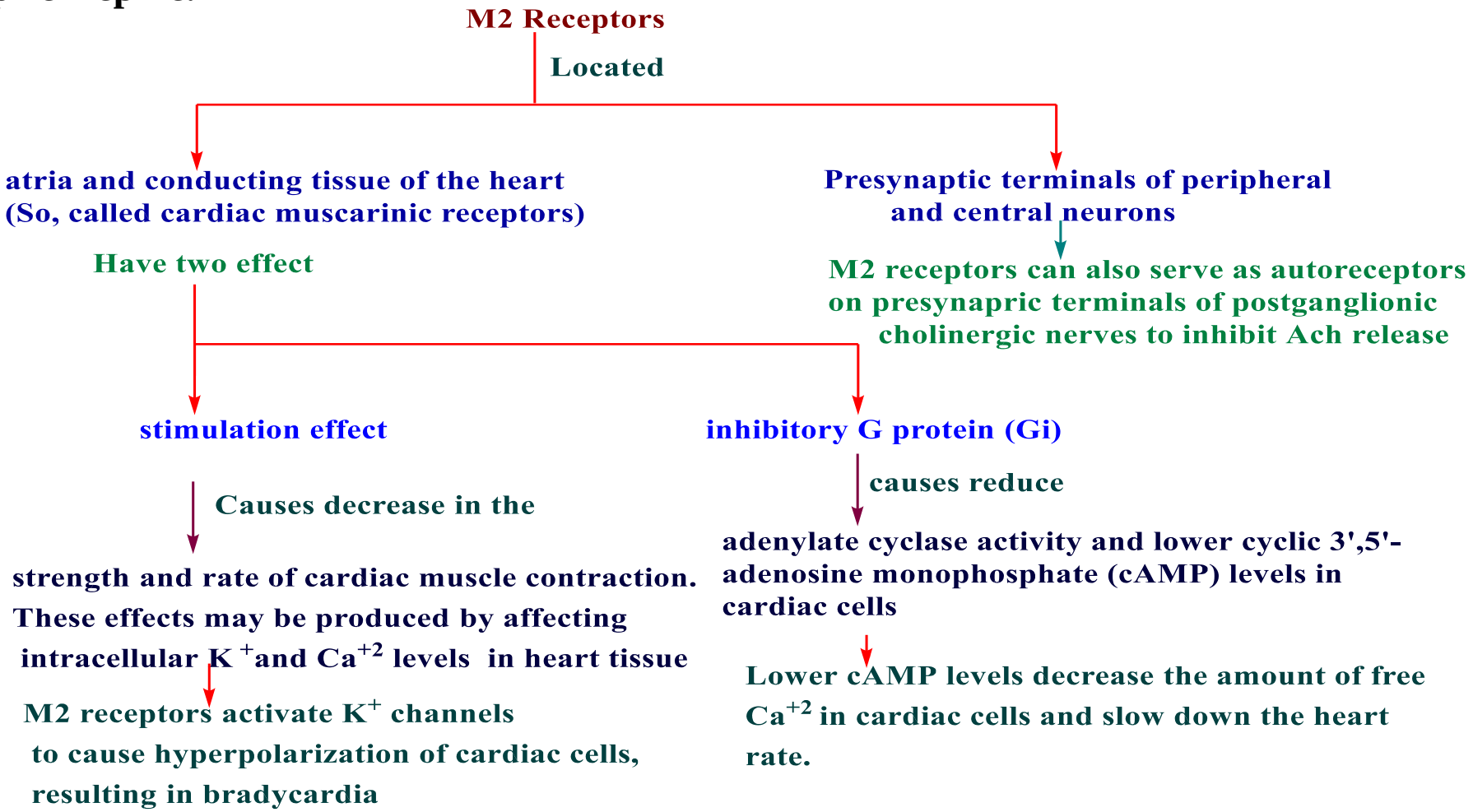
rapid eye
movement
(REM) sleep

emotional
responses

affective disorders including
depression and modulation
of stress

memory ,
learning

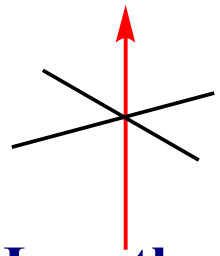
M2 receptor:- are also called cardiac muscarinic receptors because they are located in the atria and conducting tissue of the heart. M2 receptors are identified by their high affinity for methoctramine, a polyamine, and by their low affinity for pirenzepine.



The balance of the effects of multiple muscarinic receptor subtypes determines the size of the airway of the smooth muscle in the bronchioles.

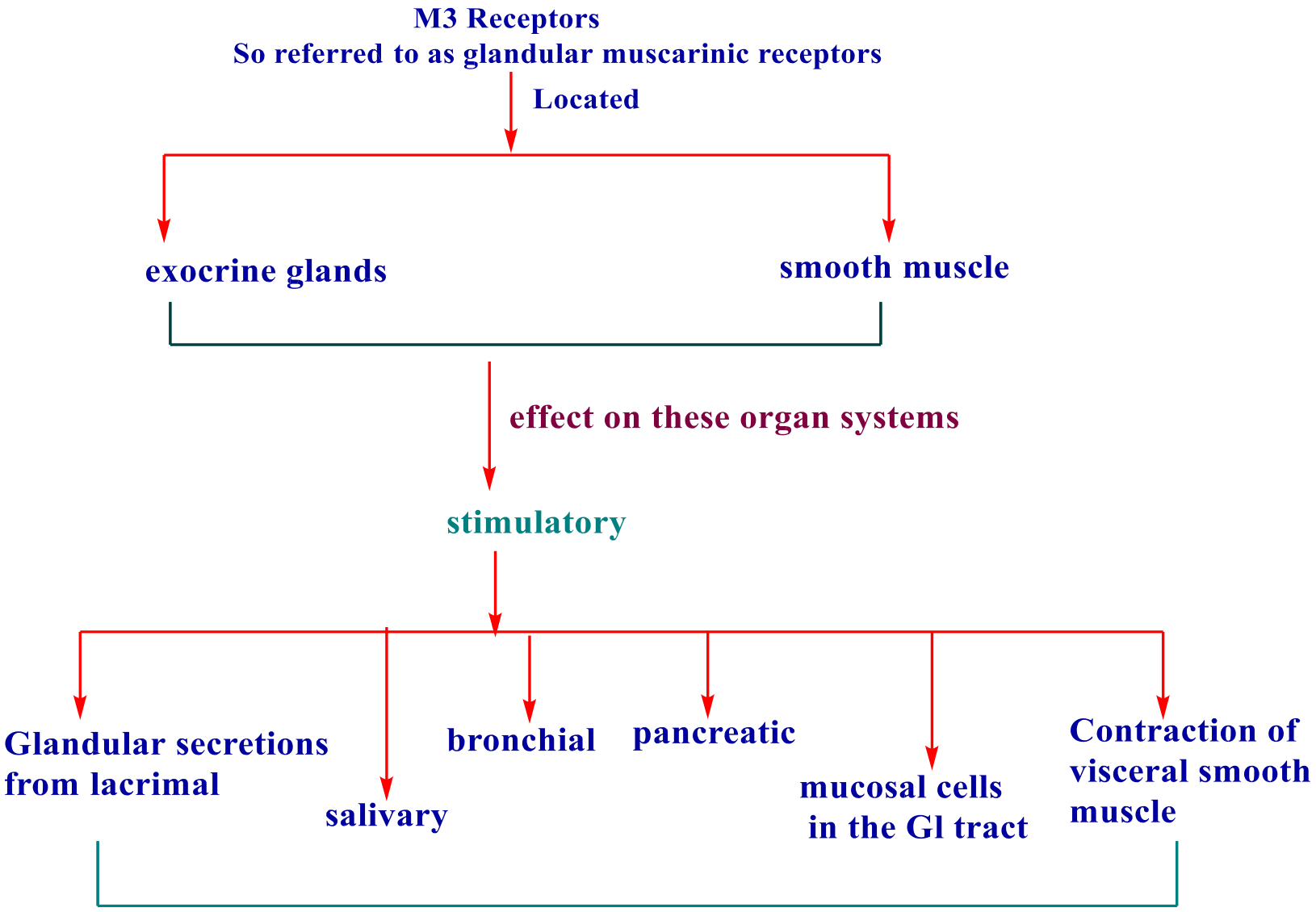
ACh → M_3 → Contraction effect

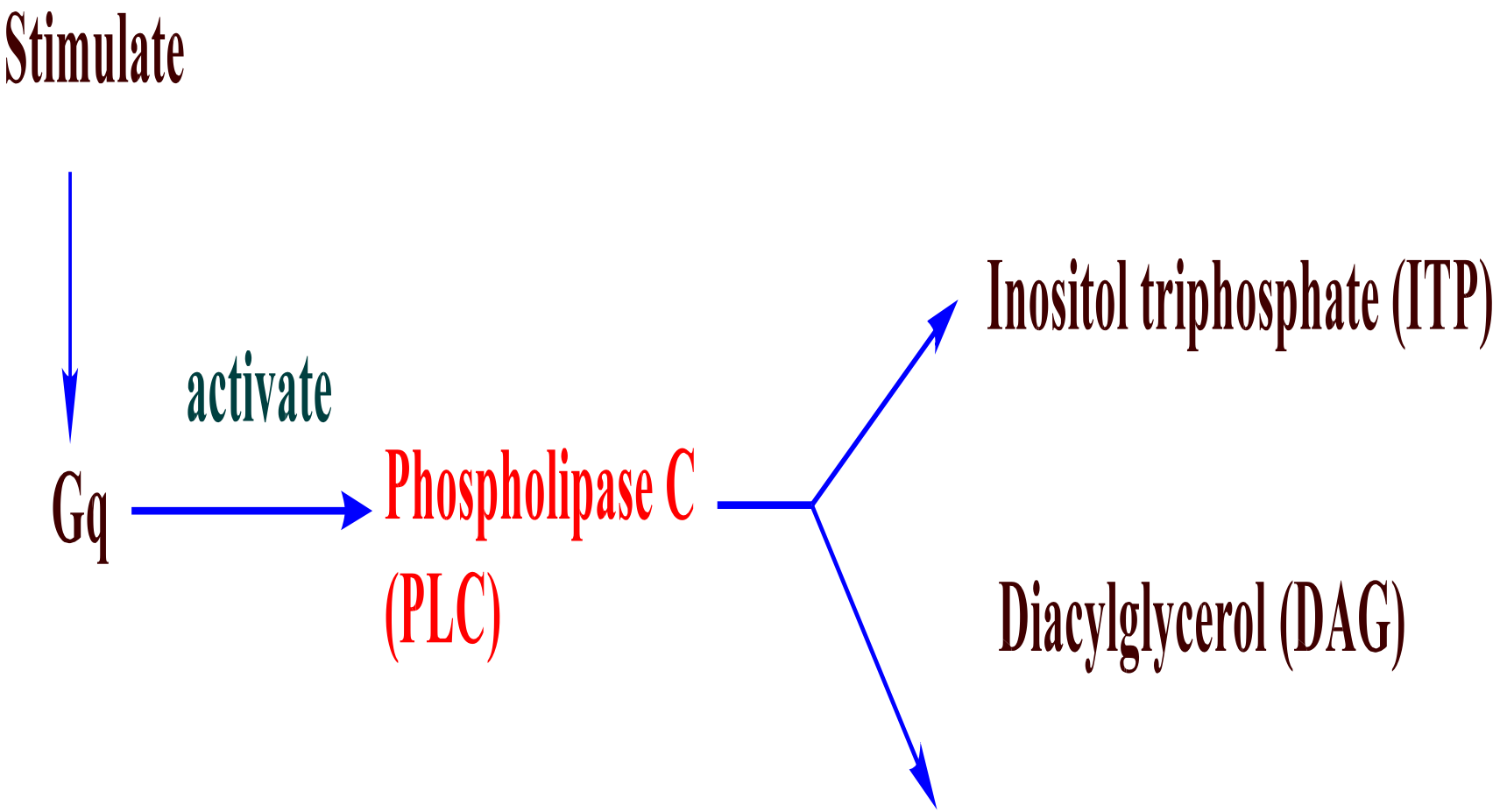
ACh → M_2 autoreceptor → Inhibit release of ACh



In asthmatics

M_2 in the lungs do not function normally.


M3 Receptors
So referred to as glandular muscarinic receptors
Located
exocrine glands
smooth muscle
effect on these organ systems
stimulatory
Glandular secretions from lacrimal
salivary
bronchial
pancreatic
mucosal cells in the GI tract
Contraction of visceral smooth muscle


Stimulate
activate
Gq
Phospholipase C
(PLC)
Inositol triphosphate (ITP)
Diacylglycerol (DAG)