UNIT-III

CHOLINERGIC NEUROTRANSMITTERS

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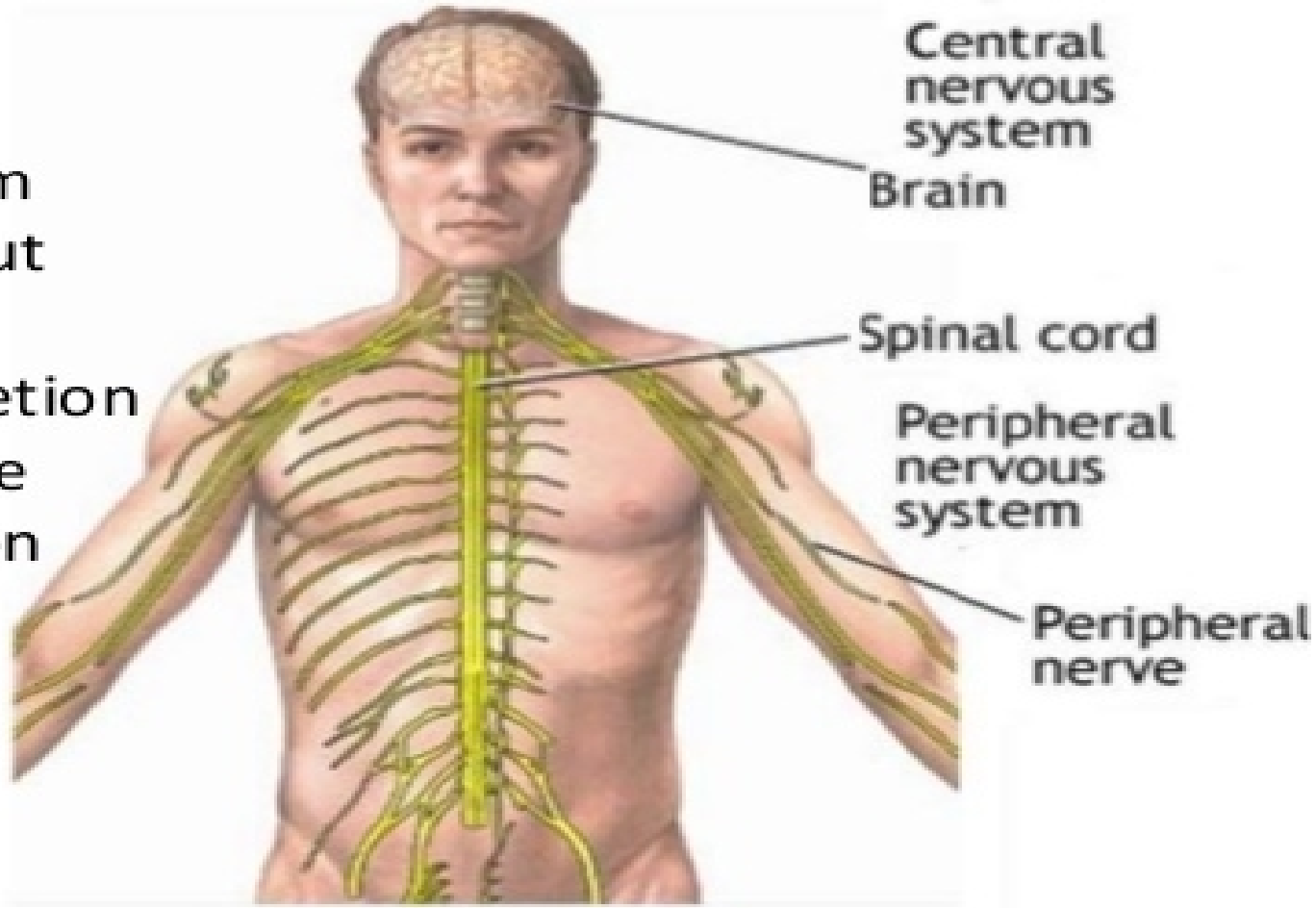
Our Nervous System

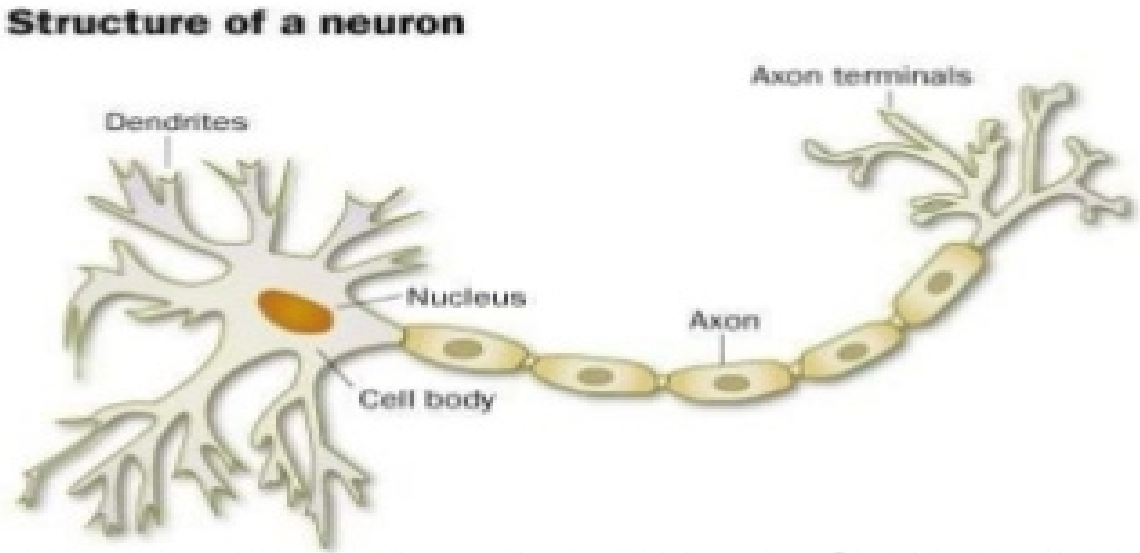
Functions –

- To transmit signals to and from body organs or cells to carry out
  - Heartbeat, Respiration
  - Digestion, Hormone secretion
  - Movement, body pressure
- To process sensory information
- Logic, Decision and Memory



Because of its wide and important involvement, understanding Nervous system is important to treat many diseases

Neurons



- Neurons are individual cells of the Nervous System that process and transmit signals by **electrical** and **chemical** process.
- Adjacent neurons are physically separated by the each other. The gap region is called **synapse.**

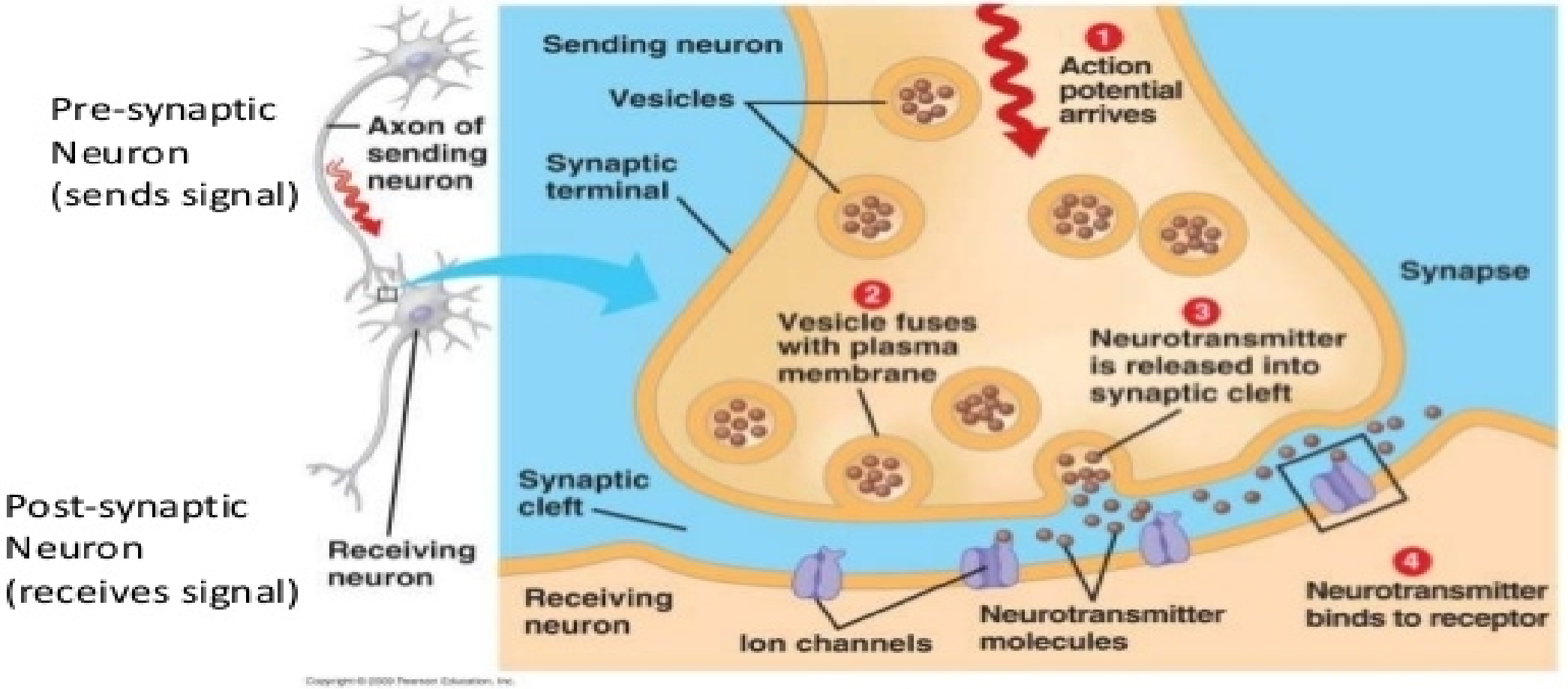
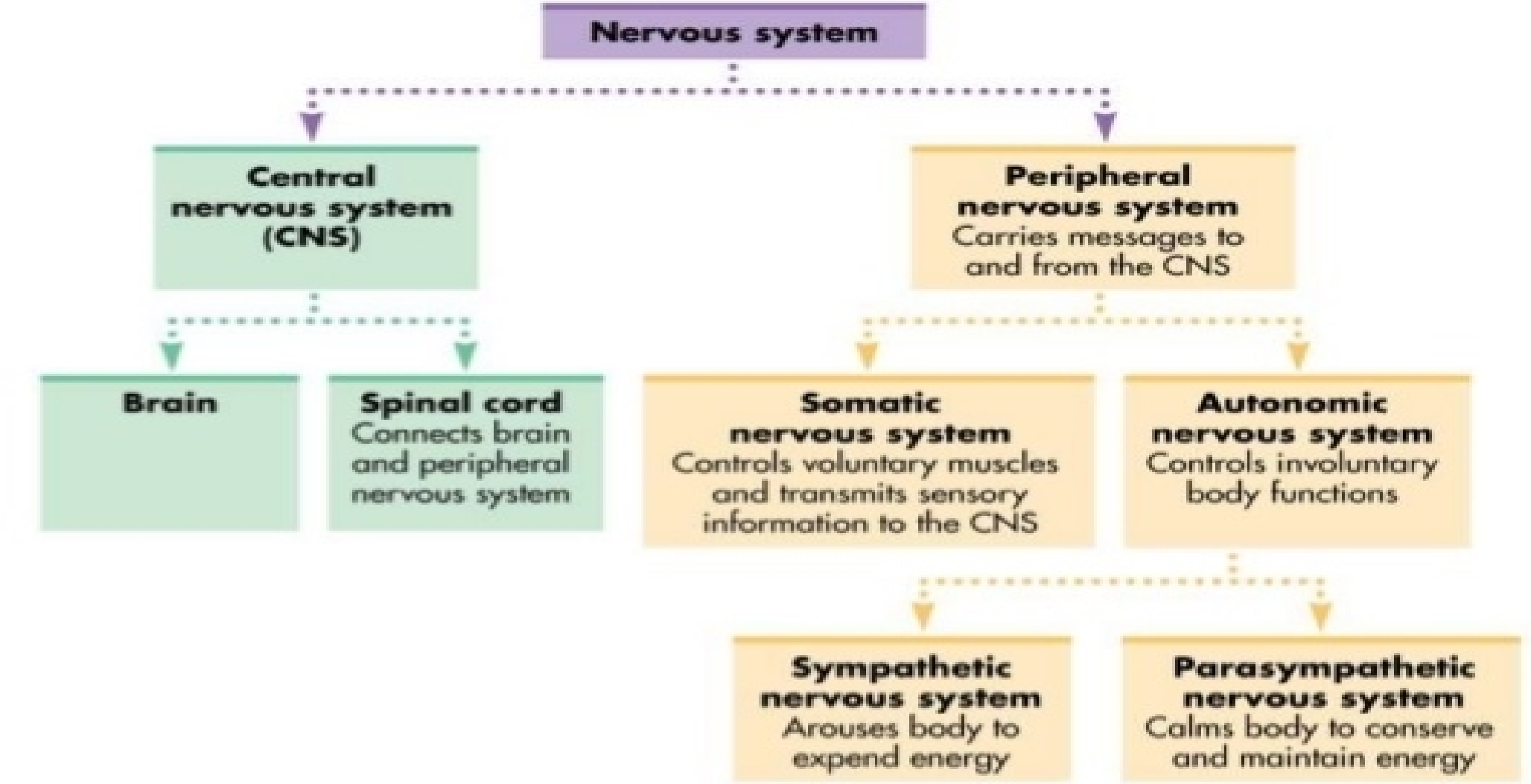


Fig: Neurotransmitters moving through Synapse between two neurons

- Neurotransmitters (NT) are *endogenous* (produced by body) chemicals that transmit signals across a synapse from sending presynaptic neuron to the target postsynaptic neuron
- They are synthesized and stored in neuron itself
- There are many NTs eg Acetylcholine, Adrenaline, serotonin, dopamine, GABA
- The process of transmission of signal along a neuron and over the synapse is called **neurotransmission**. Signal can pass over the synapse by either chemically or electrically
- One neurons interacts with many other neurons in all possible directions.

Our Nervous system



Types of peripheral NS

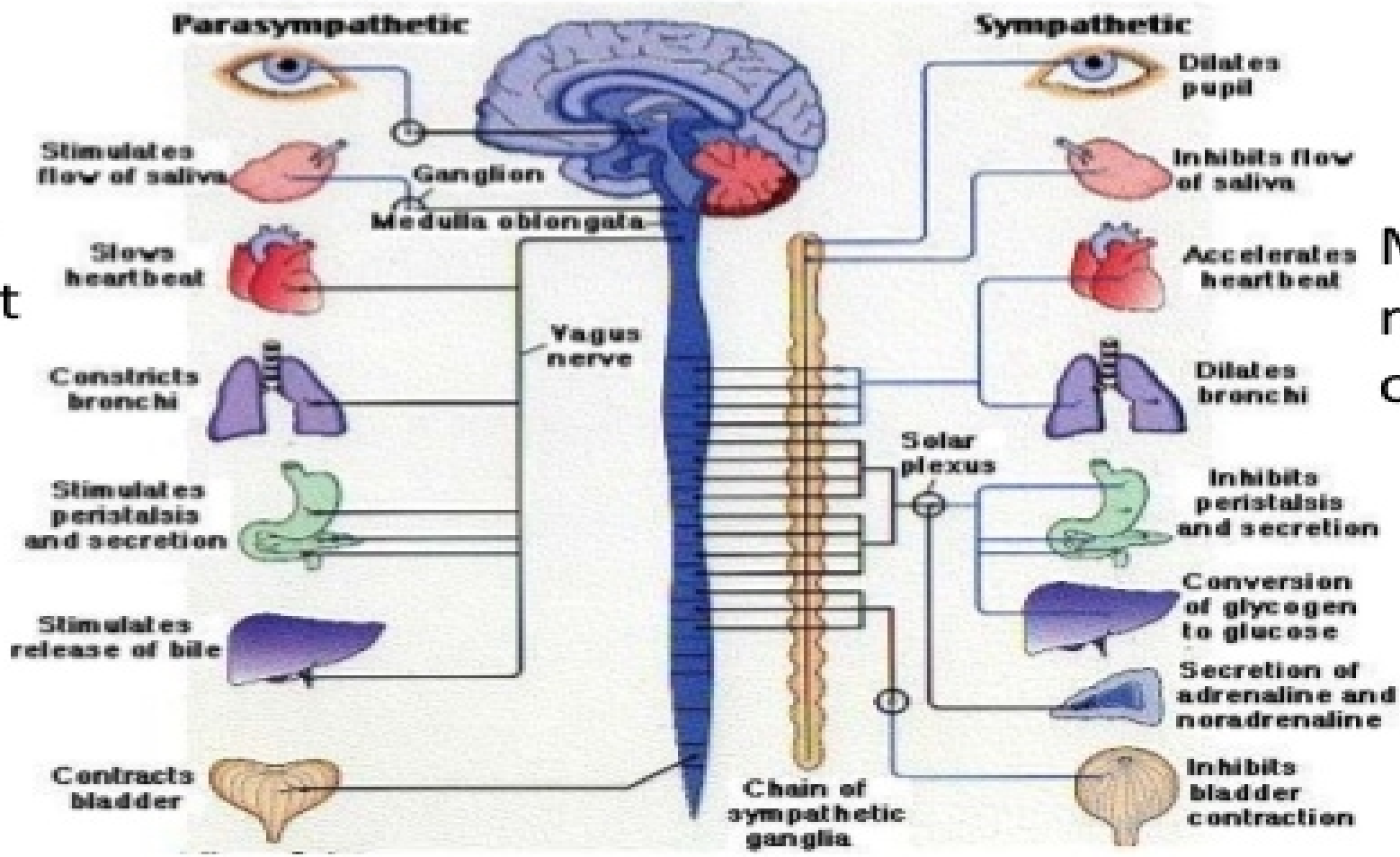
- Somatic NS-
  - controls voluntary muscle Movement
  - Transmits sensory information to brain
- Autonomic NS
  - Controls involuntary body functions such as Heart beat, secretion (GI acid/insulin), fight or flight responses

Two types of Autonomic NS

Parasympathetic NS
Uses Acetylcholine

Sympathetic NS
Uses Adrenaline

Makes body ready for rest



Makes body ready for fight or flight

Sympathetic Vs Parasympathetic

- SYMPATHETIC

Fight or Flight

- Increase BP & HR, glucose, perfusion

to skeletal muscles, Mydriasis, Bronchodilatation

- PARASYMPATHETIC

Rest and Digest

- Miosis, decreased HR, BP, bronchia secretion,

Insulin release, Digestion, excretion

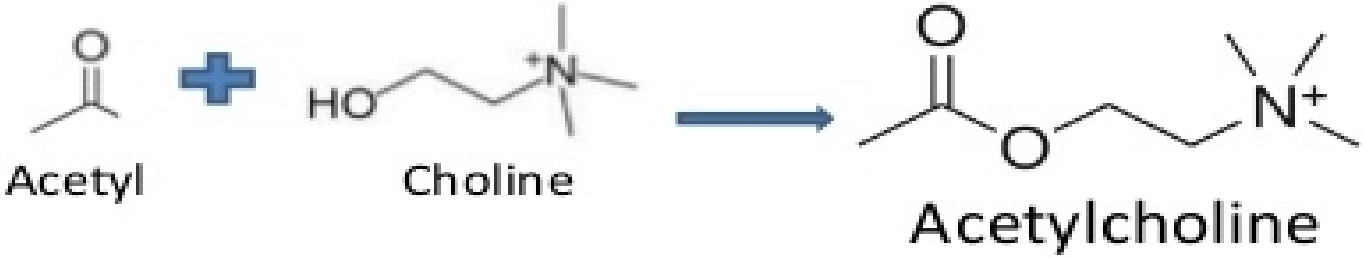
Parasympathetic Nervous System

- Works to save energy, aids in digestion, and supports restorative, resting body functions.
  - Decrease in heart rate
  - Increased gastro intestinal tract tone and peristalsis
  - Urinary sphincter relaxation
  - Vasodilation – decrease in blood pressure

Body Responses – "rest and digest"

- Dilation of blood vessels in skin
- Decrease heart rate (bradycardia)
- Increase secretion of digestive enzymes
- Constriction of smooth muscle of bronchi
- Increase in sweat glands - cooling
- Contraction of smooth muscles of urinary bladder
- Contraction of smooth muscle of skeletal system

Introduction

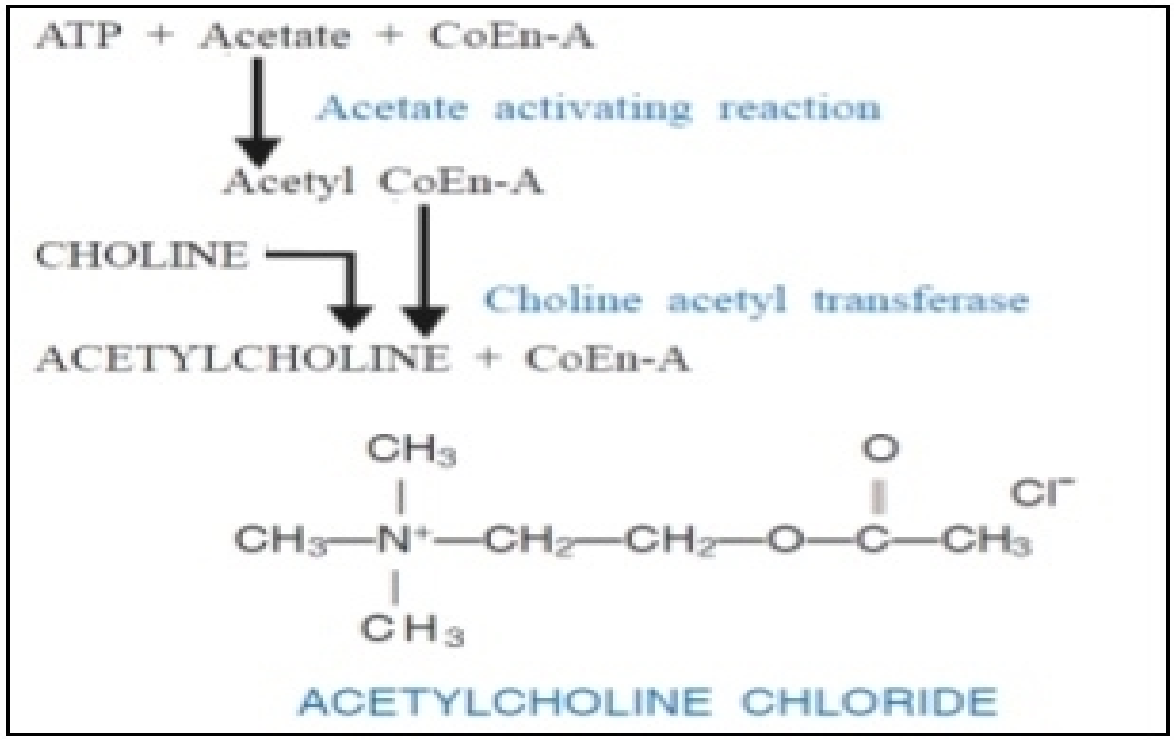


- Cholinergics refer to the part of Nervous system that utilize Acetylchlonine (Ach) as a neurotransmitter. It is key NT in the parasympathetic NS
- A unique feature of Ach is that the same molecule can bind with two different **receptors** (muscarinic and nicotinic receptor) using different **conformation**.

Cholinergic System

- **Cholinergic transmission**
  - Acetylcholine (ACh) is a major neurohumoral transmitter at autonomic, somatic as well as central sites.
- **Synthesis, storage and destruction of Ach**

Ach is synthesized locally in the cholinergic nerve endings by the following pathway

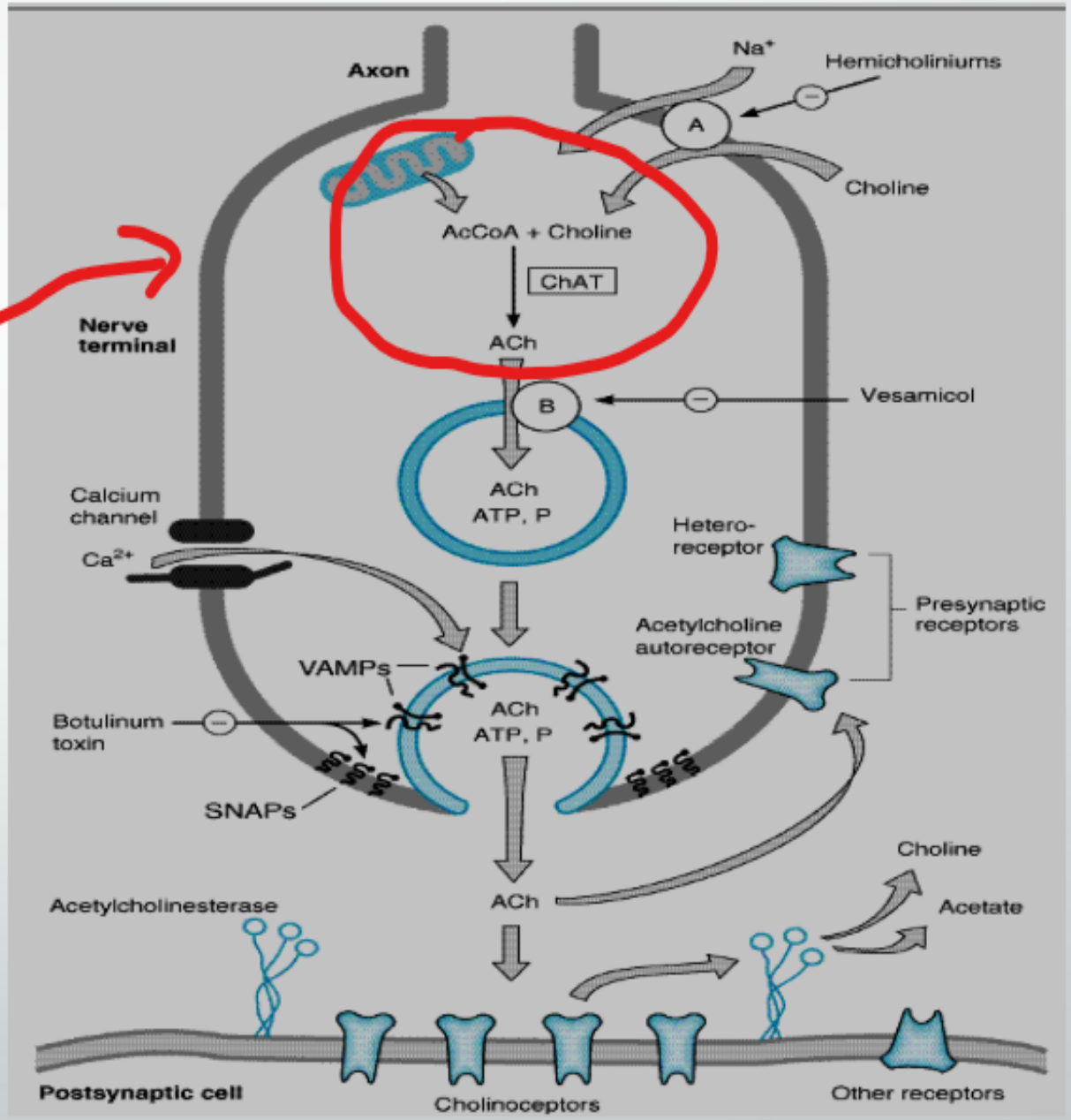


Cholinergic Transmission –

Synthesis:

- Cholinergic neurons contain large numbers of small membrane-bound vesicles (containing ACh) concentrated near the synaptic portion of the cell membrane
- ACh is synthesized in the cytoplasm from **acetyl-CoA** and **choline** by the catalytic action of Choline acetyltransferase (ChAT)
- **Acetyl-CoA** is synthesized in mitochondria, which are present in large numbers in the nerve ending
- **Choline** is transported from the extracellular fluid into the neuron terminal by a Na+-dependent membrane choline cotransporter **(Carrier A).** This carrier can be blocked by a group of drugs called hemicholiniums

❖ **The action of the choline transporter is the rate-limiting step in ACh synthesis**



Cholinergic Transmission –

Release:

• Synthesized, ACh is transported from the cytoplasm into the vesicles by an antiporter that removes **protons** (carrier B). This transporter can be blocked by **vesamicol**

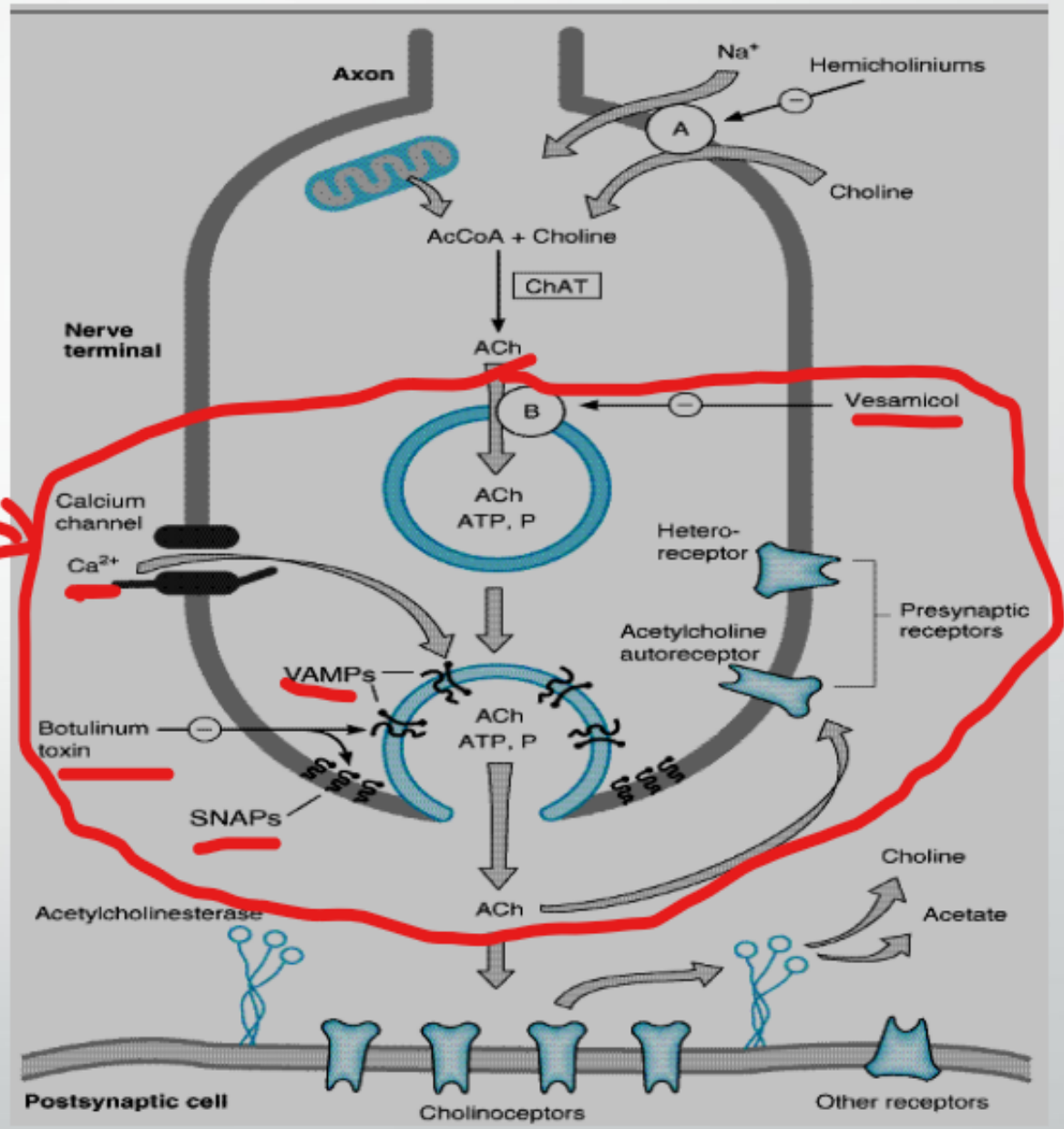
• Release is dependent on extracellular Ca^{2+}

•and occurs when an action potential reaches the terminal and triggers sufficient influx of Ca^{2+}ions

• The increased Ca^{2+}concentration **"destabilizes"** the storage vesicles by interacting with special proteins associated with the vesicular membrane **(VAMPs and SNAP- synaptosome associated protein)**

Fusion of the vesicular membranes with the terminal membrane results in exocytotic expulsion of ACh into the synaptic cleft

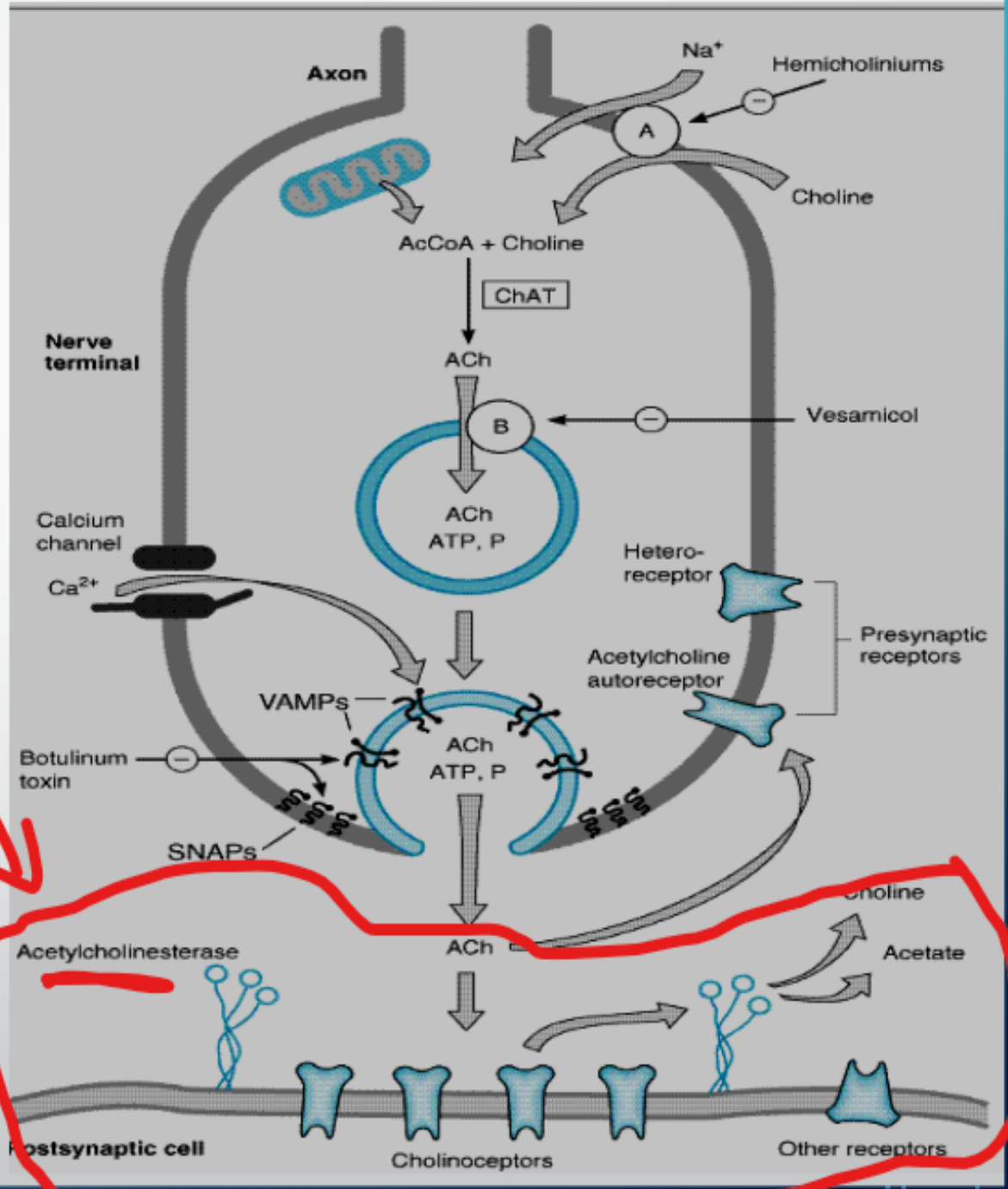
• The ACh vesicle release process is blocked by **botulinum toxin** through the enzymatic removal of two amino acids from one or more of the fusion proteins.



Cholinergic Transmission:

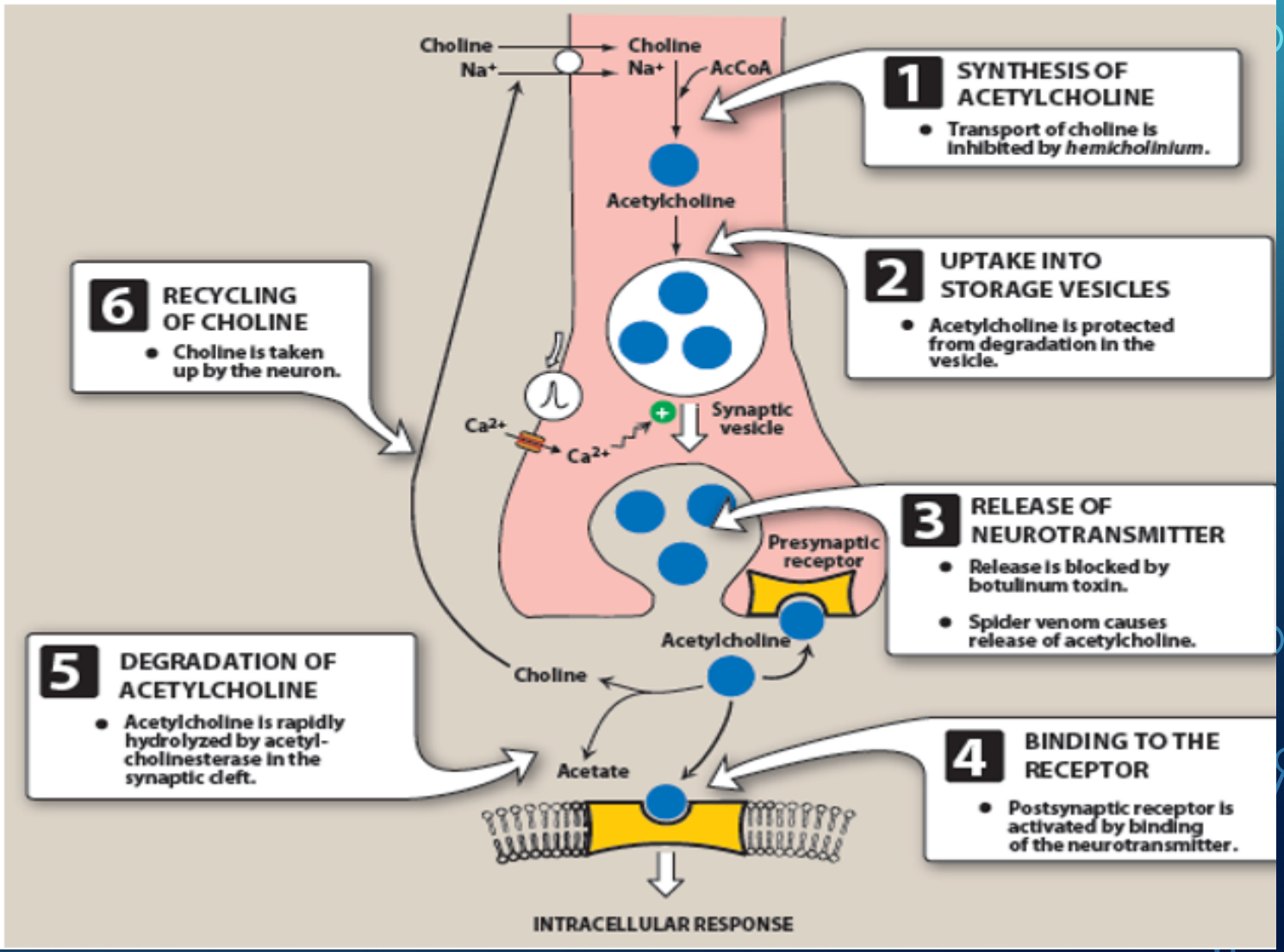
Destruction

- After release - ACh molecules may bind to and activate an ACh receptor (cholinoceptor)
- Eventually (and usually very rapidly), all of the ACh released will diffuse within range of **an acetylcholinesterase (AChE)** molecule
- AChE very efficiently splits ACh into **choline** and **acetate**, neither of which has significant transmitter effect, and thereby terminates the action of the transmitter.
- Most cholinergic synapses are richly supplied with AChE; the half-life of ACh in the synapse is therefore very short. AChE is also found in other tissues, eg, red blood cells.
- Another cholinesterase with a lower specificity for ACh, **butyrylcholinesterase [pseudo cholinesterase],** is found in blood plasma, liver, glial, and many other tissues



Neurotransmission in the cholinergic neuron

1. Synthesis of ACh
2. Storage of ACh in vesicles
3. Release of ACh
4. Binding of ACh to the receptor
5. Degradation of ACh
6. Recycling of choline and acetate



Did you note the mono-directionality ?

- Instead of a *single* light switch that you can *turn on/off* or a *single* volume knob you can *turn high/low*.....
- In this case you have *two independent* control system for doing opposing things, eg sympathetic increases heart beat while parasympathetic is required to slow heart beat, there is no way neither NS can reverse or undo it's action by itself.

Why they are called as cholinergics?

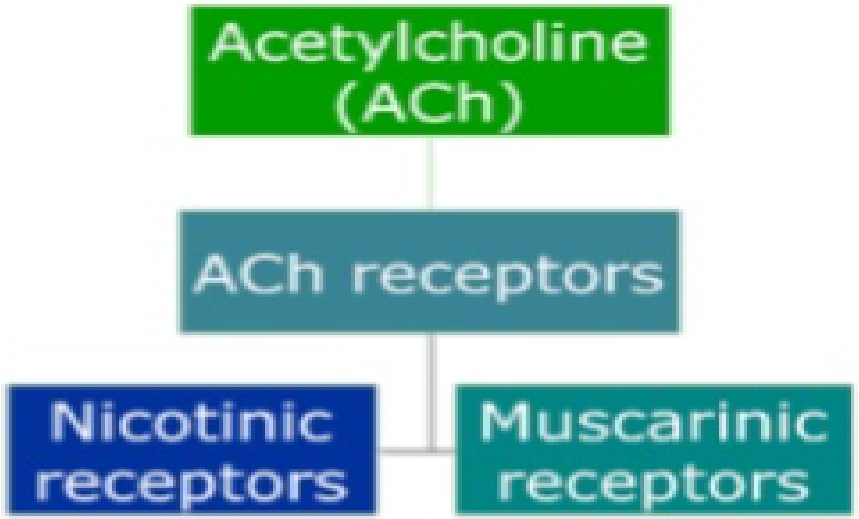
- Drugs – stimulate Parasympathetic Nervous System
- Called cholinerigics
  - Because ACh is a neurotransmitter in PNS
  - Those drugs resemble the effects produced by stimulation of PNS (cholinergic nervous system).

What is the neurotransmitter involved?

- Acetylcholine

What are the receptors involved?

- Muscarinic receptors
- Nicotinic receptors



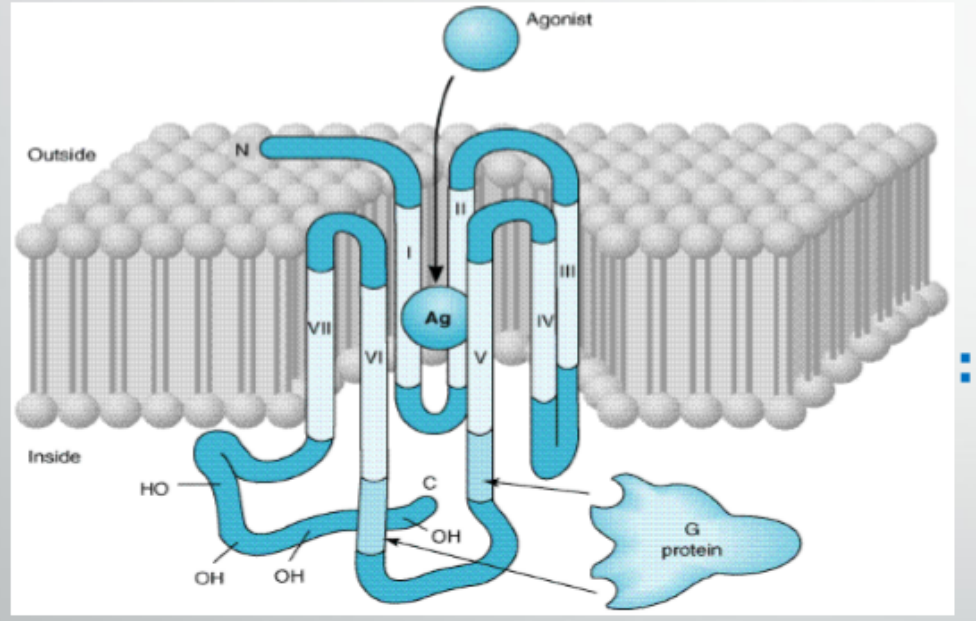
Cholinoceptors

- Two classes of receptors

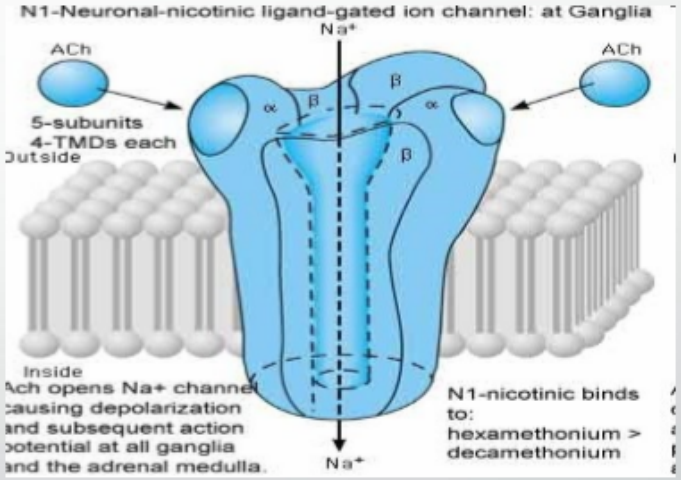
MUSCARINIC & NICOTINIC

- **Muscarinic** receptors are GPCR
- **NICOTINIC** receptors belongs to Ligand gated receptors

Cholinergic receptors - 2 types

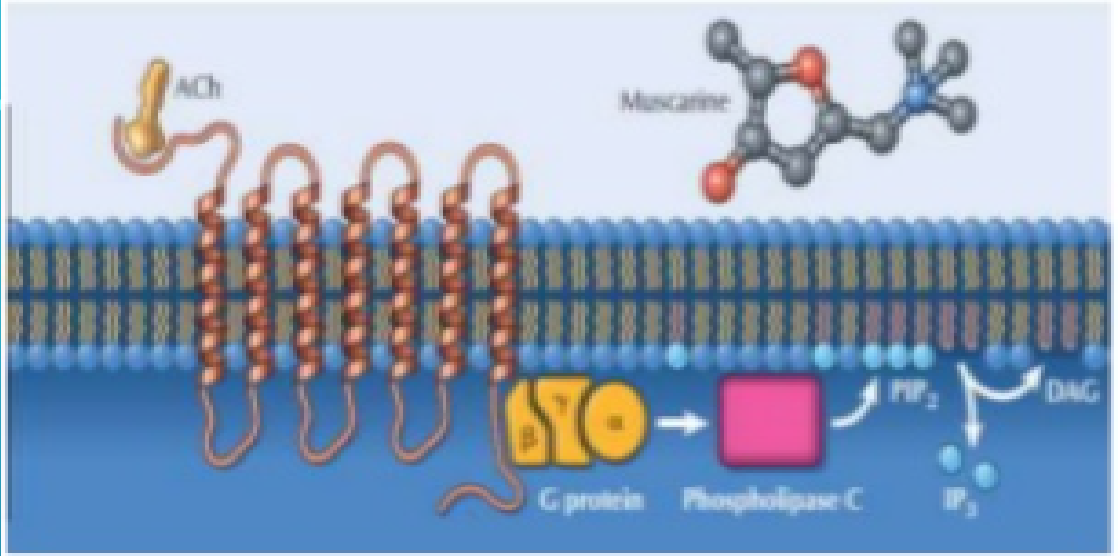


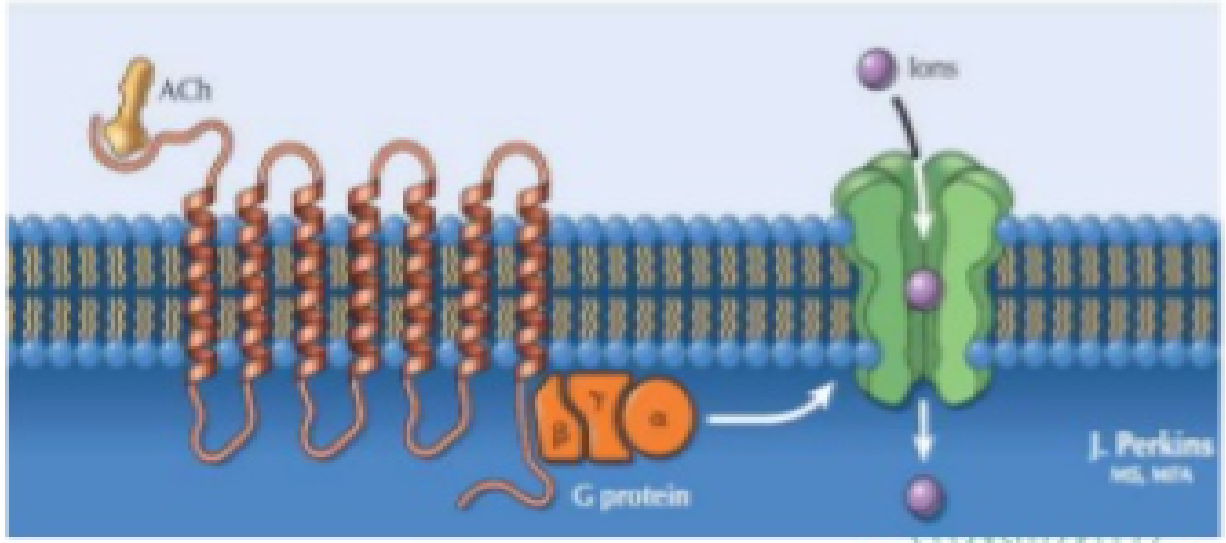
Muscarinic (M) - GPCR



Nicotinic (N) – ligand gated

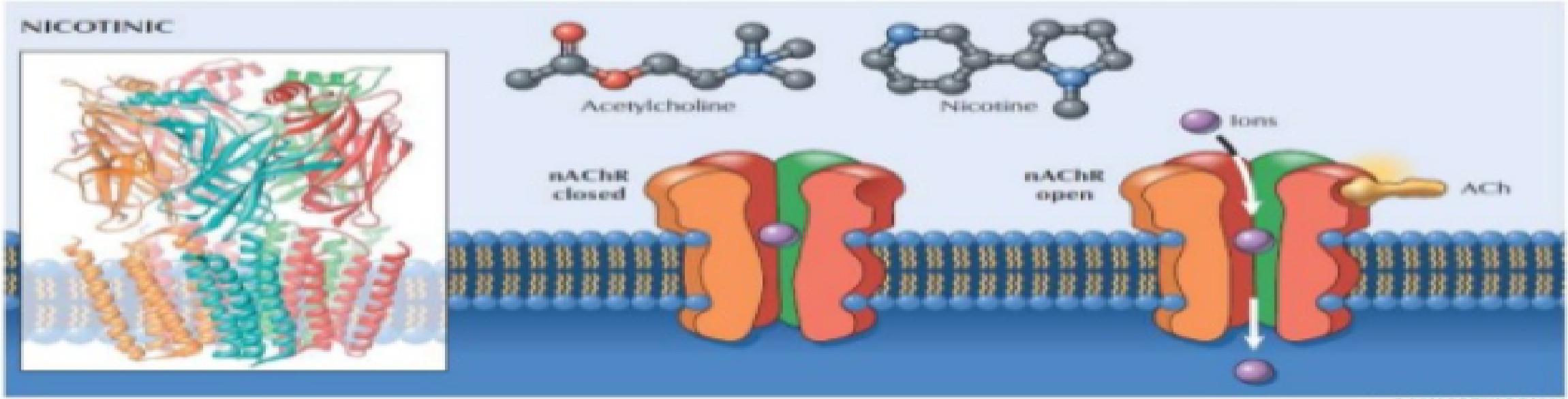
MUSCARINIC RECEPTORS





Receptors	Locations	Mechanism
M_1	ANS , CNS	Gq
M_2	Heart ,ganglia	Gi
M_3	Smooth muscle ,glands, vascular endothelium	Gg
M_4	CNS	Gi
M_5	CNS	Gq

CHOLINOCEPTORS



Receptor	Location	Mechanism
N_M	Neuromuscular junction	Ion channel
N_N	Autonomic ganglia Adrenal medulla CNS	Ion channel

- SUBTYPES of MUSCARINIC RECEPTORS:

  M_1, M_2, M_3, M_4, M_5

- SUBTYPES of NICOTINIC RECEPTORS:

  N_m, N_n

MASCARINIC RECEPTORS

- Receptors are selectively stimulated by MASCARINE
- Blocked by ATROPINE
- Located primarily on Autonomic effector cells in HEART, BLOOD VESSELS, EYE, SMOOTH MUSCLES, URINARY TRACT, SWEAT GLANDS

NICOTINIC RECEPTORS(LGCC)

- Selectively active by **NICOTINE.**
- Blocked by d-TC(d-Tubacurarine) or Hexamethonium

Activation:

- Nicotinic receptor activation
- Opening of channels
- Results rapid inflow of cations into the cell

DEPOLARISATION, Increase ACTION POTENTIAL

SUBTYPES of NICOTINIC receprors

- Nm , Nn

Nm: (Skeletal muscle end plate)

- Mediates skeletal muscle contraction
- Selectively Stimulated by **PHENYL TRIMETHYL AMMONIUM**
- Blocked by **Tubocurarine**

Nn:

- **Autonomic Ganglia**
- **Adrenal medullary cells**
- **Spinal cord**
- **Certain Areas of the Brain**
- Selectively stimulated by **Dimethyl phenyl piperazinium**
- Blocked by **Hexamethonium**

Cholinergic Receptors

M1	**Secretory glands**	salivation, stomach acid, sweating, lacrimation
M2	**Heart**	Decreases heart rate → bradycardia
M3	**Smooth muscle (GI/GU/Resp)**	Contraction of smooth muscles (some) → diarrhea, bronchospasm, urination
M3	**Pupil and ciliary muscle**	Contracts → Miosis Increased flow of aqueous humor
Nm	**Skeletal muscle end plate**	Contraction of skeletal muscle
Nn	**Autonomic ganglia, Adrenal Medulla**	Secretion of Epinephrine Controls ANS

THANK YOU