Cholinomimetic drugs (cholinergic drugs)

Cholinomimetic drugs (cholinergic drugs)

What students should know:

- Nervous system
- Classifications of autonomic nervous system
- Cholinergic nervous system
- Chemical neurotransmitters

  Synthesis – Actions – Metabolism

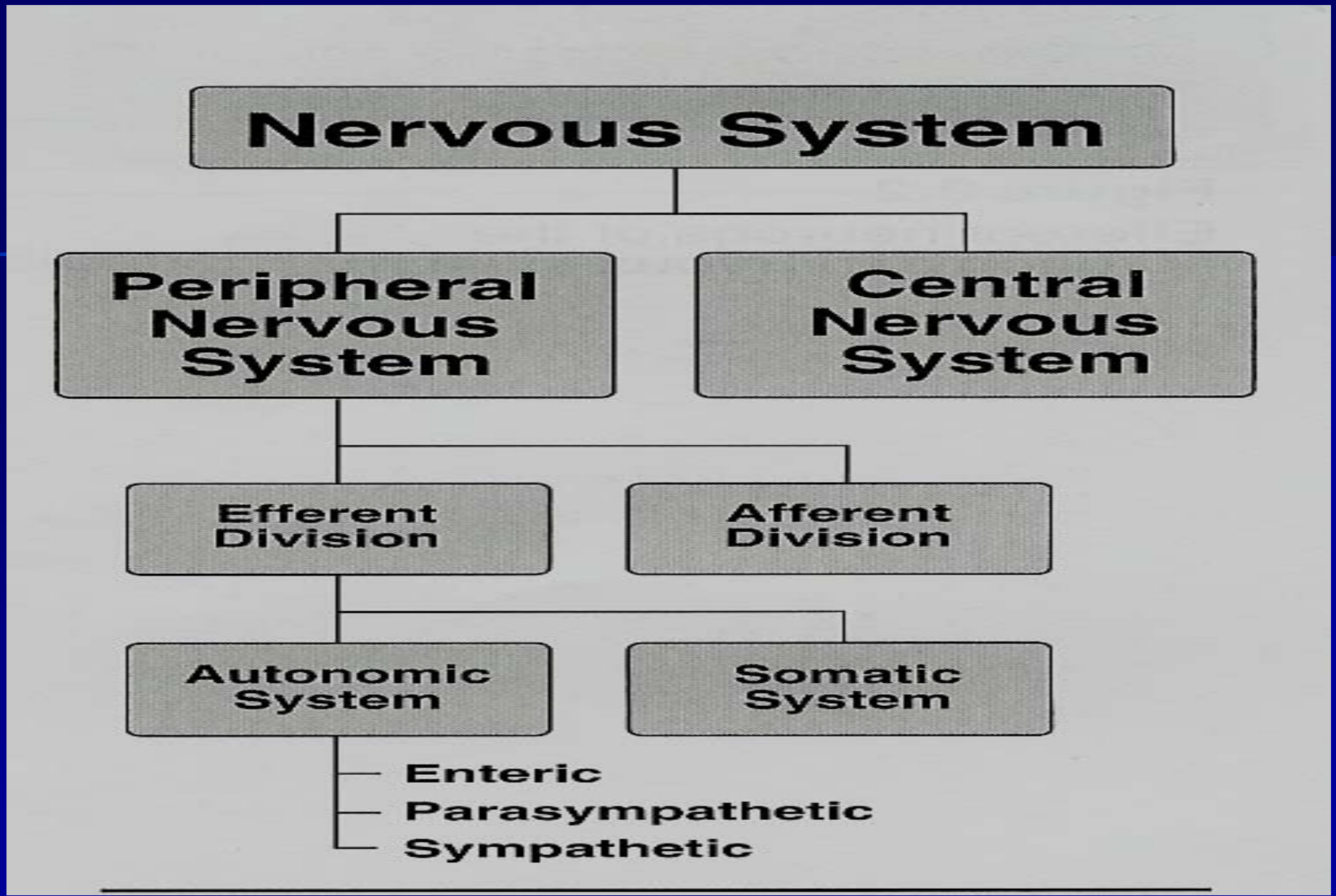
- Cholinergic receptors
- Cholinomimetic drugs & anticholinergic drugs
  - Kinetics
  - Dynamics
  - Uses
  - Adverse effects & contraindications.

The nervous system is a communication network that allow an organism to interacts with the environment in appropriate ways.

It can be classified in to **the central nervous system** and **the peripheral nervous system**.

The central nervous system is composed of brain and spinal cord.

The peripheral nervous system is somatic .N.S and the autonomic nerves system.


Nervous System
Peripheral Nervous System
Central Nervous System
Efferent Division
Afferent Division
Autonomic System
Somatic System
Enteric
Parasympathetic
Sympathetic

What are the differences between the somatic and the autonomic N.S?

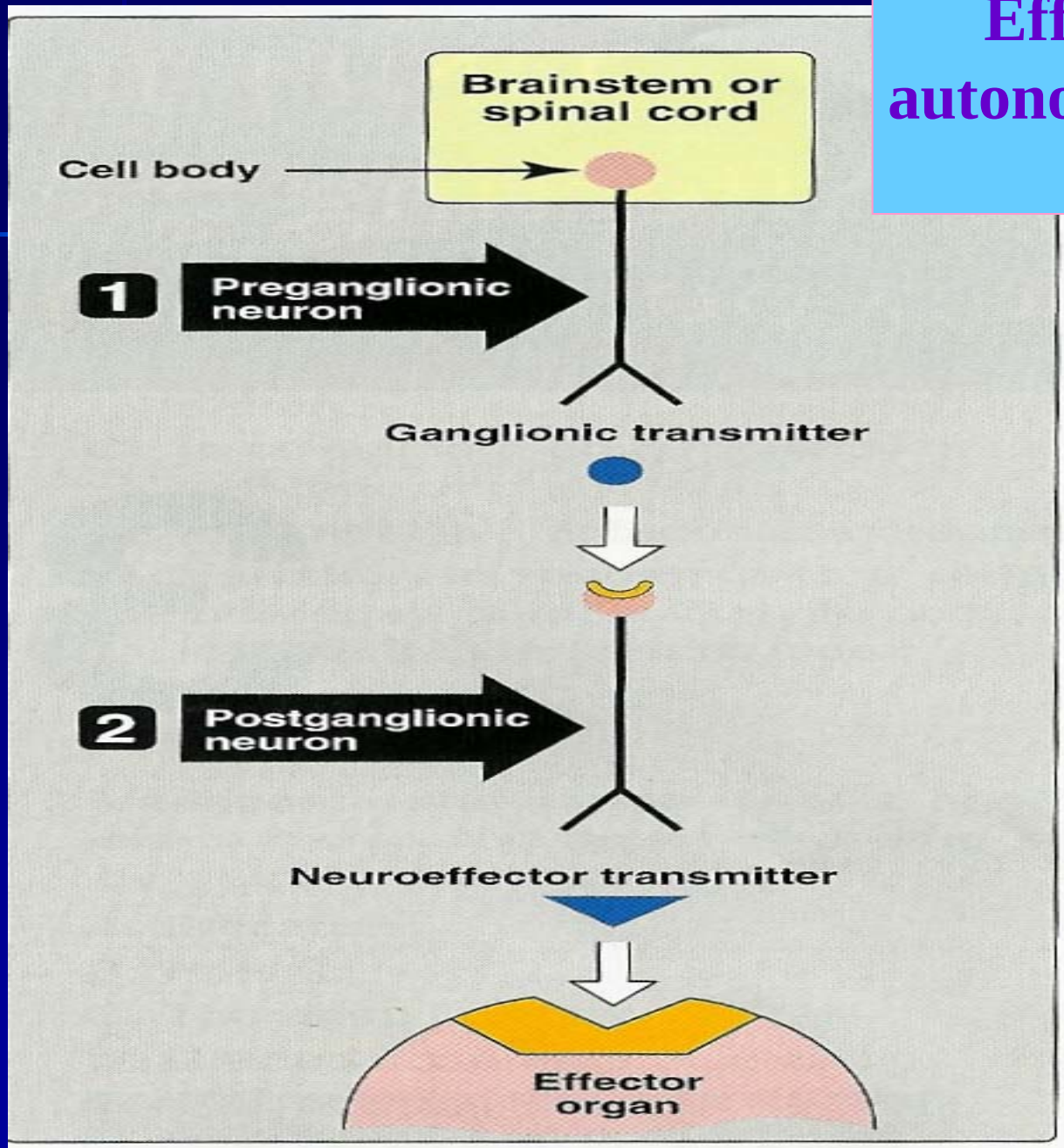
Somatic N.S

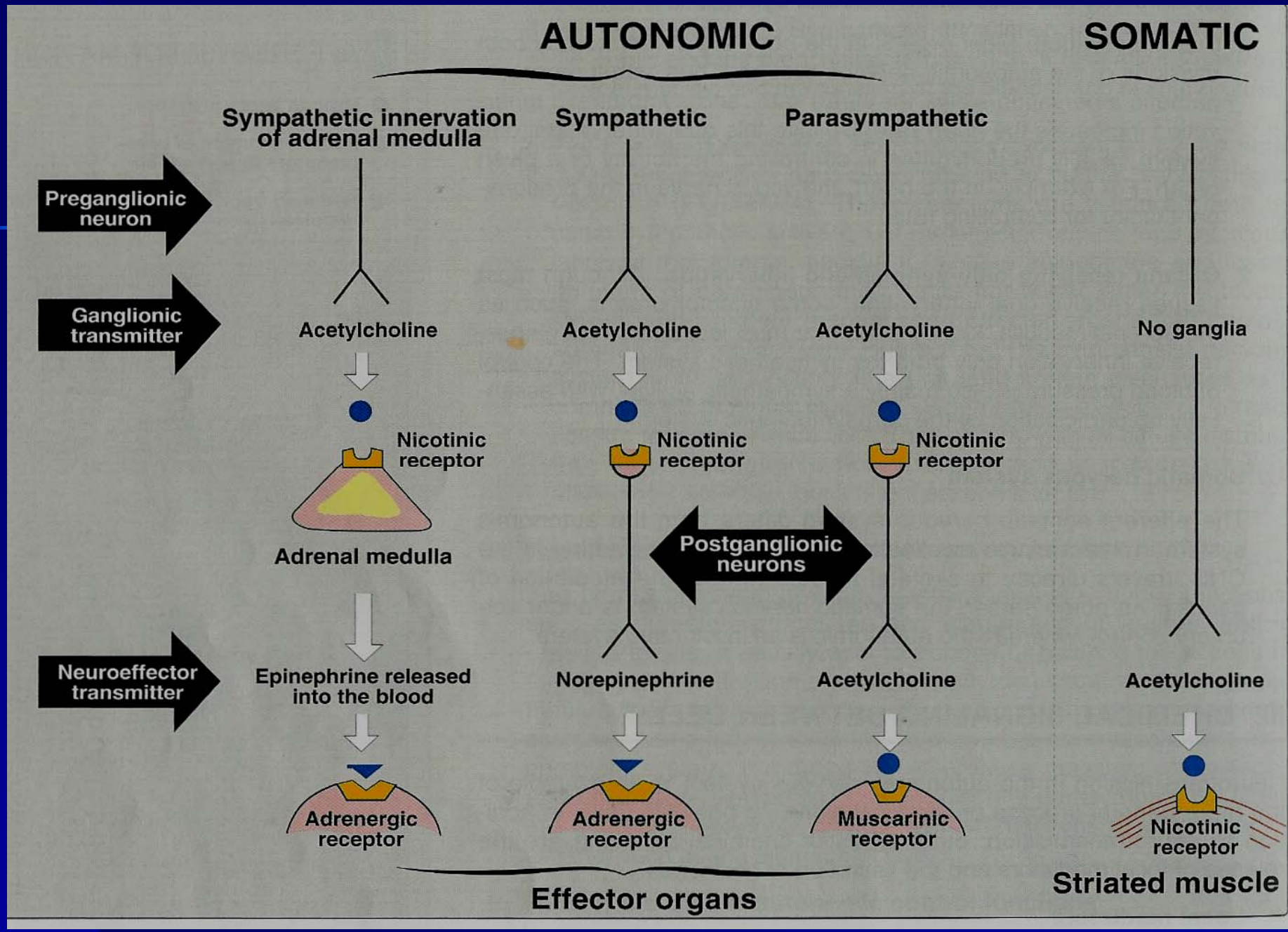
- Control skeletal muscles
- Voluntary
- Somatic nerve is one fiber

Autonomic N.S

- Control smooth muscles of viscera, blood vessels, exocrine glands & cardiac muscles
- Involuntary
- Autonomic nerves have two neurons

Efferent neurons of autonomic nervous system




AUTONOMIC
SOMATIC
Sympathetic innervation of adrenal medulla
Sympathetic
Parasympathetic
Preganglionic neuron
Ganglionic transmitter
Neuroeffector transmitter
Acetylcholine
Acetylcholine
Acetylcholine
No ganglia
Nicotinic receptor
Nicotinic receptor
Nicotinic receptor
Adrenal medulla
Postganglionic neurons
Epinephrine released into the blood
Norepinephrine
Acetylcholine
Acetylcholine
Adrenergic receptor
Adrenergic receptor
Muscarinic receptor
Nicotinic receptor
Effector organs
Striated muscle

AUTONOMIC NERVOUS SYSTEM

consists of :

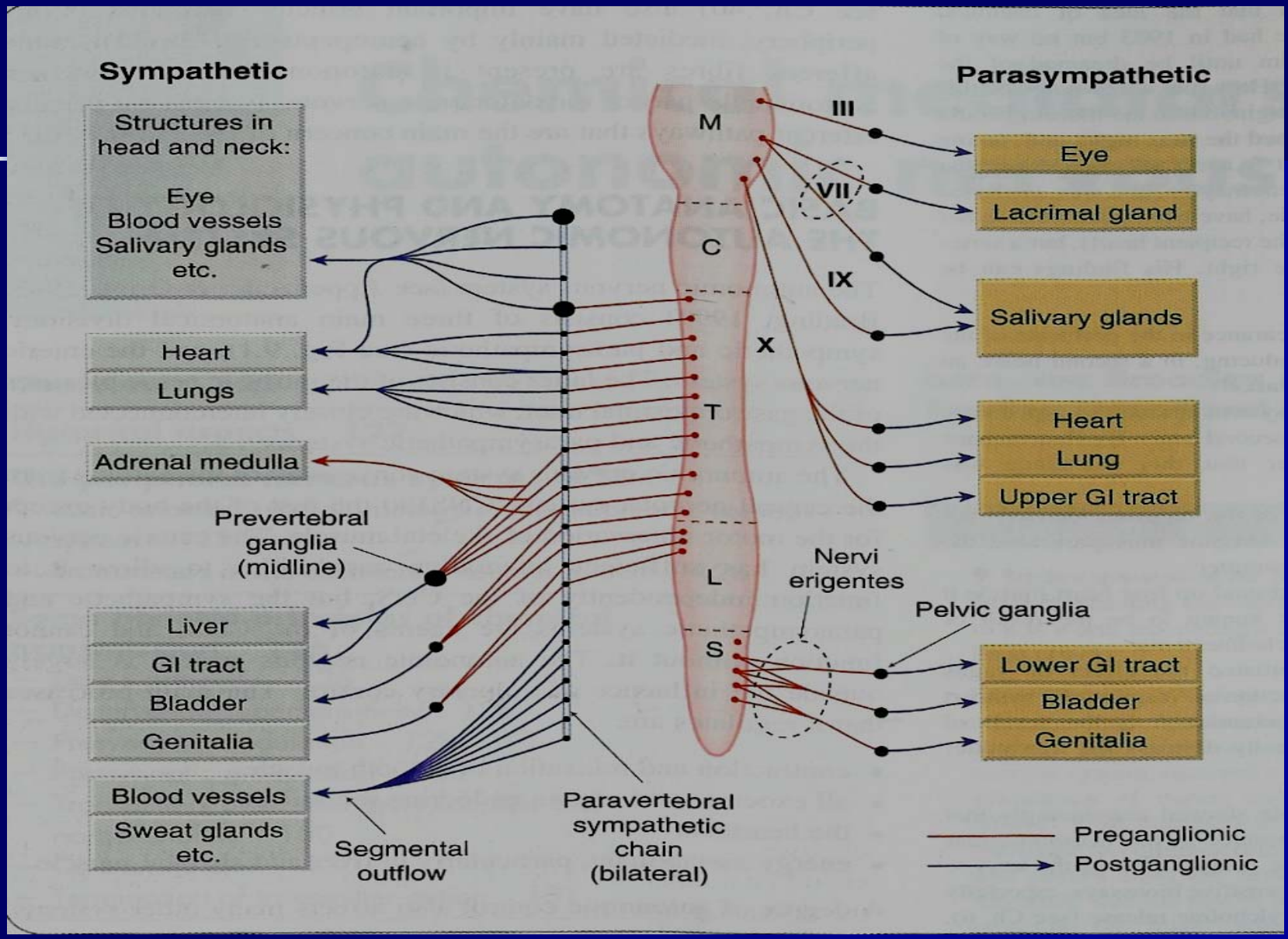
1. The sympathetic or thoracolumbar outflow.

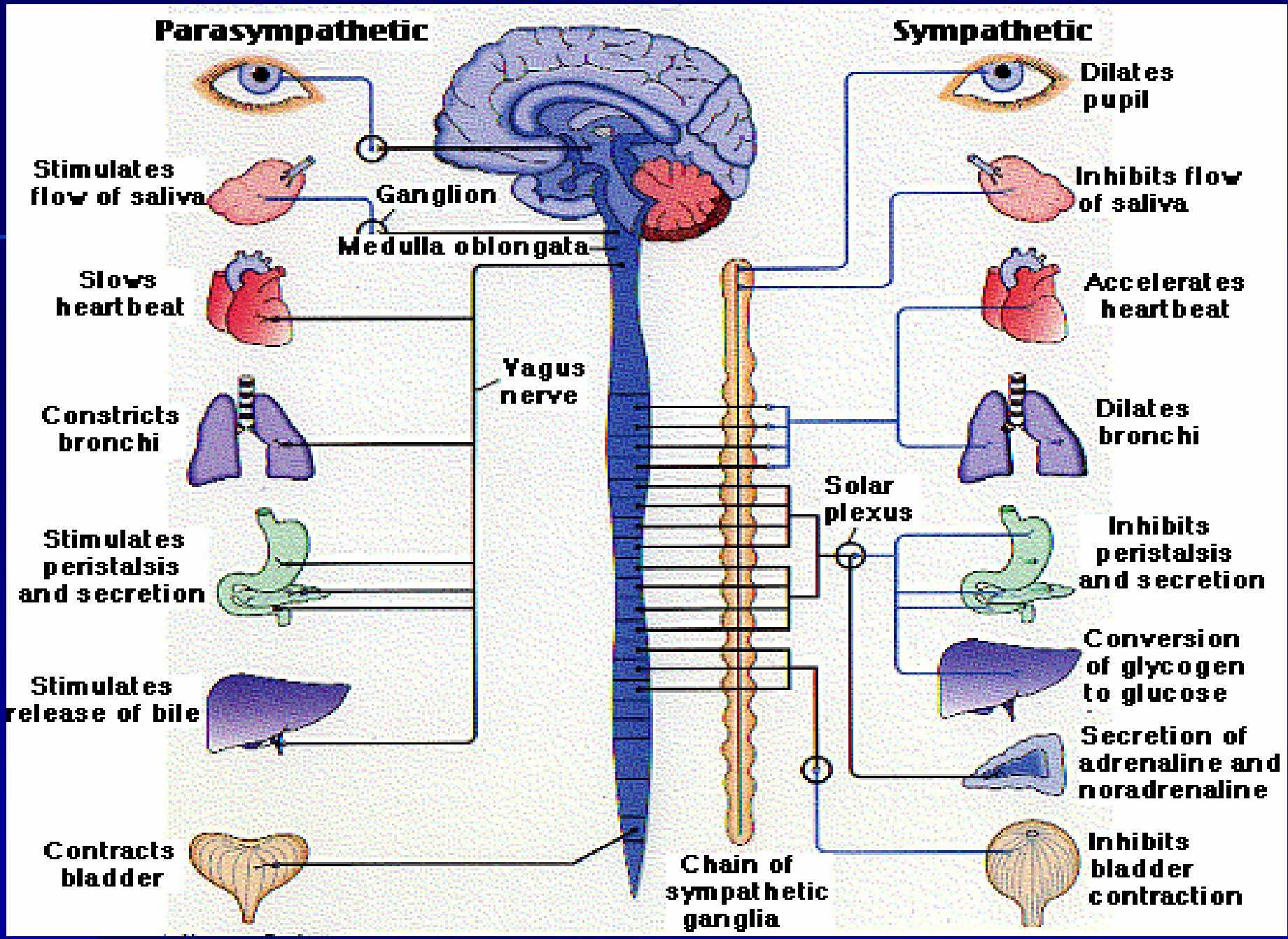
2. The parasympathetic or craniosacral outflow.

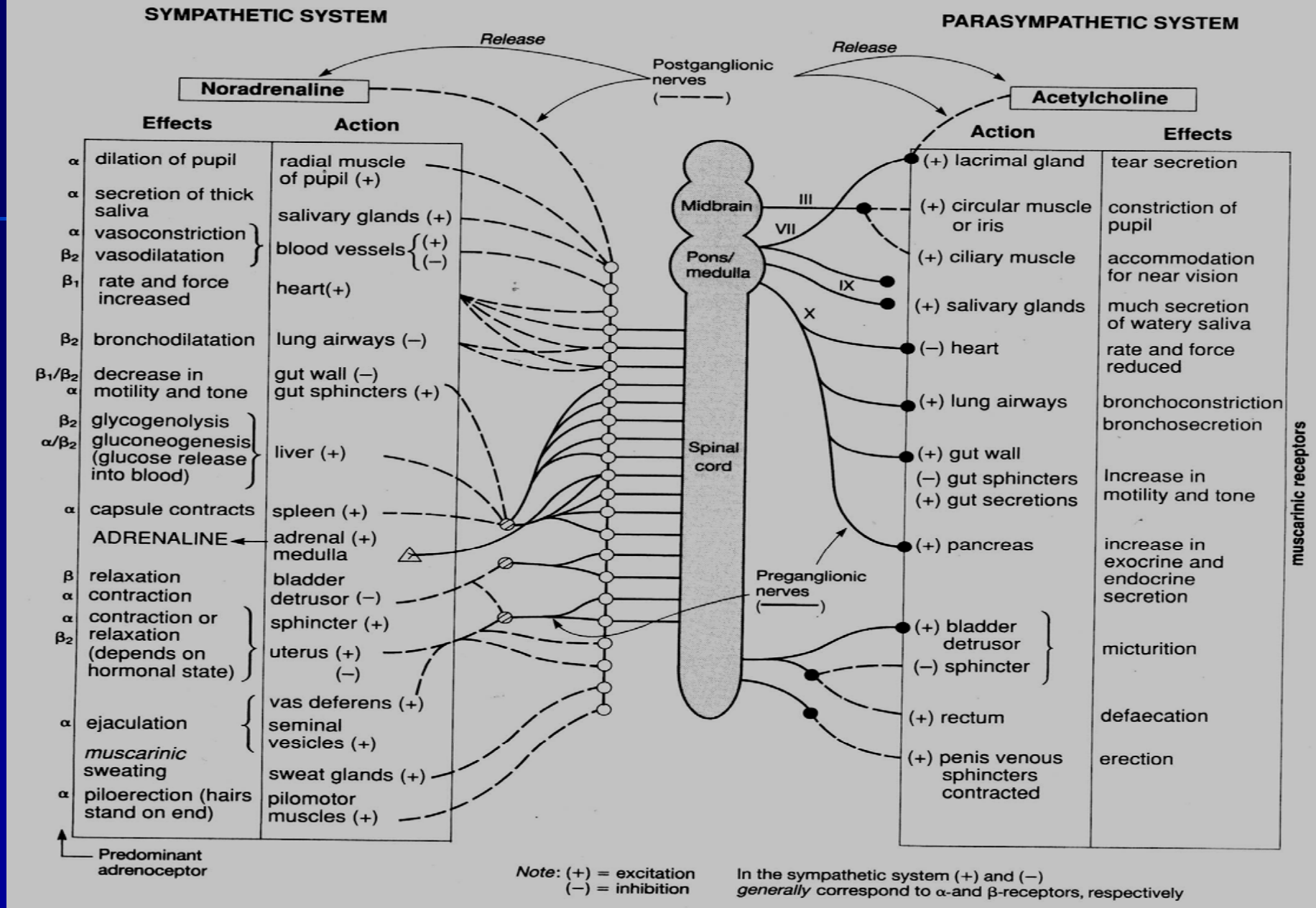
Anatomy Of The Autonomic Nervous System

Sympathetic	Parasympathetic
Thoracolumbar Preganglionic fibers leave CNS through first thoracic to second lumbar segments of spinal nerves	**Craniosacral** Preganglionic fibers leave the CNS through cranial nerves (3,7,9,10) and sacral segments of spinal cord
Preganglionic is shorter than postganglionic	Preganglionic is longer than postganglionic
Ganglia form chain near the spinal cord.	Ganglia present near organs innervated or nearly embedded in it
Ergotropic system. (Fight & flight)	Trophotropic system. (rest & digest)

ANATOMY OF THE AUTONOMIC NERVOUS SYSTEM




Parasympathetic
Sympathetic
Dilates pupil
Stimulates flow of saliva
Ganglion
Medulla oblongata
Inhibits flow of saliva
Slows heartbeat
Accelerates heartbeat
Vagus nerve
Constricts bronchi
Dilates bronchi
Solar plexus
Stimulates peristalsis and secretion
Inhibits peristalsis and secretion
Conversion of glycogen to glucose
Stimulates release of bile
Secretion of adrenaline and noradrenaline
Contracts bladder
Chain of sympathetic ganglia
Inhibits bladder contraction


SYMPATHETIC SYSTEM
PARASYMPATHETIC SYSTEM
Release
Noradrenaline
Postganglionic nerves (———)
Release
Acetylcholine
Effects
Action
Action
Effects
α dilation of pupil
radial muscle of pupil (+)
α secretion of thick saliva
salivary glands (+)
α vasoconstriction
β2 vasodilatation
blood vessels (+) (–)
β1 rate and force increased
heart(+)
β2 bronchodilatation
lung airways (–)
β1/β2 decrease in motility and tone
α
gut wall (–)
gut sphincters (+)
β2 glycogenolysis
α/β2 gluconeogenesis (glucose release into blood)
liver (+)
α capsule contracts
spleen (+)
ADRENALINE
adrenal (+) medulla
β relaxation
α contraction
bladder detrusor (–)
α contraction or
β2 relaxation (depends on hormonal state)
sphincter (+)
uterus (+) (–)
α ejaculation
vas deferens (+)
seminal vesicles (+)
muscarinic sweating
sweat glands (+)
α piloerection (hairs stand on end)
pilomotor muscles (+)
Predominant adrenoceptor
Midbrain
Pons/ medulla
Spinal cord
III
VII
IX
X
Preganglionic nerves (———)
(+) lacrimal gland
tear secretion
(+) circular muscle or iris
constriction of pupil
(+) ciliary muscle
accommodation for near vision
(+) salivary glands
much secretion of watery saliva
(–) heart
rate and force reduced
(+) lung airways
bronchoconstriction
bronchosecretion
(+) gut wall
(–) gut sphincters
(+) gut secretions
Increase in motility and tone
(+) pancreas
increase in exocrine and endocrine secretion
(+) bladder detrusor
(–) sphincter
micturition
(+) rectum
defaecation
(+) penis venous sphincters contracted
erection
muscarinic receptors
Note: (+) = excitation
(–) = inhibition
In the sympathetic system (+) and (–) generally correspond to α-and β-receptors, respectively

Innervation by autonomic nervous system

Most organs are dually innervated by both sympathetic and parasympathetic system BUT **one system** usually predominates

Some organs as <u>adrenal medulla, kidney, blood vessels, sweat glands and pilomotor muscles</u> receive only **sympathetic system.**

Neurotransmitters

Chemical substances responsible for communication between nerve cells and between nerve cells and effector organs.

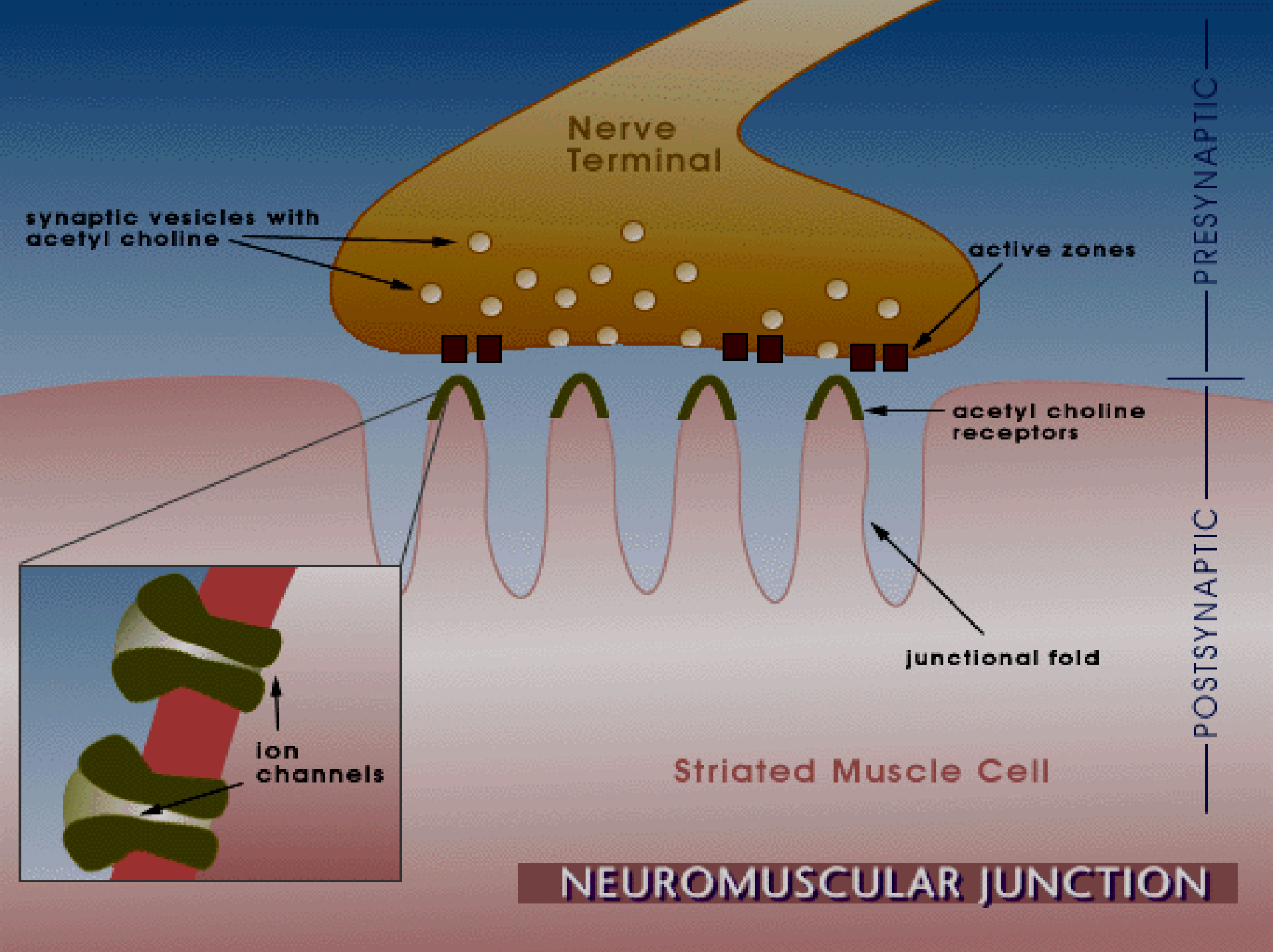
Neurotransmitter in **sympathetic** system is **noradrenaline** and nerves are **adrenergic**

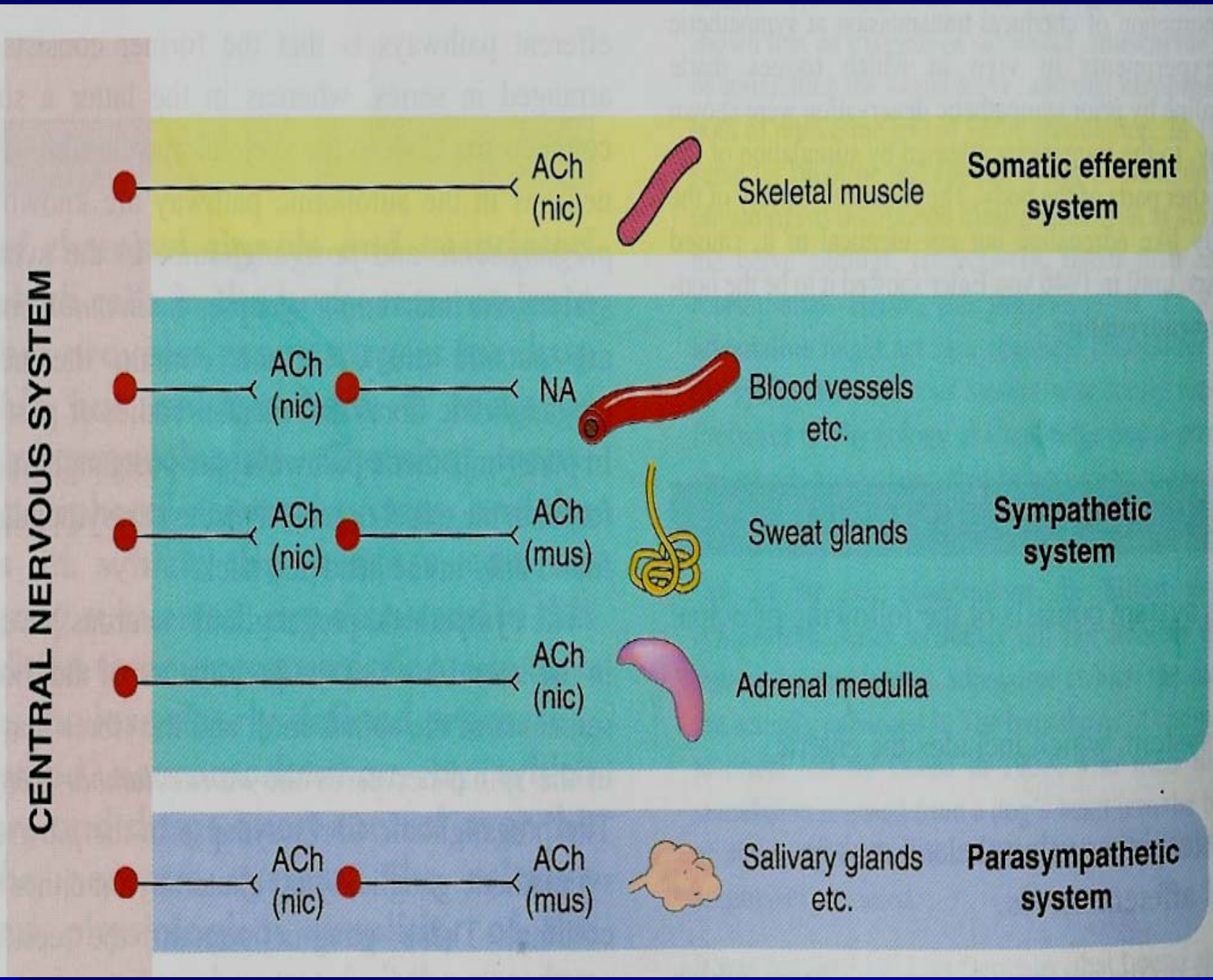
Neurotransmitter in **parasympathetic** system is **acetylcholine** and nerves are **cholinergic**

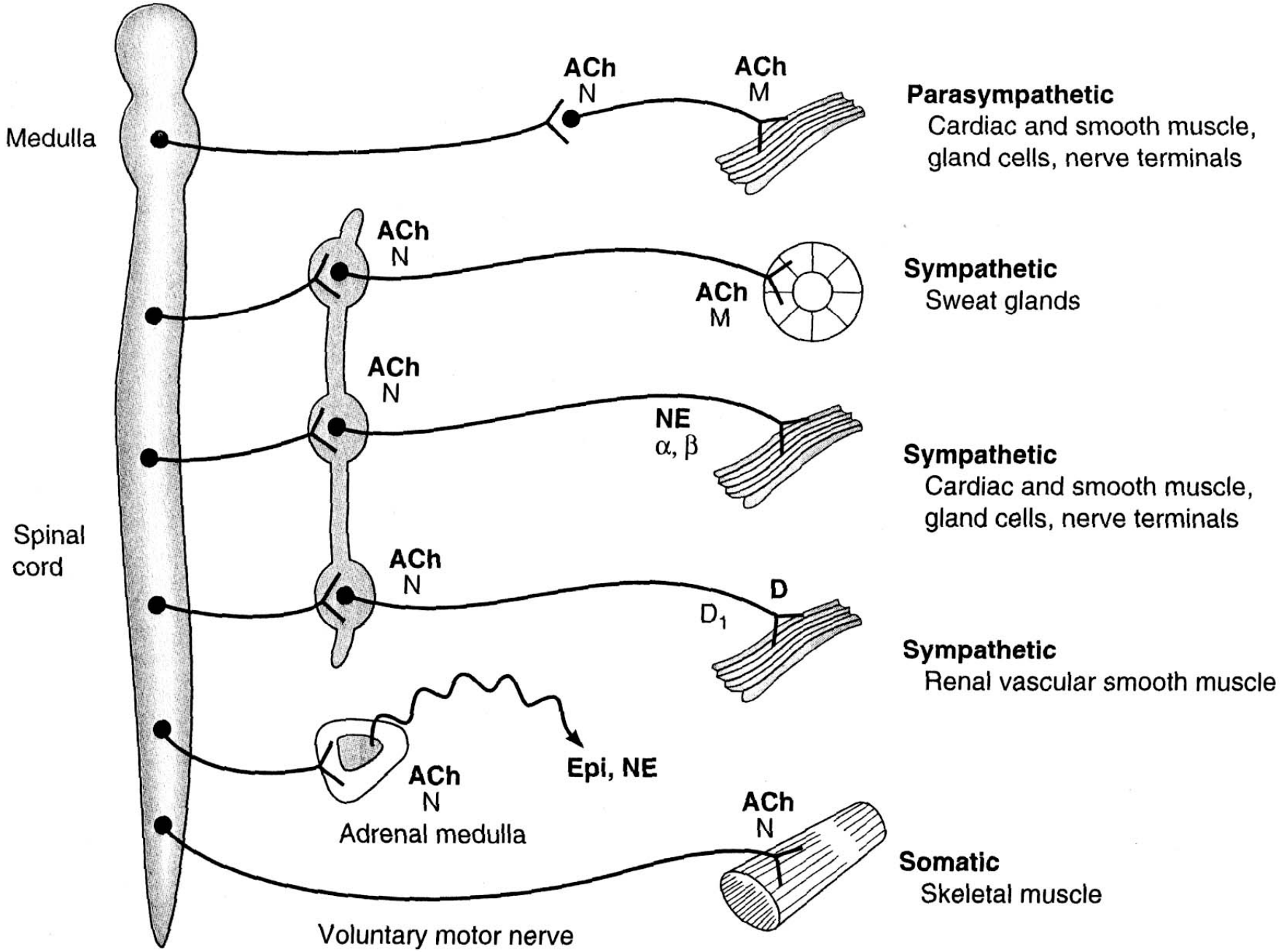
Cholinergic nervous system

Sites of Ach release

1. Neuromuscular junction.
2. **Autonomic ganglia:** all preganglionic nerve fibers of both sympathetic and parasymp nerves.
3. **Parasympathetic** postganglionic fibers.
4. **Sympathetic** postganglionic fibers to sweat glands.
5. **Preganglionic** sympathetic nerve to **Adrenal medulla.**


Nerve Terminal
synaptic vesicles with acetyl choline
active zones
PRESYNAPTIC
acetyl choline receptors
POSTSYNAPTIC
junctional fold
ion channels
Striated Muscle Cell
NEUROMUSCULAR JUNCTION


CENTRAL NERVOUS SYSTEM
ACh (nic)
Skeletal muscle
Somatic efferent system
ACh (nic)
NA
Blood vessels etc.
ACh (nic)
ACh (mus)
Sweat glands
Sympathetic system
ACh (nic)
Adrenal medulla
ACh (nic)
ACh (mus)
Salivary glands etc.
Parasympathetic system


Medulla
Spinal cord
ACh
N
ACh
M
Parasympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh
N
ACh
M
Sympathetic
Sweat glands
ACh
N
NE
α, β
Sympathetic
Cardiac and smooth muscle, gland cells, nerve terminals
ACh
N
D
D1
Sympathetic
Renal vascular smooth muscle
Epi, NE
ACh
N
Adrenal medulla
ACh
N
Somatic
Skeletal muscle
Voluntary motor nerve

CHOLINERGIC TRANSMISSION

Consists of :

- Synthesis of acetylcholine (Ach)
- Storage
- Release
- Binding to receptors
- Metabolism (fate).
- Recycling of the choline

CHOLINERGIC TRANSMISSION

1) **Synthesis**

- Choline is transported into cytoplasm of the cholinergic presynaptic nerve terminals by carrier
- Choline + acetyl CoA $\rightarrow$ ACh + CoA

(Inhibition by hemicholinium, triethylcholine)

2) Storage

ACh is transported into the storage vesicles by active transport system

(Inhibition by vesamicol)

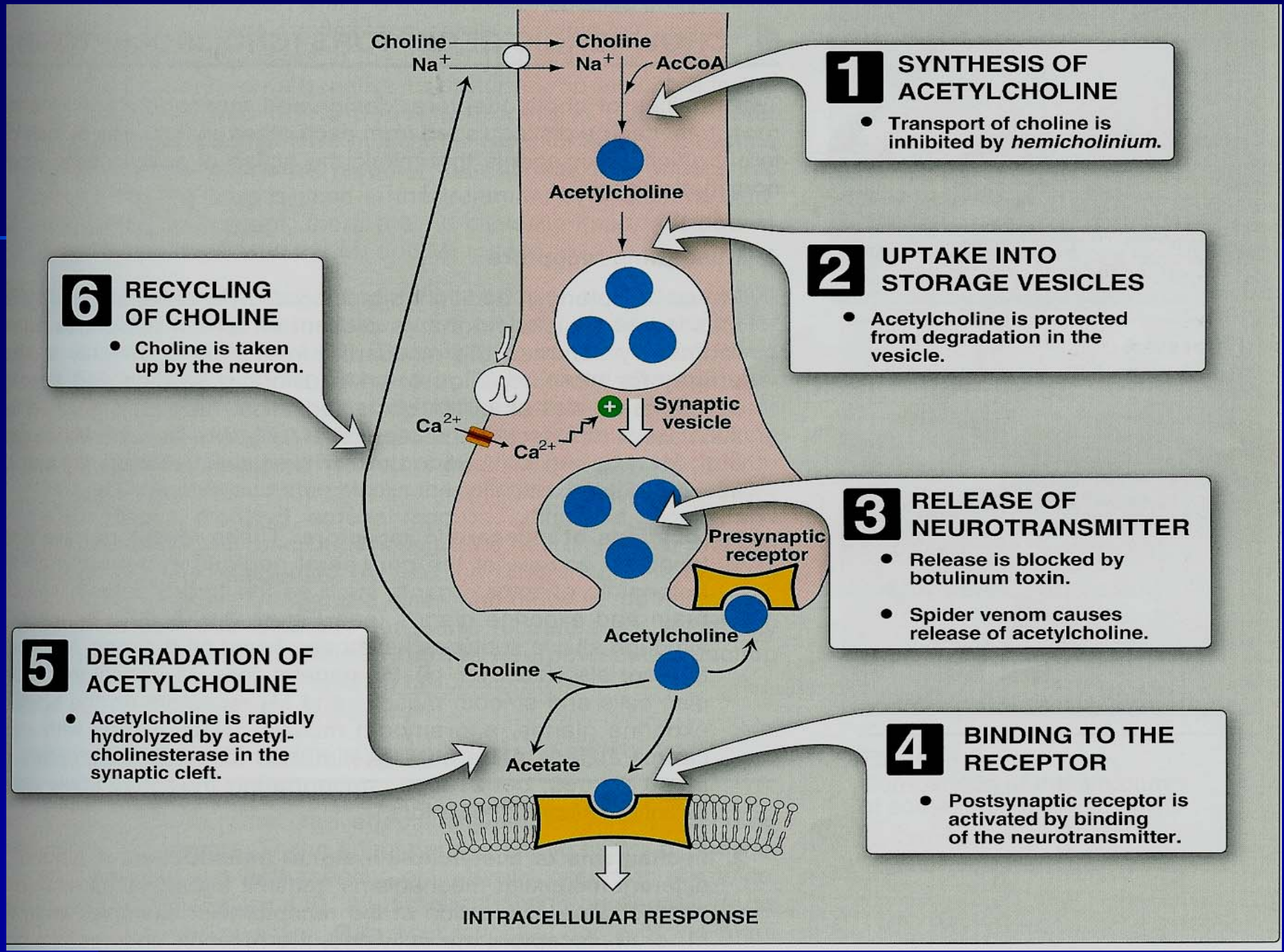
CHOLINERGIC TRANSMISSION

3) Release

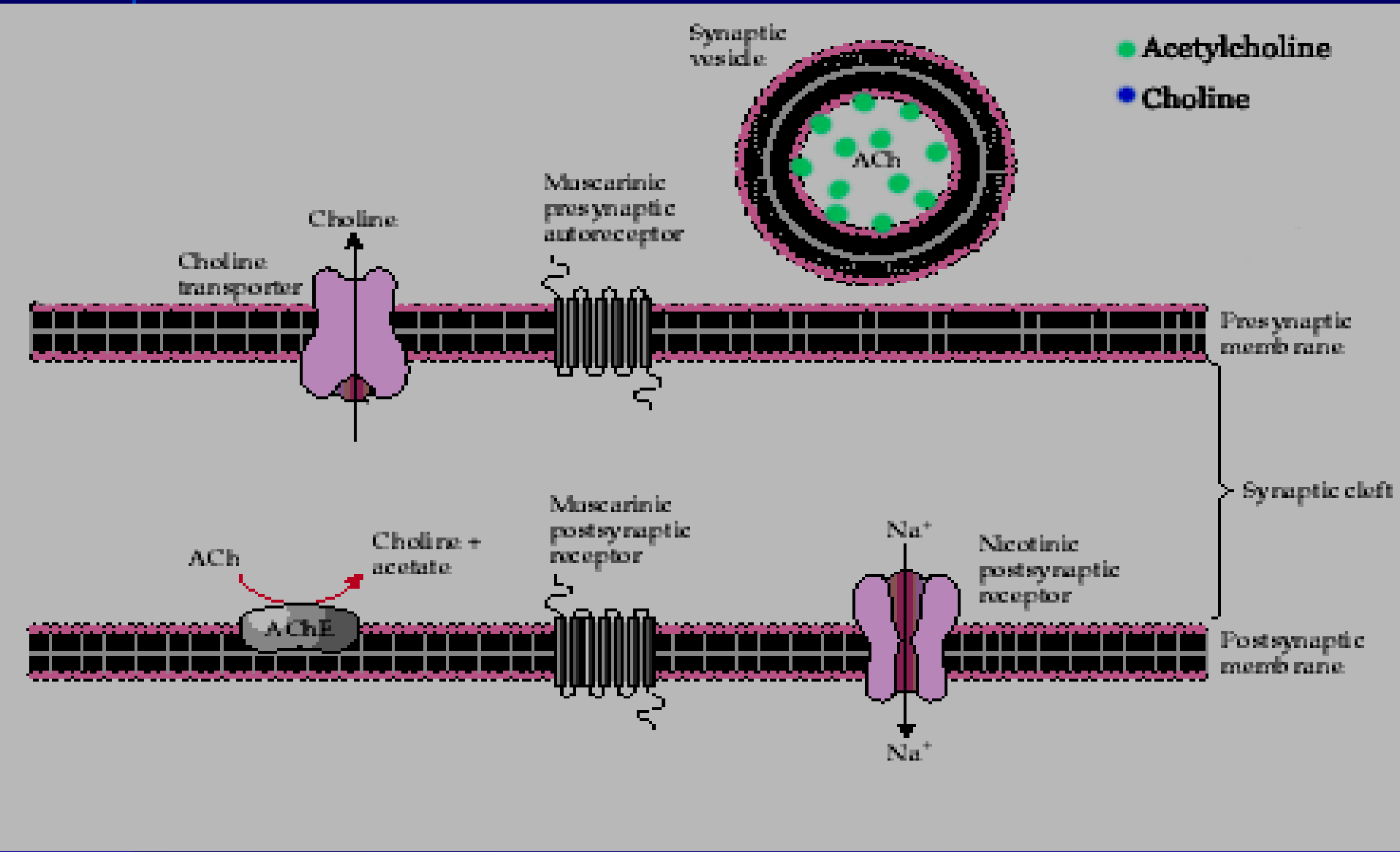
ACh is released upon nerve stimulation → influx of calcium → exocytosis → Ach release into synaptic cleft

(Inhibition by Magnesium, aminoglcosides)

3) Metabolism (FATE) **acetylcholinesterase**


Choline
Na+
Choline
Na+
AcCoA
Acetylcholine
1 SYNTHESIS OF ACETYLCHOLINE
• Transport of choline is inhibited by hemicholinium.
2 UPTAKE INTO STORAGE VESICLES
• Acetylcholine is protected from degradation in the vesicle.
6 RECYCLING OF CHOLINE
• Choline is taken up by the neuron.
Ca2+
Ca2+
Synaptic vesicle
3 RELEASE OF NEUROTRANSMITTER
• Release is blocked by botulinum toxin.
• Spider venom causes release of acetylcholine.
Presynaptic receptor
Acetylcholine
Choline
5 DEGRADATION OF ACETYLCHOLINE
• Acetylcholine is rapidly hydrolyzed by acetyl-cholinesterase in the synaptic cleft.
Acetate
4 BINDING TO THE RECEPTOR
• Postsynaptic receptor is activated by binding of the neurotransmitter.
INTRACELLULAR RESPONSE

Cholinergic nervous system
Cholinergic transmission



CHOLINERGIC TRANSMISSION

True Cholinesterase	Pseudocholinesterase
Specific	Non specific
Cholinergic fibers, RBC, CSF	Plasma, liver, skin, intestine
Slow turnover, 120 day	Rapid turnover
ACh, methacholine	Succinylcholine, Butyrylcholine

Cholinergic receptors

1. **Nicotinic** (Central cholinergic) receptors.

2. **Muscarinic** (Peripheral cholinergic) receptors.

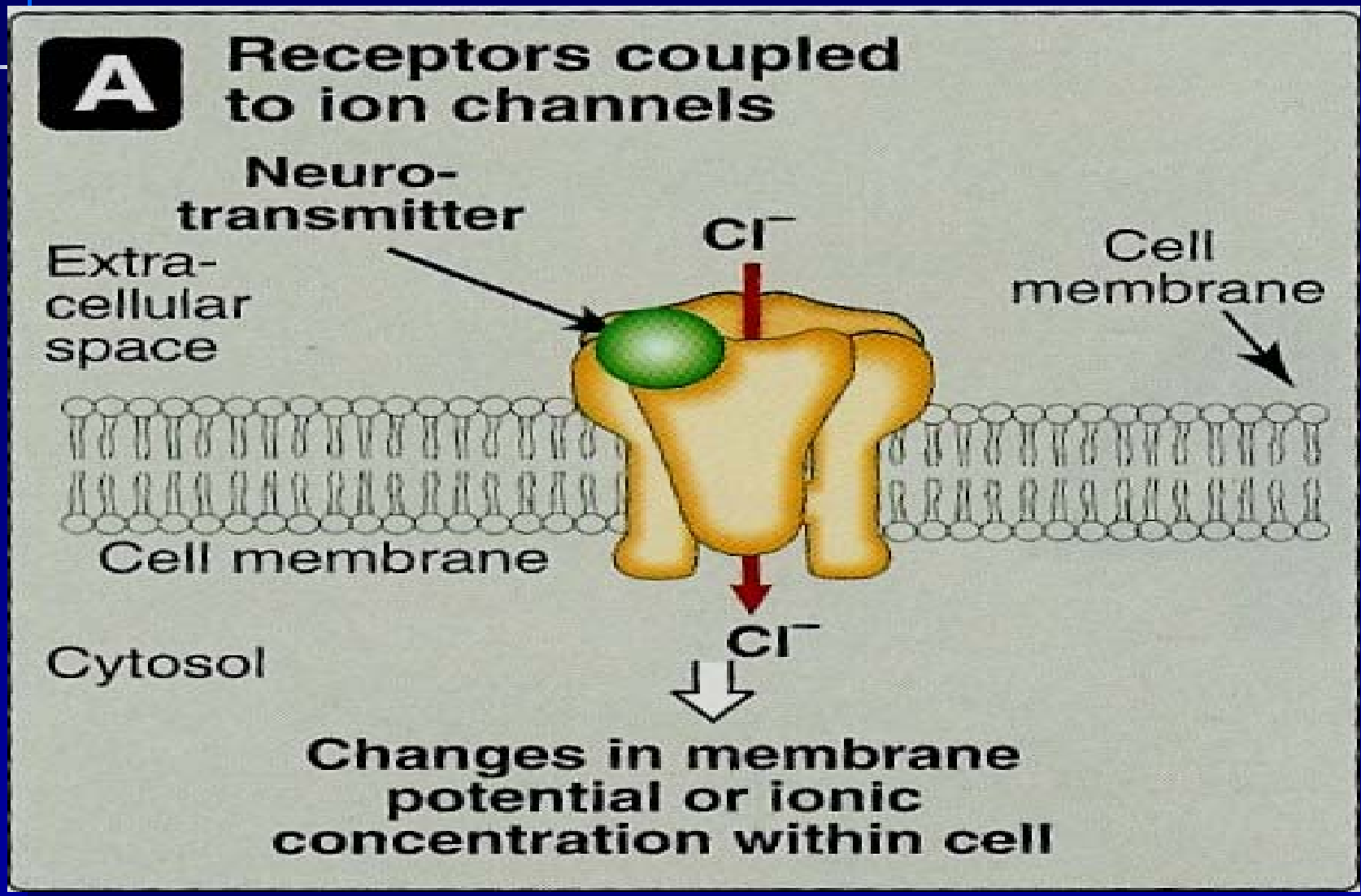
Nicotinic receptors

ion channels-linked receptors (Fast)

Types

1. Neuronal (NN).
2. Muscular (NM).

Nicotinic receptors



Locations of nicotinic receptors

1. Autonomic ganglia NN (neuronal type).
2. Adrenal medulla.
3. CNS
3. Neuromuscular junction (NM)

Cholinergic receptors
Muscarinic receptors

- M1—M5
- M1,M3,M5 are excitatory .
- M2,M4 are inhibitory .
- C.N.S has all receptors .
- Periphery i.e. G.I.T , U.T .etc have M2&M3.
- The heart mainly M2 .

Muscarinic receptors
(Peripheral cholinergic receptors)

G-protein linked receptors

Five subclasses ; M_1 - M_5

M_1,M_3,M_5 are excitatory in function.

M_2,M_4 are inhibitory in function .

Locations

in all effector organs innervated by cholinergic fibers as

- Smooth muscles (GIT, urinary tract, bronchial muscles).
- Exocrine glands, C.N.S

M1 (Neural)

Autonomic ganglia, CNS, gastric parietal cells

Excitatory

Activation of phospholipase C ↑ IP3 & DAG

CNS excitation

Gastric acid secretion

M2 (Cardiac)

Heart – Presynaptic cholinergic fibers

Inhibitory

- **Inhibition of adenyl cyclase (↓cAMP)**
- **Activation of K channels**

Cardiac inhibition

Presynaptic inhibition

M3 (Glandular)

Exocrine glands - smooth muscles

Vascular endothelium

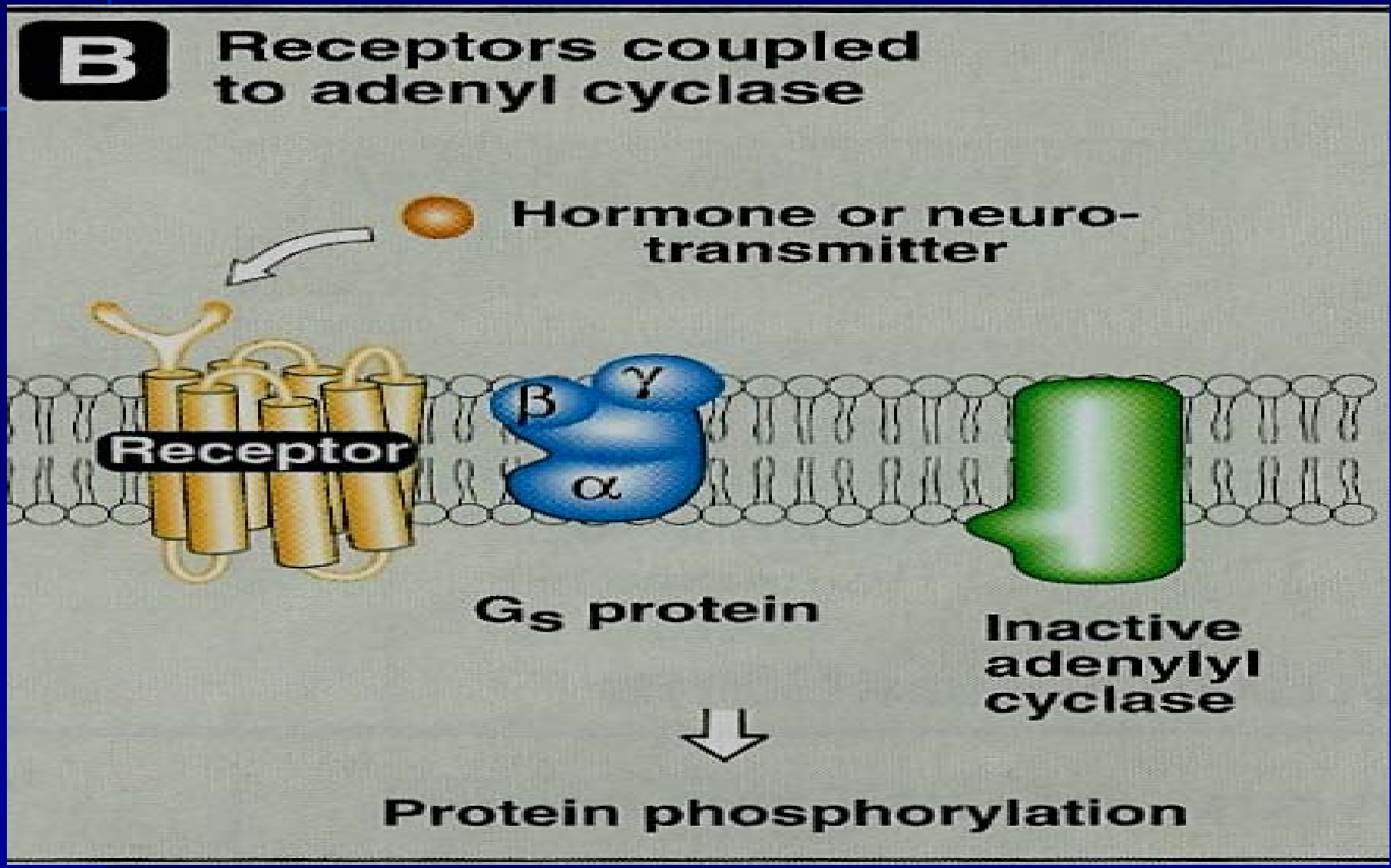
Excitatory

- **Secretion**
- **Smooth muscle contraction**
- **Vasodilatation (via NO)**

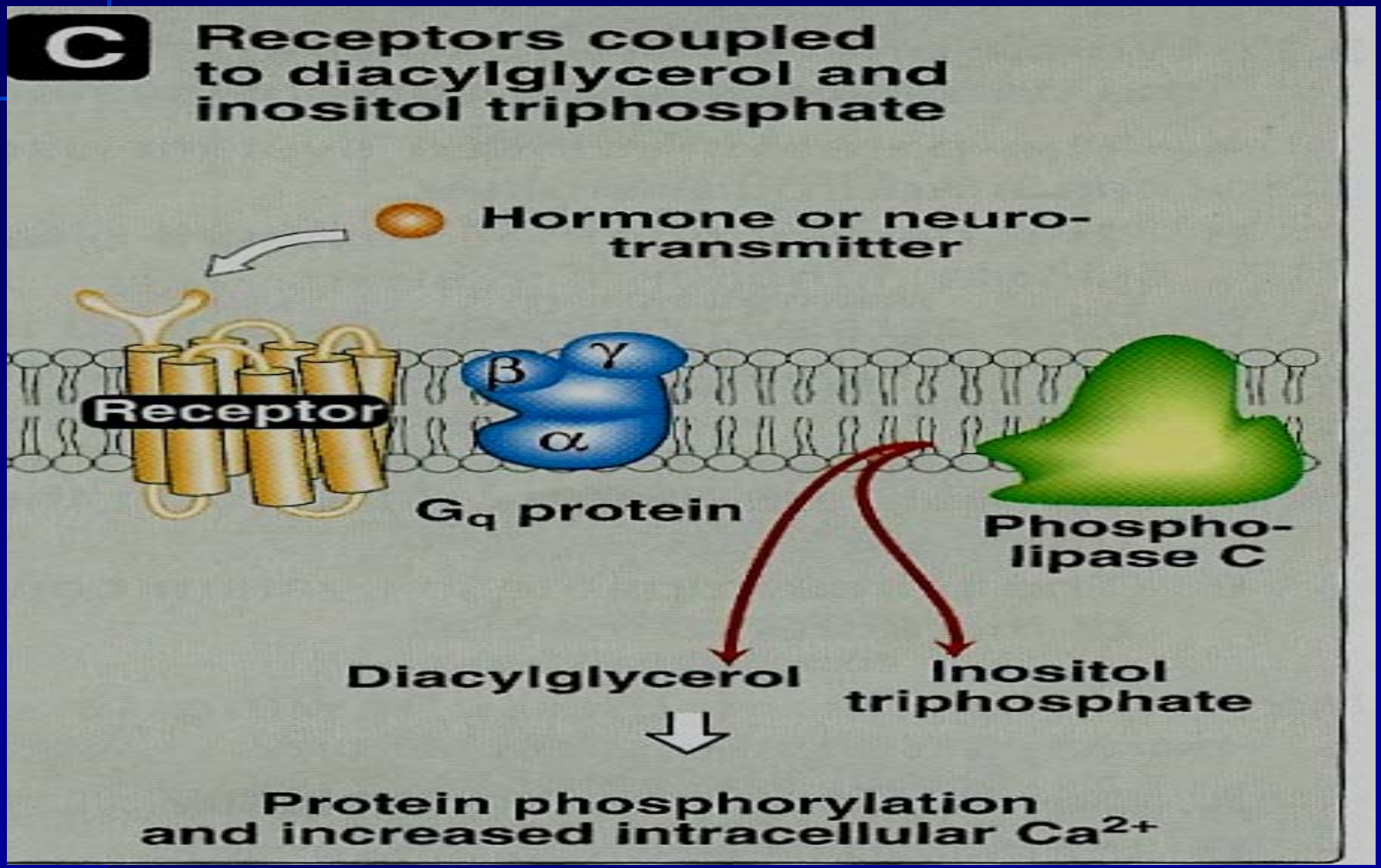
Activation of phospholipase C---increased IP3.

Receptor	Locations	Effects
M1 (Neural) Excitatory	CNS Autonomic ganglia gastric parietal cells	CNS excitation Gastric acid secretion Activation of phospholipase C ↑ IP3 &DAG → ↑ Ca
M2 (Cardiac) Inhibitory	Heart Presynaptic cholinergic fibers	Cardiac inhibition Presynaptic inhibition ▪ Inhibition of adenyl cyclase (↓ cAMP) ▪ Opening of K channels
M3 (Glandular) Excitatory	Exocrine glands Smooth muscles Vascular endothelium	▪ Secretion ▪ Smooth muscle contraction ▪ Vasodilatation (via NO) ▪ Activation of phospholipase C ↑ IP3 & DAG.

Muscarinic Receptors



Excitatory Muscarinic receptors



What are actions of cholinergic system activation?

- Nicotinic actions
- Muscarininc actions
- CNS

NICOTINIC ACTIONS OF ACH

Skeletal muscles:

- stimulation → muscle fasciculation (twitching).
- High conc → persistent depolarization & paralysis.

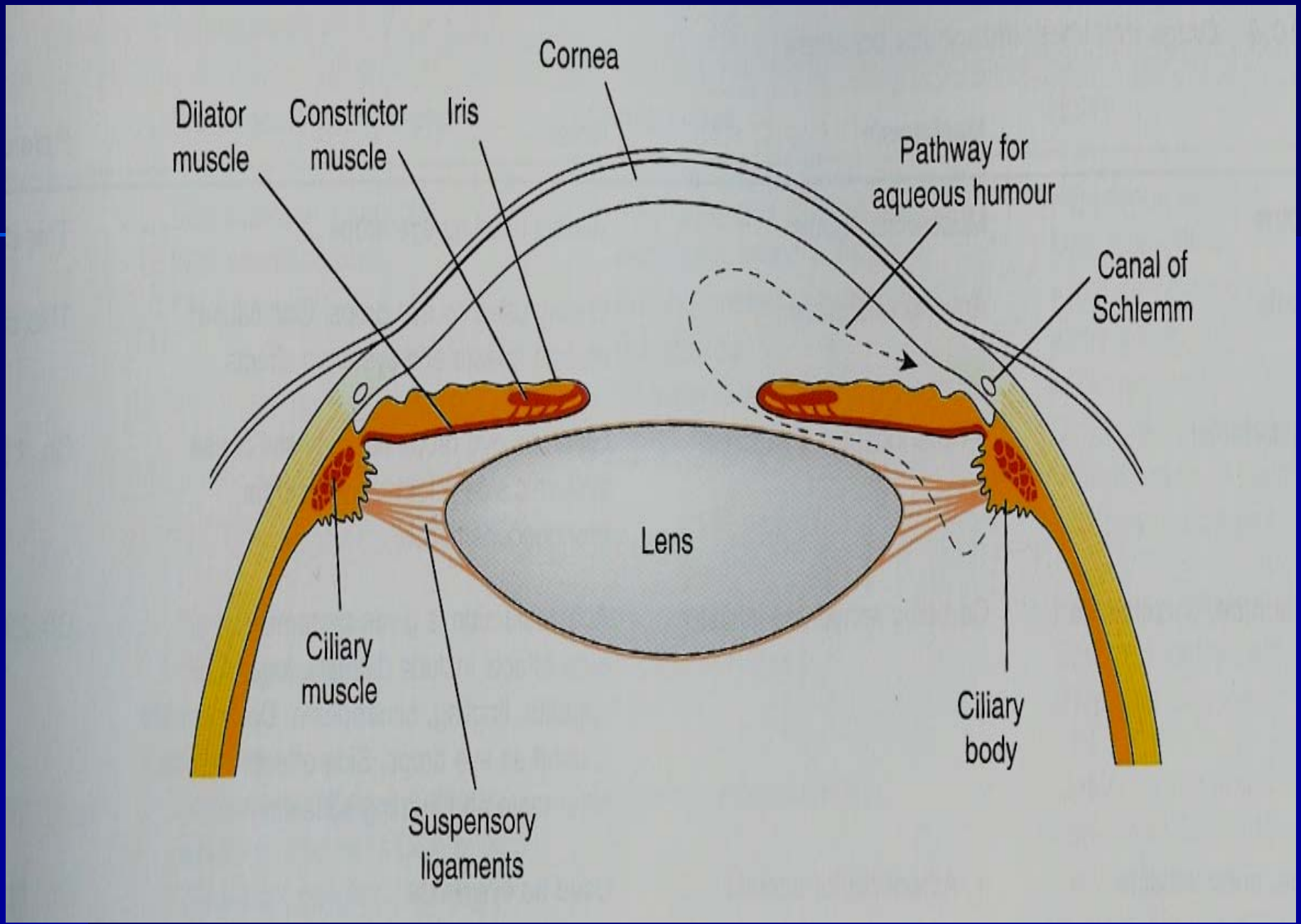
Ganglia: stimulation of sympathetic and parasympathetic ganglia

Adrenal medulla release of catecholamines (A & NA).

Muscarinic actions of Ach

Organ	Effect of			
	Sympathetic Activity		Parasympathetic Activity	
	Action[1]	Receptor[2]	Action	Receptor[2]
Eye				
Iris				
Radial muscle	Contracts	α_1	. . .	. . .
Circular muscle	. . .	. . .	Contracts	M_3
Ciliary muscle	[Relaxes]	β	Contracts	M_3
Heart				
Sinoatrial node	Accelerates	β_1,β_2	Decelerates	M_2
Ectopic pacemakers	Accelerates	β_1,β_2	. . .	. . .
Contractility	Increases	β_1,β_2	Decreases (atria)	M_2
Blood vessels				
Skin, splanchnic vessels	Contracts	α	. . .	. . .
Skeletal muscle vessels	Relaxes	β_2	. . .	. . .
	[Contracts]	α	. . .	. . .
	Relaxes	M^3	. . .	. . .
Endothelium			Releases EDRF	M_3[4]
Bronchiolar smooth muscle	Relaxes	β_2	Contracts	M_3
Gastrointestinal tract				
Smooth muscle				
Walls	Relaxes	α_2,[5] β_2	Contracts	M_3
Sphincters	Contracts	α_1	Relaxes	M_3
Secretion	. . .	. . .	Increases	M_3
Myenteric plexus			Activates	M_1
Genitourinary smooth muscle				
Bladder wall	Relaxes	β_2	Contracts	M_3
Sphincter	Contracts	α_1	Relaxes	M_3
Uterus, pregnant	Relaxes	β_2	. . .	. . .
	Contracts	α	Contracts	M_3
Penis, seminal vesicles	Ejaculation	α	Erection	M
Skin				
Pilomotor smooth muscle	Contracts	α	. . .	. . .
Sweat glands			. . .	. . .
Thermoregulatory	Increases	M	. . .	. . .
Apocrine (stress)	Increases	α	. . .	. . .
Metabolic functions				
Liver	Gluconeogenesis	β_2,α	. . .	. . .
Liver	Glycogenolysis	β_2,α	. . .	. . .
Fat cells	Lipolysis	β_3	. . .	. . .
Kidney	Renin release	β_1	. . .	. . .
Autonomic nerve endings				
Sympathetic	. . .	. . .	Decreases NE release	M[6]
Parasympathetic	Decreases ACh release	α	. . .	. . .

Organ	Parasympathetic Activity	
	Action	Receptor[2]
Eye		
Iris		
Radial muscle	. . .	. . .
Circular muscle	Contracts	M_3
Ciliary muscle	Contracts	M_3
Heart		
Sinoatrial node	Decelerates	M_2
Ectopic pacemakers	. . .	. . .
Contractility	Decreases (atria)	M_2
Blood vessels		
Skin, splanchnic vessels	. . .	. . .
Skeletal muscle vessels	. . .	. . .
	. . .	. . .
	. . .	. . .
Endothelium	Releases EDRF	M_3[4]
Bronchiolar smooth muscle	Contracts	M_3
Gastrointestinal tract		
Smooth muscle		
Walls	Contracts	M_3
Sphincters	Relaxes	M_3
Secretion	Increases	M_3
Myenteric plexus	Activates	M_1
Genitourinary smooth muscle		
Bladder wall	Contracts	M_3
Sphincter	Relaxes	M_3
Uterus, pregnant	. . .	. . .
	Contracts	M_3
Penis, seminal vesicles	Erection	M
Skin		
Pilomotor smooth muscle	. . .	. . .
Sweat glands	. . .	. . .
Thermoregulatory	. . .	. . .
Apocrine (stress)	. . .	. . .
Metabolic functions		
Liver	. . .	. . .
Liver	. . .	. . .
Fat cells	. . .	. . .
Kidney	. . .	. . .
Autonomic nerve endings		
Sympathetic	Decreases NE release	M^6
Parasympathetic	. . .	. . .


Cornea
Dilator muscle
Constrictor muscle
Iris
Pathway for aqueous humour
Canal of Schlemm
Lens
Ciliary muscle
Ciliary body
Suspensory ligaments

CNS actions

Nicotinic actions:

- ADH secretion from hypothalamus
- Inhibition of motor fibers

Muscarinic actions:

- ACh is involved in memory and arousal
- Parkinsonism
- Dementia of Alzheimer: loss of cholinergic neurons.

Cholinomimetics = Parasympathomimetics

These drugs produce actions similar to cholinergic system stimulation

Types

1. Direct cholinomimetics

Act by direct stimulation of nicotinic or muscarinic receptors.

2. Indirect cholinomimetics

They act indirectly by inhibiting acetylcholinesterase thus prevent the degradation of Ach.

Cholinomimetic drugs

Direct cholinomimetics

- Naturally occurring alkaloids e.g. Pilocarpine
- Choline esters
  - Acetylcholine
  - Methacholine
  - Carbachol
  - Bethanechol

Indirect cholinomimetics (anticholinesterases)

- Reversible indirect cholinomimetics
  - Edrophonium
  - Ambenonium
  - Physostigmine
  - Pyridostigmine
  - Neostigmine

- Irreversible indirect cholinomimetics
  - Ecothiophate
  - Isoflurophate

Direct cholinomimetics

Classification

- Naturally occurring alkaloids e.g. Pilocarpine

- Synthetic Choline esters
  - Acetylcholine
  - Methacholine
  - Carbachol
  - Bethanechol

Cholinomimetic drugs

Mechanism of action

Muscarinic agonists

- Activation of phospholipase C → ↑ IP3 & DAG → contraction of smooth muscles
- Increase cGMP → NO release → relaxation
- Inhibition of adenyl cyclase (cAMP)
- Opening of K channels → Hyperpolarization

Nicotinic agonists

- Opening of ion channels → Depolarization

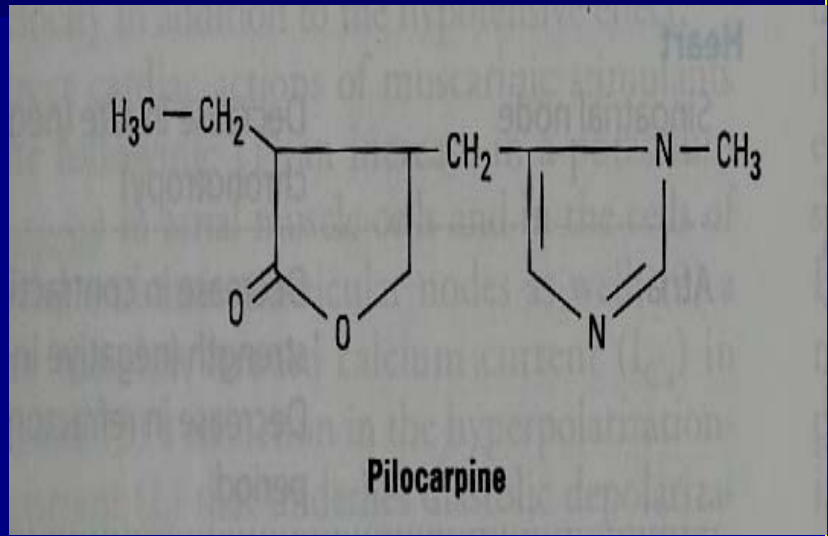
Organ	Response
Eye	
Sphincter muscle of iris	Contraction (miosis)
Ciliary muscle	Contraction for near vision
Heart	
Sinoatrial node	Decrease in rate (negative chronotropy)
Atria	Decrease in contractile strength (negative inotropy). Decrease in refractory period.
Atrioventricular node	Decrease in conduction velocity (negative dromotropy). Increase in refractory period.
Ventricles	Small decrease in contractile strength

Blood vessels Arteries	Dilation (via EDRF). Constriction (high-dose direct effect).
Veins	Dilation (via EDRF). Constriction (high-dose direct effect).
Lung Bronchial muscle	Contraction (bronchoconstrictor)
Bronchial glands	Stimulation
Gastrointestinal tract Motility	Increase
Sphincters	Relaxation
Secretion	Stimulation
Urinary bladder Detrusor	Contraction
Trigone and sphincter	Relaxation
Glands Sweat, salivary, lacrimal, nasopharyngeal	Secretion

Direct Cholinomimetic drugs
1. Naturally occurring alkaloids
Pilocarpine

Chemistry

- Tertiary amine - basic



Pilocarpine

Pharmacokinetics

- It is well absorbed orally
- Can cross BBB.
- Good distribution
- Not degraded by cholinesterases
- Long duration of action
- Excreted unchanged in the urine

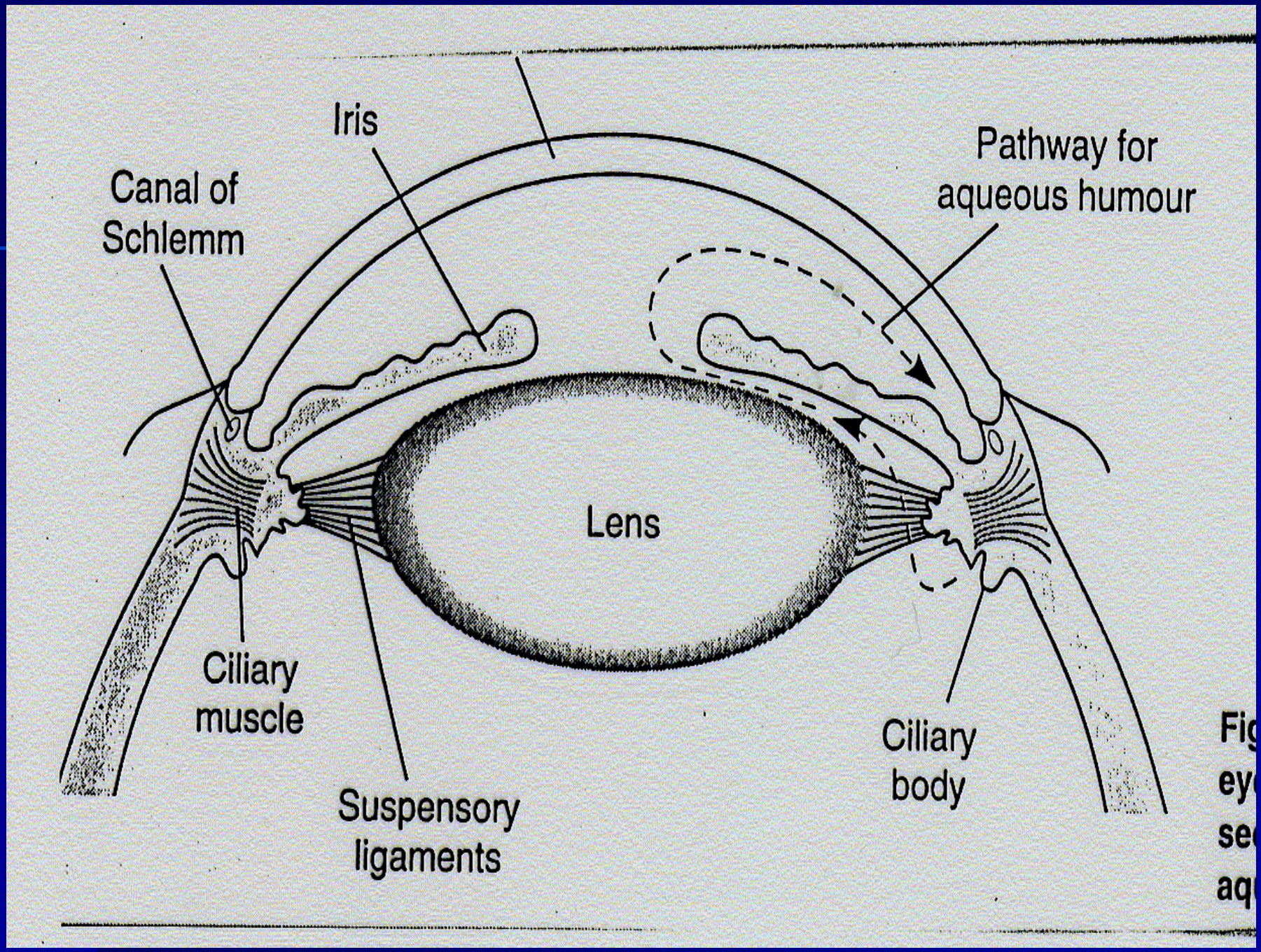
(acidification ↑ excretion).

Pharmacodynamics

1. Direct muscarinic agonist mainly on eye & secretions (saliva, tears, sweat).
2. No nicotinic action.
3. CNS actions

Uses

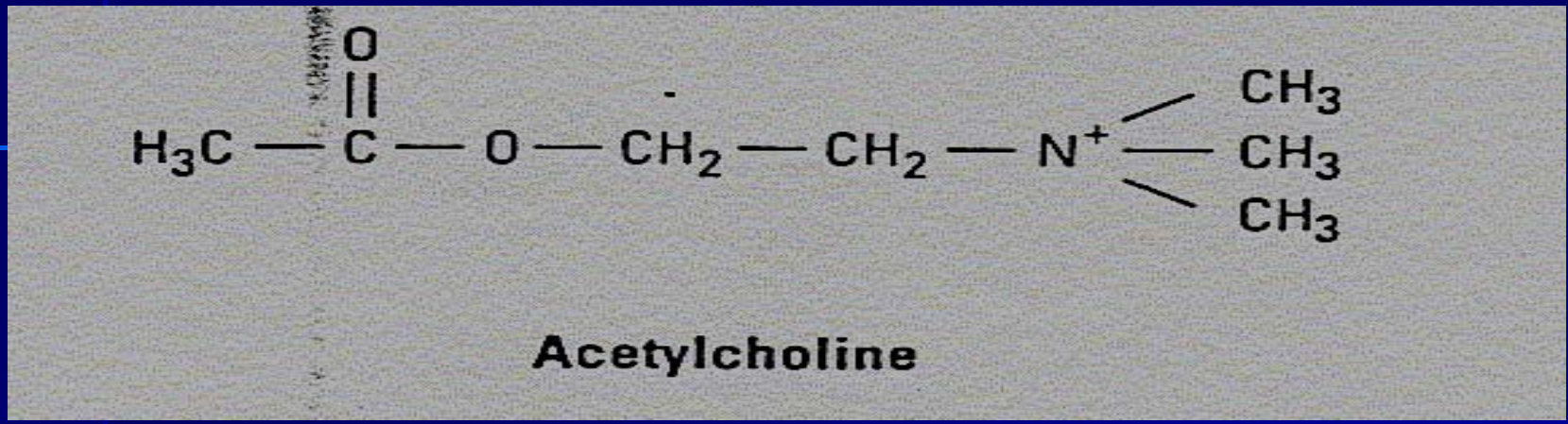
1. Glaucoma
2. Xerostomia (dry mouth).
3. To counteract mydriatics after fundus examination.


Iris
Canal of Schlemm
Pathway for aqueous humour
Lens
Ciliary muscle
Suspensory ligaments
Ciliary body

Direct cholinomimetics

- Acetylcholine & Synthetic Choline esters
  - Acetylcholine
  - Methacholine
  - Carbachol
  - Bethanechol

Acetylcholine (Ach)



Acetylcholine

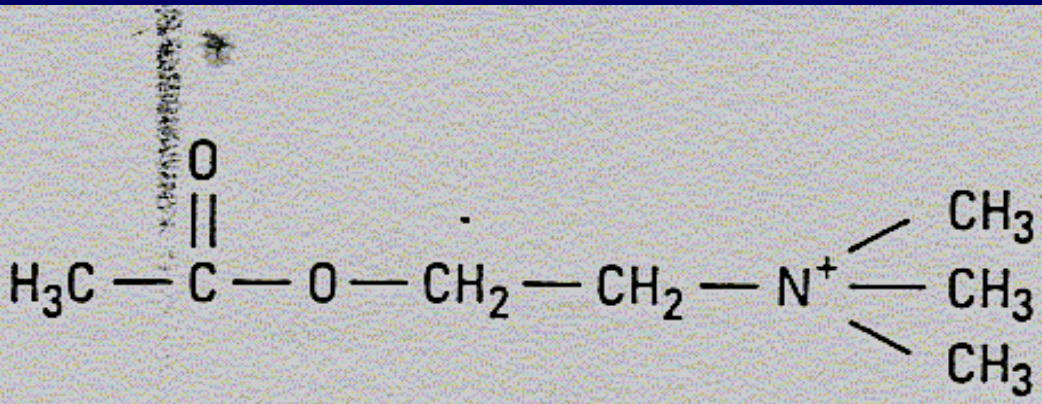
- Quaternary ammonium compound
- Not absorbed orally (given by injection)
- Muscarinic and nicotinic agonist
- Not used due to
  - non selectivity **Why?**
  - short duration of action **Why?**

Synthetic choline esters

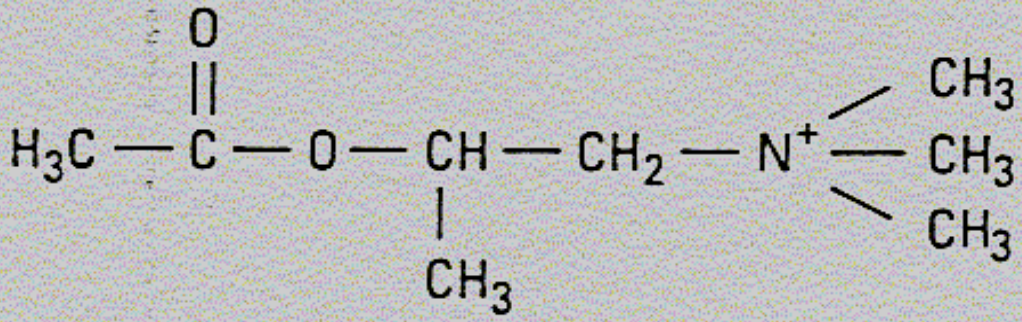
Chemistry

Quaternary ammonium compounds

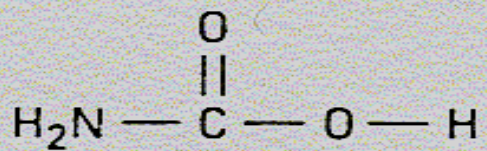
- Methacholine
- Carbachol
- Bethanechol



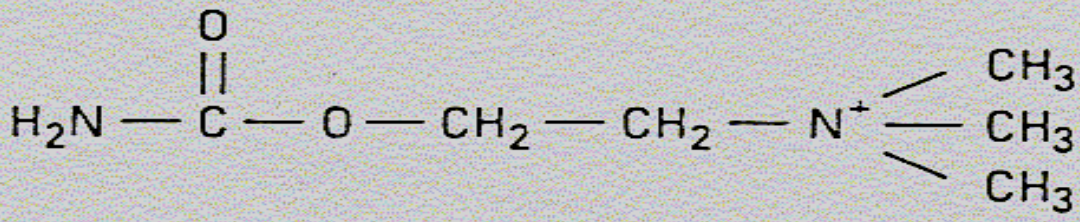
Acetylcholine



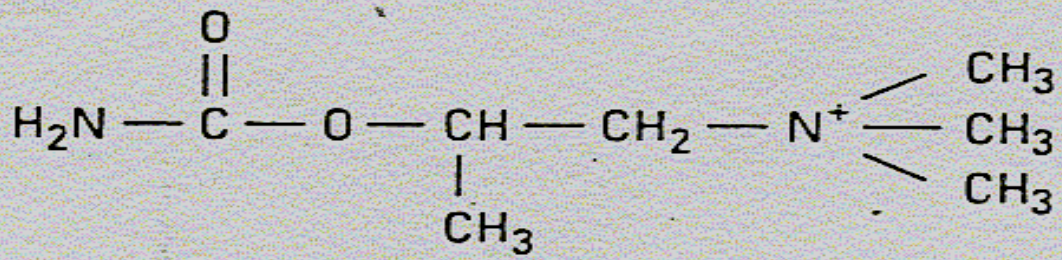
Methacholine
(acetyl-β-methylcholine)



Carbamic acid



Carbachol
(carbamoylcholine)



Bethanechol
(carbamoyl-β-methylcholine)

Kinetics

1. Polar
2. Poor distribution
3. can not cross BBB
4. Metabolized by cholinesterase (variable degree).

Pharmacodynamics

1. Muscarinic agonists

   Methacholine - Bethanechol

2. Muscarinic and Nicotinic agonists

   Acetylcholine - Carbachol

What are the differences between Ach and synthetic choline esters ?

Synthetic choline esters are:

1. More specific.
2. Less or not metabolized by acetylcholinesterase.
3. Have longer duration of action
4. Never given I.V. or I.M.

Methacholine (Muscarinic agonist)

1. Orally-SC.
2. Metabolized by true cholinesterase.
3. Longer duration of action
4. More specific
5. Muscarinic actions on CVS than GIT& UT
6. No nicotinic action.
7. Used for
   - Peripheral vascular disease
   - Paroxysmal atrial tachycardia.

Carbachol (nicotinic & Muscarinic)

1. Not a substrate to acetylcholinesterase.
2. Longer duration of action than Ach
3. Has both muscarinic & nicotinic actions.
4. Muscarinic actions mainly on **Eye, GIT, urinary tract.**
5. Used for
   - Glaucoma
   - Urinary retention & paralytic ileus

Bethanechol (Muscarinic agonist)

- Similar to carbachol **But** it has no effect on **nicotinic receptors**
- Orally- S.C.
- More Preferred than carbachol for paralytic ileus & urinary retention.

	ACh	Methacholine	Carbachol	Bethanechol
Absorption	NOT	Irregular	Complete	Complete
Metabolism	True (+++) Pseudo	True + only	NOT metabolized (Resistant)	NOT metabolized (Resistant)
Duration	Very short	Longer (+)	Longer (++)	Longer (++)
Administ.	I.V.	Oral, S.C.	Oral, S.C., eye drops	Oral, S.C.

	ACh	Methacholine	Carbachol	Bethanechol
Muscarinic	+++	+++	+++	+++
Selectivity	NOT	More on CVS than GIT and urinary bladder	Eye, GIT Urinary bladder	GIT, Urinary bladder
Nicotinic	+++	NO	+++	NO
Uses	NO	•Paroxysmal atrial tachycardia •Peripheral vascular disease	•Glaucoma •Urinary retention •Paralytic ileus	•Urinary retention •Paralytic ileus

Uses

1. Glaucoma (pilocarpine).
2. Paralytic ileus (bethanechol, carbachol).
3. Urinary retention (bethanechol, carbachol).

Contraindications

1. Bronchial asthma.
2. Peptic ulcer.
3. Angina pectoris


Thank you