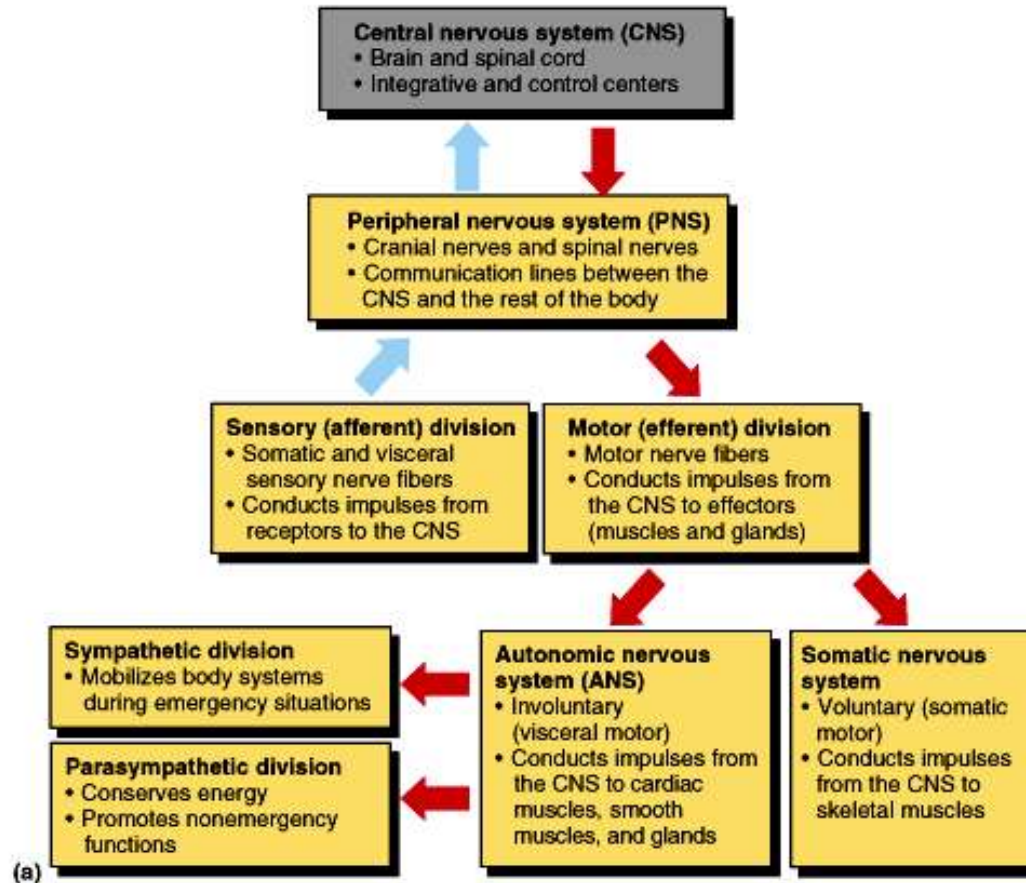


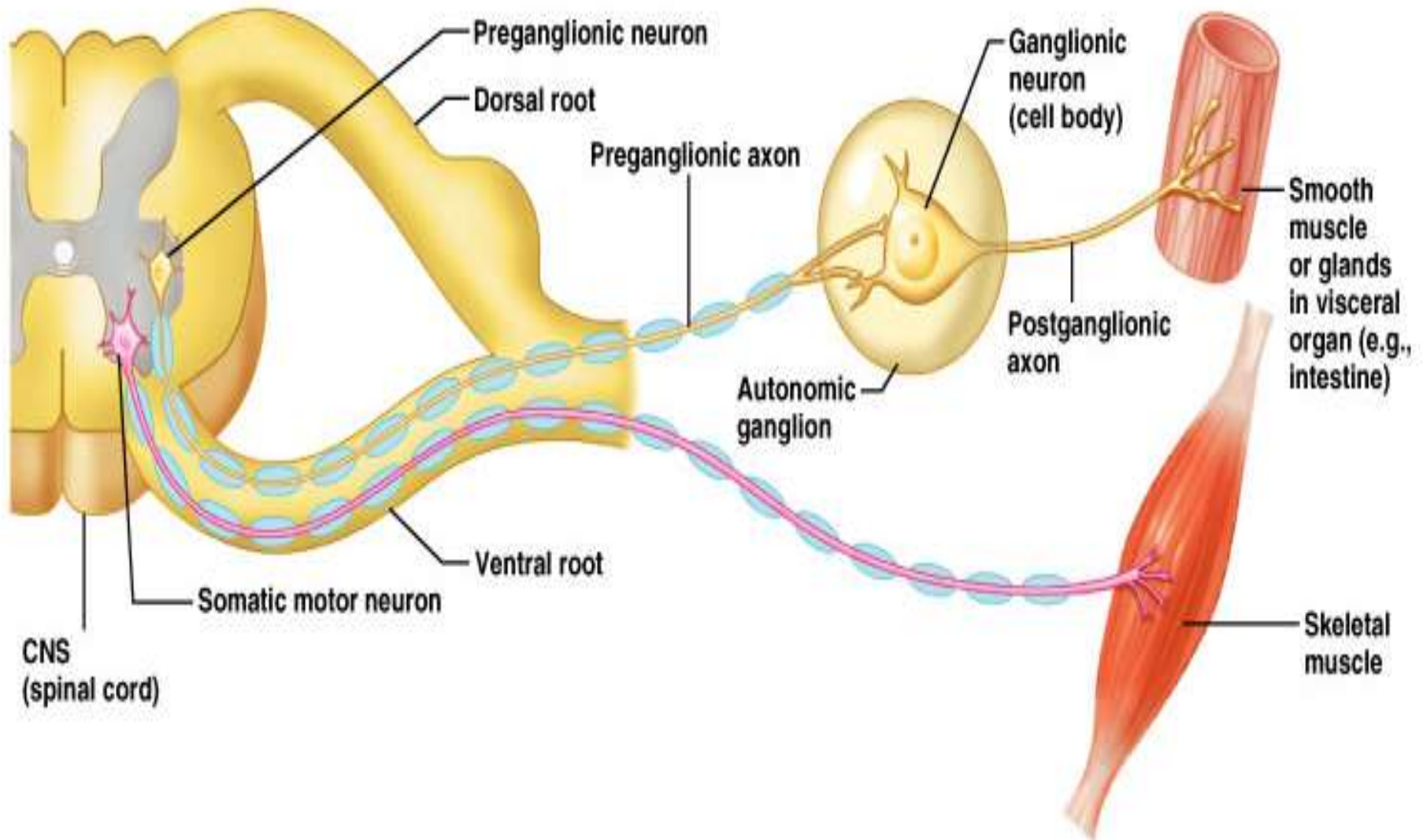
FARMAKODINAMIK SSO

SISTEM KOLINERGIK



Organization of the Nervous System





SSO/ANS : AUTONOMIC NERVOUS SYSTEM

Terdiri dari 2 divisi :

1. Simpatis ANS (SANS)

disebut juga divisi

Thoracolumbalis

(N.spinalis Th 1 s/d 12 & L
1,2,3)

Fungsi : Fight or Flight system

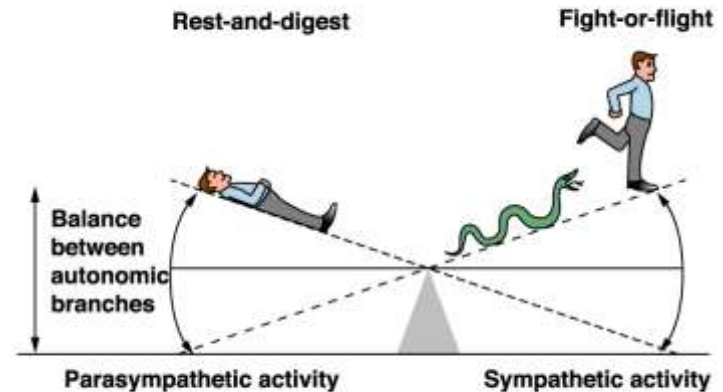
2. Parasimpatis ANS (PANS)

disebut juga divisi

Craniosacralis

(Cranio : Nc. N III, VII, IX, X ,
Sacral : S2,3,4)

Fungsi : Rest and Digest



The physiologic response to flight or fight stimuli

Mental activity increases

Eyes

Pupils dilate
Ciliary muscle relaxed (for far sightedness)

Mouth

Saliva production stops

Heart

Heart output increases
Blood pressure rises

Lungs

Breathing increases
Airways dilate

Under arms

Sweat glands: increase secretion
Apocrine glands: increase secretion

Muscles

Blood vessels mostly constrict, except to some muscles
Muscle: increased strength

Gastrointestinal

Digestion shuts down

Kidneys

Kidneys decrease output

Bladder

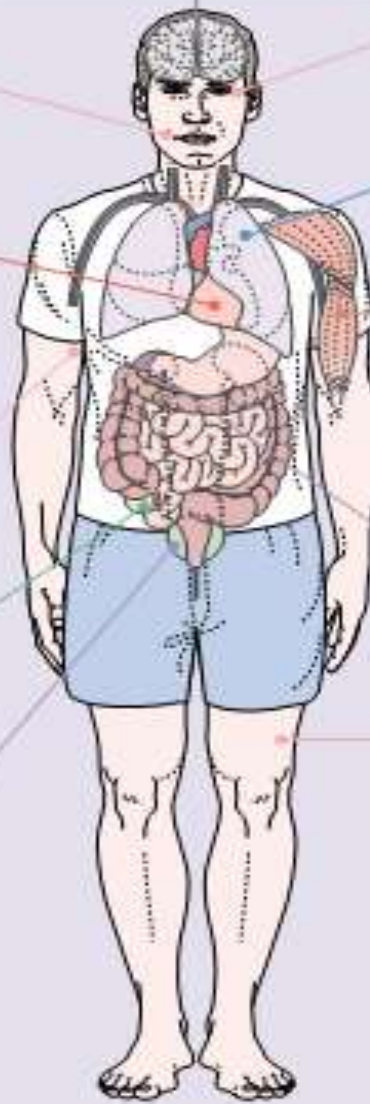
Bladder sphincters contract

Skin

Blood flow to skin increases
Blood coagulation increases

General unspecific

Metabolism: glucose mobilized
Immune system suppressed



Jenis Neurotransmitter (NT) & Reseptor (R)

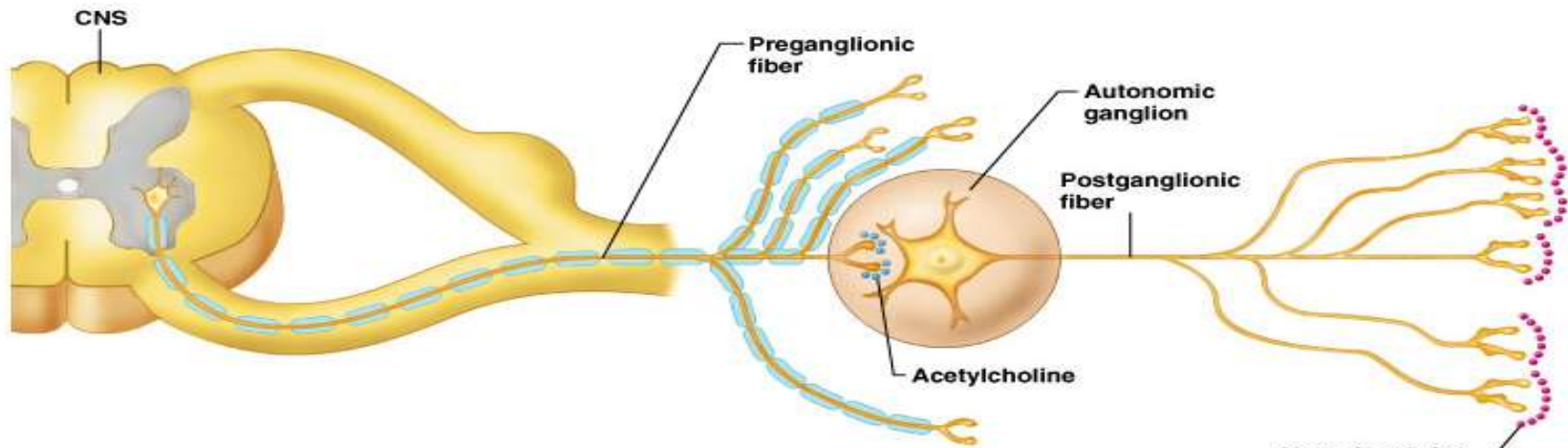
PNAS

- ▶ NT = Asetil kolin (**Ach**)
- ▶ R / Nikotinic (N)
 - Nikotinic neural (**N_N**)
 - Nikotinic muscular (**N_M**)
- ▶ R / Muscarinic (M)
 - Muscarinic -1 (**M₁**)
 - Muscarinic-2 (**M₂**)
 - Muscarinic-3 (**M₃**)
 - Muscarinic-4 (**M₄**)
 - Muscarinic-5 (**M₅**)

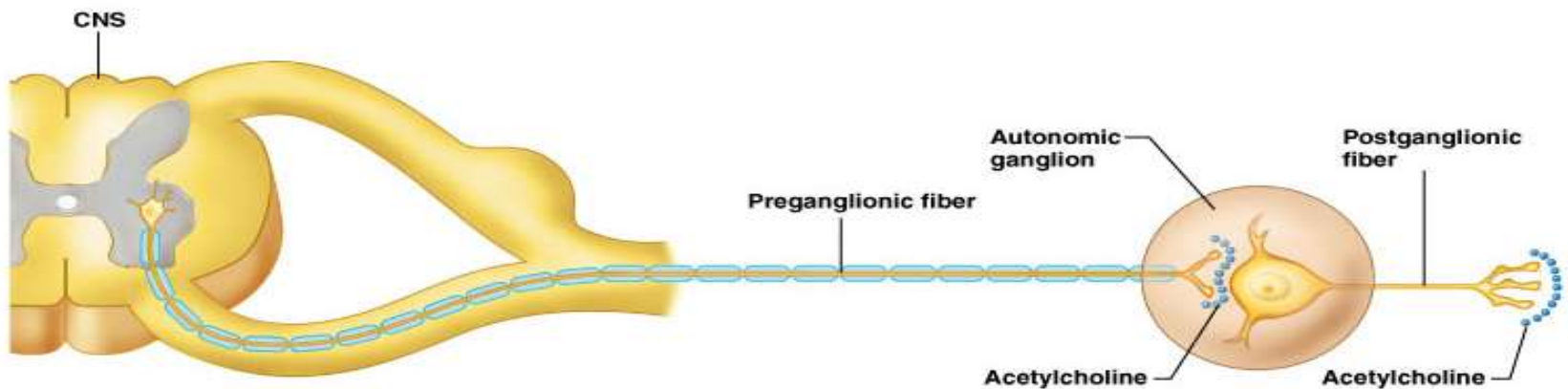
SNAS

- ▶ NT = nor adrenalin / nor epinephrine (**NE**)
- ▶ R / α
 - Alfa-1 (**α 1**)
 - Alfa-2 (**α 2**)
- ▶ R / β
 - Beta-1 (**β 1**)
 - Beta-2 (**β 2**)

Perbedaan Anatomi Parasimpatis dan Simpatis

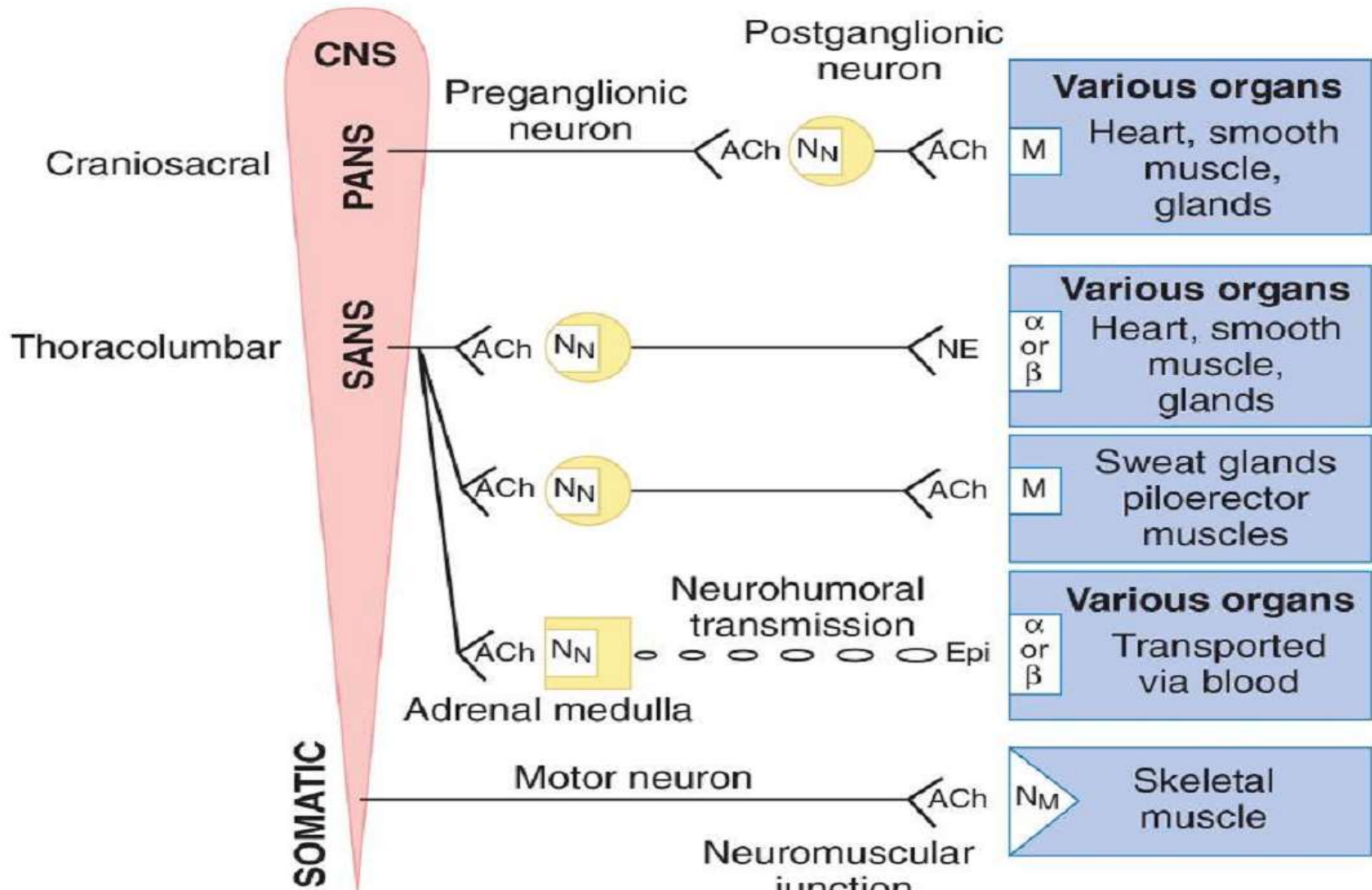


(a) Sympathetic pathway



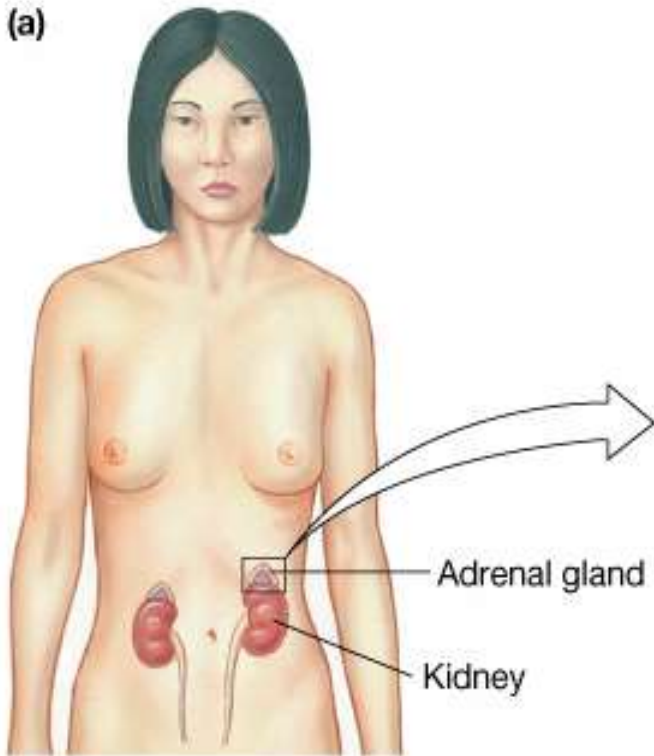
(b) Parasympathetic pathway

Anatomi SSO

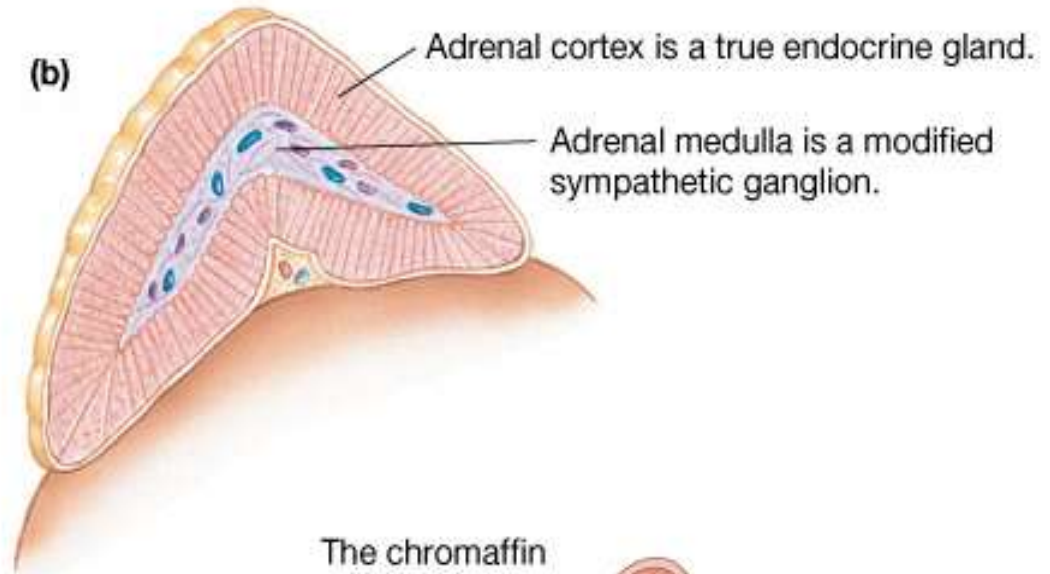


Adrenal Medulla: A Modified Sympathetic Ganglion

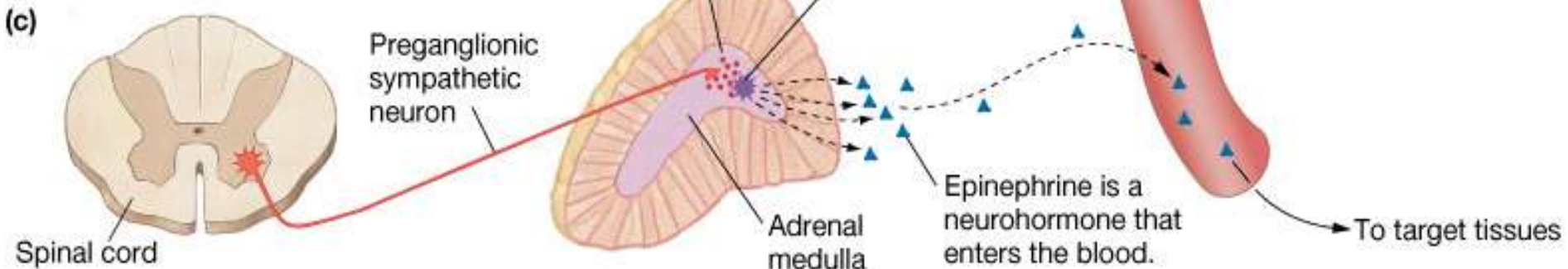
(a)



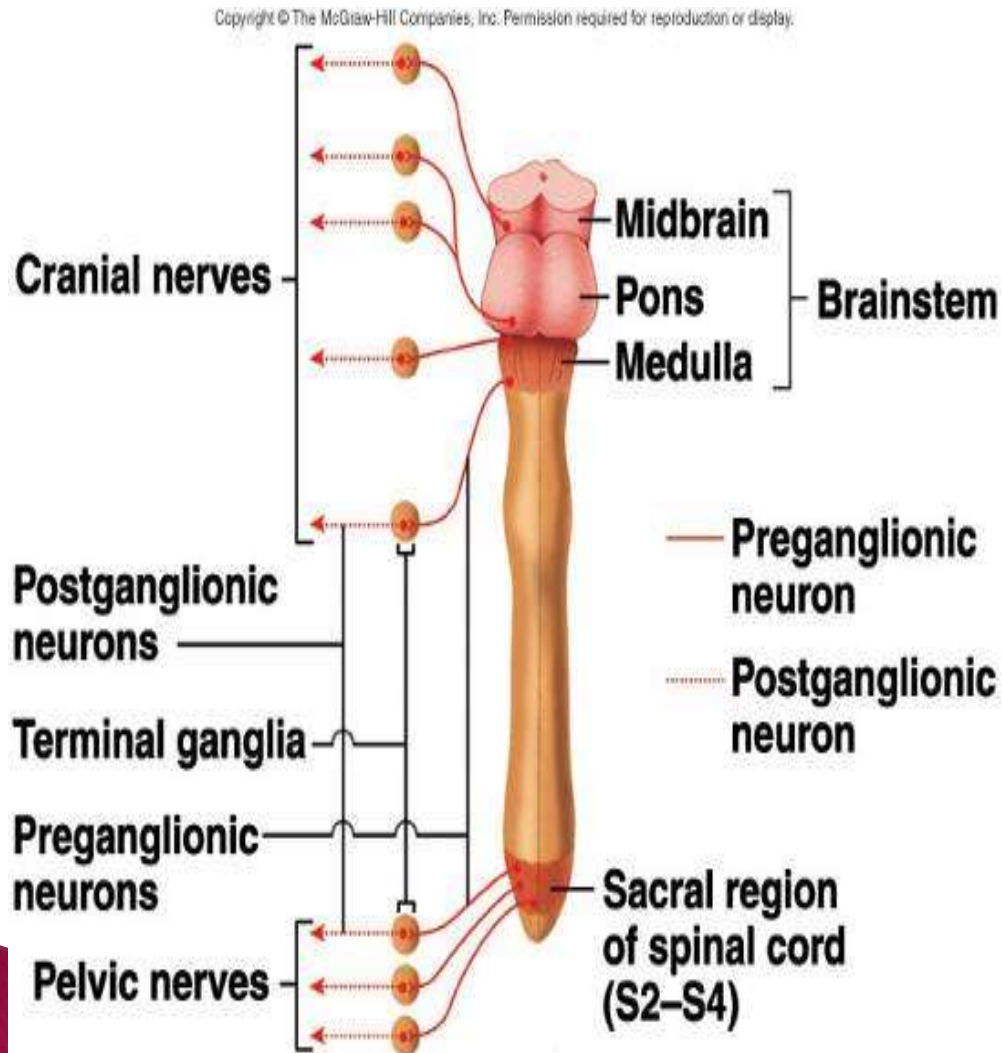
(b)



(c)

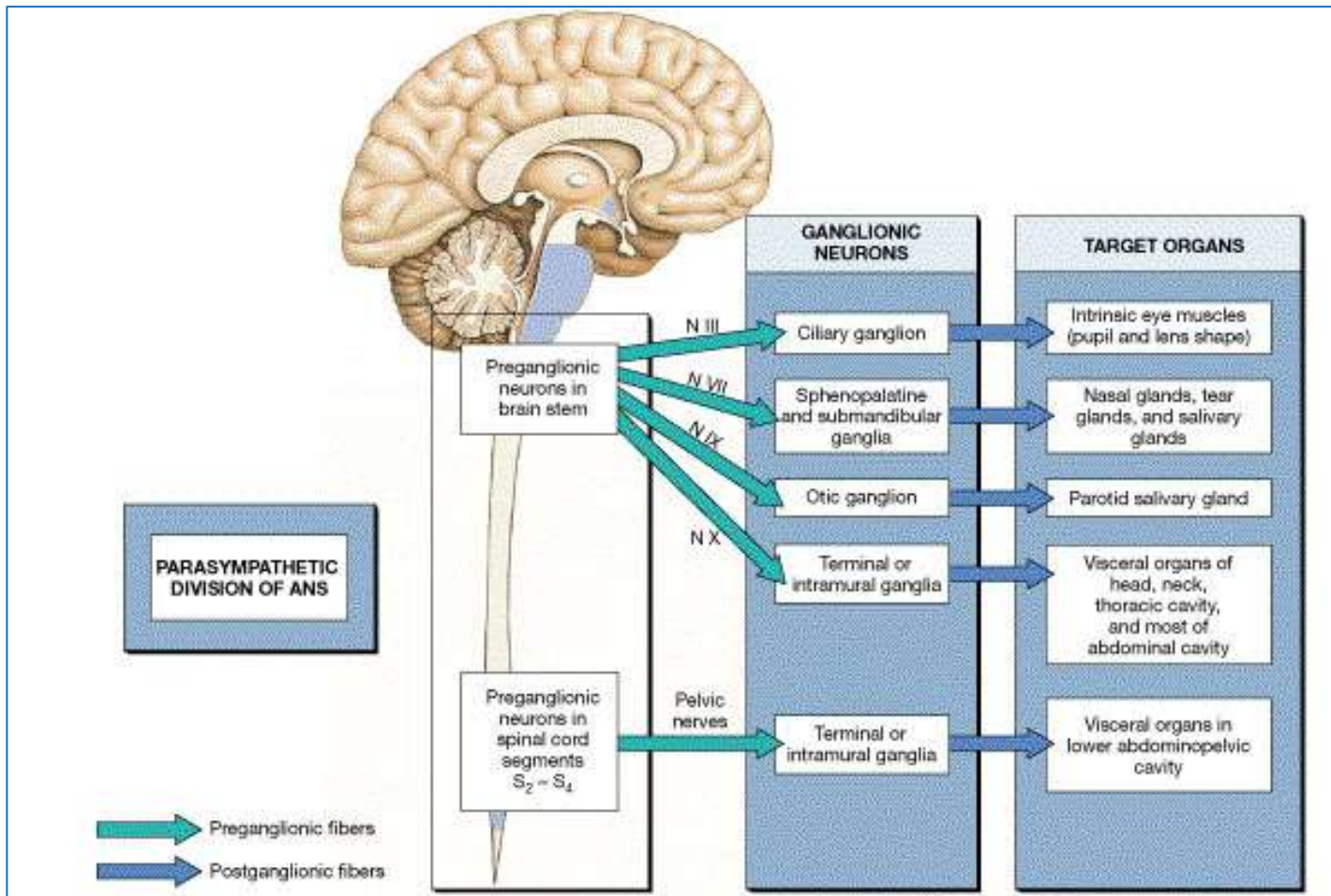


Divisi Parasimpatis

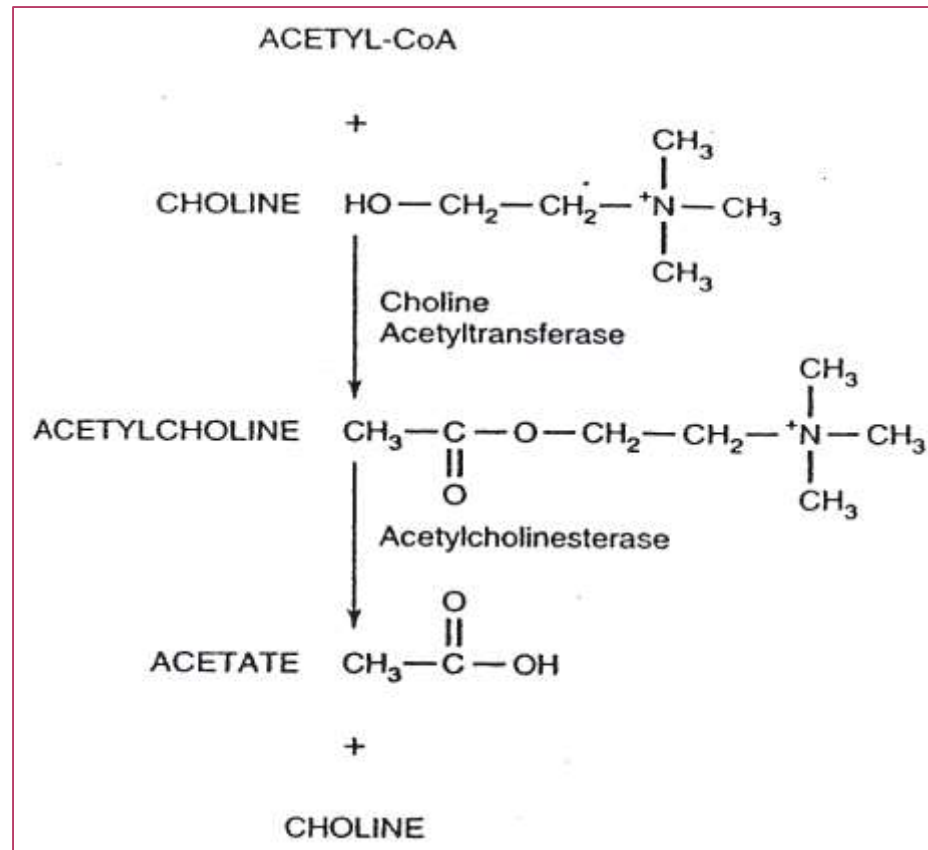


- ▶ Sel bodi preganglionik terletak di brainstem dan bagian lateral spinal cord gray matter S2–S4
- ▶ Ganglion terletak di dinding atau dekat organ yang diinervasi.
 - Akson Preganglionik dari otak menuju ke ganglion melalui Nn cranial.
 - Akson Preganglionik dari regio sakral menuju ganglion melalui Nn Pelvic

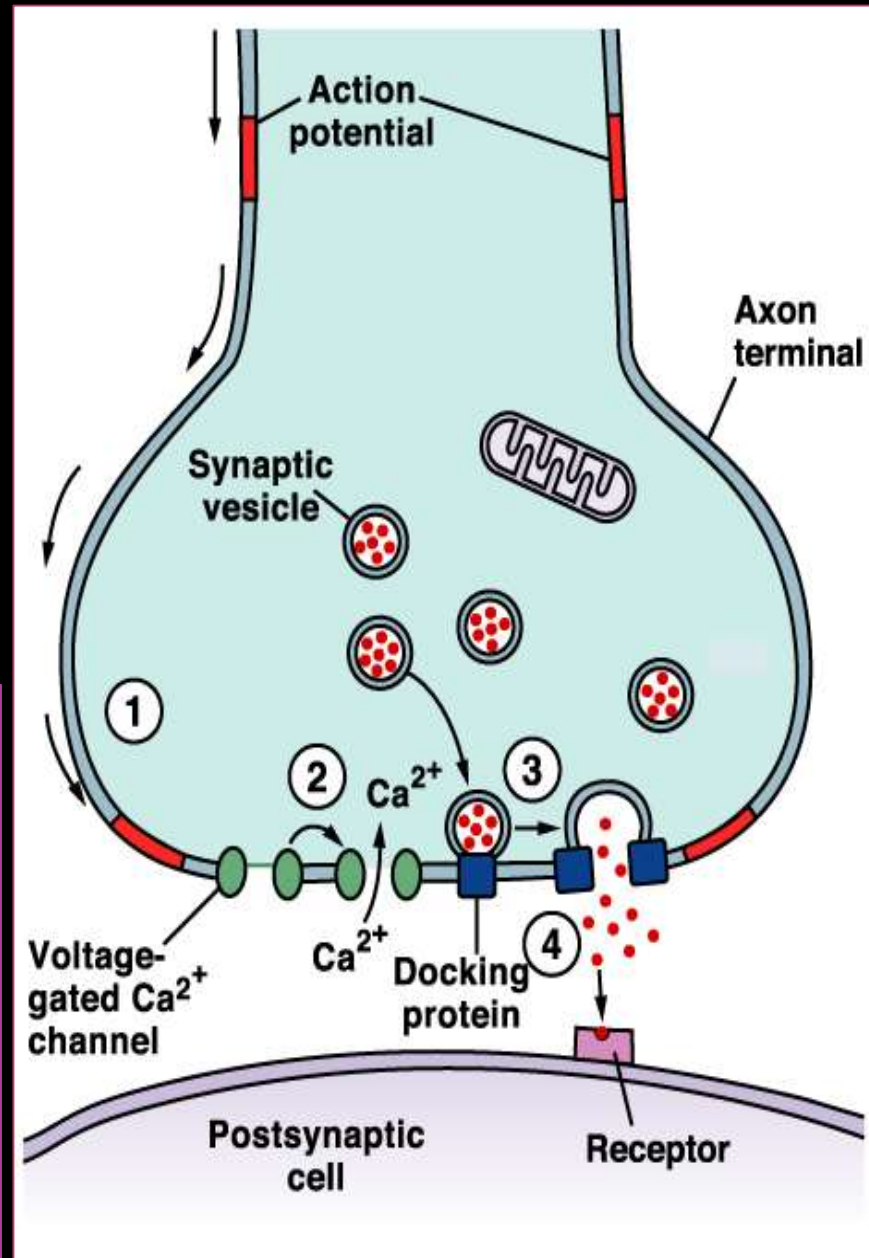
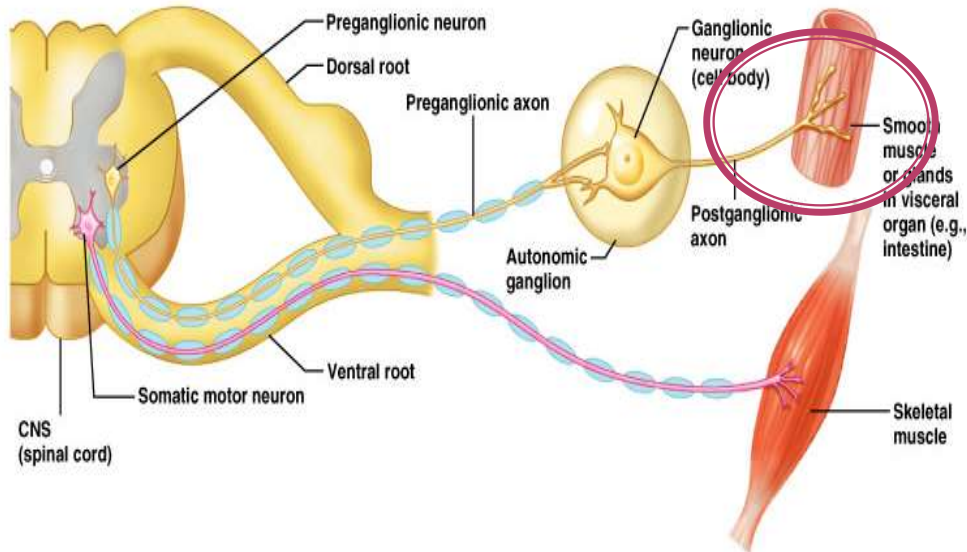
ORGANISASI DIVISI PARASIMPATIS



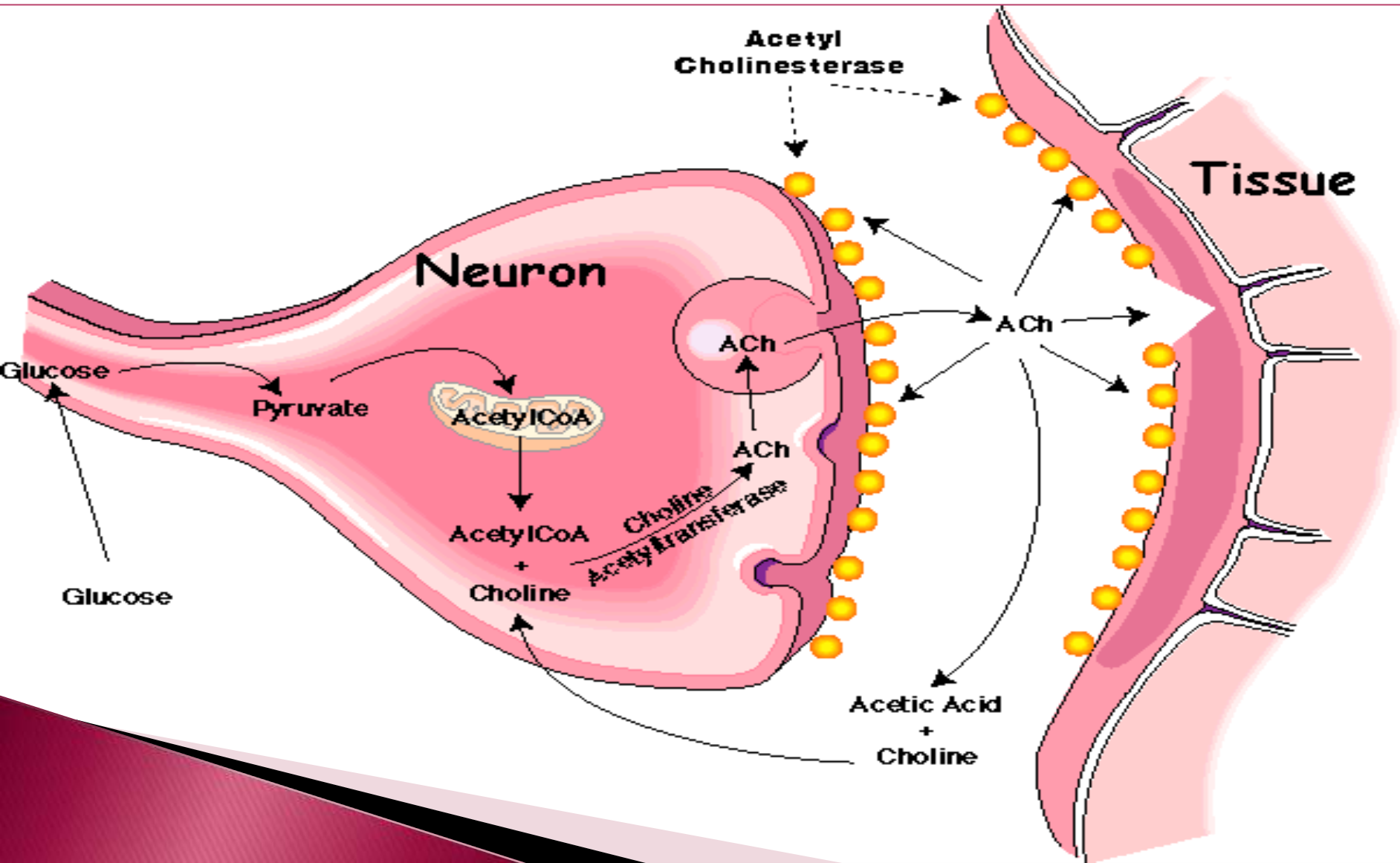
SINTESA NEUROTRANSMITTER ACh



TRANSMISI SINYAL



TRANSMISI KOLINERGIK

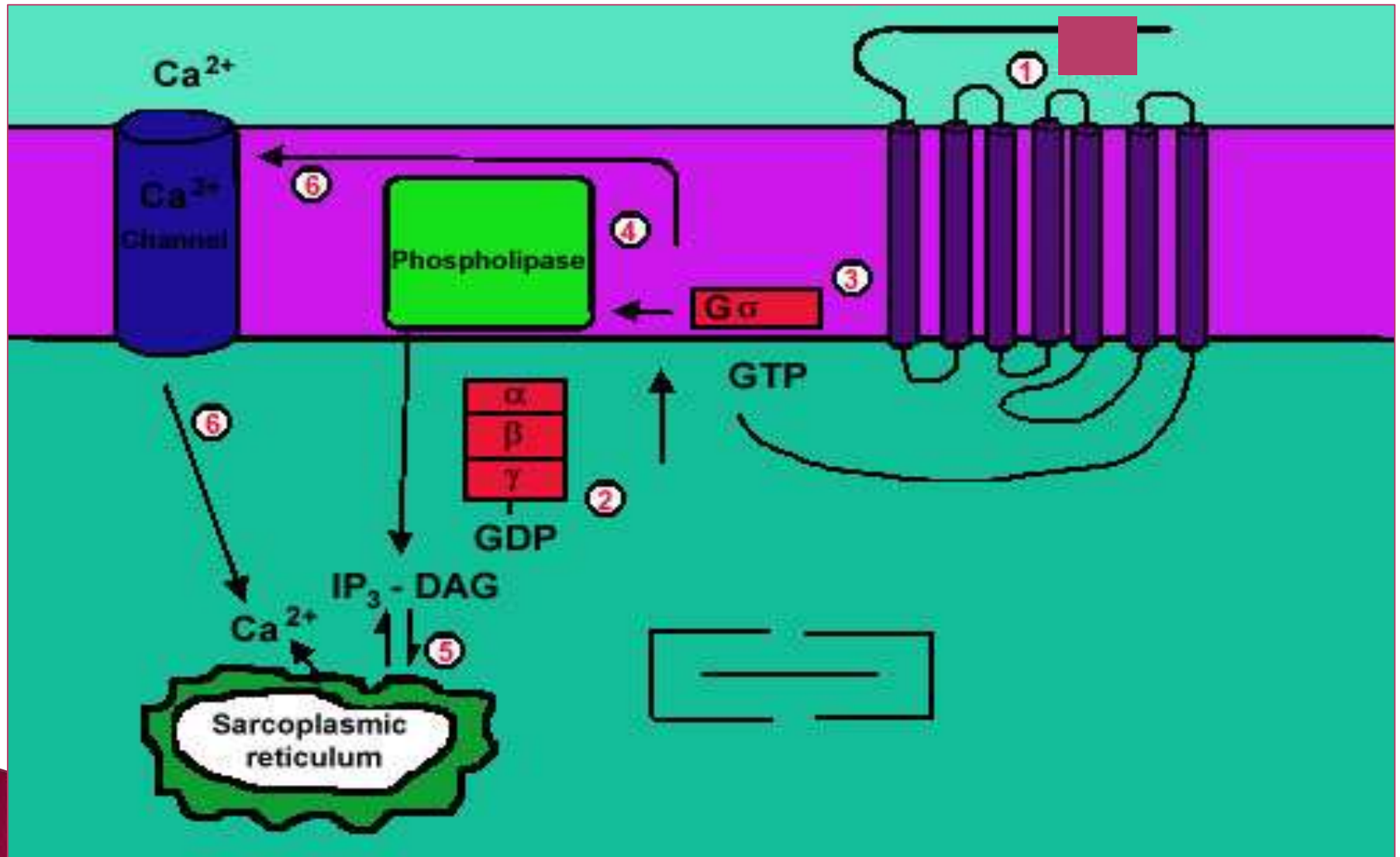


RESEPTOR KOLINERGIK

RESEPTOR	SUBTIPE	LOKASI
MUSKARINIK	M1	Lambung, ganglion otonom, CNS
	M2	Miocard, ganglion otonom, CNS
	M3	Otot Polos, Kelenjar eksokrin, Endothel p.d, CNS
	M4	Pleksus myenteric, CNS
	M5	CNS
NIKOTINIK	Nn	Ganglion Otonom, Medula Adrenal, CNS
	Nm	Neuromuskular Junction Otot Skelet

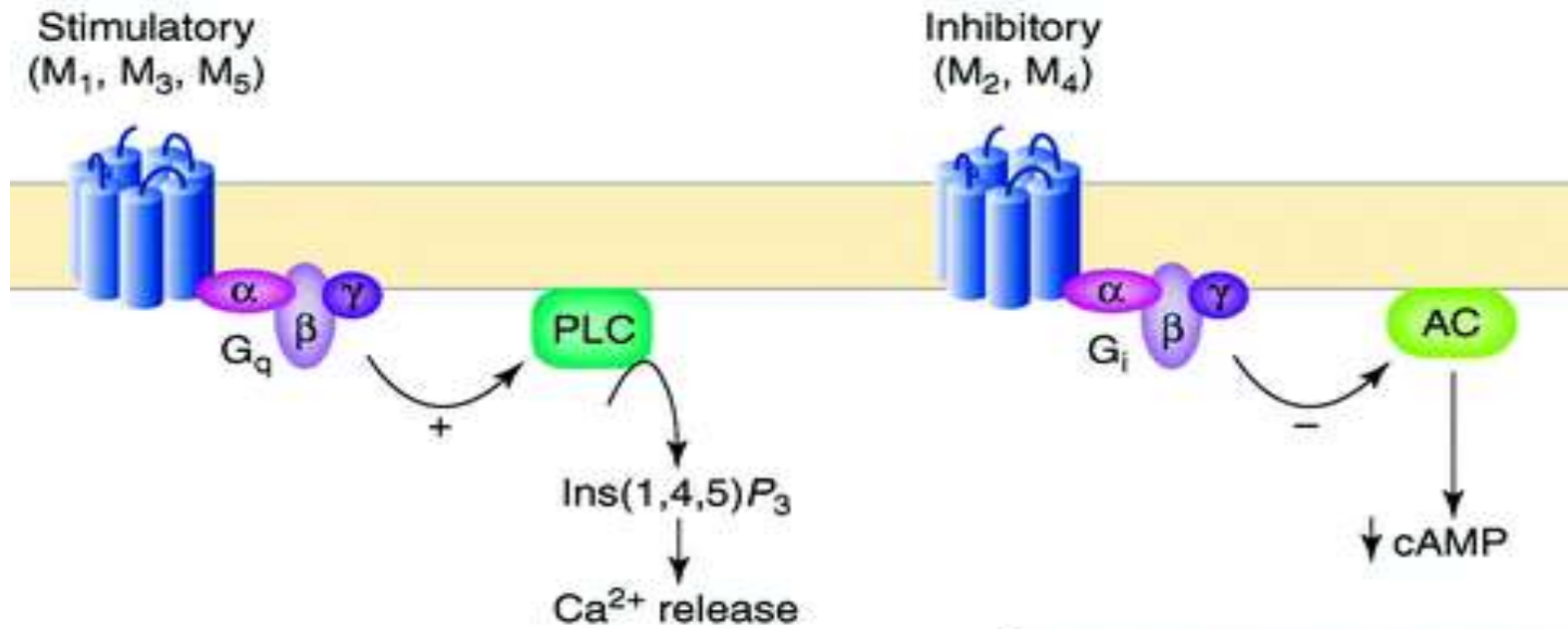
RESEPTOR MUSKARINIK (M1, M3, M5)

G Protein-Linked Receptor



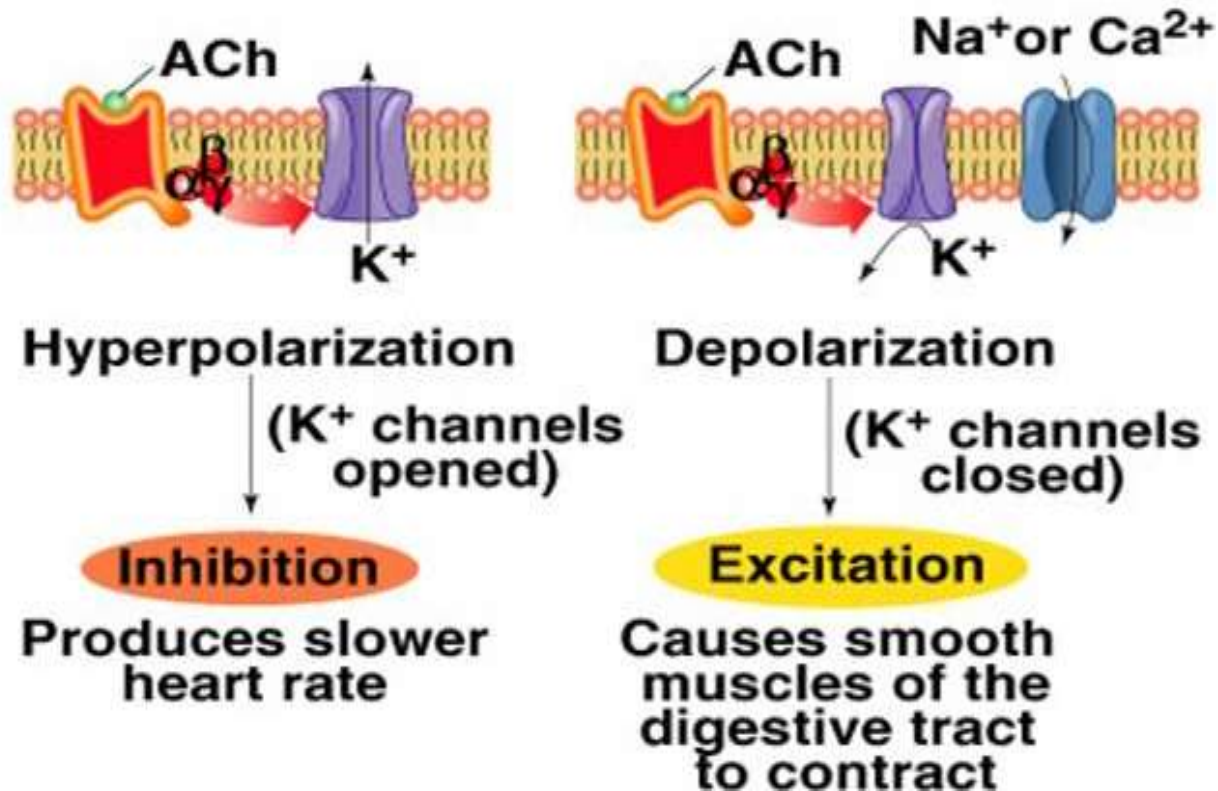
RESEPTOR MUSKARINIK (M1 s.d M5)

G Protein-Linked Receptor



RESEPTOR MUSKARINIK M1 s.d M5

G Protein-Linked Receptor Influence Ion Channel



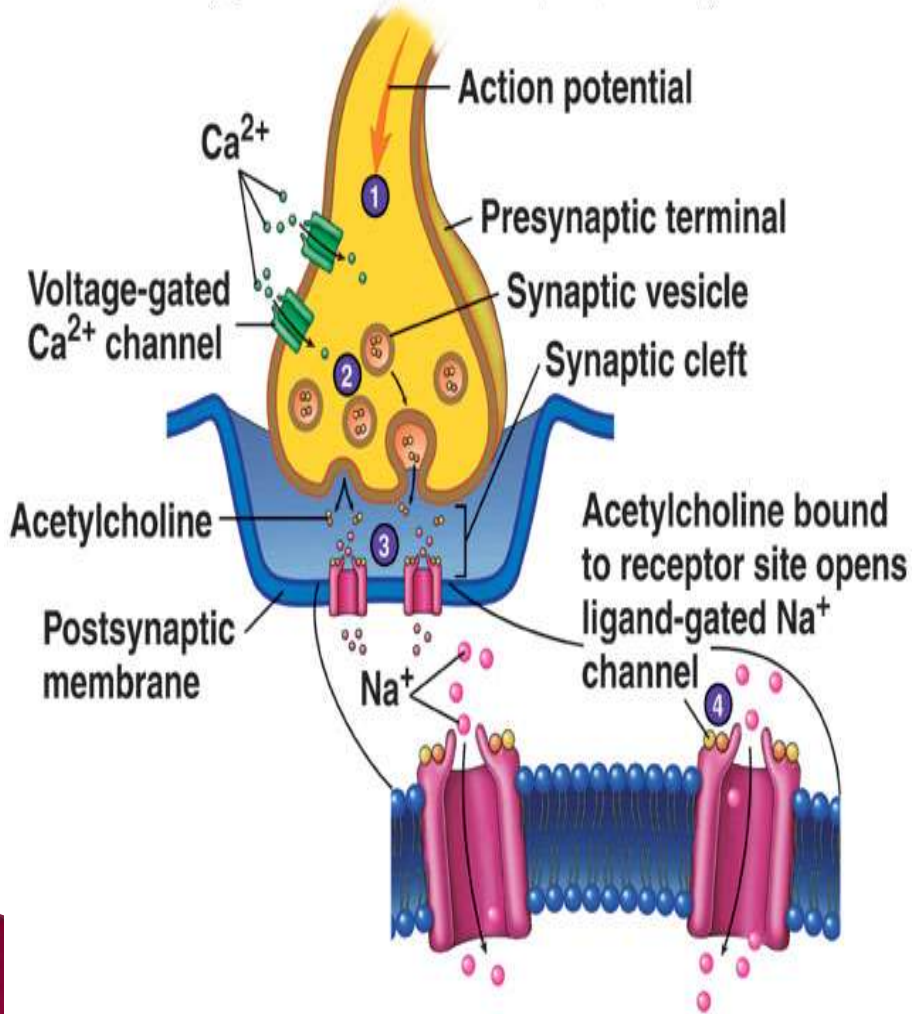
M2 dan M4

M1, M3 dan M5

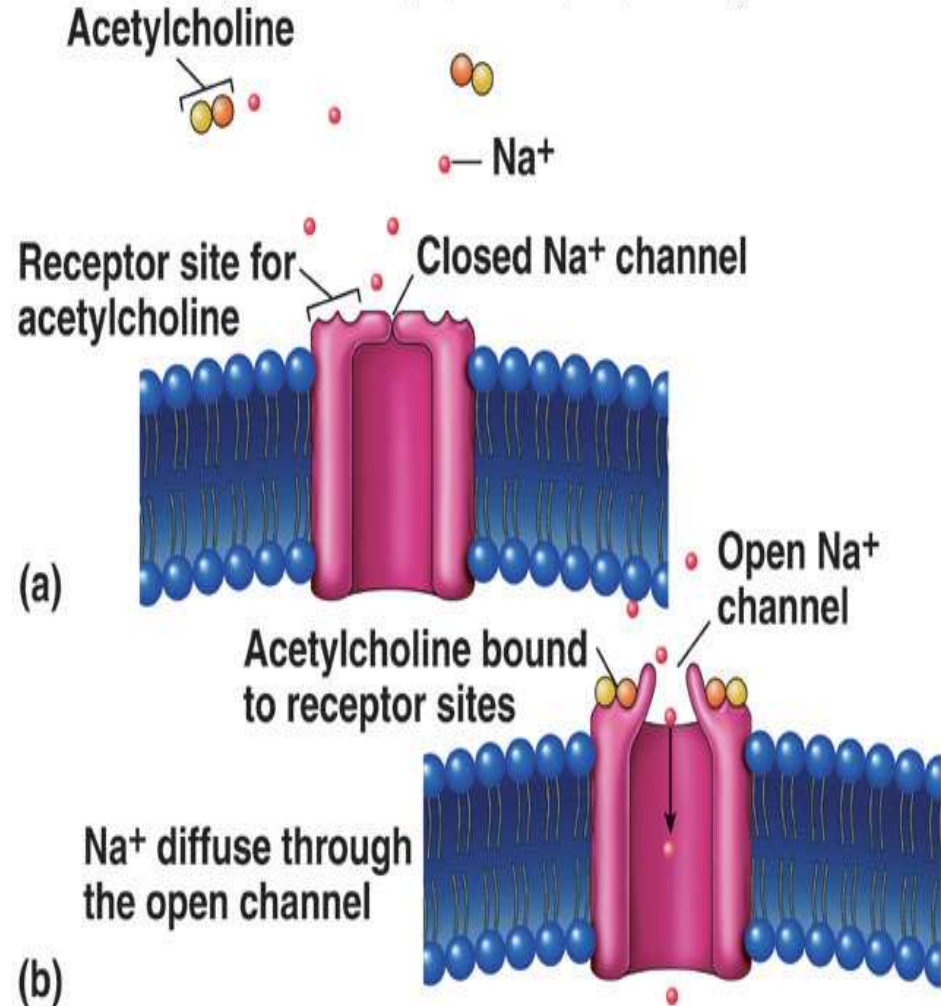
RESEPTOR NIKOTINIK

Ion Channel-Linked Receptor

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RESEPTOR NIKOTINIK

Ion Channel-Linked Receptor

- Ada 2 tipe :
 - a. Tipe neuronal (Nn): subunit bervariasi
 - ✓ lokasi : semua ganglion otonom, sel bodi serabut post ganglion S & PS
 - ✓ antagonis selektif : hexamethonium, trimethaphan
 - ✓ agonis selektif : ion dimethylphenyl piperazinium (DMPP)
 - b. Tipe Muscular (Nm): subunit $\alpha 1$ dan $\beta 1$
 - ✓ Lokasi : skeletal muscle
 - ✓ Antagonis selektif : d-tubokurarin, vecuronium, decamethonium
 - ✓ Agonis selektif : phenilmethyl ammonium

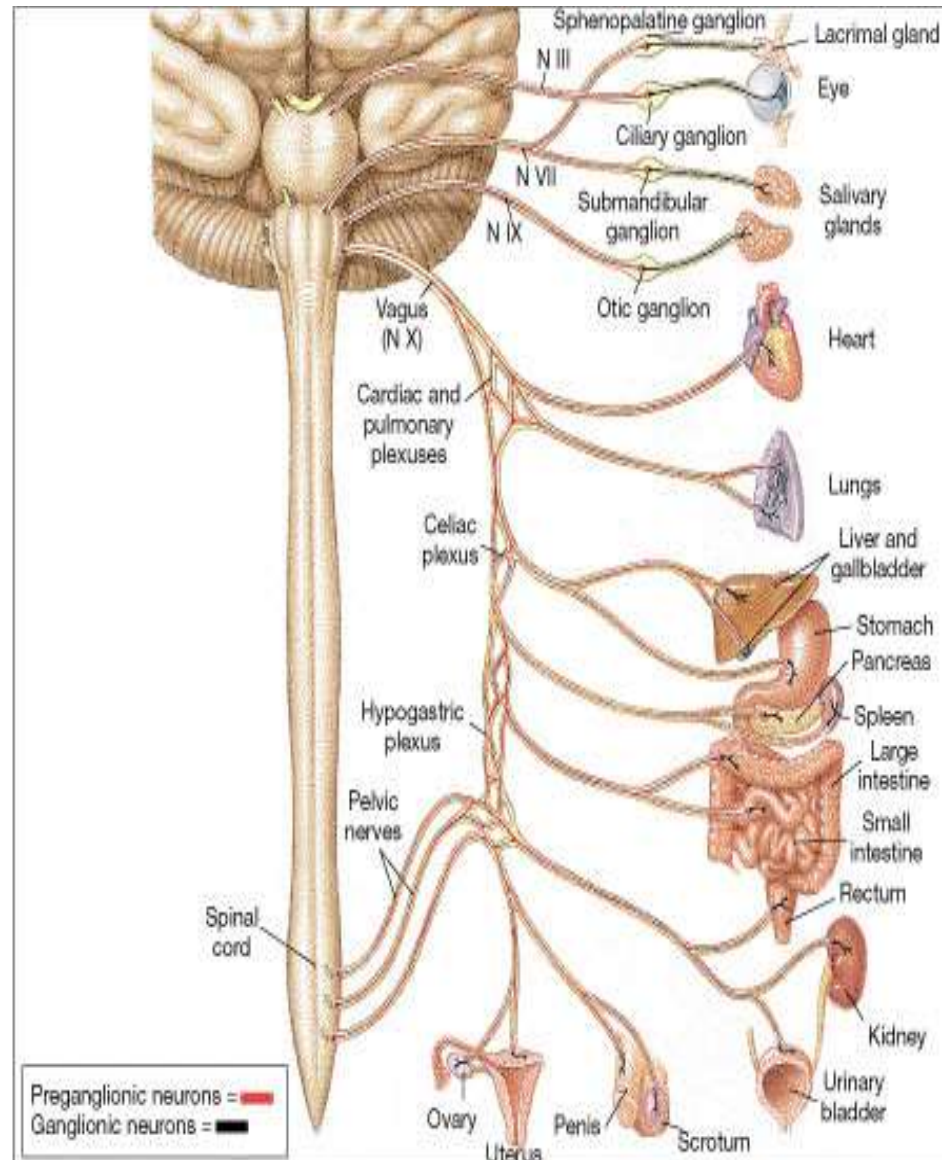
Mekanisme Sinyal Transduksi Reseptor Kolinergik

M_1 and M_3	G_q coupled	\uparrow phospholipase C \rightarrow \uparrow IP_3 , DAG, Ca^{2+}
M_2	G_i coupled	\downarrow adenylyl cyclase \rightarrow \downarrow cAMP
N_N and N_M	No 2nd messengers	activation (opening) of Na/K channels

EFEK STIMULASI R/MUSKARINIK DAN R/ NIKOTINIK

ORGAN	SUB TIPE RESEPTOR	RESPON
Otot Polos - Mata (otot sirkuler & siliar) - Saluran nafas - GIT, GU - <i>Pembuluh Darah</i>	M3 <i>M3 (mel EDRF)</i>	Eksitasi <i>Vasodilatasi</i>
Kelenjar (saliva, bronkus, gaster)	M3, M1	Eksitasi (Sekresi ↑)
Jantung (SA node, AV node, Otot atrium, ventrikel)	M2	Inhibisi (kronotropik -, inotropik -, dromotropik -)
Ganglion otonom Med Adrenal, CNS	Nn	Depolarisasi Sekresi katekolamin
Neuromusk Junction	Nm	Depolarisasi end plate Kontraksi otot skelet

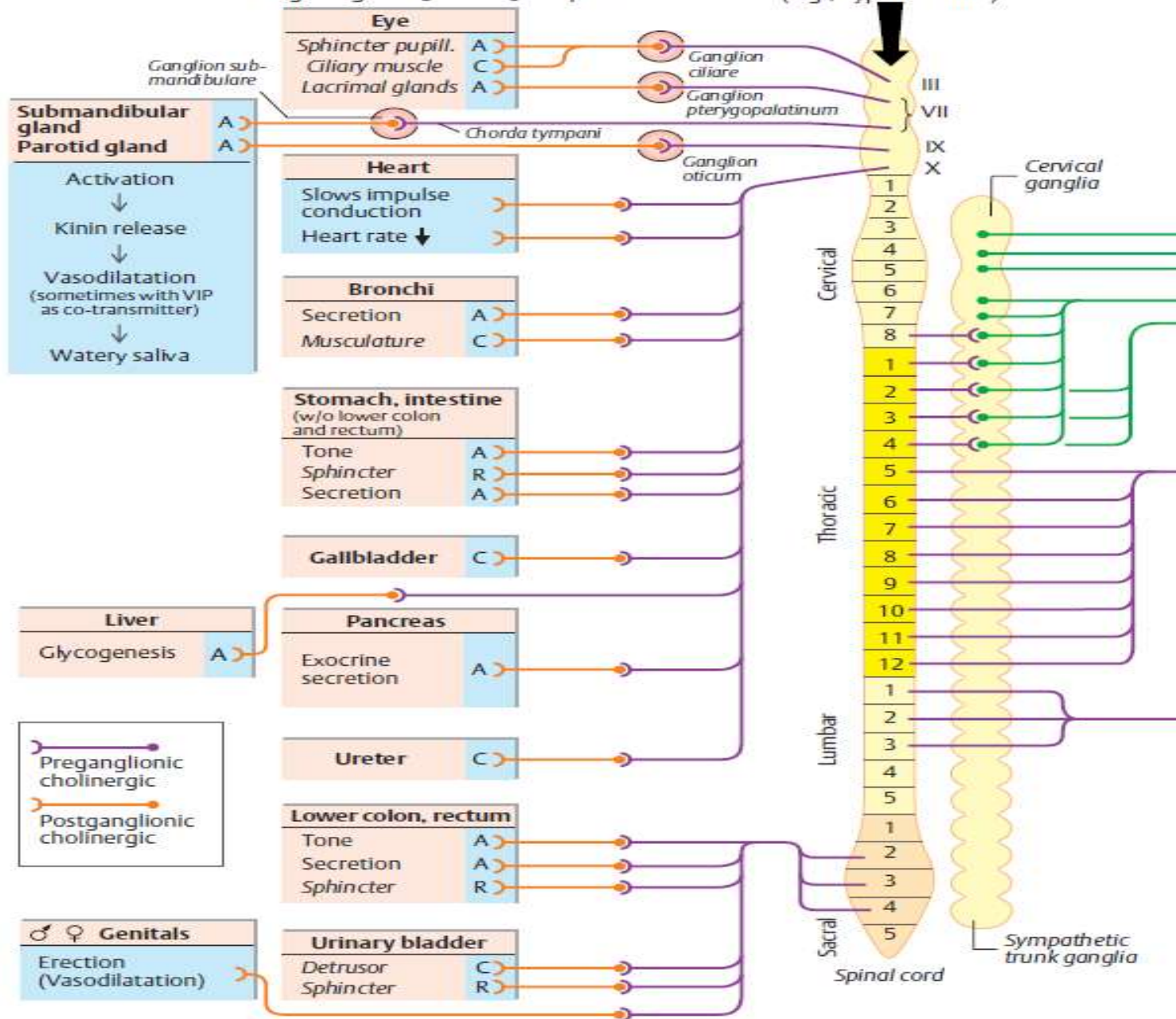
DISTRIBUSI RESEPTOR MUSKARINIK PARASIMPATIS



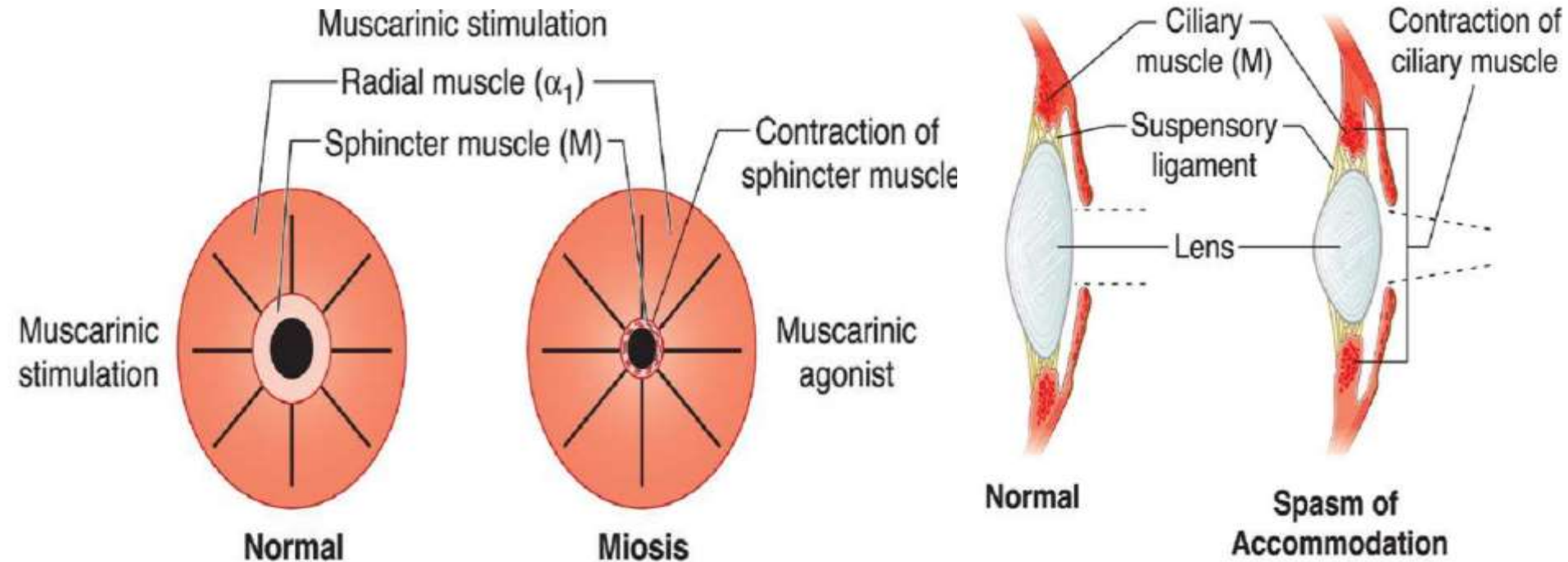
Parasympathetic division (cholinergic)

Ganglia: N_N and M₁ receptors
 Target organ: M₂ oder M₃ receptors

Controlled by
 superordinate centers
 (e.g., hypothalamus)



Pengaruh PNAS pada Mata : ukuran pupil dan akomodasi



Muscarinic stimulation

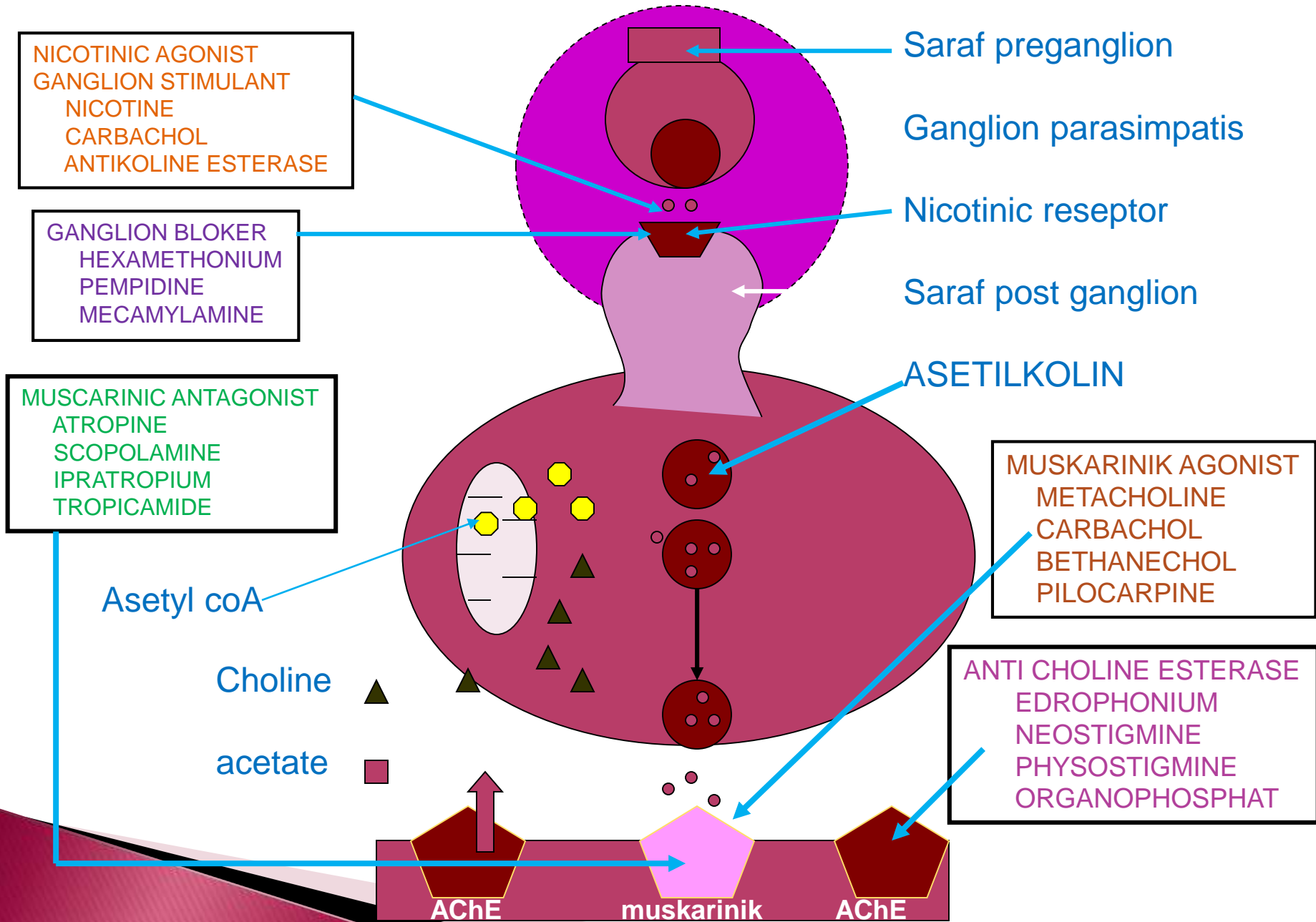
1. Miosis
2. Accommodation (near vision)

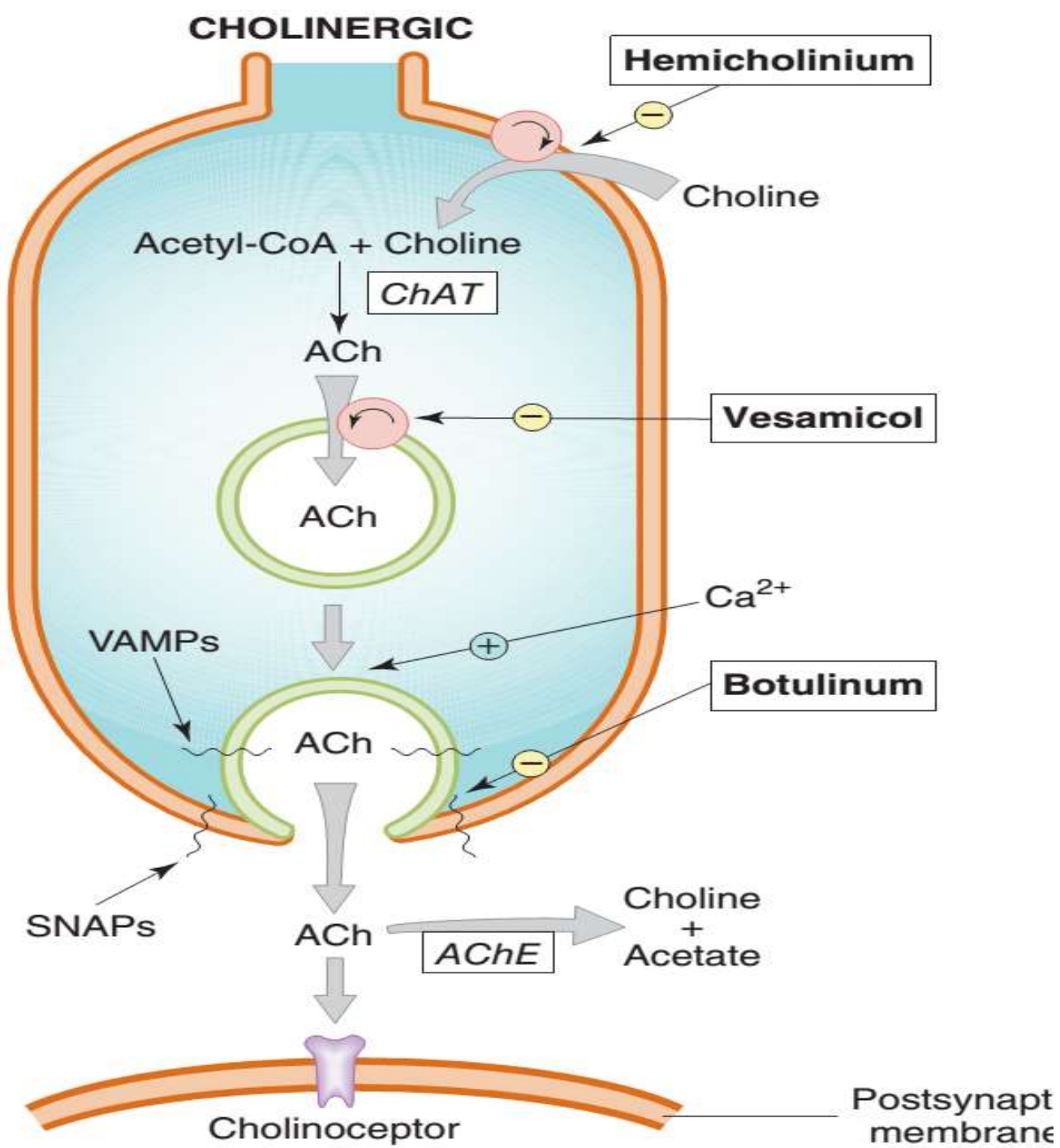
Muscarinic antagonism

1. Mydriasis
2. Accommodation to far vision, leading to cycloplegia (paralysis of accommodation)

Target		Receptor	Response
Eye	Sphincter Ciliary muscle	M ₃ M ₃	Contraction—miosis Contraction—accommodation for near vision
Heart	SA node AV node	M ₂ M ₂	↓Heart rate (HR)—negative chronotropy ↓ Conduction velocity—negative dromotropy No effects on ventricles, Purkinje system
Lungs	Bronchioles Glands	M ₃ M ₃	Contraction—bronchospasm ↑ Secretion
GI tract	Stomach Glands Intestine	M ₃ M ₁ M ₃	↑ Motility—cramps ↑ Secretion Contraction—diarrhea, involuntary defecation
Bladder		M ₃	Contraction (detrusor), relaxation (trigone/sphincter), voiding, urinary incontinence
Sphincters		M ₃	Relaxation, except lower esophageal, which contracts
Glands		M ₃	↑ Secretion—sweat (thermoregulatory), salivation, and lacrimation
Blood vessels (endothelium)		M ₃	Dilation (via NO/endothelium-derived relaxing factor)—no innervation, no effects of indirect agonists

OBAT YANG BEKERJA PADA SISTEM SARAF PARA SIMPATIS

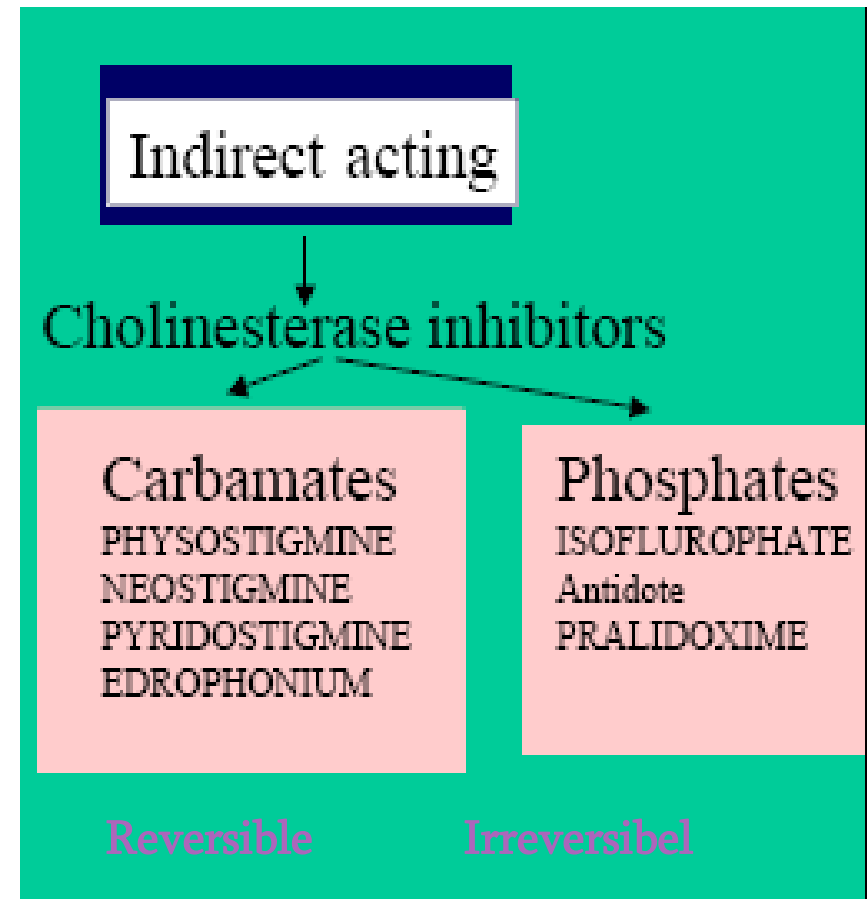
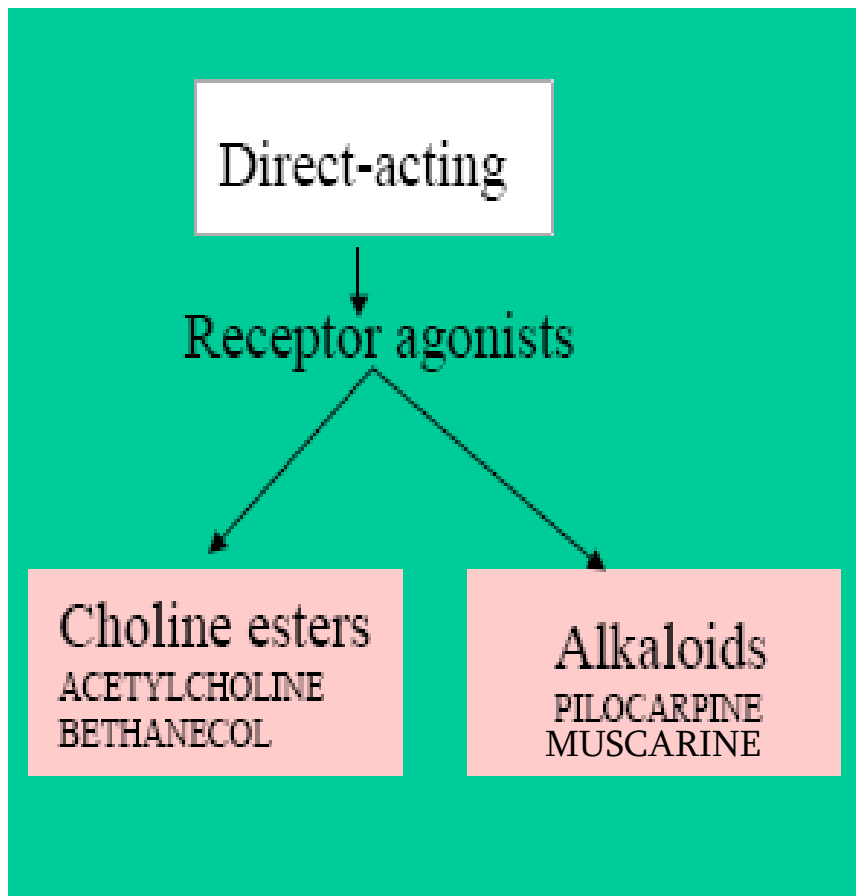




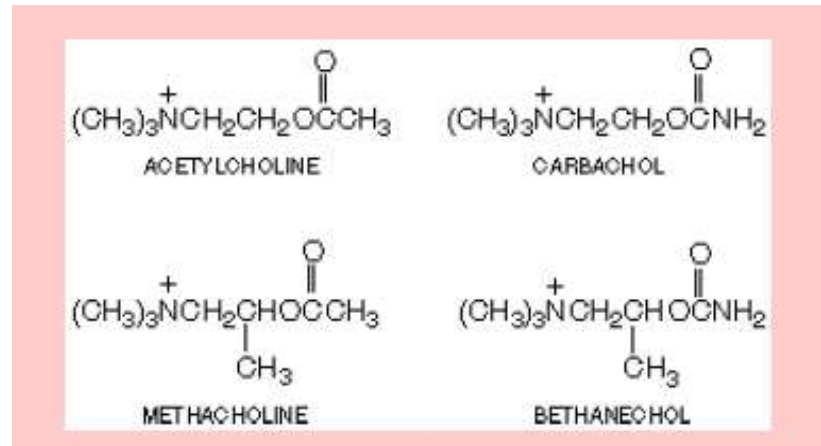
OBAT YANG BEKERJA PADA SISTEM KOLINERGIK

- A. Cholinoceptor Stimulant
(Cholinomimetic)**
- B. Cholinergic Antagonis**

Cholinomimetic Drug



AGONIS MUSKARINIK



PHARMACOLOGICAL ACTIONS

CHOLINE ESTER	SUSCEPTIBILITY TO CHOLINESTERASE	CARDIO-VASCULAR	GI	GU	EYE (TOPICAL)	ANTAGONISM BY ATROPINE
ACETYLCHOLINE	+++	++	++	++	+	+++
METACHOLINE	+	++++	+++	++	+	+++
CARBACHOL	-	+	+++	+++	++	+
BETHANECHOL	-	±	+++	+++	++	+++

APLIKASI KLINIK CHOLINOMIMETIC DRUGS :

MUSCARINIC AGONIST

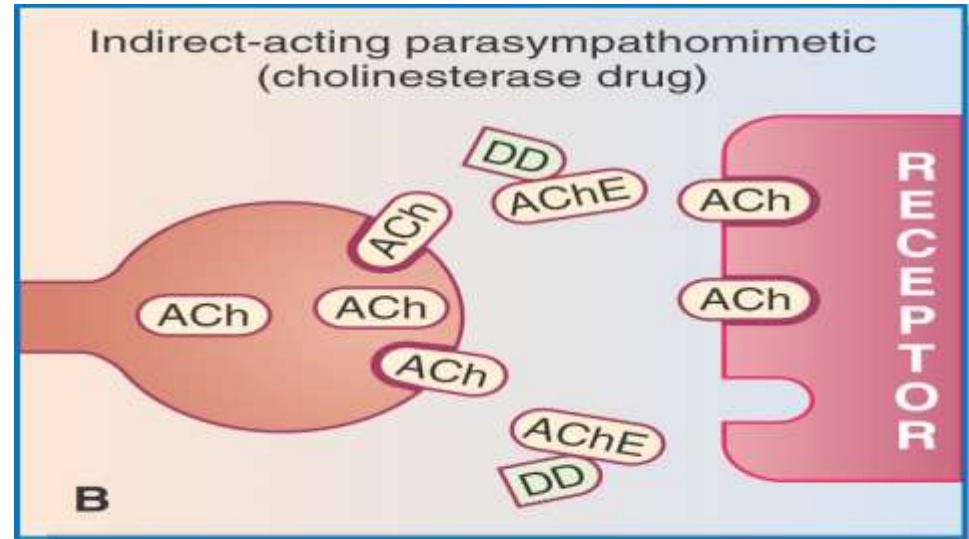
Drug	Activity	AChE Hydrolysis	Clinical Uses
ACh	M and N	+++	Short half-life—no clinical use
Bethanechol	M	-	Rx—ileus (postop/neurogenic), urinary retention
Methacholine	M > N	+	Dx—bronchial hyperreactivity
Pilocarpine, cevimeline	M	-	Rx—xerostomia, glaucoma (pilocarpine)

CHOLINESTERASE INHIBITOR

► Mekanisme Kerja :

Mengikat enzim AChE di tempat kerjanya, sehingga AChE tidak bisa menjalankan tugasnya dalam menghidrolisa ACh menjadi Choline dan Asetat dan terjadi penumpukan ACh di celah sinap

(AChE mampu memetabolisme 25.000 molekul ACh / detik)



REVERSIBLE INHIBITORS	IRREVERSIBLE INHIBITOR
<i>Water-Soluble</i>	<i>Lipid Soluble (dpt melewati BBB)</i>
Edrophonium Neostigmine Pyridostigmine Physostigmine	Insektisida Organophospat Isoflurophate

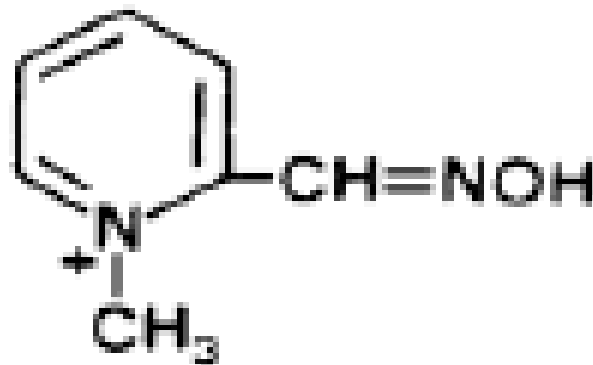
INTOKSIKASI CHOLINESTERASE INHIBITOR

D H U M B E L S

- ▶ Diare
- ▶ Hipotensi
- ▶ Urinasi
- ▶ Miosis
- ▶ Bronkhokonstriksi, Bradikardi
- ▶ Eksitasi (otot skelet : fasikulasi ; CNS: tremor, ansietas, konvulsi, koma)–nicotinic effect
- ▶ Lakrimasi
- ▶ Salivasi, Sweating

Obat yang digunakan pada Intoksikasi Insektisida Organofosfat

- ▶ Antimuskarinik : **ATROPIN**
=mengurangi efek Ach di tempat kerjanya
- Cholinesterase Reactivator : **PRALIDOXIME (2-PAM)**
=melepas ikatan enzim AChE yang terikat Cholinesterase inhibitor sehingga AChE bebas.



Pralidoxime

APLIKASI KLINIK CHOLINOMIMETIC DRUGS : KOLINESTERAE INHIBITOR

Drug	Characteristics	Clinical Uses
Edrophonium	Short-acting	Dx—myasthenia gravis
Physostigmine	Tertiary amine (enters CNS)	Rx—glaucoma; antidote in atropine overdose
Neostigmine, pyridostigmine	Quaternary amines (no CNS entry)	Rx—ileus, urinary retention, myasthenia gravis, reversal of nondepolarizing NM blockers
Donepezil, rivastigmine	Lipid-soluble (CNS entry)	Rx—Alzheimer disease
Organophosphates	Lipid-soluble, irreversible inhibitors	Note: used as insecticides (malathion, parathion) and as nerve gas (sarin)

CHOLINERGIC ANTAGONISTS



```
graph TD; A[CHOLINERGIC ANTAGONISTS] --> B[MUSCARINIC ANTAGONISTS]; A --> C[NICOTINIC ANTAGONISTS]; C --> D[GANGLIONIC BLOCKING AGENTS]; C --> E[NEUROMUSCULAR BLOCKING AGENTS];
```

The diagram is a hierarchical flowchart. At the top is a teal box with the text 'CHOLINERGIC ANTAGONISTS'. Two arrows point downwards from this box to two pink boxes: 'MUSCARINIC ANTAGONISTS' on the left and 'NICOTINIC ANTAGONISTS' on the right. From the 'NICOTINIC ANTAGONISTS' box, two arrows point downwards to two yellow boxes: 'GANGLIONIC BLOCKING AGENTS' on the left and 'NEUROMUSCULAR BLOCKING AGENTS' on the right.

MUSCARINIC
ANTAGONISTS

NICOTINIC
ANTAGONISTS

GANGLIONIC
BLOCKING AGENTS

NEUROMUSCULAR
BLOCKING AGENTS

Cholinergic Antagonis

A. MUSCARINIC ANTAGONISTS

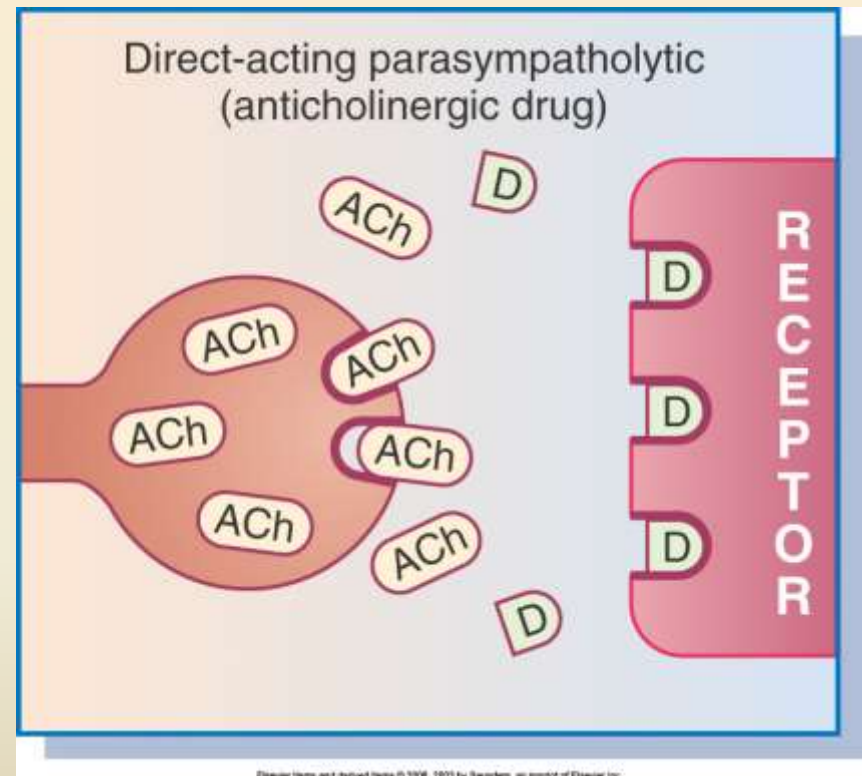
- Natural alkaloid : Atropin , Scopolamine (Hyoscine)
- Semisintetik analog tersier ammonium :
Scopolamin
metilbromid, Homatropin metilbromid, Pirenzepin,
Benztropin
- Semisintetik analog kuaterner ammonium :
Eprophanthelin, Metantelin metilbromid,
Ipratropium
bromida, Propanthelin, Tiotropium

B. NICOTINIC ANTAGONISTS

1. Ganglion Bloker : Hexamethonium, Trimethapan,
Mecamylamine
2. Neuromuskular Junction Bloker
 - Depolarizing : Succinylcholine
 - Nondepolarizing : Tubocurare

A. MUSCARINIC ANTAGONISTS

- ▶ **Mekanisme kerja :**
menghambat ACh menduduki reseptor muskarinik secara kompetitif
- ▶ Contoh : Atropin, Scopolamine yang berasal dari alkaloid belladonna
- ▶ Atropin dan Scopolamine berbeda dalam memberikan efek CNS (Scopolamine dapat melewati BBB)



EFEK ANTAGONIS MUSKARINIK

ORGAN	EFEK	MEKANISME
CNS	Sedasi, anti motion sickness action, amnesia, delirium, antiparkinson	Blok M (subtipe ?)
Mata	Siklopegi, midriasis	Blok M3
Bronkhus	Bronkodilatasi	Blok M3
GIT	Peristaltik ↓, konstipasi	Blok M1 dan M3
Genitourinari	Relaksasi dinding VU, Retensi urine	Blok M3
Jantung	Awalnya bradikardi, selanjutnya takikardi Vasodilatasi & hipertermia	Bradikardi akibat stim vagus, takikardi akibat blok M2 Blok M3
Kelenjar	Sekresi saliva, keringat ↓	Blok M1 dan M3

APLIKASI KLINIS ANTAGONIS MUSKARINIK

Drug	Clinical Uses and/or Characteristics
Atropine	Antispasmodic, antisecretory, management of AChE inhibitor OD, antidiarrheal, ophthalmology (but long action)
Tropicamide	Ophthalmology (topical)
Ipratropium, tiotropium	Asthma and COPD (inhalational)—no CNS entry, no change in mucus viscosity
Scopolamine	Used in motion sickness, causes sedation and short-term memory block
Benztropine, trihexyphenidyl	Lipid-soluble (CNS entry) used in parkinsonism and in acute extrapyramidal symptoms induced by antipsychotics
Oxybutynin	Used in overactive bladder (urge incontinence)

INTOKSIKASI ANTAGONIS MUSKARINIK

- ▶ **Kering** karena pe↓ sekresi saliva, keringat, airmata, bronkus
- ▶ **Merah** karena dilatasi pembuluh darah kulit di kepala, leher, lengan, tubuh (“atropin flush”), hipertermia
- ▶ **Midriasis dan sikloplegi**
- ▶ **Gangguan di SSP** : sedasi, amnesia, delirium, halusinasi

OBAT GANGLION

Nicotinic Receptor Activation

Target	Receptor	Response
Adrenal medulla	N_N	Secretion of epinephrine and NE
Autonomic ganglia	N_N	Stimulation—net effects depend on PANS/SANS innervation and dominance
Neuromuscular junction	N_M	Stimulation—twitch/hyperactivity of skeletal muscle

Note: N receptors desensitize very quickly upon excessive stimulation.

Bloker pada Ganglion

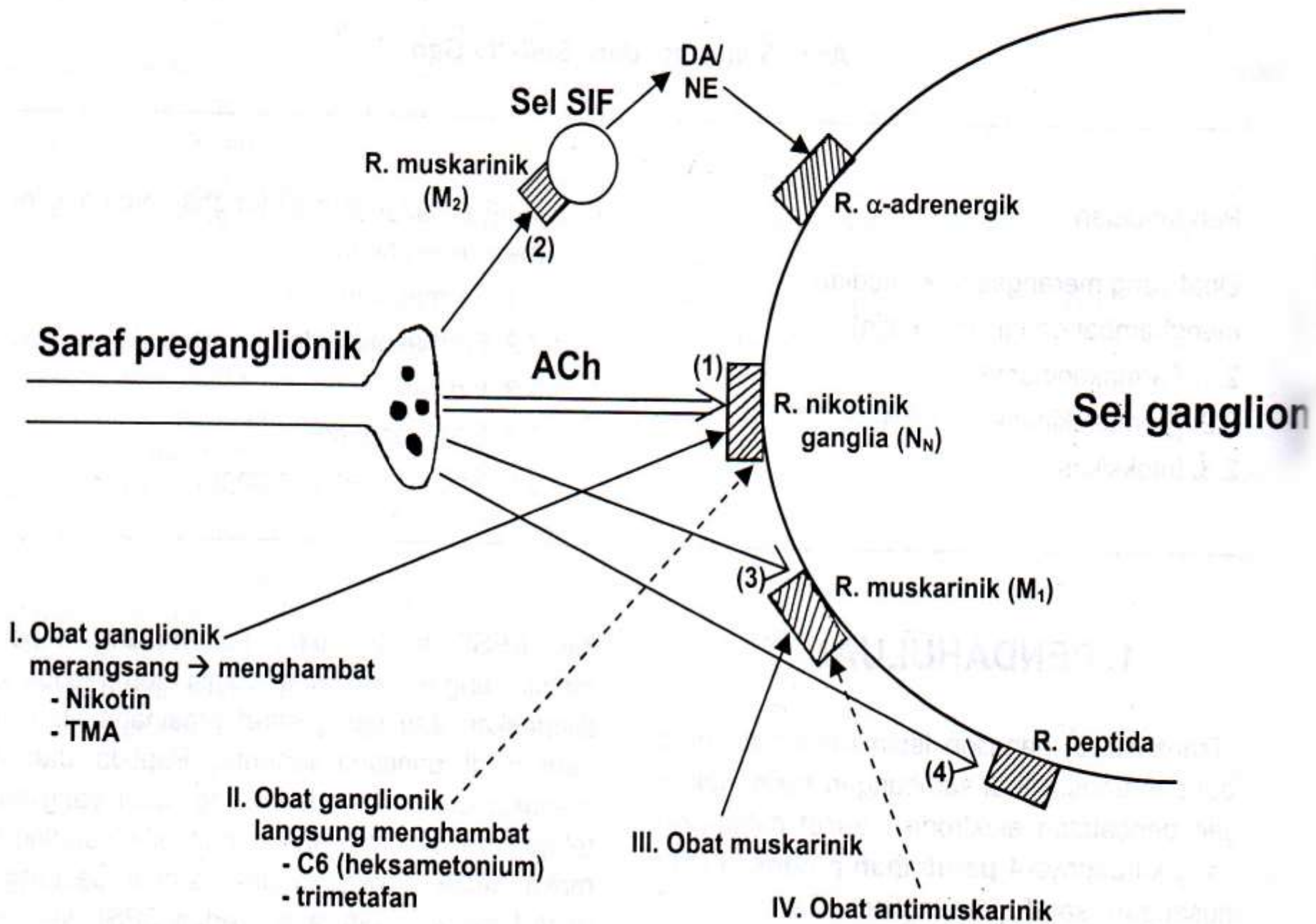
```
graph TD; A([Bloker pada Ganglion]) --> B[Merangsang kemudian menghambat]; A --> C[Langsung menghambat]; B --> D(Nikotin); C --> E["Ganglionik bloker : heksamethonium"];
```

Merangsang kemudian menghambat

Nikotin

Langsung menghambat

**Ganglionik bloker :
heksamethonium**

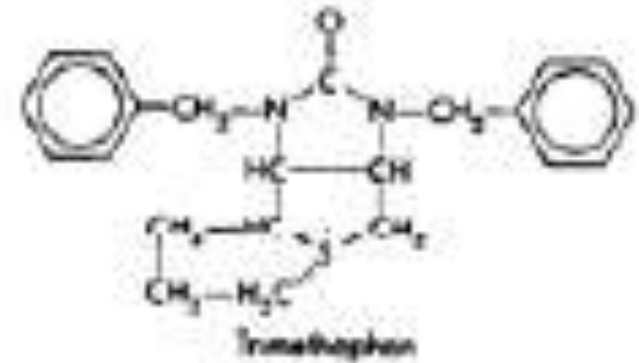


Obat Yang Merangsang Kemudian Menghambat Ganglion (NIKOTIN)

- ➡ Bekerja seperti ACh pada N_N .
- ➡ Menimbulkan EPSP awal → mencapai ambang rangsang → terjadi perangsangan ganglion.
- ➡ EPSP (depolarisasi) persisten menimbulkan hambatan ganglion (desensitisasi kolinoseptor).
- ➡ Bersifat toksik, menimbulkan ketergantungan psikis.
- ➡ Pertama kali diisolasi dari *Nicotiana tabacum* oleh Posselt dan Reiman (1828).

GANGLIONIC BLOCKER

- ▶ Menghambat secara kompetitif ACh bekerja pada reseptor nikotinik di ganglion
- ▶ Contoh : Hexamethonium, Trimethaphan, Mecamylamine
- ▶ Efek : sangat banyak, meliputi sistem simpatis dan parasimpatis.
- ▶ Efek pada organ : tergantung dominasi innervasi pada masing-masing organ



EFEK GANGLIONIC BLOCKER

Effector	System	Effect of Ganglion Blockade
Arterioles	SANS	Vasodilation, hypotension
Veins	SANS	Dilation, ↓ venous return, ↓ CO
Heart	PANS	Tachycardia
Iris	PANS	Mydriasis
Ciliary muscle	PANS	Cycloplegia
GI tract	PANS	↓ tone and motility—constipation
Bladder	PANS	Urinary retention
Salivary glands	PANS	Xerostomia
Sweat glands	SANS	Anhidrosis

Terima Kasih

by Fath's @ 2020