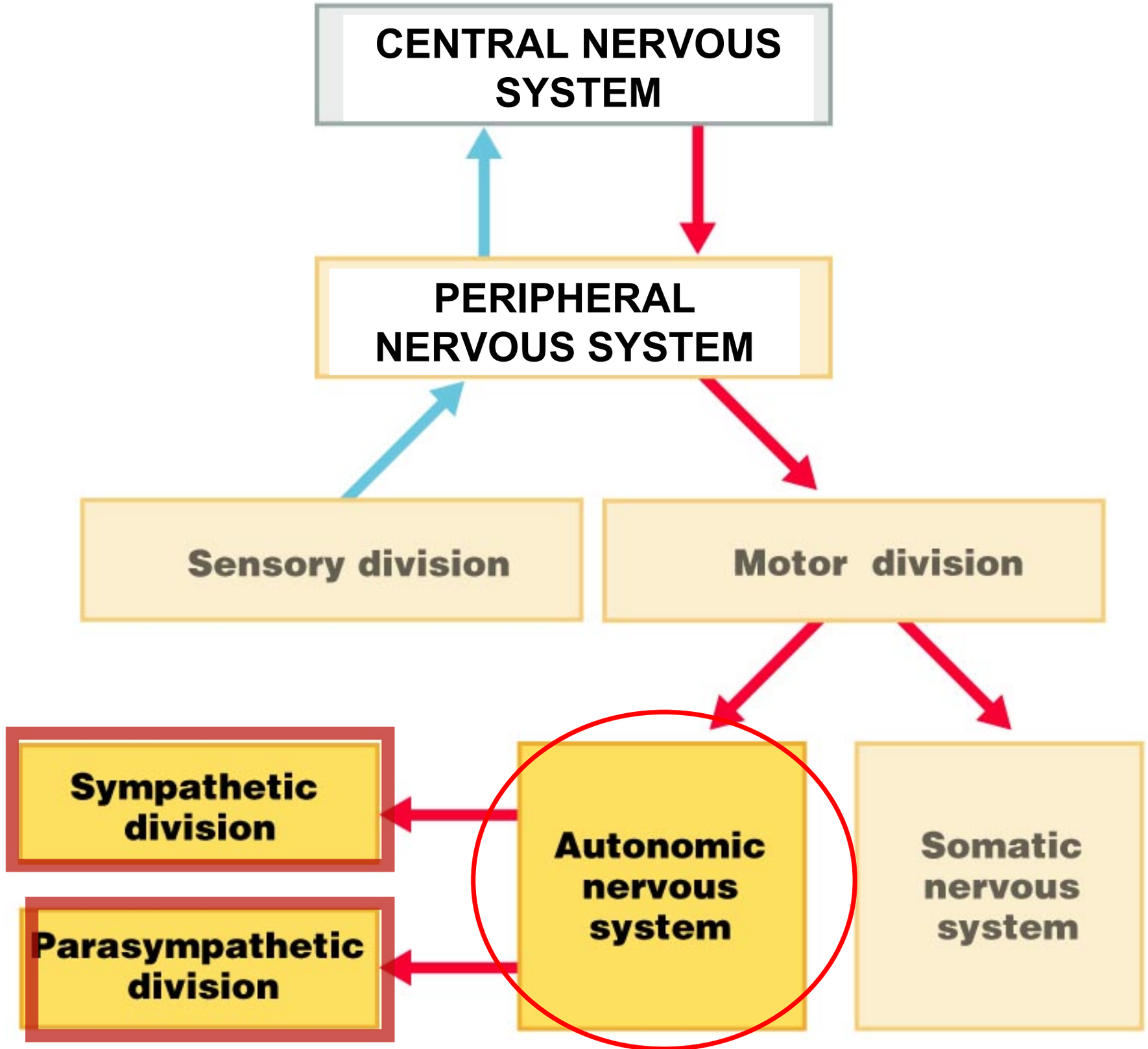
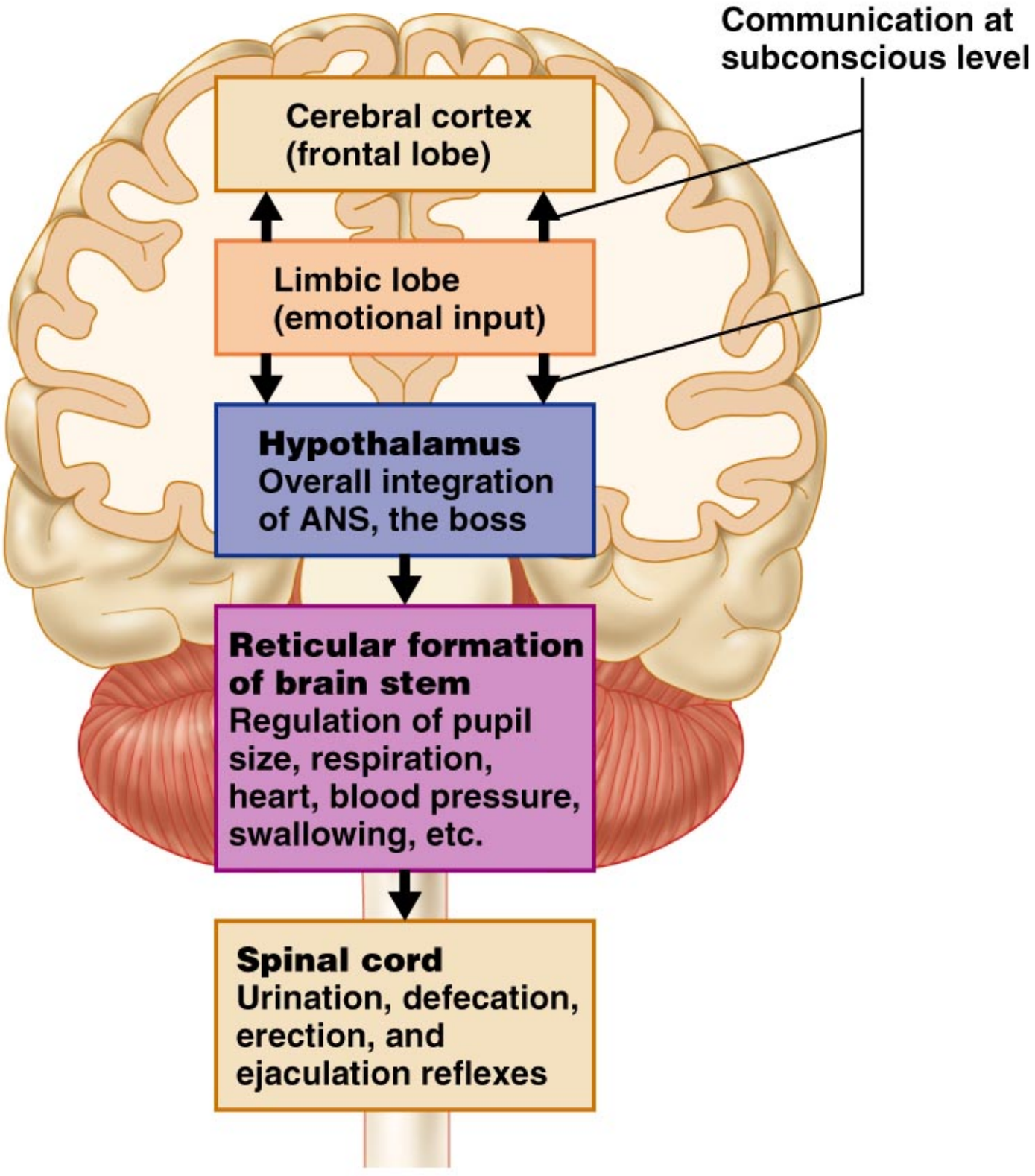
AUTONOMIC NERVOUS SYSTEM

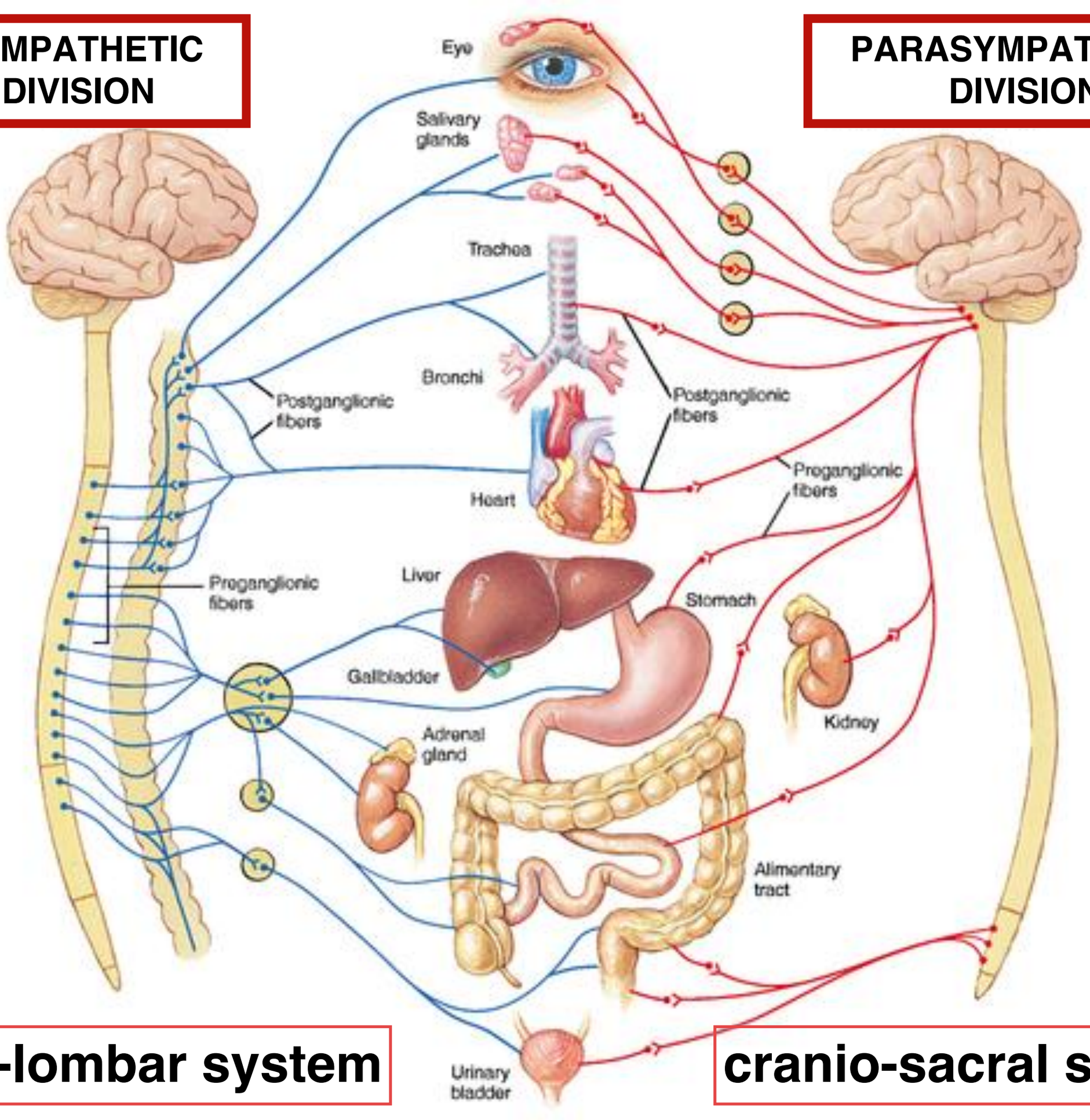


The Autonomic Nervous System (ANS) is under control of the Central Nervous System (CNS)



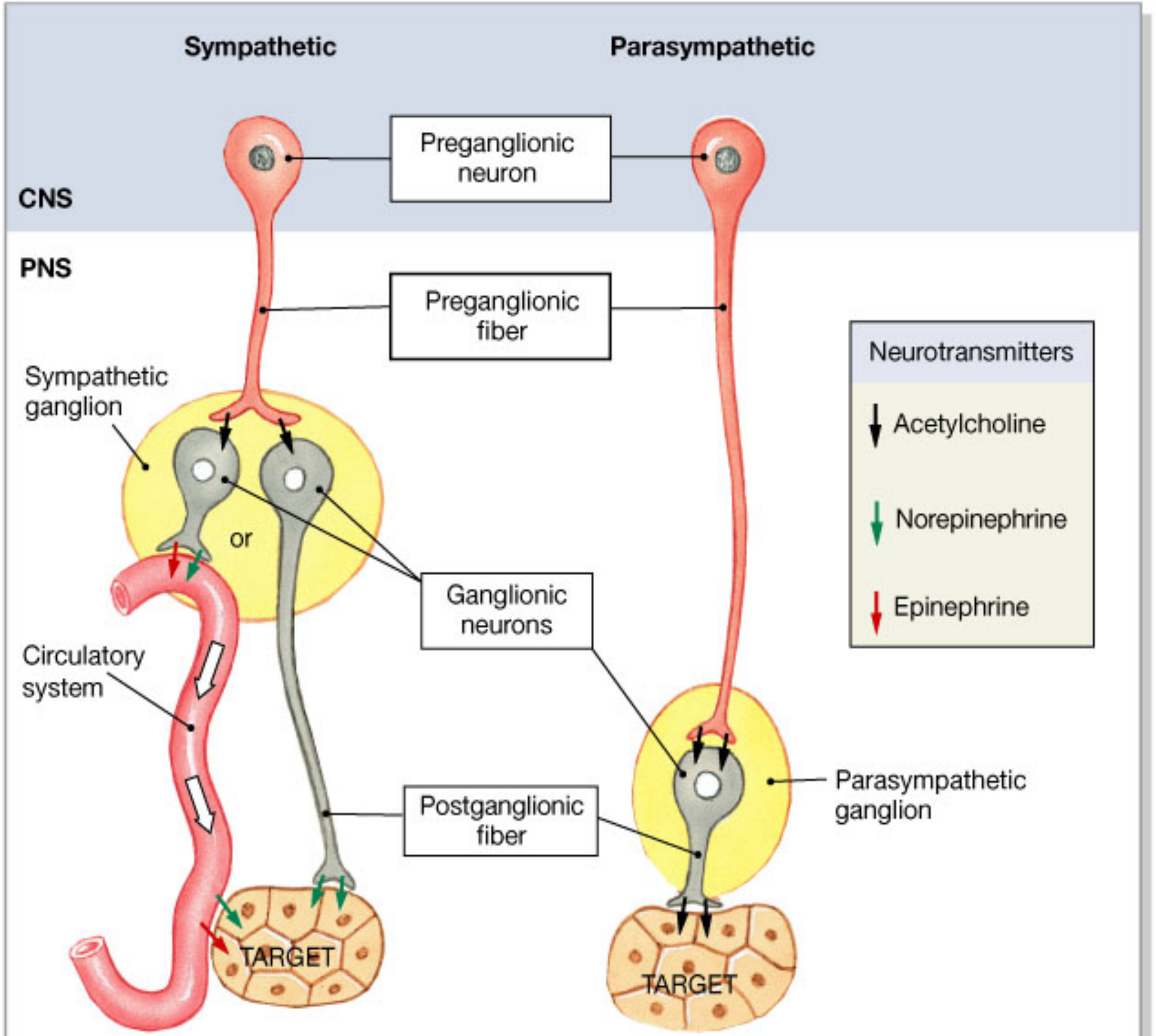
SYMPATHETIC DIVISION

PARASYMPATHETIC DIVISION

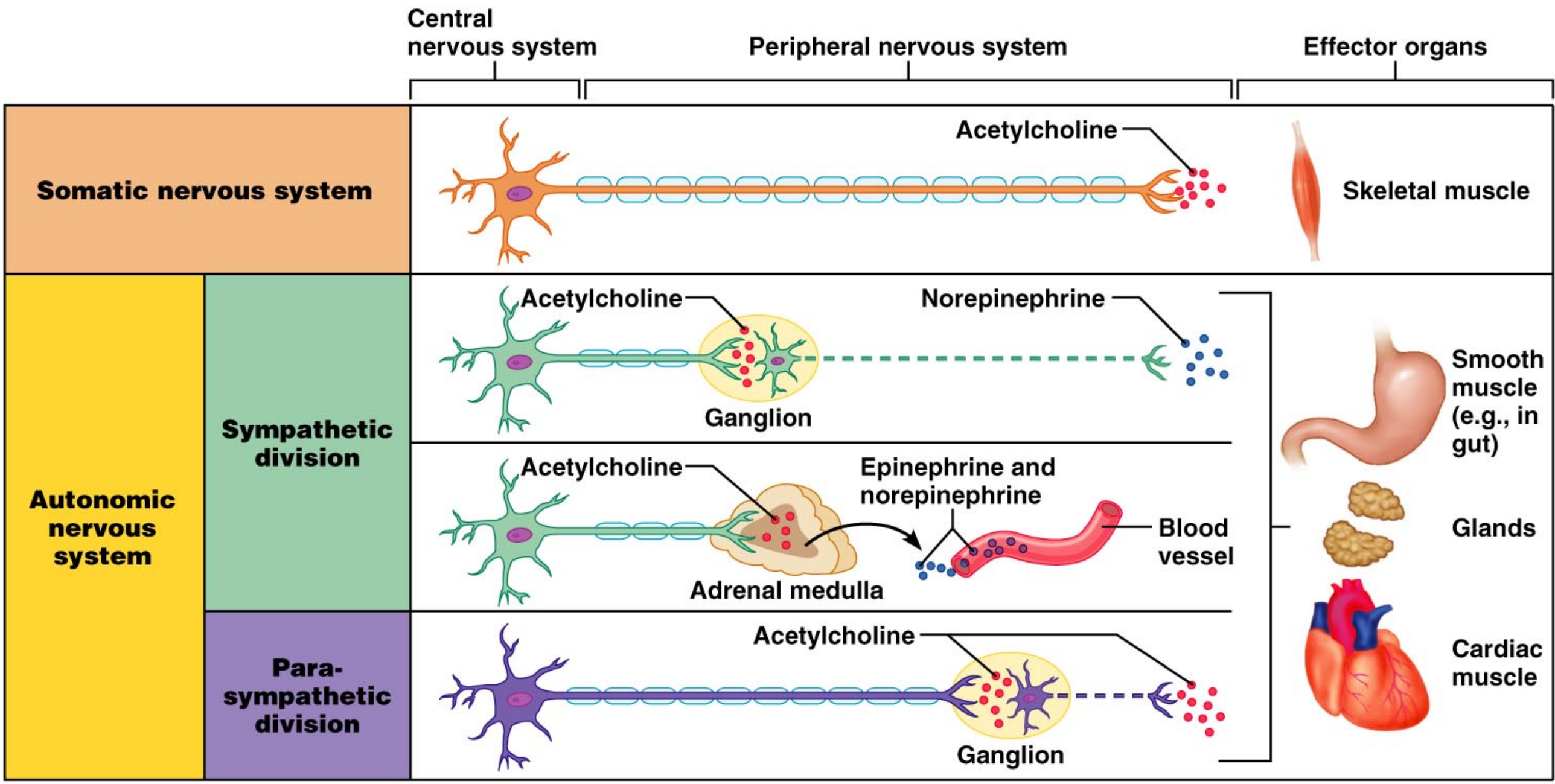


toraco-lombar system

cranio-sacral system


Sympathetic
Parasympathetic
CNS
PNS
Preganglionic neuron
Preganglionic fiber
Sympathetic ganglion
or
Ganglionic neurons
Circulatory system
Postganglionic fiber
Parasympathetic ganglion
TARGET
TARGET
Neurotransmitters
Acetylcholine
Norepinephrine
Epinephrine

Autonomic Nervous System fibers



Key:

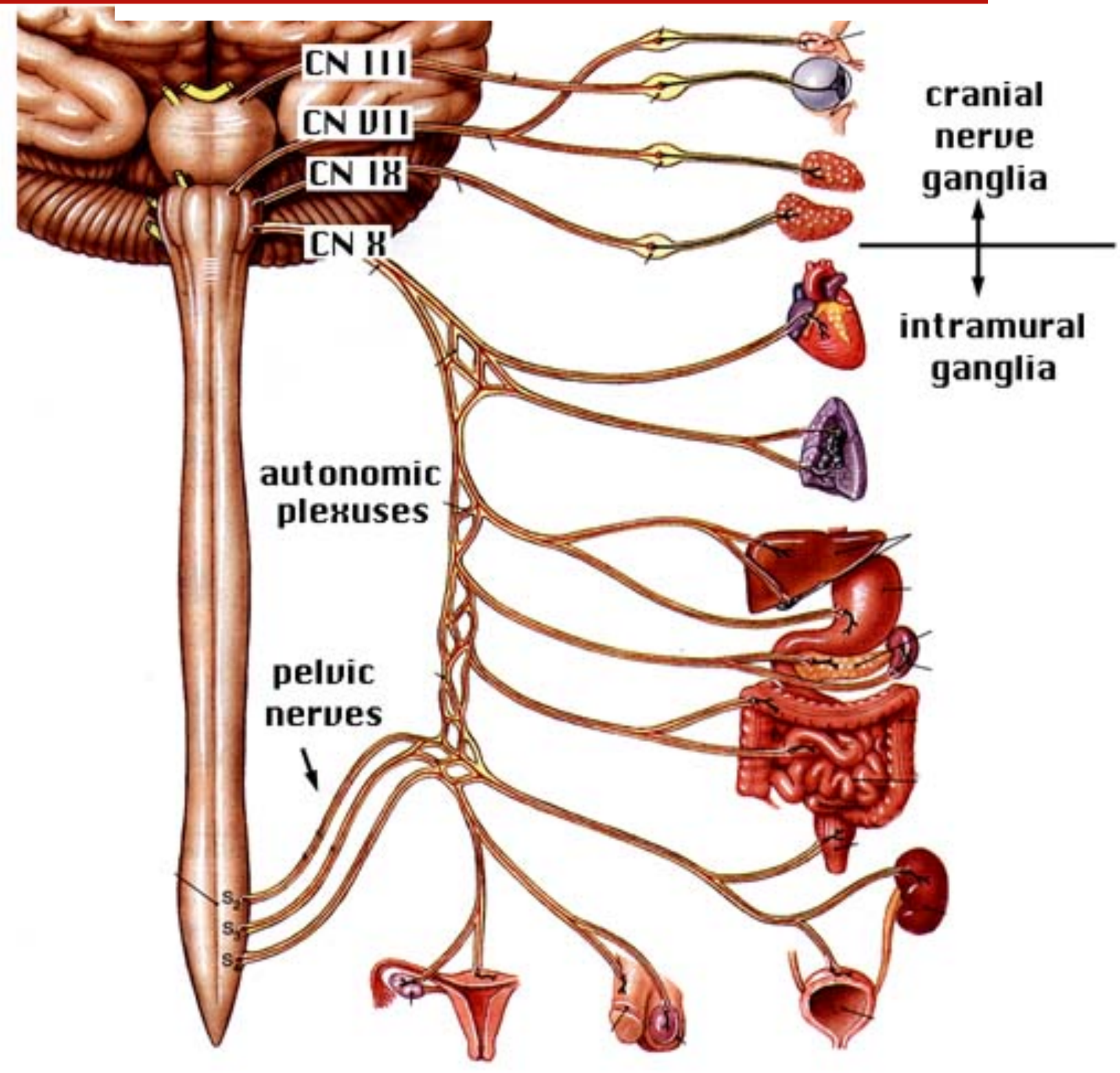
= Preganglionic axons (sympathetic) = Postganglionic axons (sympathetic) = Myelination = Preganglionic axons (parasympathetic) = Postganglionic axons (parasympathetic)

PNS vs SNS

The parasympathetic nervous system (PNS) controls homeostasis of the body at rest and is responsible for the "rest and digest" function

The sympathetic nervous system (SNS) controls the body's responses to a perceived threat and is responsible for the "fight or flight" response

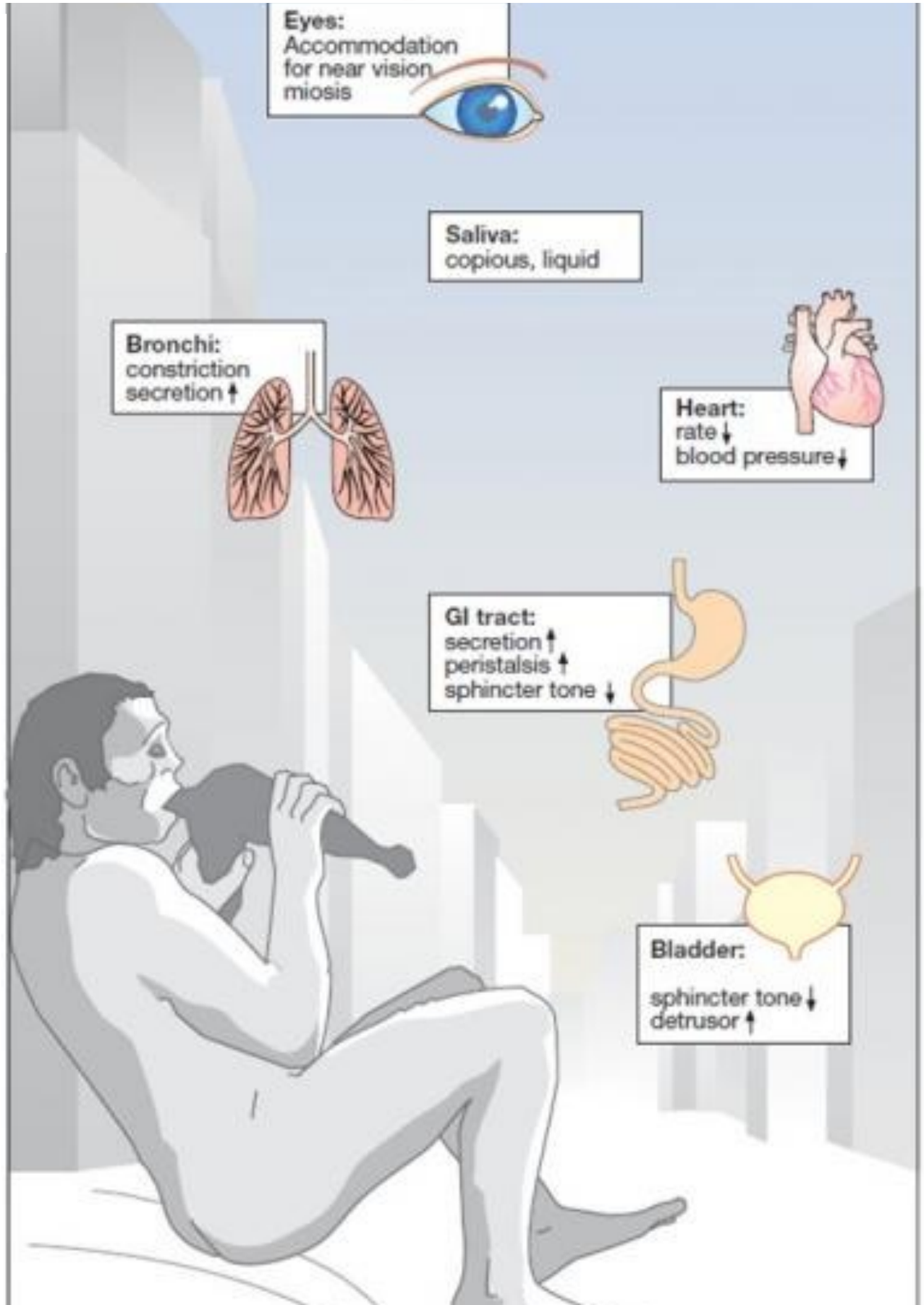
PARASYMPATHETIC DIVISION



"rest and digest" functions:

Eyes:
Accommodation for near vision
Miosis

Bronchi:
Constriction
Increased secretion



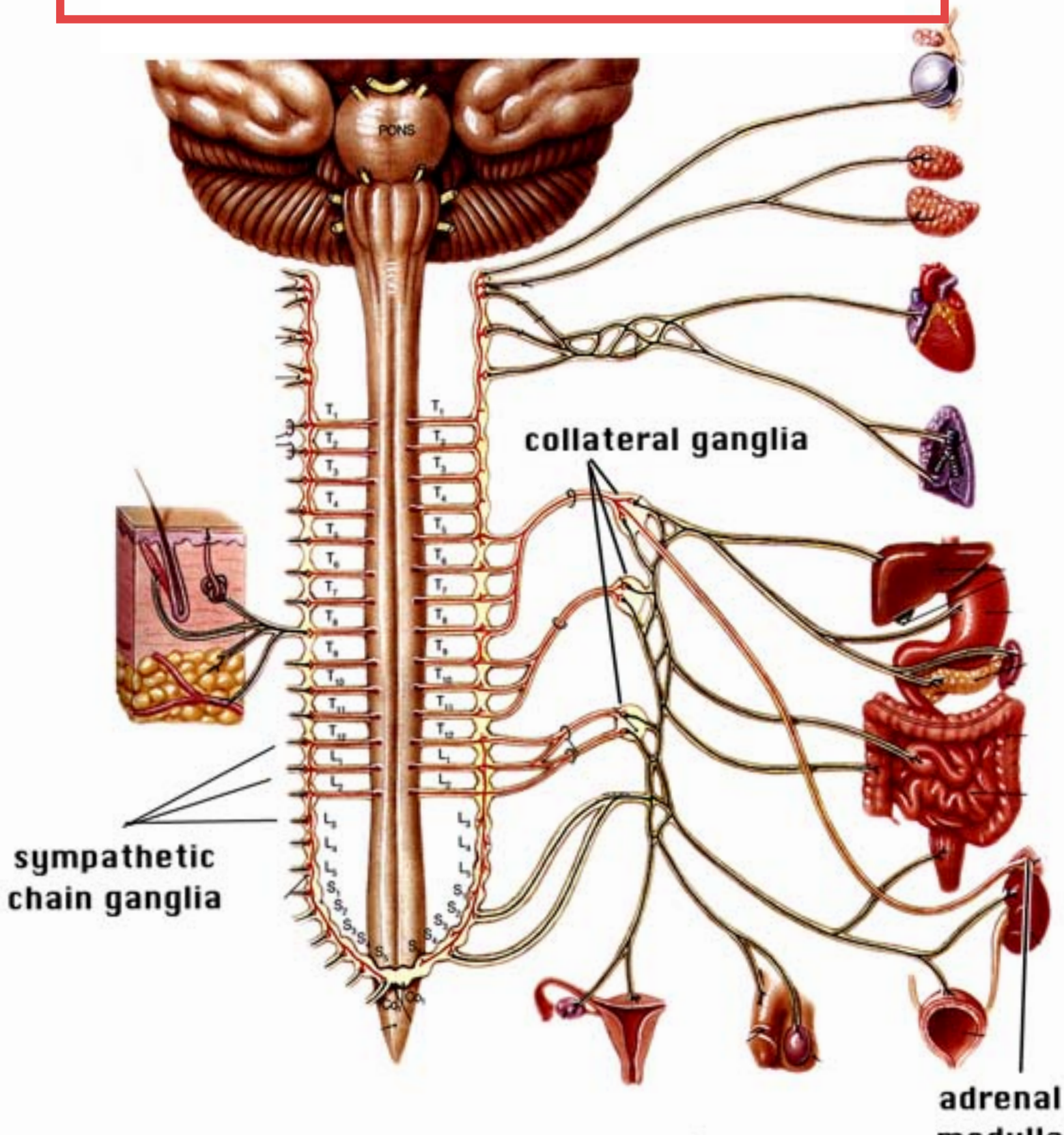
Saliva:
Copious, liquid

Heart:
Decreased rate
Decreased blood pressure

Gastro-intestinal tract:
Increased secretion
Increased peristalsis
Decreased sphincter tone

Bladder:
Increased detrusor tone
Decreased sphincter tone

SYMPATHETIC DIVISION



Modified from Fig. 17-5, Prentice Hall, Martini/Timmons 1997

SNC:
Increased drive and alertness

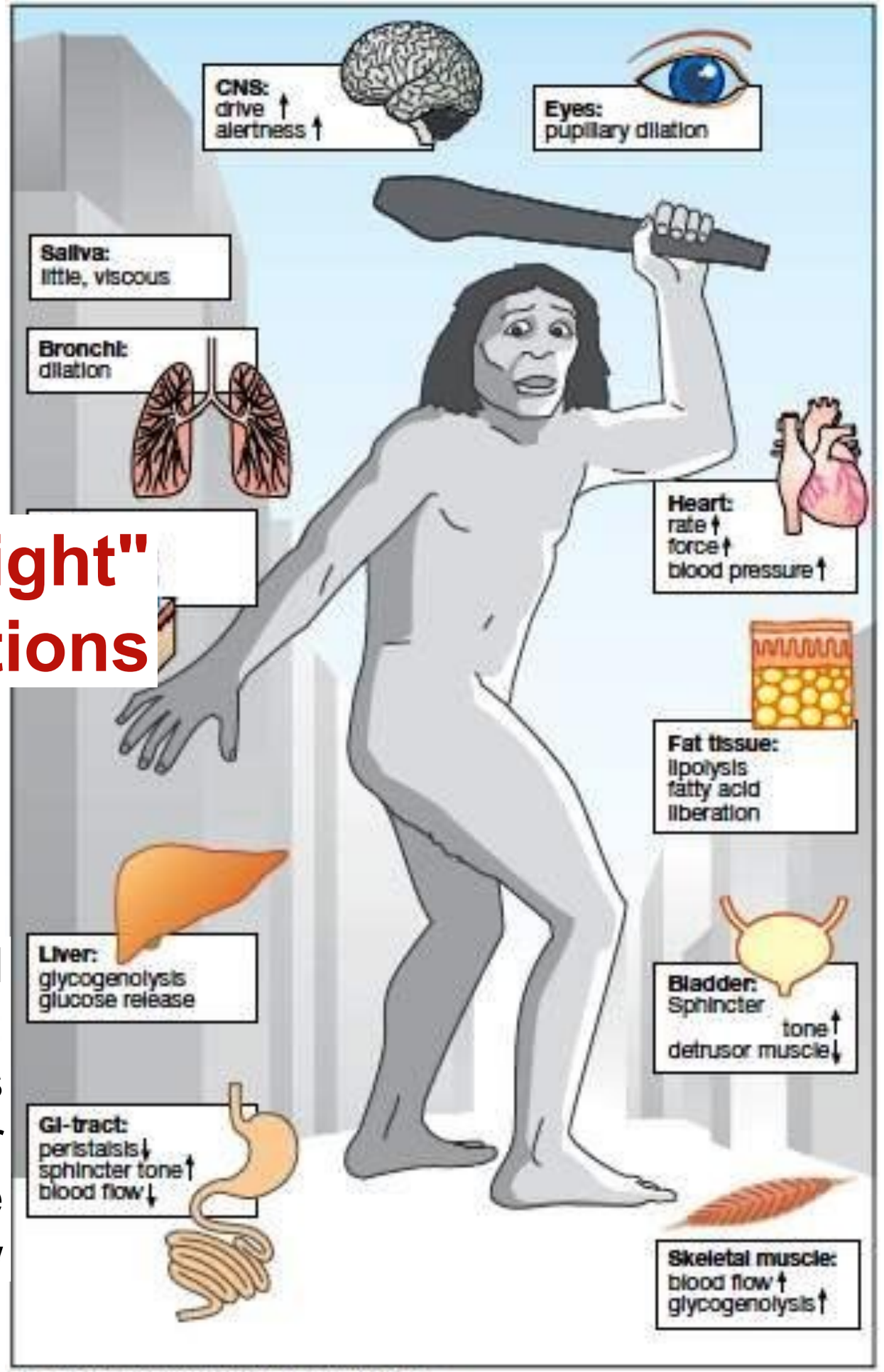
Saliva:
Little, viscous

Bronchi:
Dilatation

"Fight or flight" functions

Liver:
Glycogenolysis
Glucose release

Gastrointestinal tract:
Decreased peristalsis
Increased sphincter tone
Decreased blood flow



Eyes:
Pupillary dilation

Heart:
Increased rate
Increased force
Increased blood pressure

Fat tissue:
Lipolysis
Fatty acids liberation

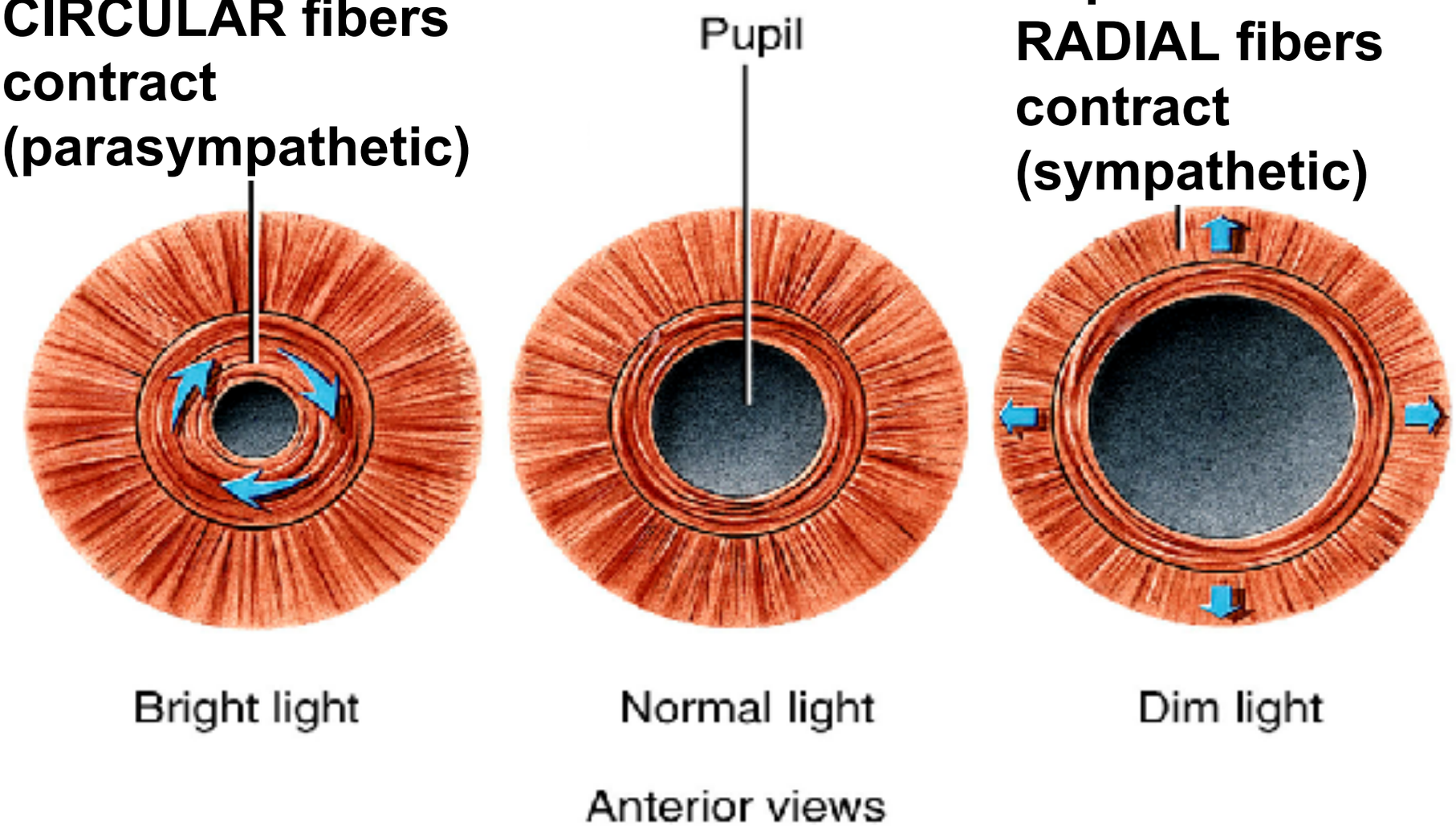
Bladder:
Decreased detrusor tone
Increased sphincter tone

Skeletal muscle:
Increased blood flow
Increased glycogenolysis

The circular and radial muscles control the size of the pupil

Pupil constricts as CIRCULAR fibers contract (parasympathetic)

Pupil dilates as RADIAL fibers contract (sympathetic)

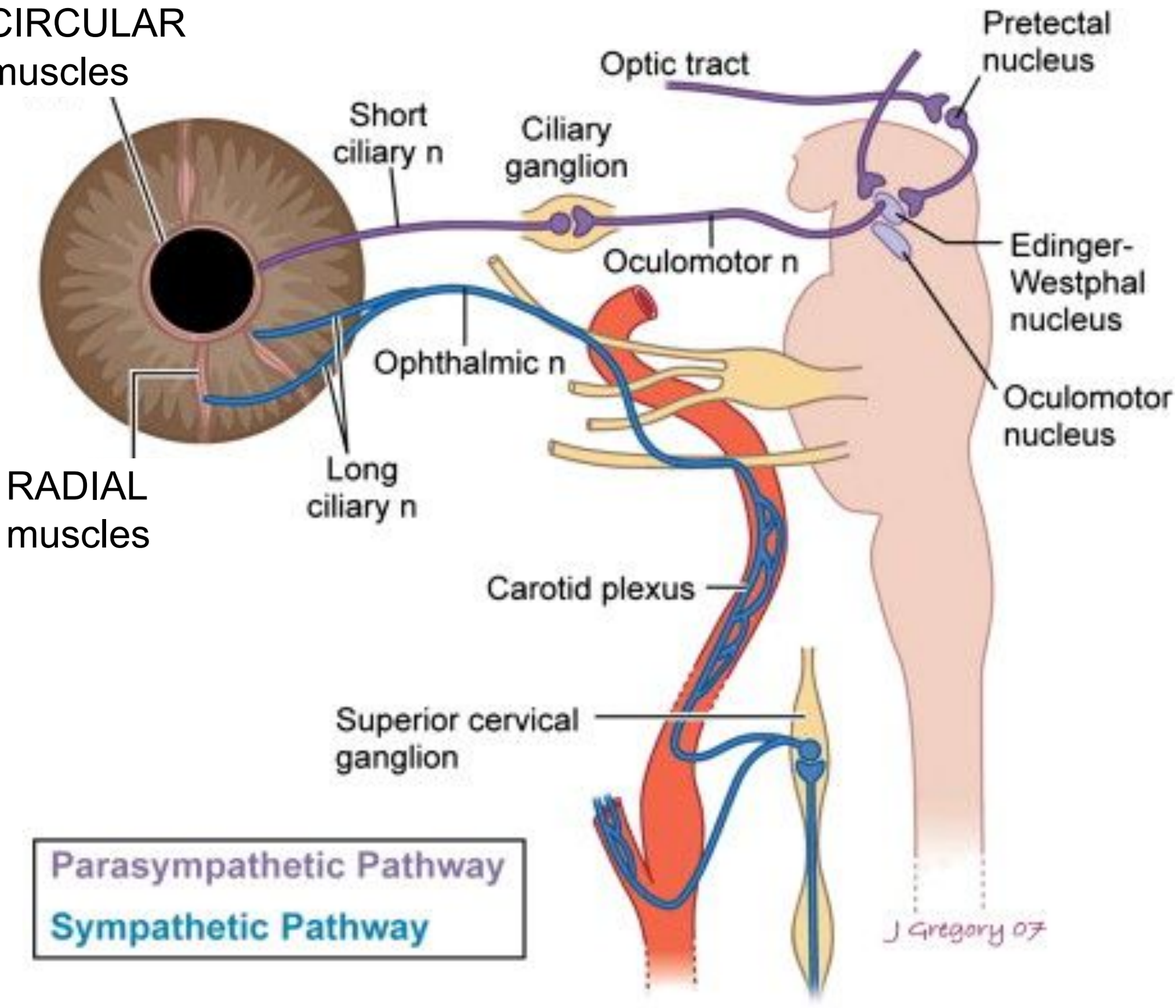


Miosis

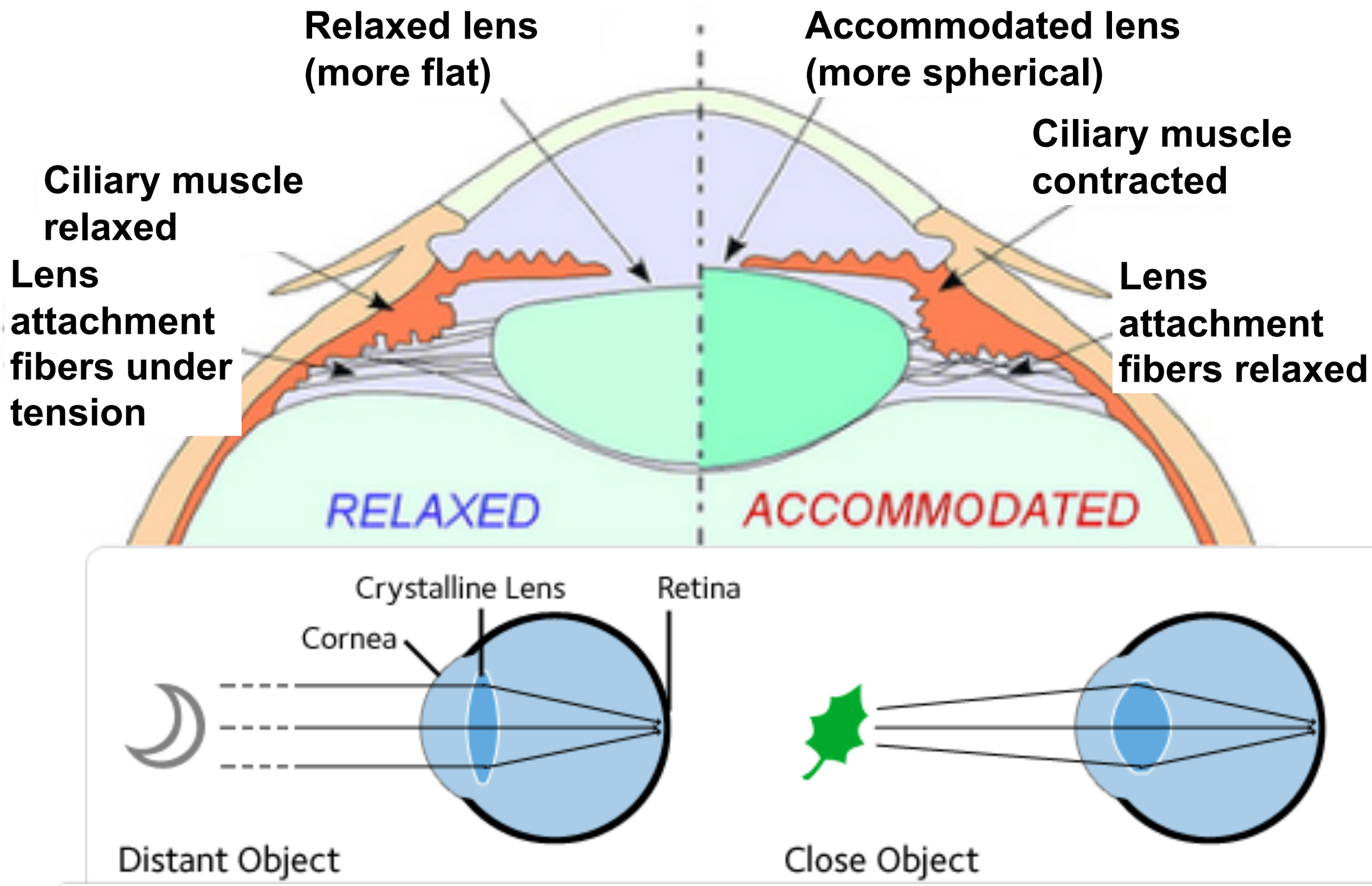
Midriasis

CIRCULAR muscles

RADIAL muscles



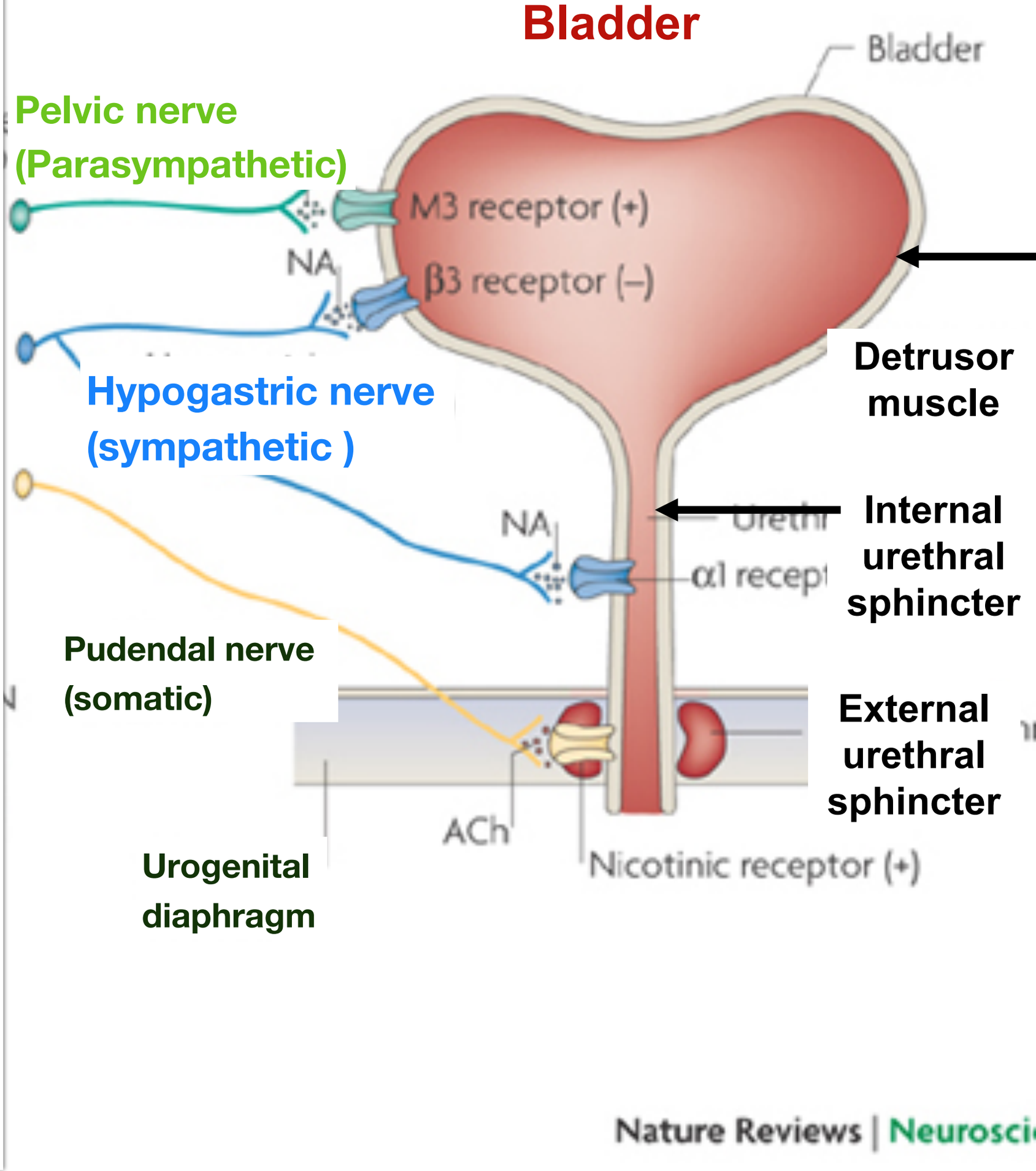
The ciliary muscles control the shape of the lens



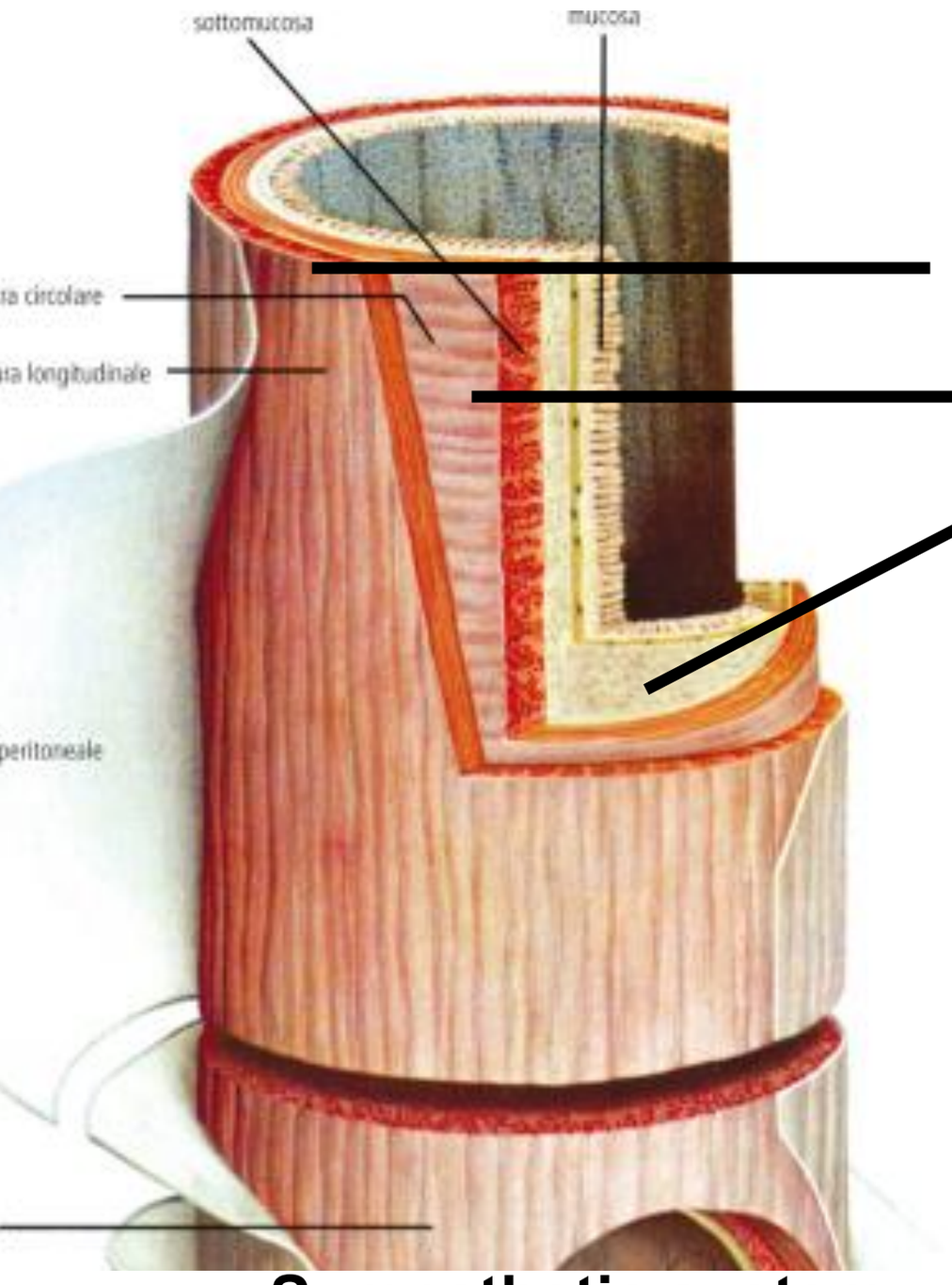
Sympathetic system	Parasympathetic system

Parasympathetic system:
Detrusor muscle contracts

Sympathetic system:
Detrusor muscle relax
Internal urethral sphincter contracts



Intestinal tract



Longitudinal muscle

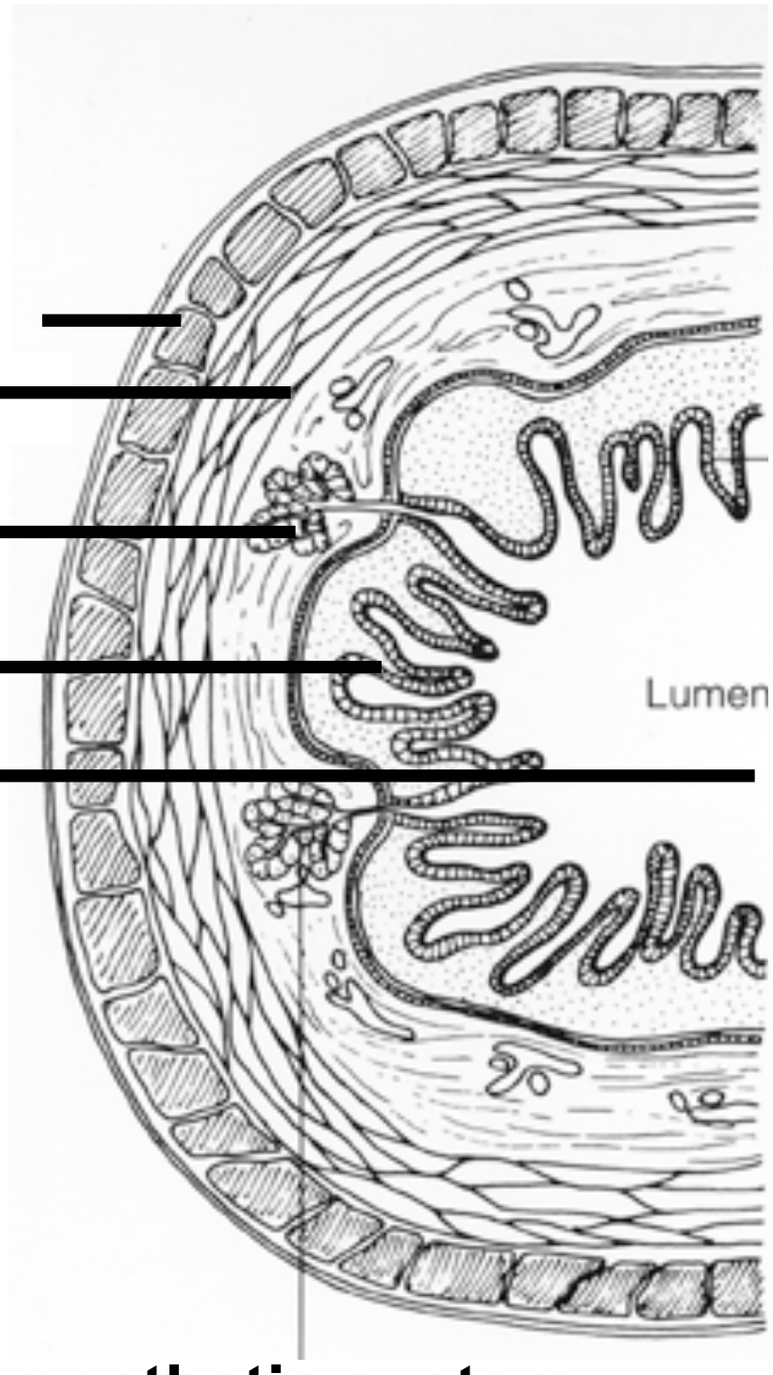
Circular muscle

Submucosa

Gland

Epithelium

Lumen



Sympathetic system:
Decreased peristalsis
Increased sphincter tone

Parasympathetic system:
Increased peristalsis
Decreased sphincter tone

SYMPATHETIC

PARASYMPATHETIC

Sympathetic Ganglia

Dilates Pupils

Constricts Pupils

Inhibits Salivation

Stimulates Salivation

Bronchial Dilation

Decreases Heart Rate

Increases Heart Rate

Decreases Contractility

Bronchial Constriction

Inhibits Digestion

Increases Contractility

Stimulates Digestion

Stimulates Glucose Release by Liver

Stimulates Epinephrine & Norepinephrine Release

Stimulates Gallbladder

Relaxes Bladder

Contracts Bladder

Contracts Rectum

Relaxes Rectum

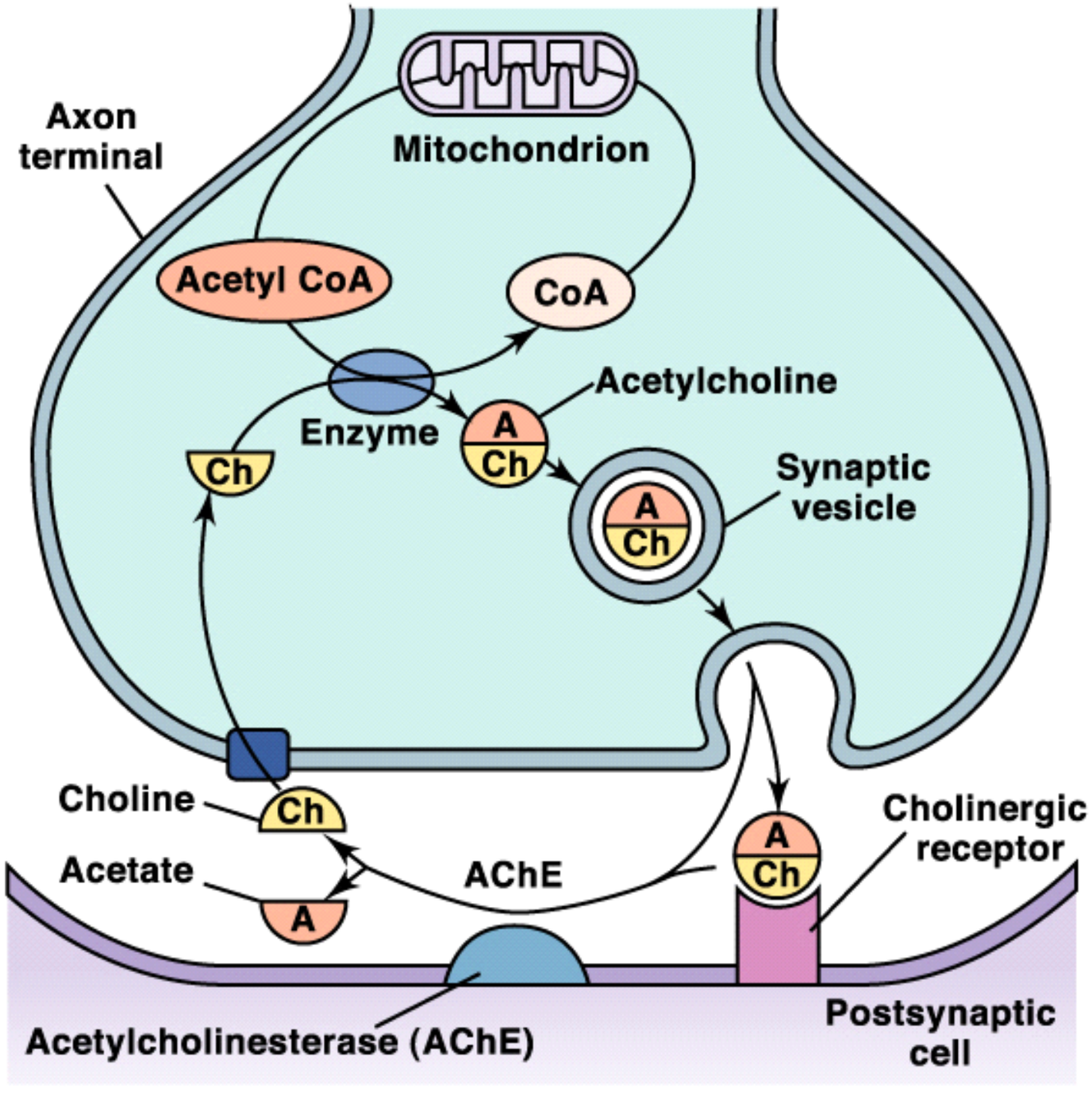
Orgasm Ejaculation

Vaginal Lubrication Erection

Peripheral Vasoconstriction

Peripheral Vasodilation

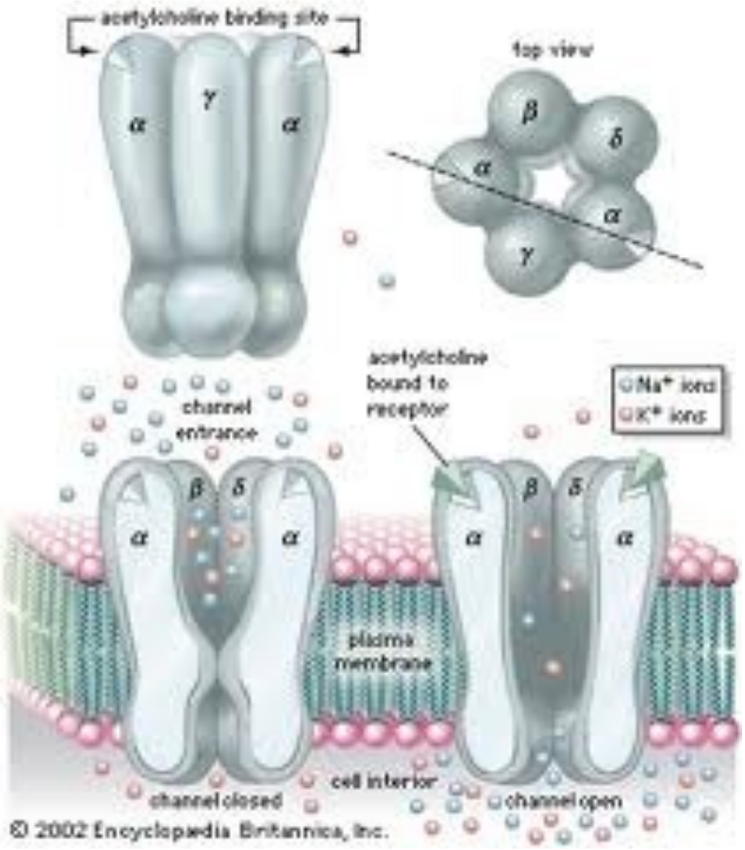
CHOLINERGIC TRANSMISSION
ACETYLCHOLINE SYNTHESIS AND DEGRADATION

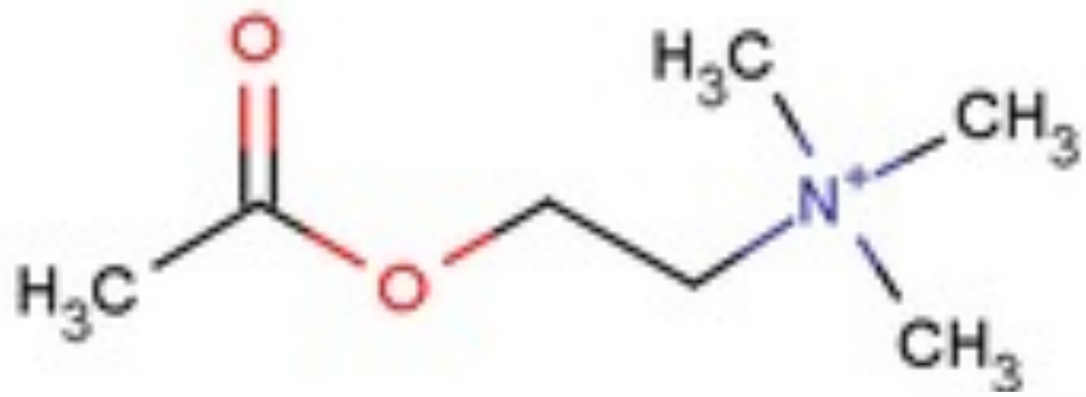


ACETYLCHOLINE RECEPTORS
(Dale, 1914)

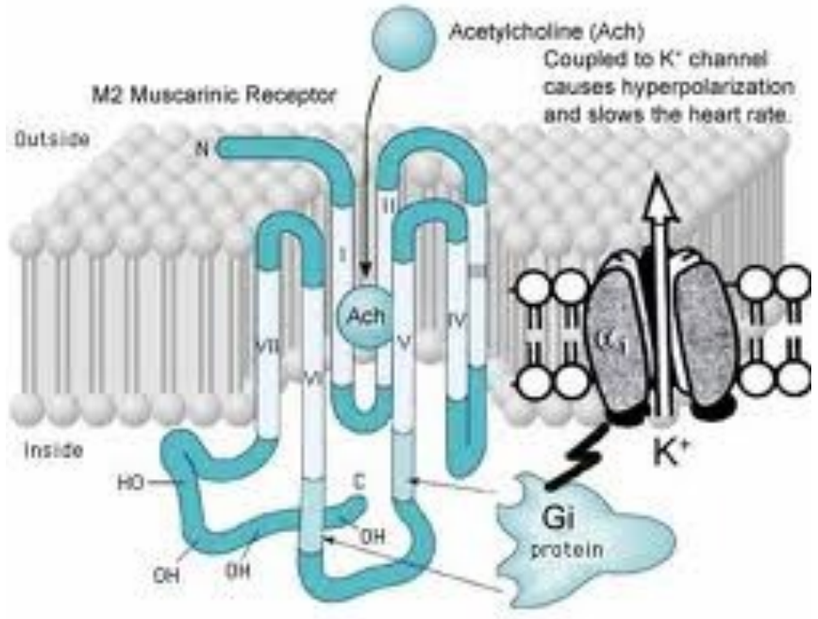
NICOTINIC
ionotropic

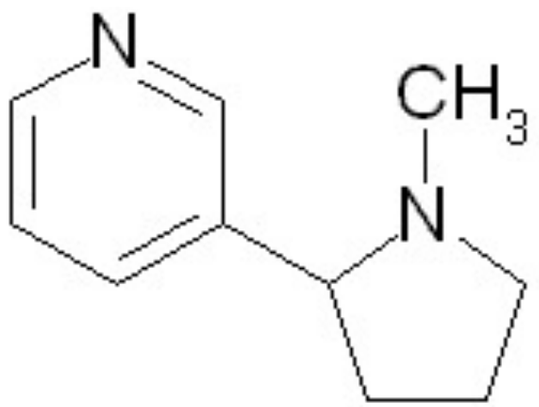
MUSCARINIC
metabotropic



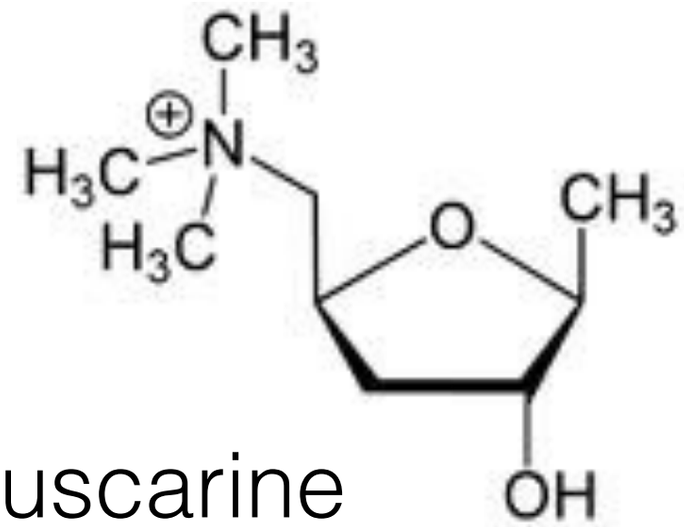


Acetylcholine



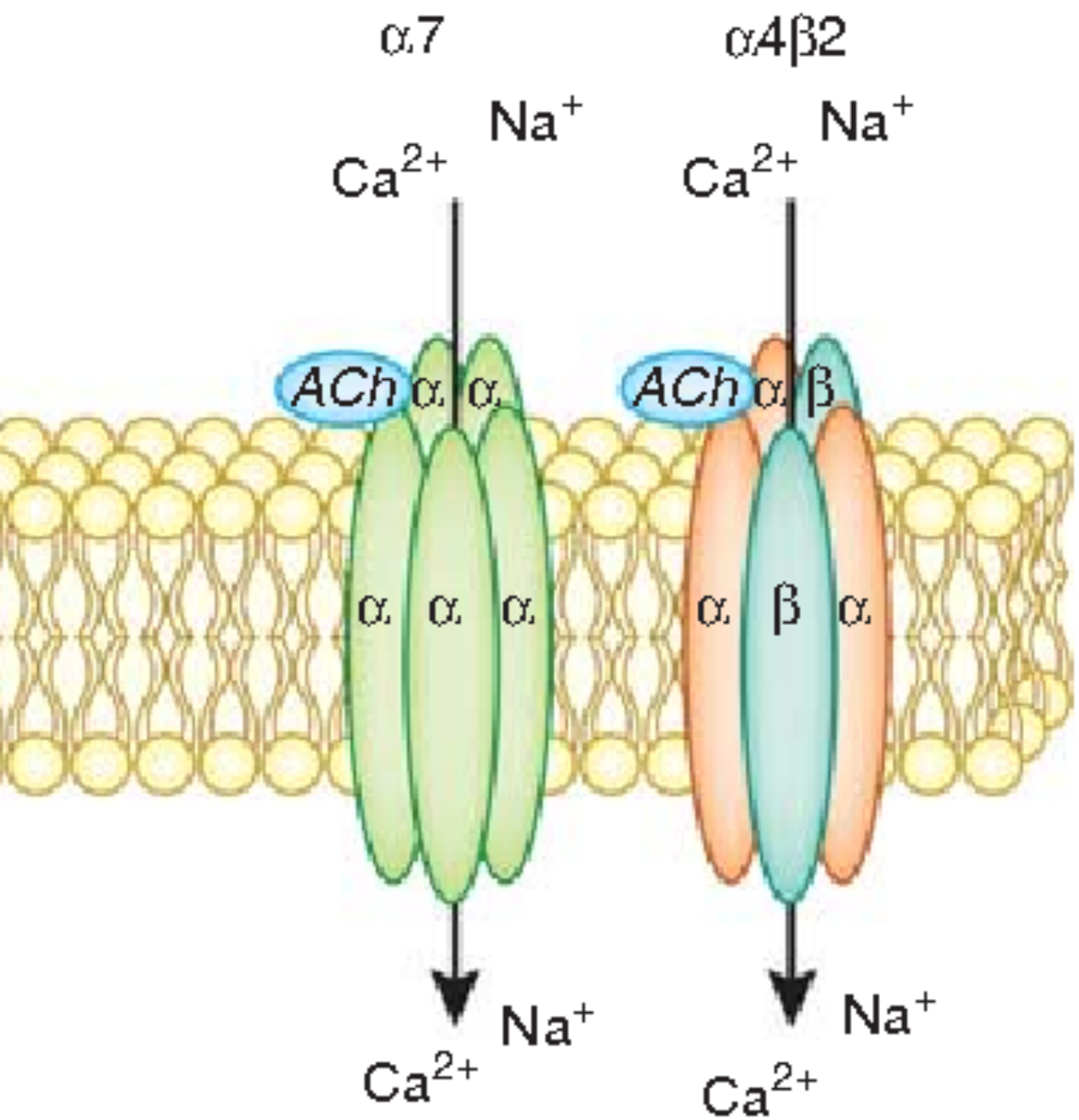


Nicotine



Muscarine

NICOTINIC RECEPTORS



Key effectors (examples)

↑ $[Ca^{2+}]i$

↑ VDCC

↑ PKC

SUBTYPE	MAIN LOCALIZATION	MEMBRANE RESPONSE
Muscle type **(alpha1)2-beta1-delta- epsilon**	Skeletal neuromuscular junction (mainly post-synaptic)	Excitatory
Ganglion type **(alpha3)2-(beta2)3**	Autonomic ganglia (mainly post-synaptic)	Excitatory
CNS type **(alpha4)2-(beta2)3** **(alpha7)5**	Many brain regions: pre- and post-synaptic	Excitatory

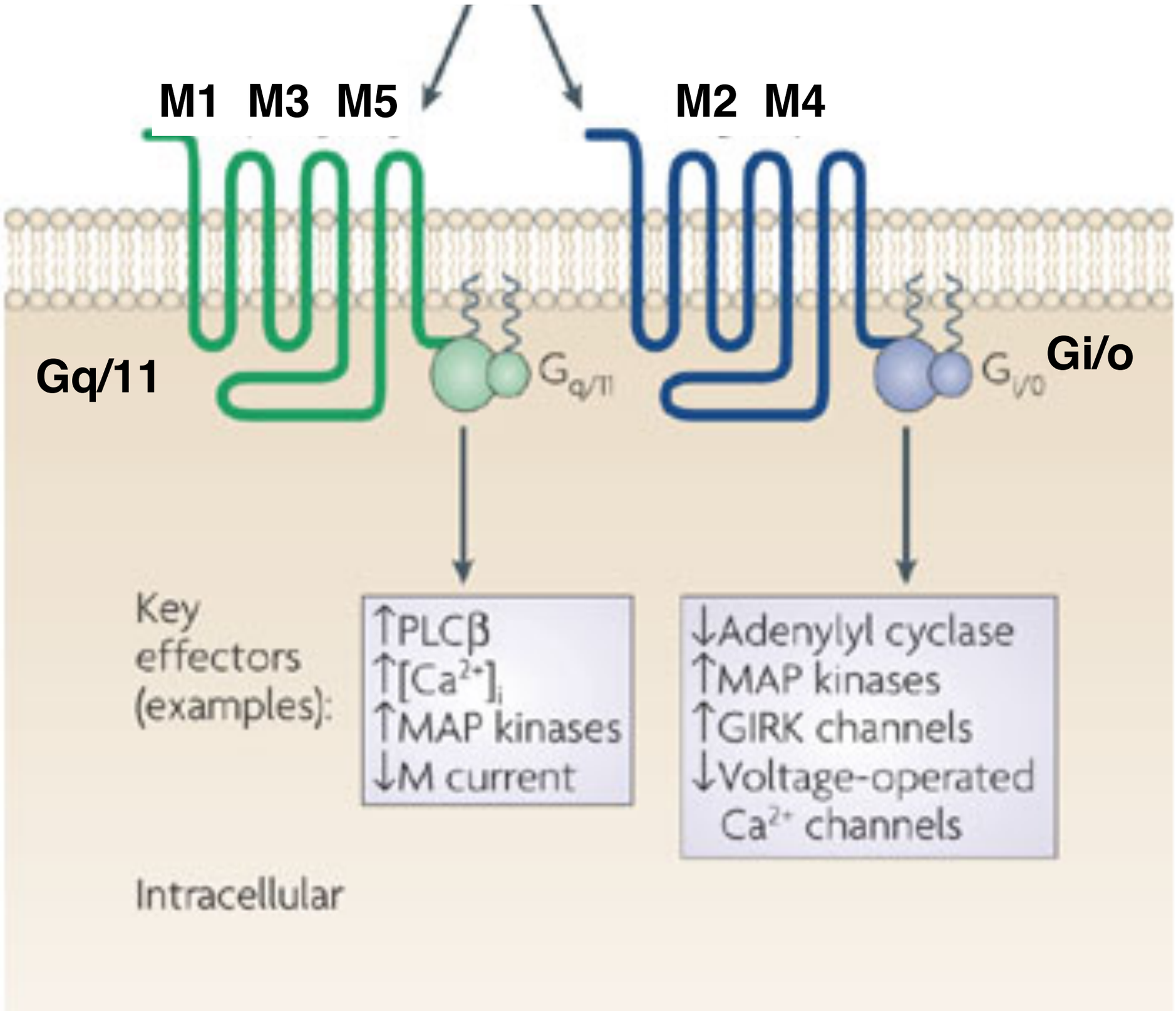
NICOTINIC RECEPTORS

SUBTYPE	AGONISTS	CLINICAL USE
Muscle type **(alpha1)2-beta1-delta-epsilon**	Acetylcholine Carbachol **Succinylcholine** Suxamethonium	None None **Paralysis during anaesthesia (short acting)**
Ganglion type **(alpha3)2-(beta2)3**	Acetylcholine Carbachol Nicotine Epibatidine	None None Smoke cessation None
CNS type **(alpha4)2-(beta2)3** **(alpha7)5**	Nicotine Epibatidine Acetylcholine Varenicline	None None None Smoke cessation

NICOTINIC RECEPTORS

SUBTYPE	ANTAGONISTS	CLINICAL USE
Muscle type **(alpha1)2-beta1-delta-epsilon**	**Tubocurarine** **Pancuronium** **Atracurium** **Vecuronium**	**Paralysis during anaesthesia**
Ganglion type **(alpha3)2-(beta2)3**	Mecamylamine Trimetaphan Hexamethonium	Obsolete anti-hypertensive drug
CNS type **(alpha4)2-(beta2)3** **(alpha7)5**	Mecamylamine Methylaconitine Alpha-bungarotoxin Alpha-conotoxin	Crosses the BBB (antagonizes nicotine CNS effects) None

MUSCARINIC RECEPTORS



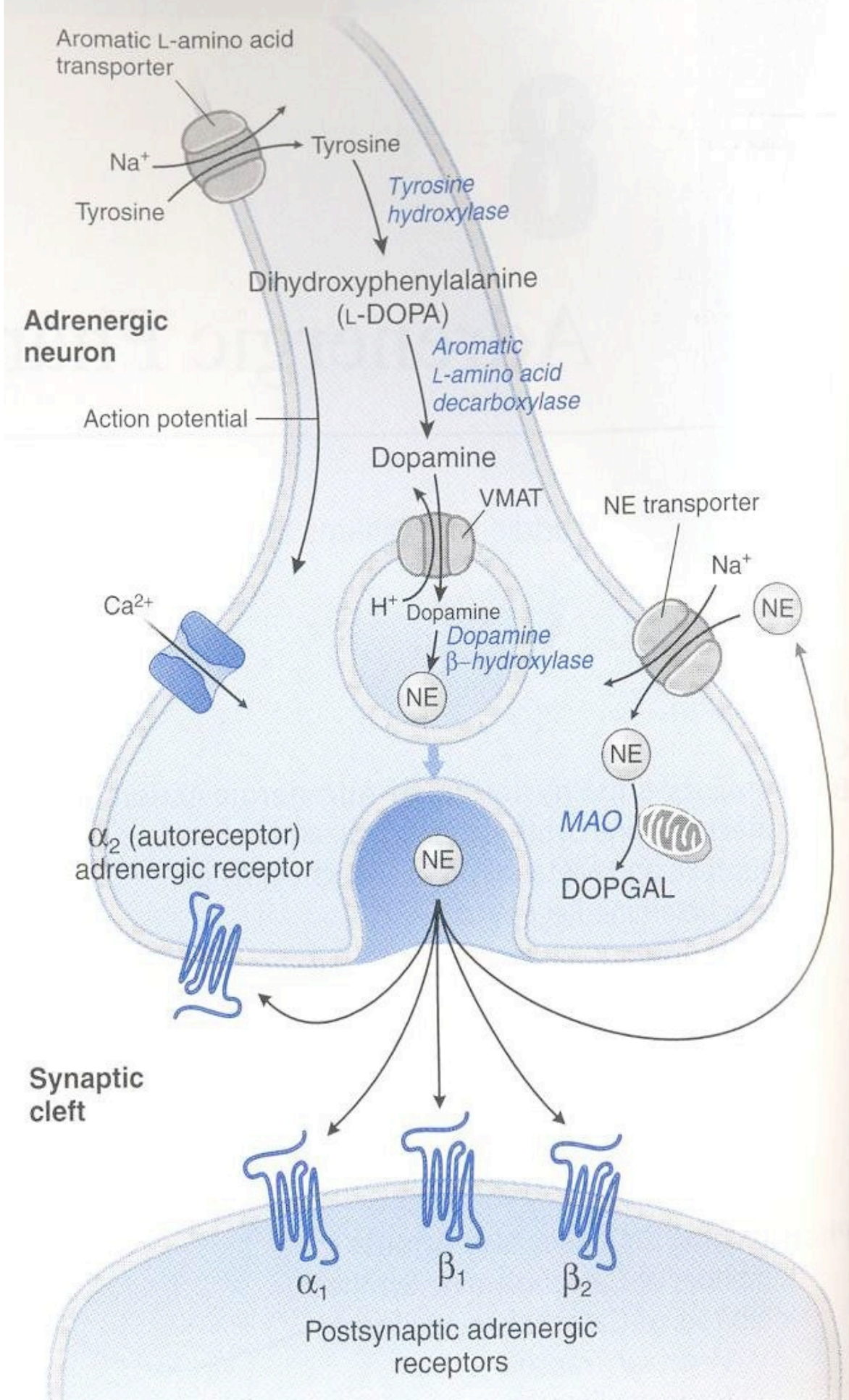
MUSCARINIC RECEPTOR		
SUBTYPE	**MAIN LOCATION**	**FUNCTIONAL RESPONSE**
M1 ("neural)	Cerebral cortex Autonomic ganglia	CNS excitation Gastric secretion
M2 ("cardiac")	**Heart: atria** CNS	**Cardiac inhibition (bradicardia)** Neural inhibition
M3 ("Glandular - Smooth muscle")	**Exocrine glands: gastric, salivary, etc** **Smooth muscle: GI tract, eye, airways, bladder** **Blood vessel (endothelium)**	**Gastric, salivary secretion** **Contraction, ocular accomodation** **Vasodilatation (NO-mediated)**
M4	CNS	Enhanced locomotion
M5	CNS (very localized expression)	Not known

SUBTYPE	MUSCARINIC RECEPTOR AGONISTS	CLINICAL USE
M1 ("neural)	NON-SELECTIVE: Acetylcholine **Carbachol** **Pilocarpine** **Bethanechol**	- - **Glaucoma** **Treatment of bladder and gastrointestinal hypotonia**
M2 ("cardiac")	Not known	
M3 ("Glandular - Smooth muscle")	SELECTIVE: Cevimeline	Sjögren'syndrome (to increase salivary and lacrimal secretion)
M4	Not known	Not known
M5	Not known	Not known

MUSCARINIC RECEPTOR		
SUBTYPE	**ANTAGONISTS**	**CLINICAL USE**
M1 ("neural)	NON-SELECTIVE: **Atropine** **Oxibutynin** **Ipatropium** SELECTIVE: Pirenzepine	**Ophthalmic (midriasis and paralisis of accomodation)** **Prevention of motion sickness** **COPD and Asthma** **Anaesthetic premedication** Inhibition of gastric secretion
M2 ("cardiac")	Gallamine	
M3 ("Glandular - Smooth muscle")	SELECTIVE **Darifenacin**	**Urinary incontinence**
M4	Not known	
M5	Not known	

Antimuscarinic drug side effects: dry mouth and skin (dry as a bone), cyclopegia (blind as a bat), bradicardia, urinary retention (full as s flask), constipation, restlessness, irritability (mad as a hatter)

ADRENERGIC TRANSMISSION NORADRENALINE SYNTHESIS AND DEGRADATION



ADRENERGIC RECEPTOR CLASSIFICATION

Epinephrine and Norepinephrine show relatively little receptor **selectivity**

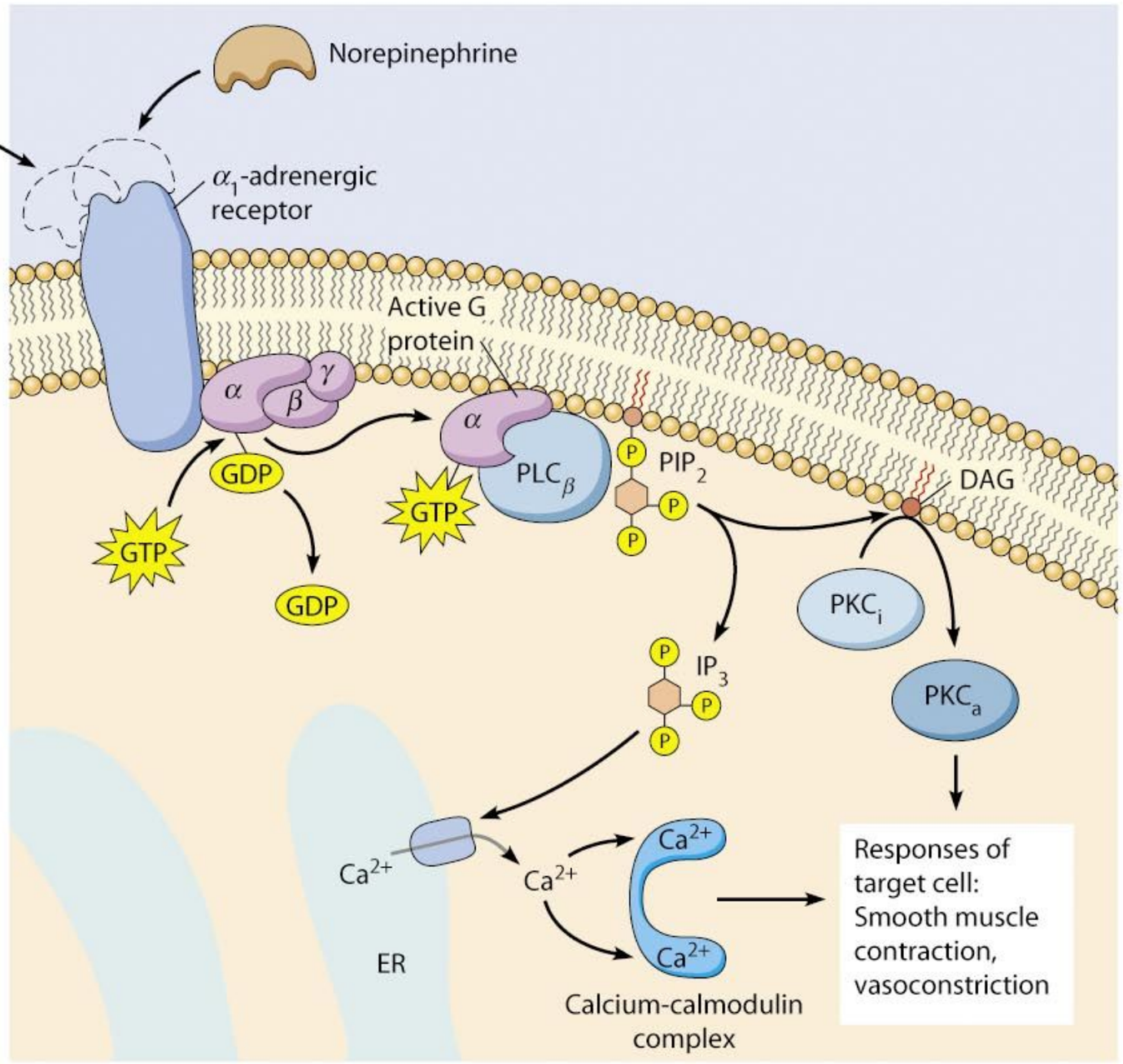
The main pharmacological classification into alfa (α) and beta (β) was originally based on order of potency of agonists:

alfa (α): Epinephrine = NE > dopamine > isoproterenol
beta (β): Isoproterenol = Epineprine > NE > dopamine

	α_1	α_2	β_1	β_2	DA
Norepinephrine	+++	+++	+	-	-
Epinephrine	+++	++	+++	++	-
Dopamine	++	+	++	+++	+++
Dobutamine	+	-	+++	+	-
Isoproterenol	-	-	++	++	-

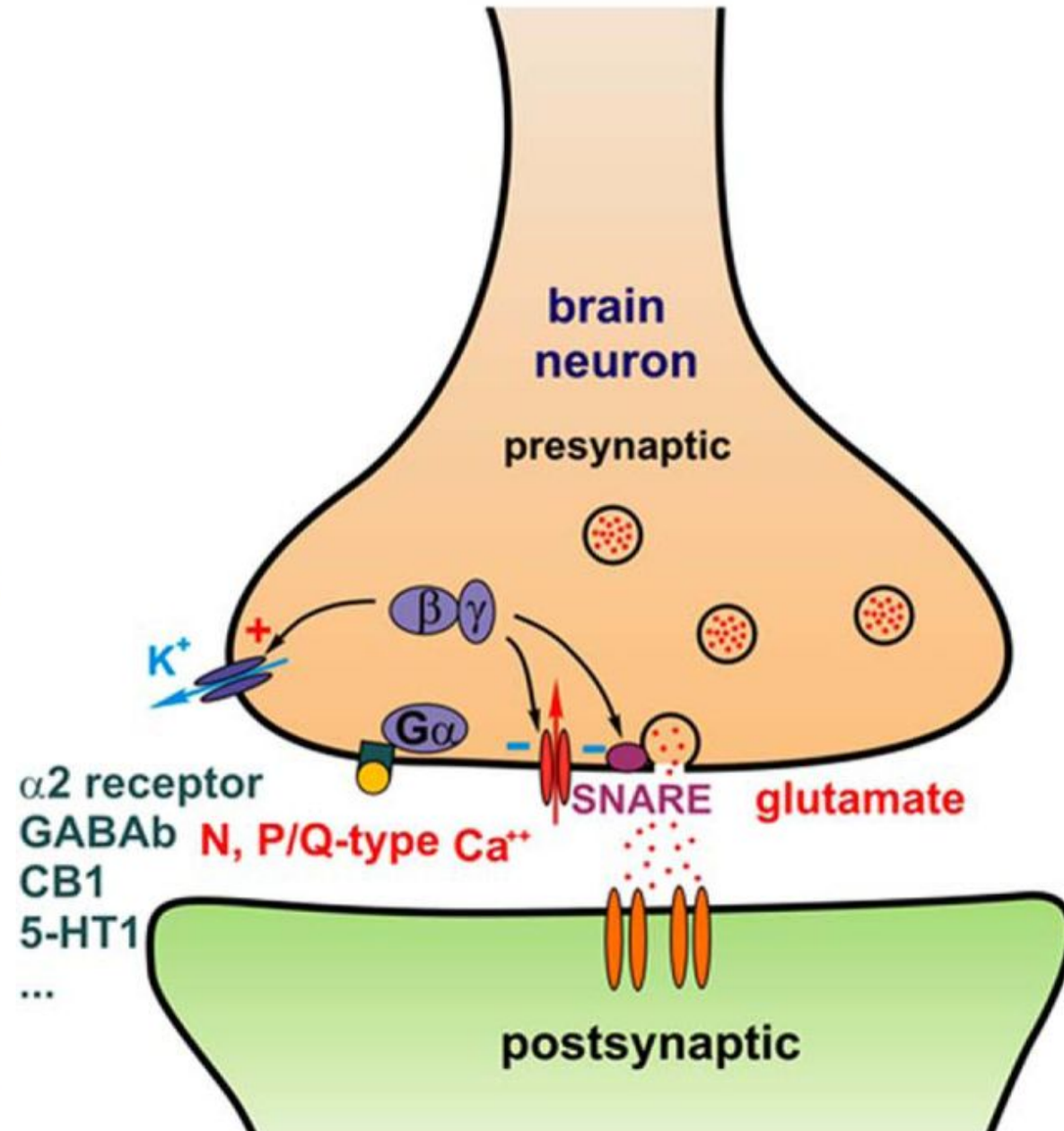
AlphaADRENERGIC RECEPTORS

alpha (α)1: Gq/11



alpha (α)2: Gi/o

- N or P/Q-type Ca^{++} channel mediated release
- Gβγ mediated inhibition via
  - either inhibition of N or P/Q type Ca^{++} channel
  - or activation of K^+ channel
  - or inhibition of key synaptic proteins



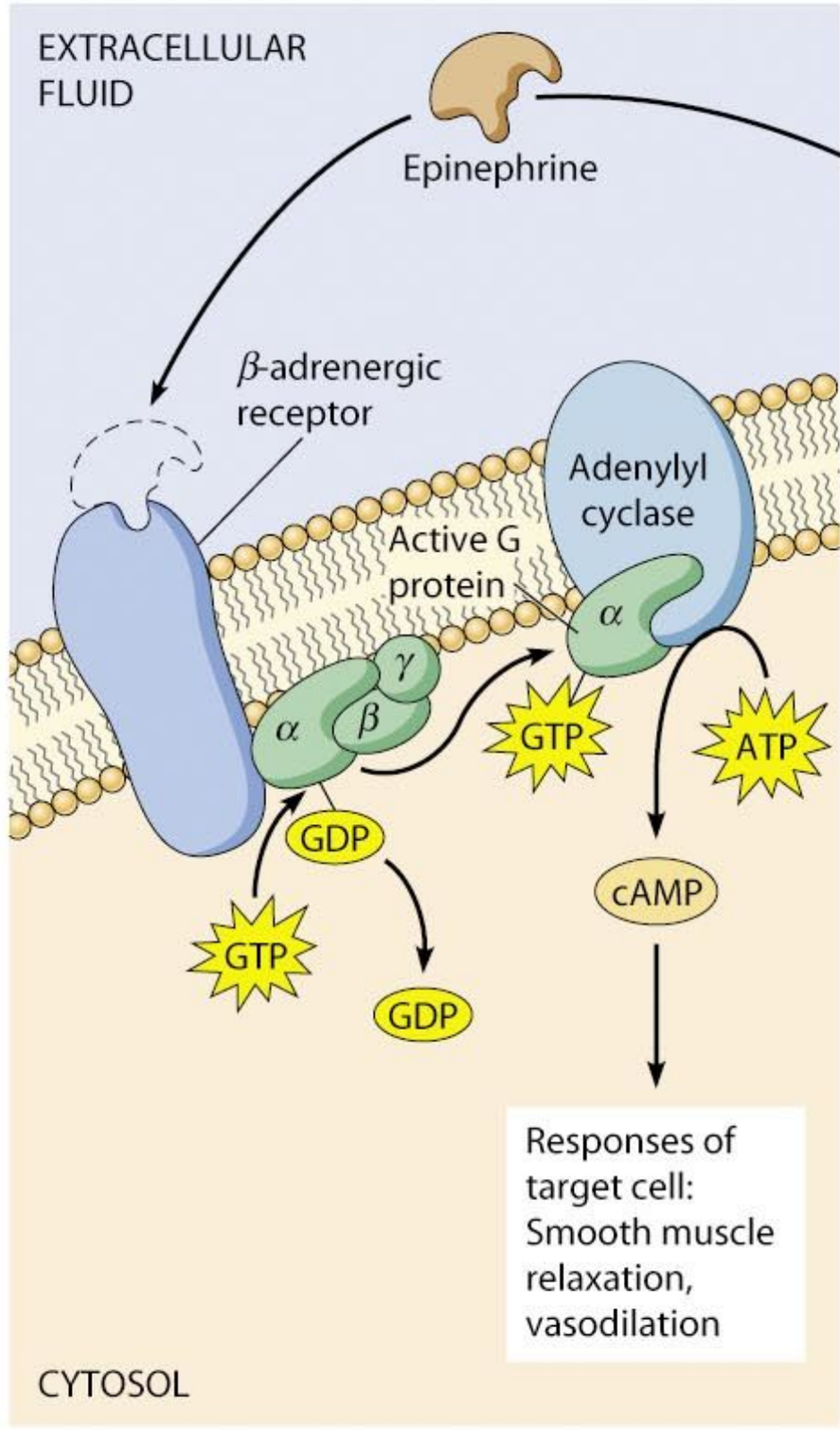
Alpha ADRENERGIC RECEPTOR		
SUBTYPE	**MAIN LOCATION**	**FUNCTIONAL RESPONSE**
Alpha 1	**Blood vessels** GI tract GI sphincters Bladder sphincter Iris	**Contraction** Relaxation Contraction Contraction Contraction (midriasis)
Alpha 2	**Presynaptic brain stem** **Presynaptic nerve terminals**	Inhibition of sympathetic outflow Decreased release of neurotransmitters

Alpha ADRENERGIC RECEPTOR

SUBTYPE	AGONISTS	CLINICAL USES
Alpha 1	**Phenylephrine** Methoxamine	**Nasal decongestion**
Alpha 2	**Clonidine**	**Hypertension**

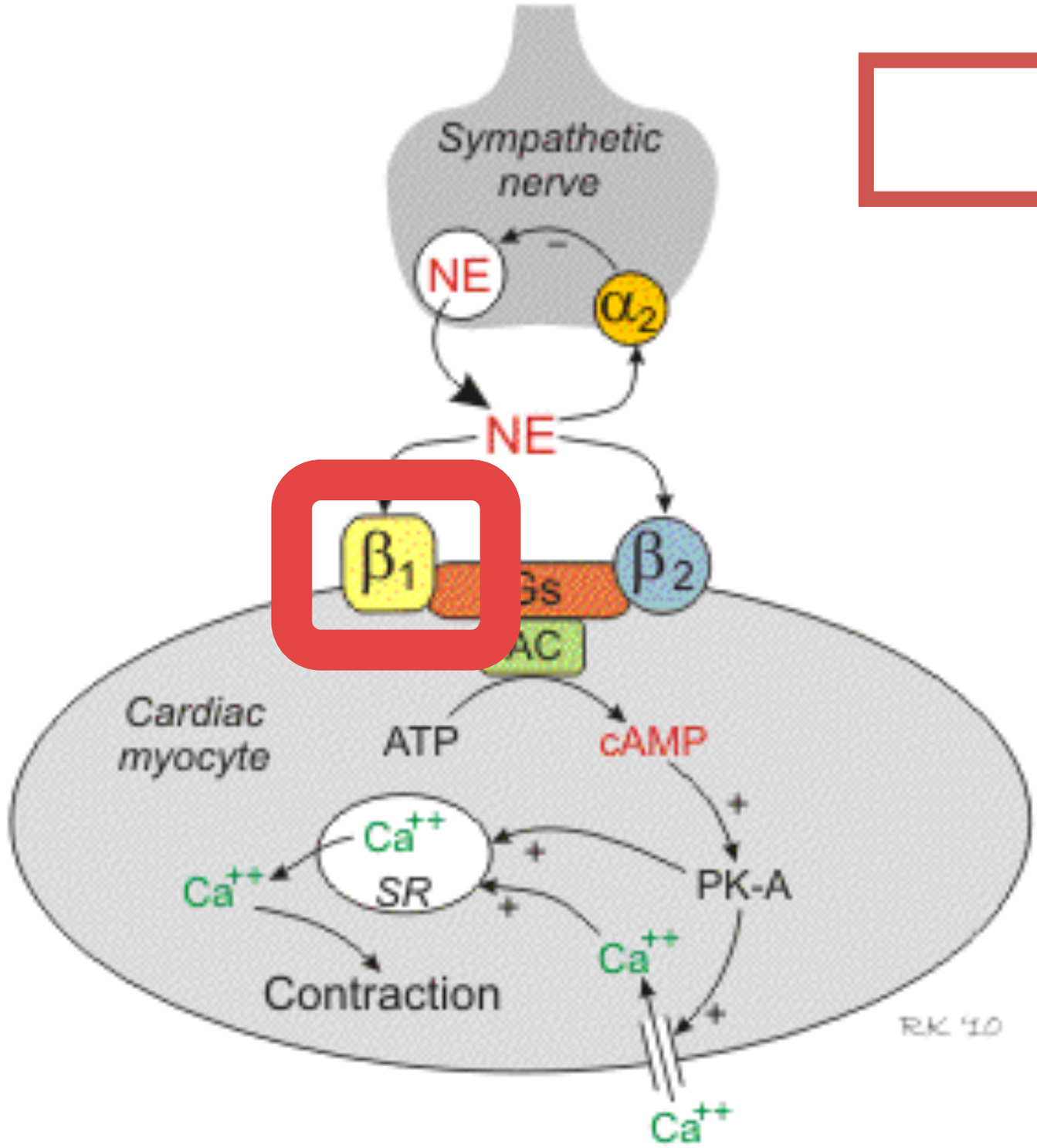
	ANTAGONISTS	CLINICAL USES
Alpha 1	**Prazosin** Doxazocin Tamsulosin	**Hypertension** Benign prostatic hypertophy
Alpha 2	Yohimbine	No clinical use

Beta ADRENERGIC RECEPTOR		
SUBTYPE	**MAIN LOCATION**	**FUNCTIONAL RESPONSE**
Beta 1	**Heart**	Increase rate and force of contraction
	Kidney (iuxtaglomerular apparatus)	Renine release
Beta 2	**Smooth muscle: bronchi**, blood vessel ciliary, GI tract, bladder detrusor	Relax
	Skeletal muscle	Increase mass, tremor
	Liver	Glycogenolysis
Beta 3	Fat tissue	Lipolysis, thermogenesis



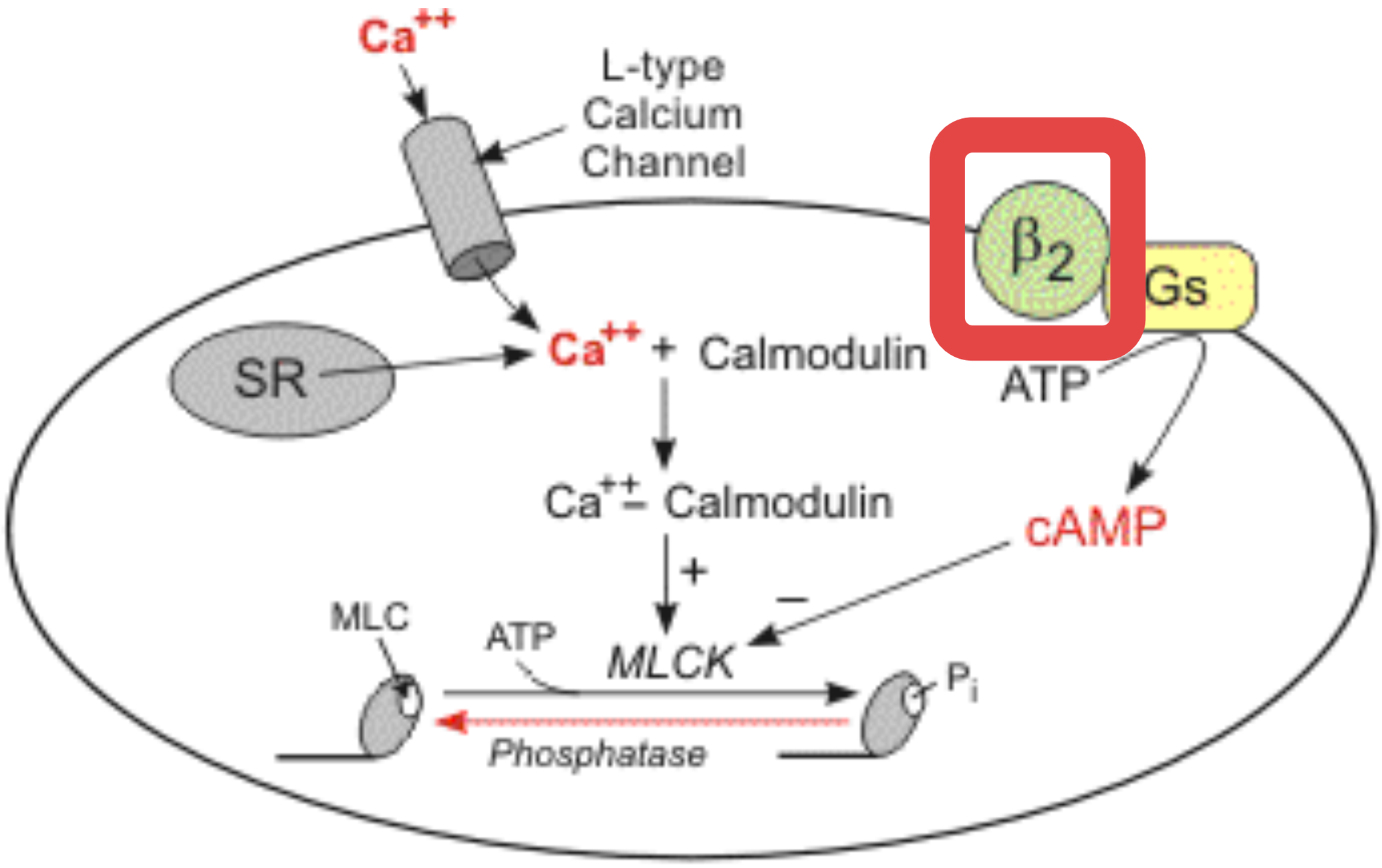
beta (β) 1, 2, 3 : Gs

HEART



PHOSPHORYLATION OF L-TYPE CALCIUM CHANNELS
INCREASE OF CICR (CALCIUM INDUCED CALCIUM RELEASE)
----> POSITIVE INOTROPIC EFFECT

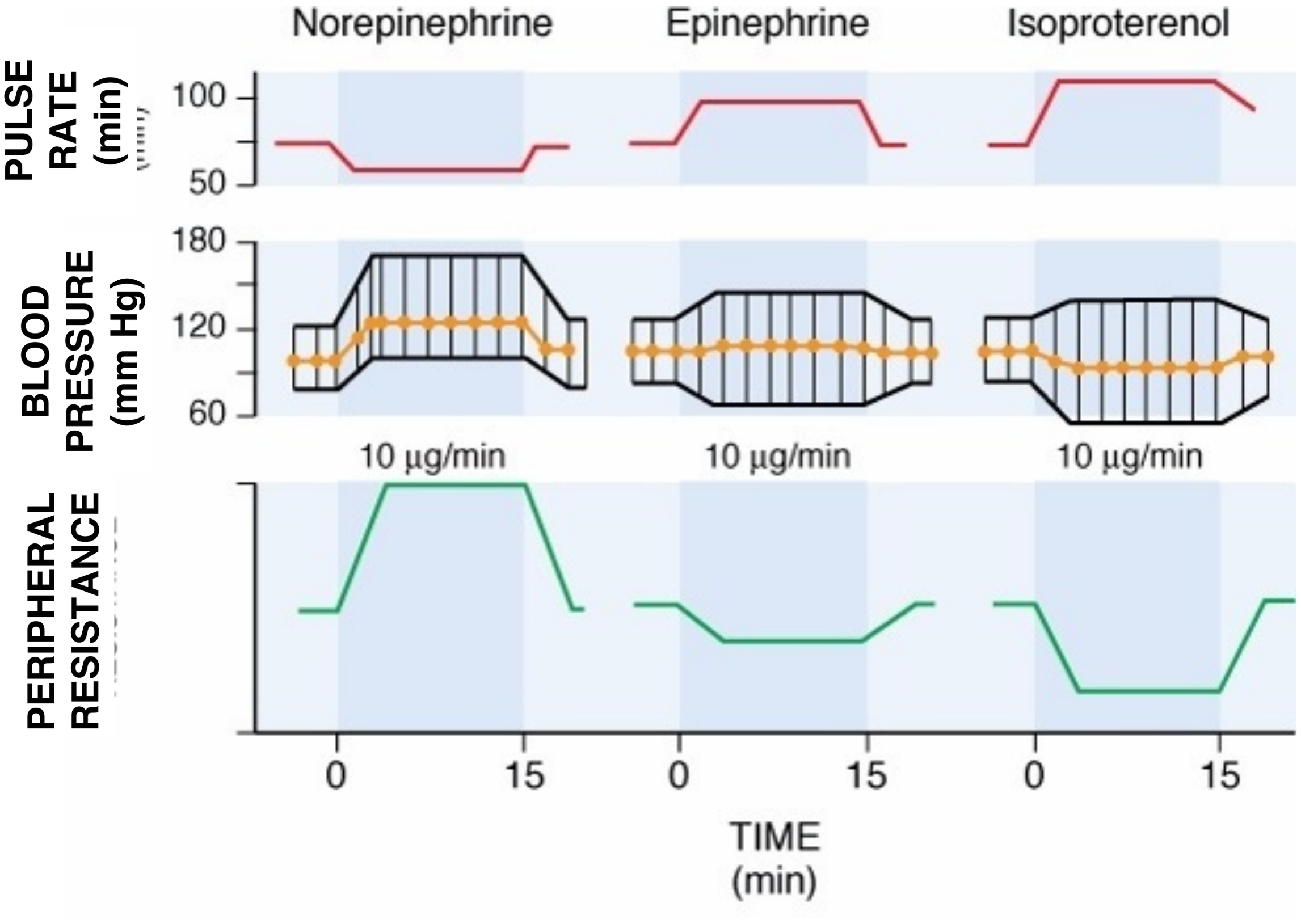
VASAL SMOOTH MUSCLE



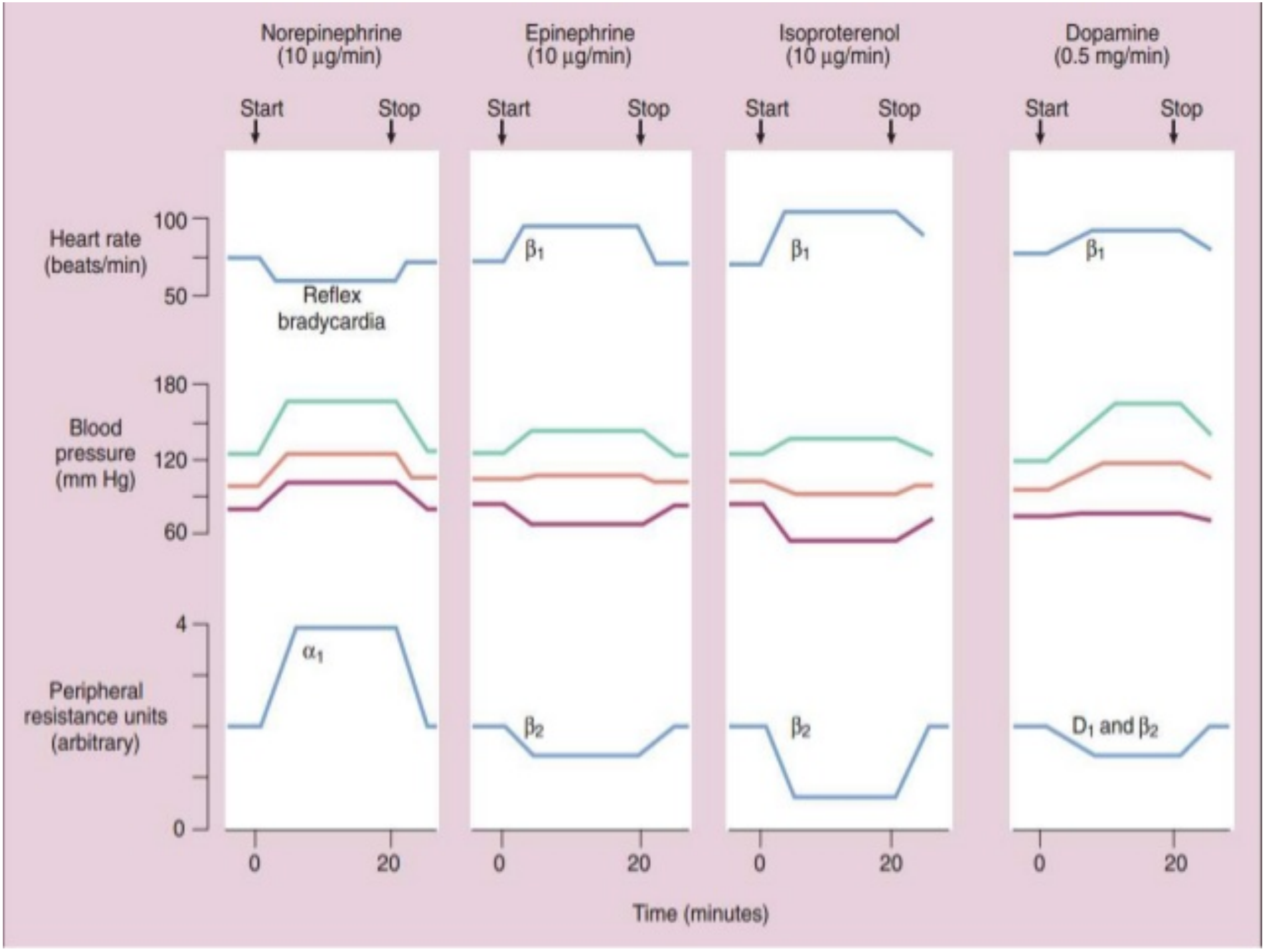
INHIBITION OF MLCK (MYOSIN LIGHT CHAIN KINASE) -----> VASODILATATION

Beta ADRENERGIC RECEPTOR		
SUBTYPE	**AGONISTS**	**CLINICAL USES**
Beta 1	Dobutamine	Cardiogenic shock
Beta 2	**Salbutamol** **Terbutaline** **Formoterol**	**Asthma**
Beta 3	Mirabegron	Symptoms of overactive bladder

SUBTYPE	ANTAGONISTS	CLINICAL USES
Beta 1	**Propranolol** **Alprenolol** **Metoprolol** **Nevibolol**	**Angina pectoris** **Hypertension** **Cardiac dysrhytmias** **(Anxiety, tremor)**
Beta 2	Butoxamine	None
Beta 3	None	



Effect of intravenous infusion of Norepinephrine, Epinephrine or Isoproterenol in human beings



Effect of intravenous infusion of Norepinephrine, Epinephrine or Isoproterenol in human beings

BAROCEPTOR, CHEMOCEPTOR AND CARDIOVASCULAR REGULATION