Introduction to Autonomic Nervous System Pharmacology

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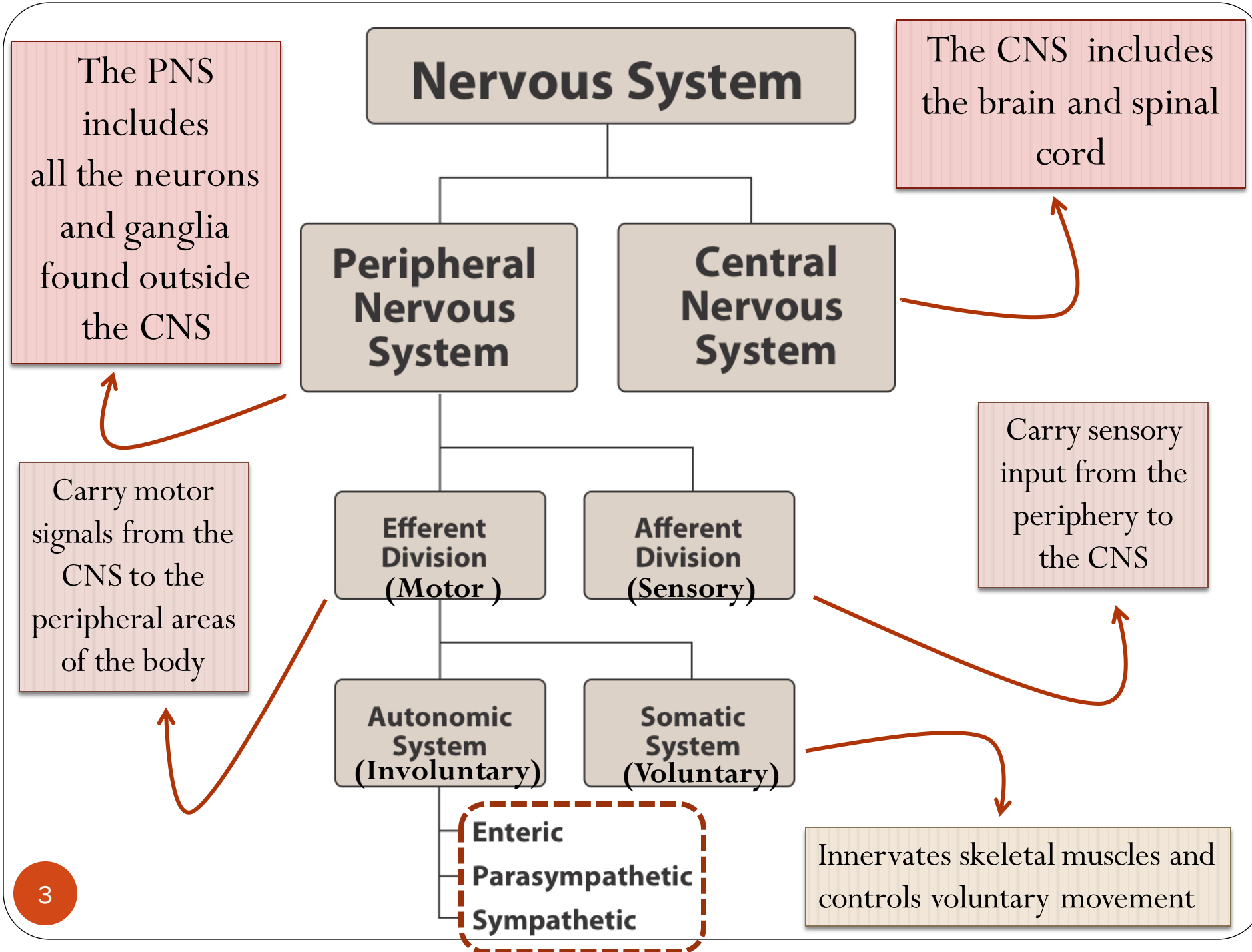
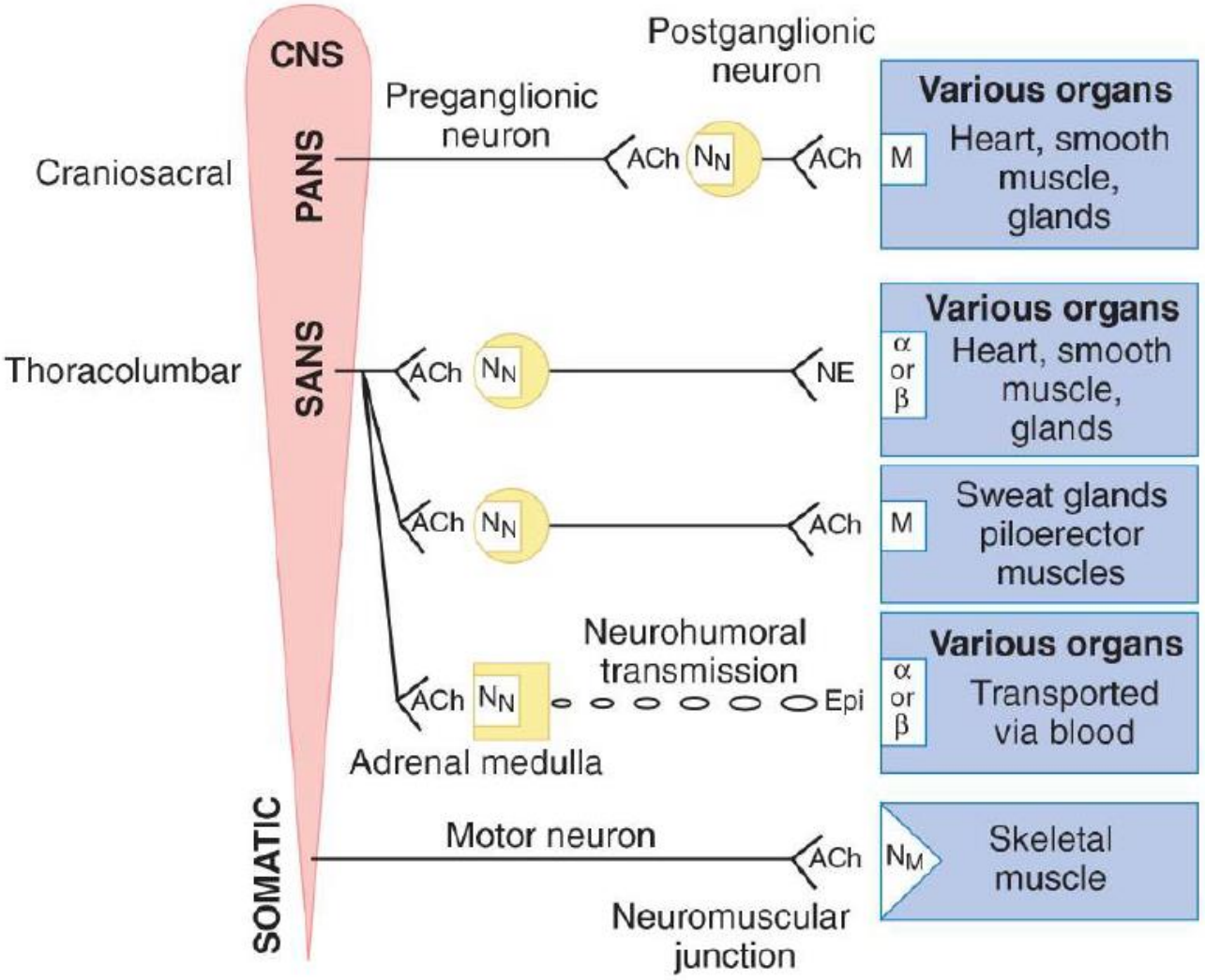
Objectives

- 1- Autonomic nervous system anatomy
- 2- Transmitter types
- 3- Transmitters synthesis, storage and release
- 4-Receptor types
- 5- Functions of autonomic nervous system


Nervous System
Peripheral Nervous System
Central Nervous System
The PNS includes all the neurons and ganglia found outside the CNS
The CNS includes the brain and spinal cord
Carry motor signals from the CNS to the peripheral areas of the body
Carry sensory input from the periphery to the CNS
Efferent Division (Motor)
Afferent Division (Sensory)
Autonomic System (Involuntary)
Somatic System (Voluntary)
Enteric
Parasympathetic
Sympathetic
Innervates skeletal muscles and controls voluntary movement



Divisions of nervous system

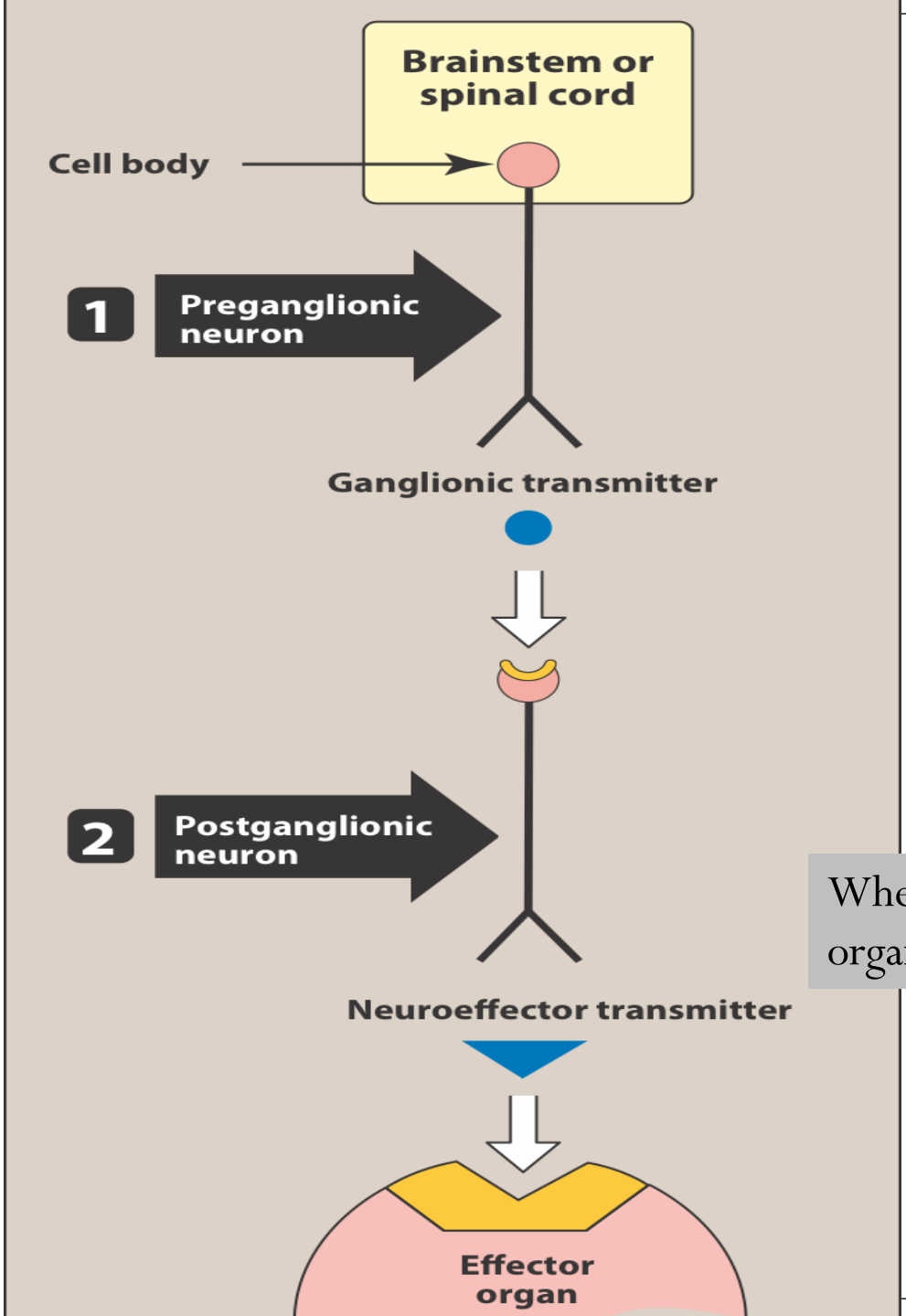
Autonomic nervous system (ANS)

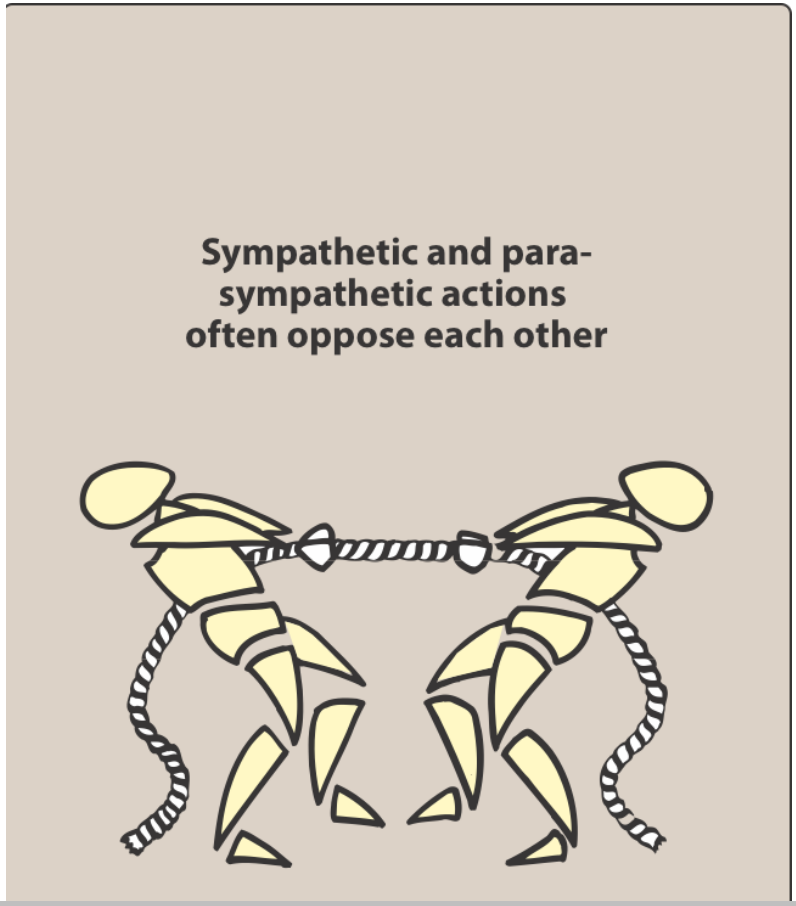
- The autonomic nervous system (ANS) carries the output of the central nervous system (CNS) to all peripheral organs except voluntary muscle.
- Automatically react to changes in the internal and external environments
- The ANS, without conscious thought or effort, controls involuntary activities in the visceral organs of the body (such as the heart, breathing, digestion, blood vessels), contraction and relaxation of smooth muscle, and secretory glands
- The ANS is regulated by centers in the CNS, including the hypothalamus, brain stem, and spinal cord.
- It is organised anatomically and functionally into sympathetic and parasympathetic divisions.

- **N_N** Nicotinic receptors are located on cell bodies in ganglia of both PANS and SANS and in the adrenal medulla.
- **N_M** Nicotinic receptors are located on the skeletal muscle motor end plate innervated by somatic motor nerves.
- **M_{1-3}** Muscarinic receptors are located on all organs and tissues innervated by postganglionic nerves of the PANS and on thermoregulatory sweat glands innervated by the SANS.

Organization of ANS

- Autonomic nerve impulses are carried through preganglionic fibers, ganglia, and postganglionic fibers
- Preganglionic impulses travel from the CNS along the preganglionic nerves to ganglia. Ganglia are composed of the terminal end of the preganglionic nerve and clusters of postganglionic cell bodies.
- A neurotransmitter is released from the terminal end of the preganglionic nerve allowing the nervous impulse to bridge the synapse between the preganglionic and postganglionic nerve.
- The postganglionic impulses travel from ganglia to effector tissues of the heart, blood vessels, glands, other visceral organs, and smooth muscle





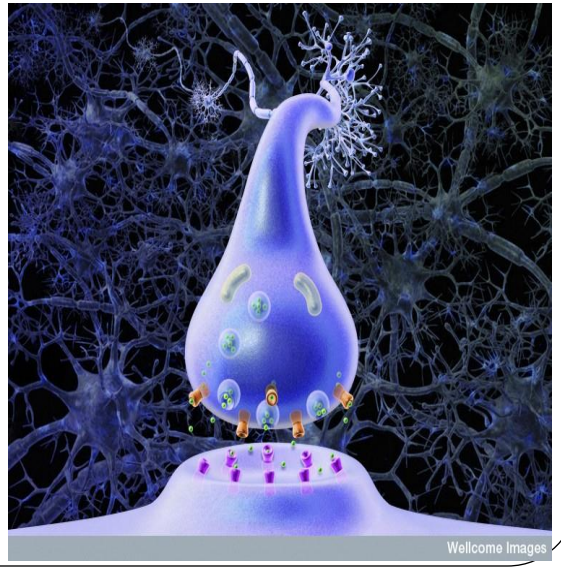
When the sympathetic system excites a particular organ, the parasympathetic system often inhibits it.

The two divisions of the ANS are usually antagonistic in their actions on a particular organ

- Acetylcholine (ACh) is the neurotransmitter at both nicotinic and muscarinic receptors in tissues that are innervated.
- Note that all direct transmission from the CNS (preganglionic and motor) uses ACh, but postganglionic transmission in the SANS system may use one of the organ-specific transmitters described below:
- **Norepinephrine** (NE) is the neurotransmitter at most adrenoceptors in organs, as well as in cardiac and smooth muscle.
- **Dopamine** (DA) activates D1 receptors, causing vasodilation in renal and mesenteric vascular beds.
- **Epinephrine** (E, from adrenal medulla) activates most adrenoceptors and is transported in the blood.

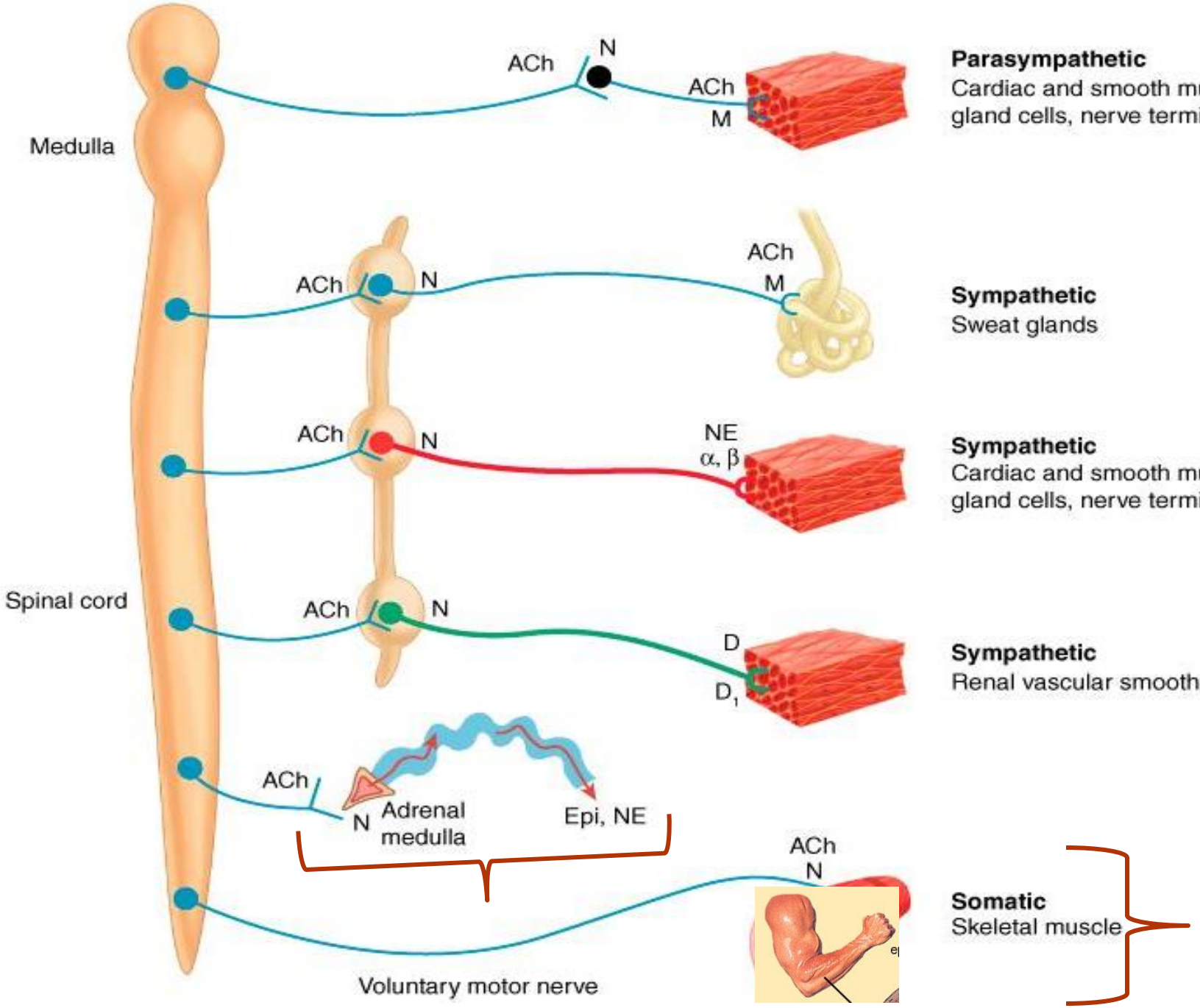
Neurotransmitters

- Communication between nerve cells and between nerve cells and effector organs occurs through the release of specific chemical signals, called neurotransmitters, from the nerve terminals.
- The neurotransmitters rapidly diffuse across the synaptic cleft or space (synapse) between neurons and combine with specific receptors on the postsynaptic (target) cell
- The main neurotransmitters of the ANS are acetylcholine and norepinephrine
- The nerve fibers that secrete acetylcholine are called cholinergic fibers
- Nerve fibers secreting norepinephrine are called adrenergic fibers.



Sympathetic Nervous System

- The preganglionic neurons of the sympathetic system come from thoracic and lumbar regions of the spinal cord (Thoracolumbar)
- The preganglionic neurons are short in comparison to the postganglionic ones.
- Axons of the postganglionic neuron extend from these ganglia to the tissues that they innervate and regulate
- Lacking axons, the **adrenal medulla**, in response to stimulation by the ganglionic neurotransmitter acetylcholine, influences other organs by secreting the hormone epinephrine (adrenaline), and lesser amounts of norepinephrine (noradrenaline) into the blood
- Norepinephrine is released at most postganglionic fibers of the sympathetic nervous 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
ACh
N
Adrenal medulla
Epi, NE
ACh
N
Somatic
Skeletal muscle
Voluntary motor nerve

Function of sympathetic neurons

- Although continually active to some degree (for example, in maintaining the tone of vascular beds), the sympathetic division has the property of adjusting in response to stressful situations, such as trauma, fear, pain, hemorrhage, hypoglycemia, cold, or extraneous exercise or work (Fight or flight response)

Sympathetic System

(Thoracolumbar) Division

Alertness ??

↑ blood flow (vasodilatation) to the brain, heart, and skeletal muscles; ↓ blood flow (vasoconstriction) to viscera, skin, and other organs not needed for fight-or-flight

B_2

α_1

Thoracic

Lumbar

T1

T12

leading to energy expenditure

Glycogenolysis
Gluconeogenesis

Tachycardia
↑myocardial contractility

Dilates pupils
(Mydriasis)
Inhibits salivation

↑ sweating

B_2

Relaxes bronchi
↓Secretion

Accelerates heartbeat
[↑ CO & HR]
↑ BP

B_1

Inhibits peristalsis and secretion (every)
[Relaxation, ↑sphincter tone]

Stimulates glucose production and release
[↑ BG]

& muscle

Secretion of adrenaline and noradrenaline

Secretion of renin ← B_1

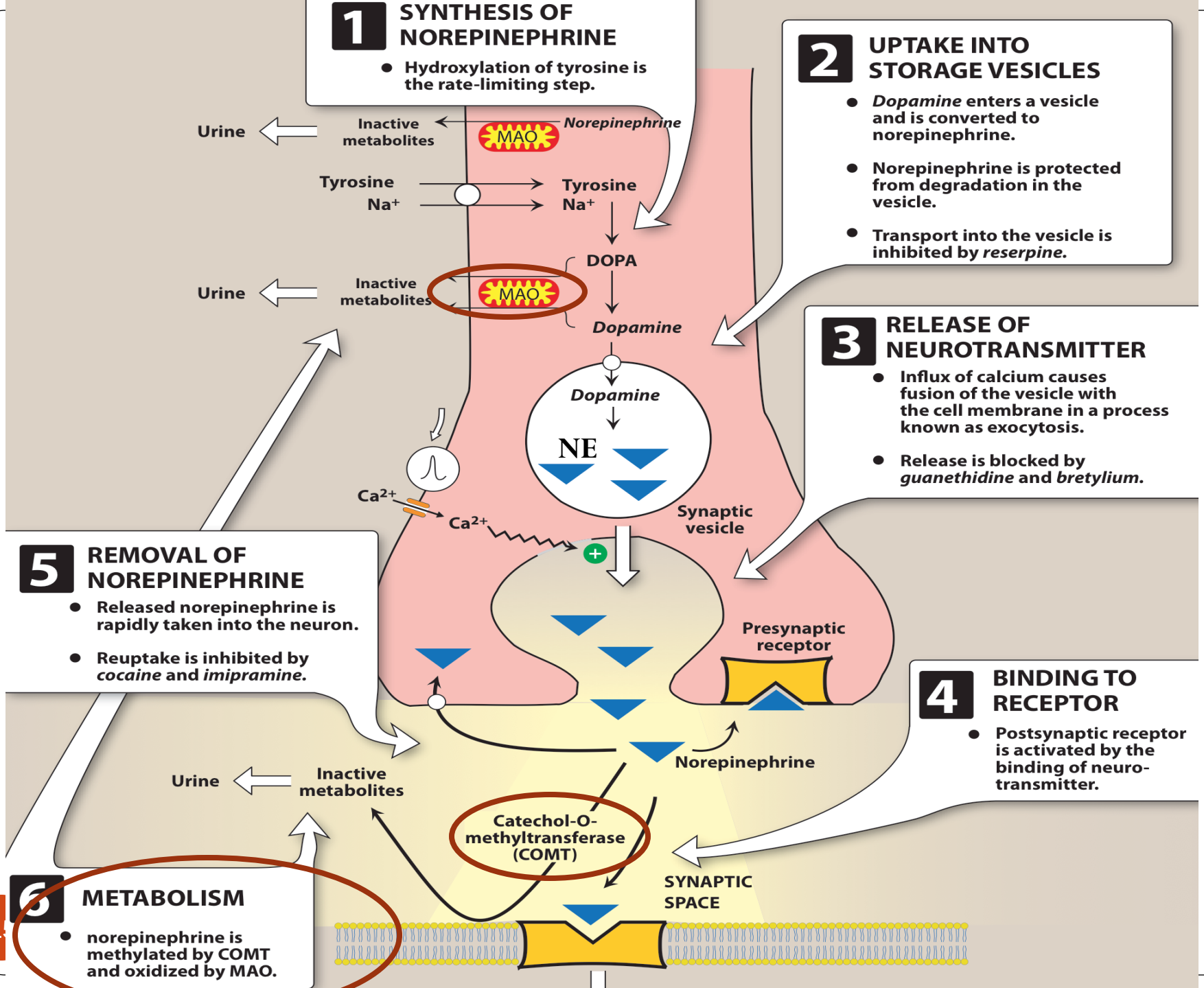
Inhibits bladder contraction

Lipolysis
(↑ FFA)

Uterus relaxation

Stimulates orgasm

Ejaculation


1 SYNTHESIS OF NOREPINEPHRINE
Hydroxylation of tyrosine is the rate-limiting step.
2 UPTAKE INTO STORAGE VESICLES
Dopamine enters a vesicle and is converted to norepinephrine.
Norepinephrine is protected from degradation in the vesicle.
Transport into the vesicle is inhibited by reserpine.
3 RELEASE OF NEUROTRANSMITTER
Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis.
Release is blocked by guanethidine and bretylium.
4 BINDING TO RECEPTOR
Postsynaptic receptor is activated by the binding of neuro-transmitter.
5 REMOVAL OF NOREPINEPHRINE
Released norepinephrine is rapidly taken into the neuron.
Reuptake is inhibited by cocaine and imipramine.
6 METABOLISM
norepinephrine is methylated by COMT and oxidized by MAO.
Urine
Inactive metabolites
MAO
Norepinephrine
Tyrosine
Na+
DOPA
Dopamine
NE
Ca2+
Synaptic vesicle
Presynaptic receptor
Catechol-O-methyltransferase (COMT)
SYNAPTIC SPACE

Adrenergic receptors

Receptor	Response
α_1	
Eye: radial (dilator) muscle	Contraction: mydriasis
Arterioles (skin, viscera)	Contraction: ↑ TPR, ↑ diastolic pressure, ↑ afterload

Veins	Contraction: ↑ venous return, ↑ preload
Bladder trigone and sphincter and prostatic urethra	Contraction: urinary retention
Male sex organs	Vas deferens: ejaculation
Liver	↑ glycogenolysis
Kidney	↓ renin release
α_2	
Prejunctional nerve terminals	↓ transmitter release and NE synthesis
Platelets	Aggregation
Pancreas	↓ insulin secretion
β_1	
Heart SA node	↑ HR (positive chronotropy)
AV node	↑ conduction velocity (positive dromotropy)
Atrial and ventricular muscle	↑ force of contraction (positive inotropy), conduction velocity, CO and oxygen consumption
His-Purkinje	↑ automaticity and conduction velocity
Kidney	↑ renin release
β_2 (mostly not innervated)	
Blood vessels (all)	Vasodilation: ↓ TPR: ↓ diastolic pressure, ↓ afterload
Uterus	Relaxation
Bronchioles	Dilation
Skeletal muscle	↑ glycogenolysis: contractility (tremor)
Liver	↑ glycogenolysis
Pancreas	↑ insulin secretion

D_1 (peripheral)	
Renal, mesenteric, coronary vasculature	Vasodilation: in kidney ↑ RBF, ↑ GFR, ↑ Na^+ secretion

Table II-3-1. Adrenergic Receptor Activation

Adrenoceptors: vasomotor function

of alpha vs. beta

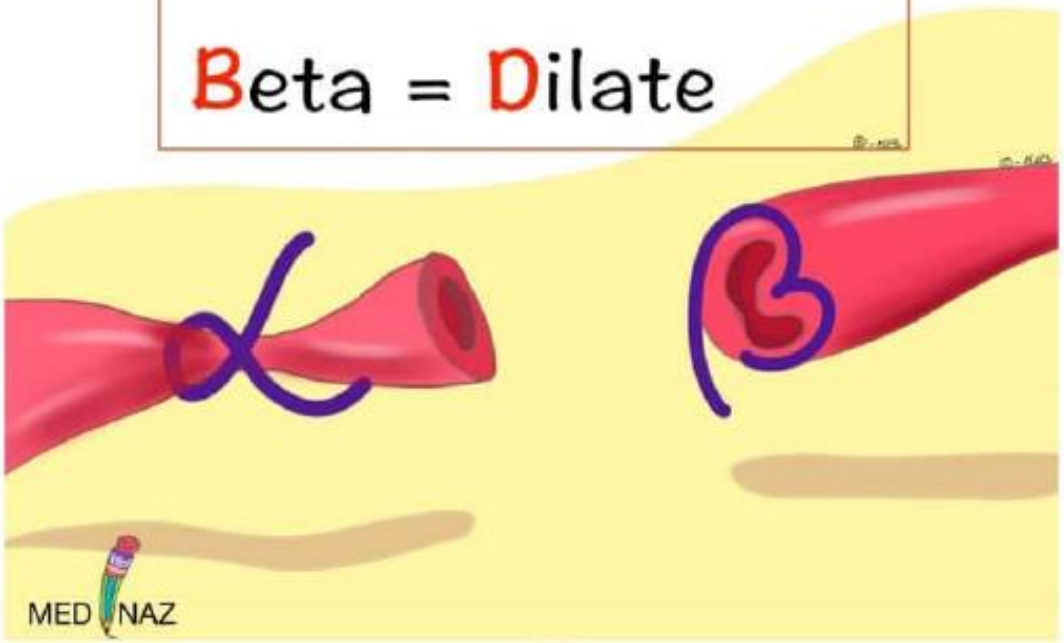
www.medinaz.com

A
B

C
D

Alpha = Constrict

Beta = Dilate

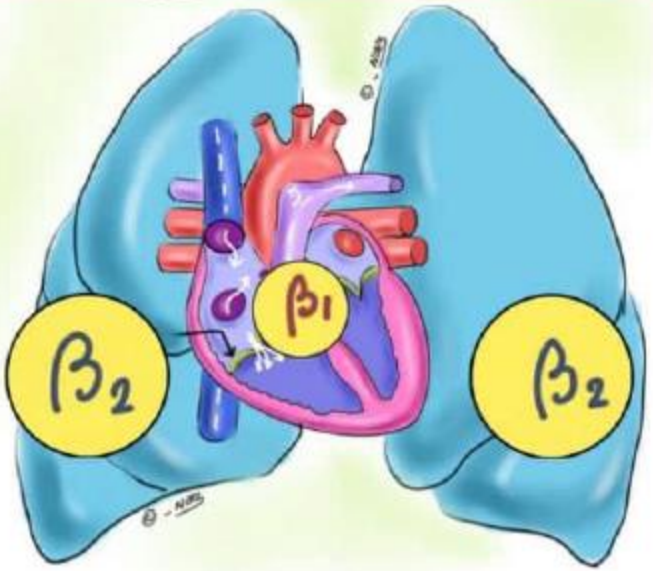


Beta 1 & 2 Receptors

Beta 1 receptor = Heart

Beta 2 receptor = Lungs

We have 1 heart and 2 lungs



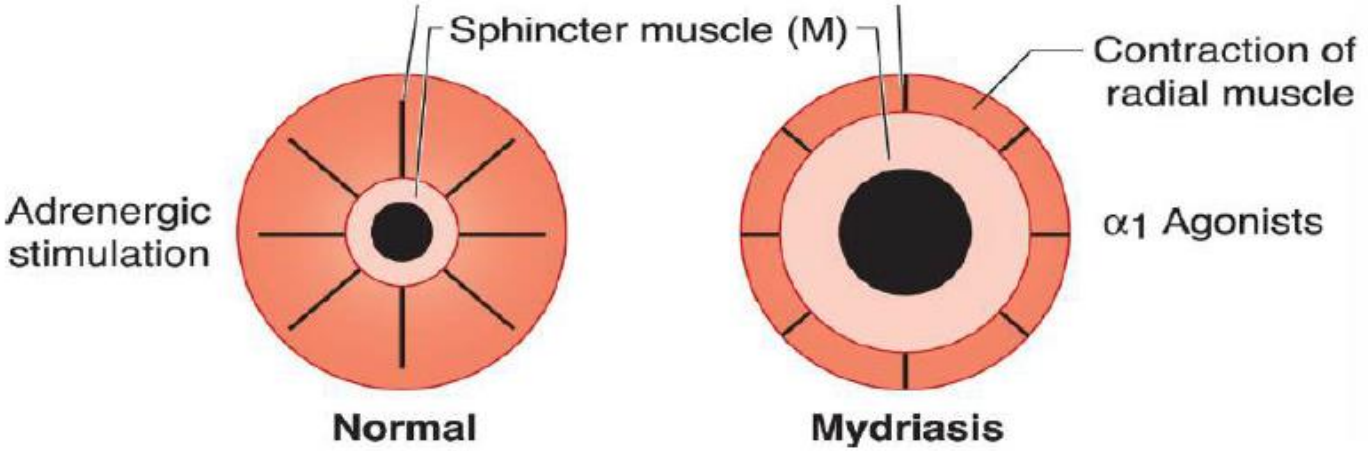


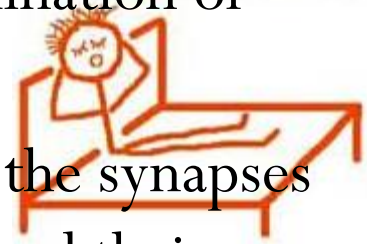
Figure II-1-5. Effect of ANS Drugs on the Eye

α_1	G_q coupled	↑ phospholipase C →↑ IP_3, DAG, Ca^{2+}
α_2	G_i coupled	↓ adenylyl cyclase → ↓ cAMP
$\beta_1\beta_2 D_1$	G_s coupled	↑ adenylyl cyclase → ↑ cAMP

Table II-3-2. Mechanisms Used by Adrenergic Receptors

Parasympathetic Nervous System

- The parasympathetic pre-ganglionic motor fibers originate in cranial nerve and in sacral segments of the spinal cord
- Parasympathetic ganglia usually lie close to or within the target organ (preganglionic fibers are longer and postganglionic fibers are short)
- The parasympathetic division maintains essential bodily functions, and dominant over the sympathetic system in "rest and digest" situations (digestive processes and elimination of wastes) … [Rest … Relax …. Repair …Renew]
- Acetylcholine (ACh) is the primary transmitter in the synapses between parasympathetic postganglionic neurons and their effector cells (also in brain and neuromuscular jun.)



Function of parasympathetic nervous system (Craniosacral) Division

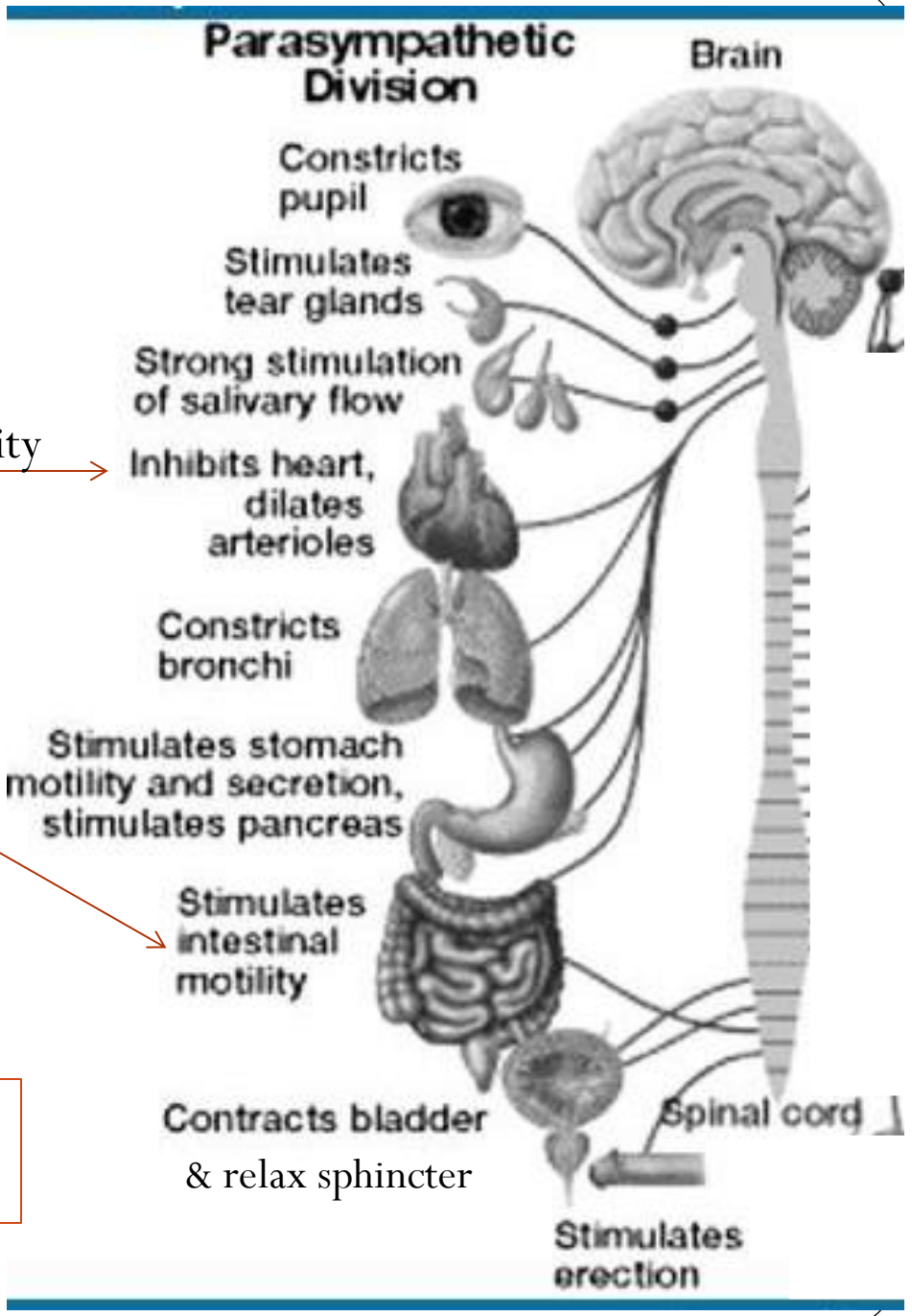
Slowing HR and ↓ contractility

Contraction of smooth muscle and relaxation of sphincters

↑ secretion

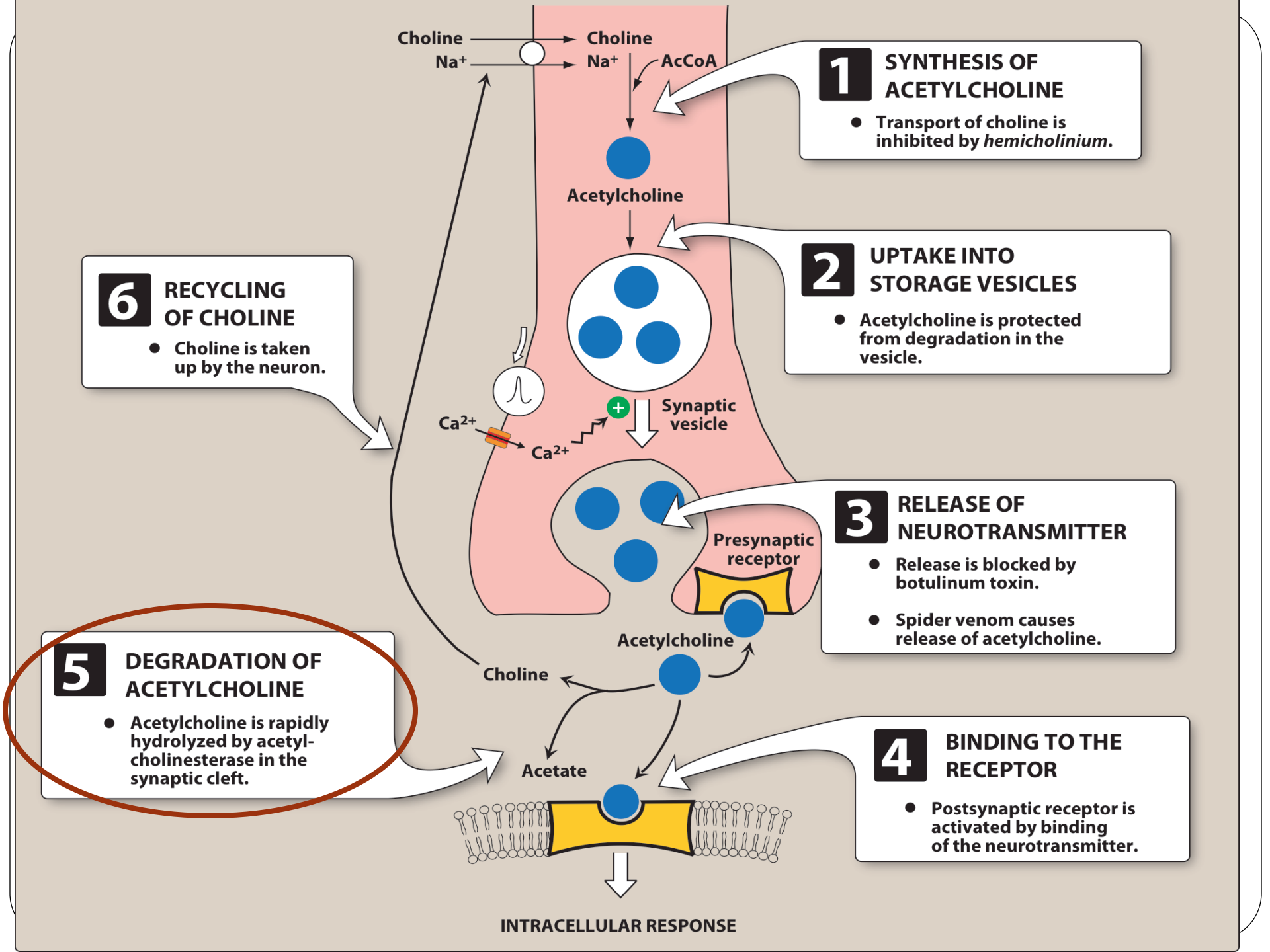
Energy-conserving and storing

Increased secretions from glands in the lungs, stomach, intestines, and skin (sweat glands)



Synthesis of acetylcholine:

- **In mitochondria:**
- CO A + ATP + Acetate $\xrightarrow{\text{Acetyl thiokinase}}$ Acetyl CO A+H2O+ADP
- **In plasma:**
- Acetyl COA+ Choline $\xrightarrow{\text{Choline transferase}}$ Acetyl choline +COA
- **<u>Acetyl choline hydrolysis:</u>**
- In tissues by cholinesterase enzyme which has 2 types
- **True cholineesterase, Pseudo-cholineesterase**


Choline
Na+
Choline
Na+
AcCoA
1 SYNTHESIS OF ACETYLCHOLINE
Transport of choline is inhibited by hemicholinium.
Acetylcholine
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
Presynaptic receptor
3 RELEASE OF NEUROTRANSMITTER
Release is blocked by botulinum toxin.
Spider venom causes release of acetylcholine.
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

Drugs affecting acetylcholine

1 Hemicholinium

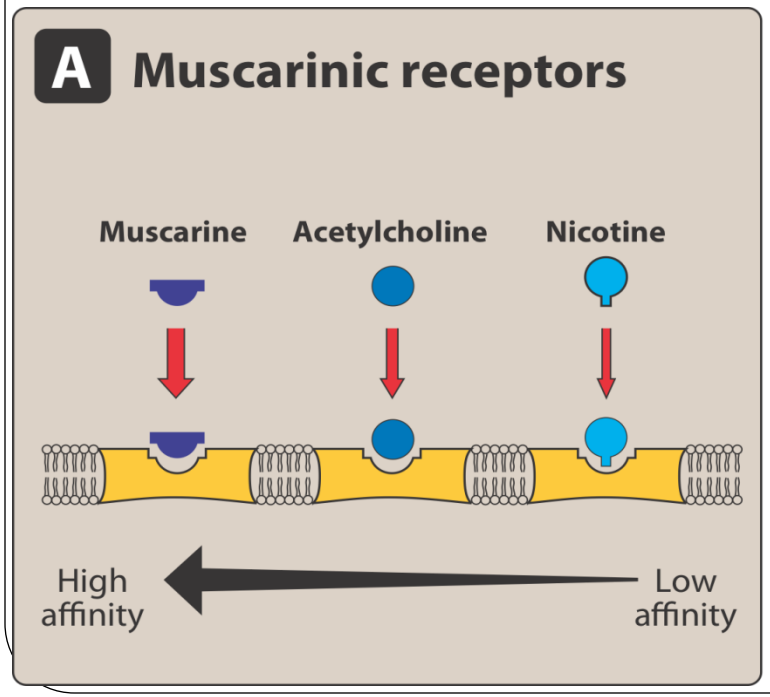
2 Botulinum toxin

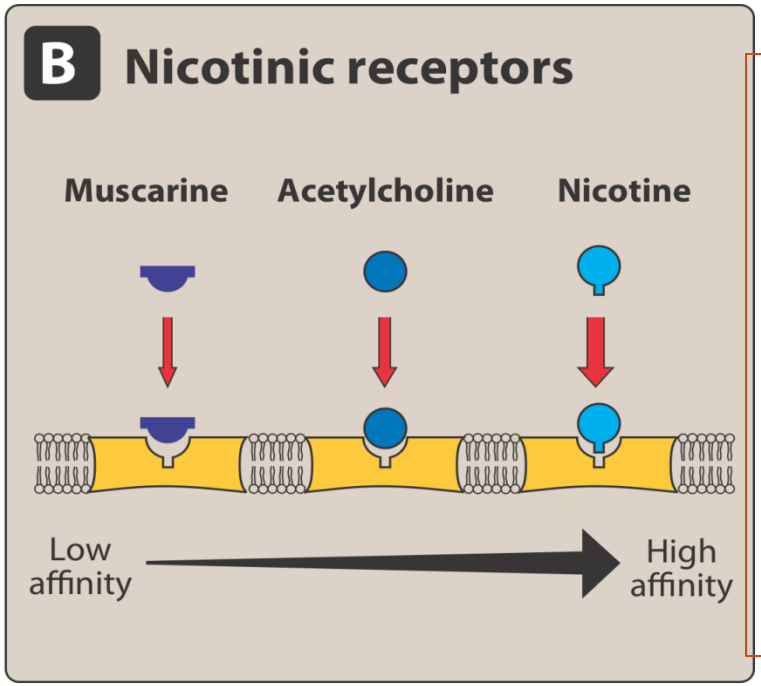
3 Acetylcholinesterase (AChE) inhibitors

4 Receptor agonists and antagonists

Cholinergic receptors

- The receptors for acetylcholine and related drugs is (*cholinoreceptors*). *They are 2 types:*
- Muscarinic acetylchline receptors (M1-M5) and
- Nicotinic cholinoreceptors (or nicotinic receptor of acetylcholine)



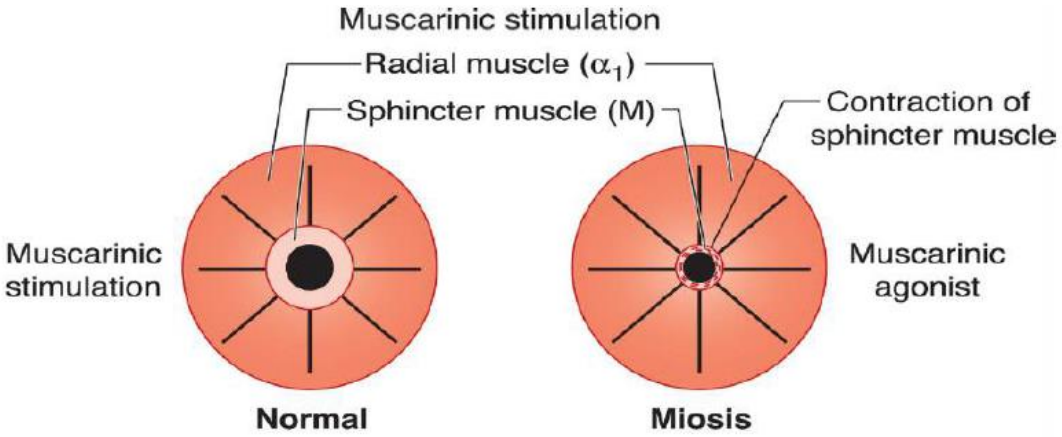


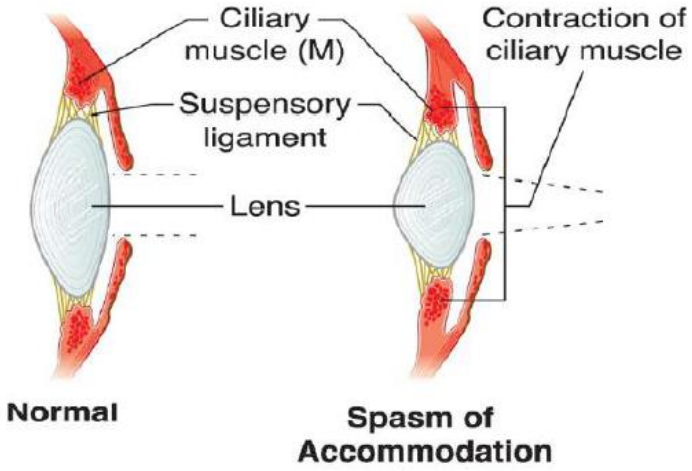
Nicotinic n= located on autonomic ganglia and the adrenal medulla

Nicotinic m = *located at neuromuscular* junctions in skeletal muscle.

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

Table II-2-1. Muscarinic Receptor Activation


Muscarinic stimulation
Radial muscle (α_1)
Sphincter muscle (M)
Contraction of sphincter muscle
Muscarinic stimulation
Muscarinic agonist
Normal
Miosis


Ciliary muscle (M)
Contraction of ciliary muscle
Suspensory ligament
Lens
Normal
Spasm of Accommodation

Autonomic effects on eye

Muscarinic stimulation

1. Miosis
2. Accommodation (near vision)

Muscarinic antagonism

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

α1-agonists

1. Mydriasis
2. No cycloplegia

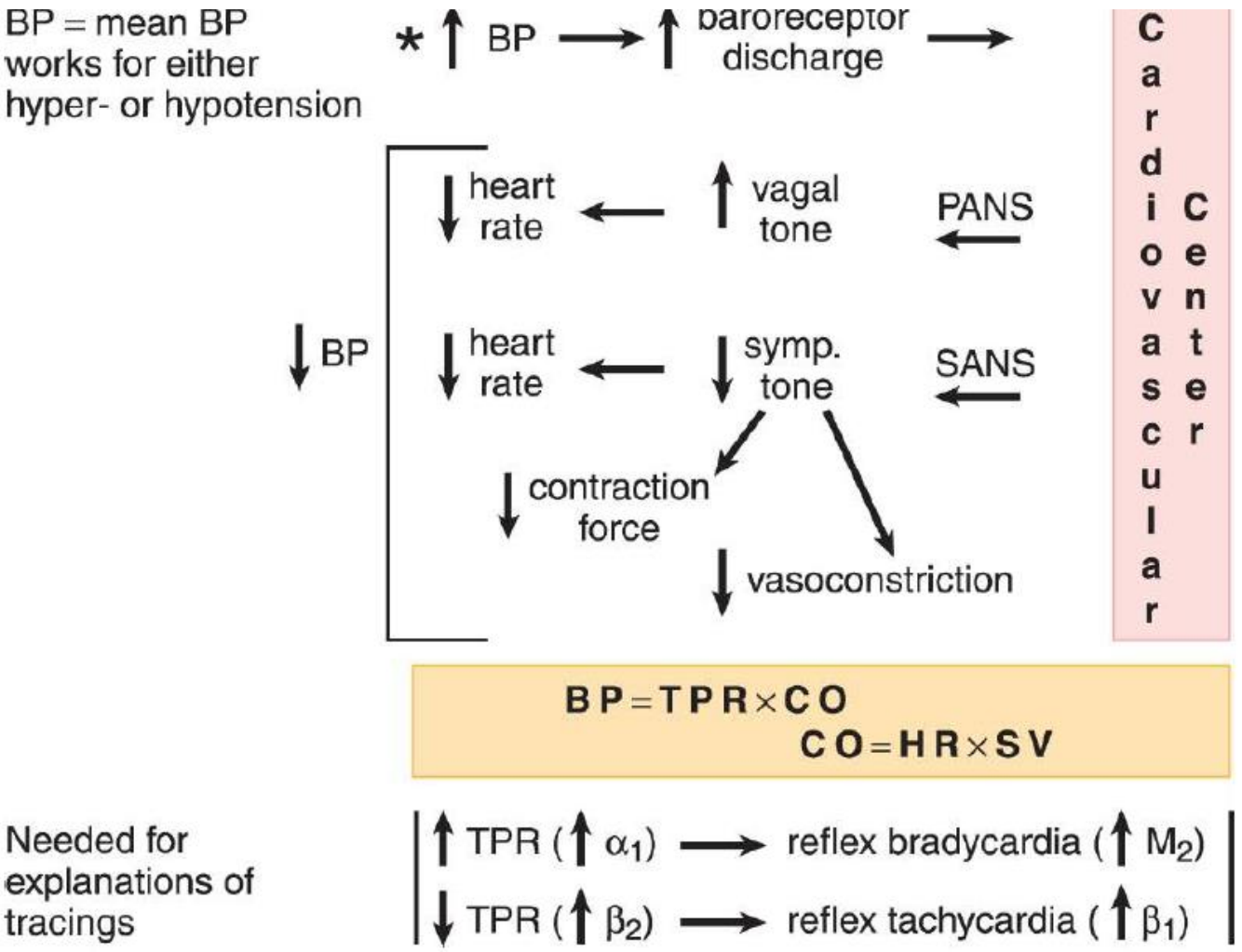


Figure II-1-2. Autonomic Feedback Loop

Activity

- Baroreceptor reflexes can be blocked at the ganglionic synapse with ……?
- Alternatively, a reflex bradycardia can be blocked with……?
- a reflex tachycardia can be blocked with ……?

Answer

- Baroreceptor reflexes can be blocked at the ganglionic synapse with **N_N receptor Antagonists**
- a reflex bradycardia can be blocked with **muscarinic antagonists**
- a reflex tachycardia can be blocked with **β_1 antagonists.**

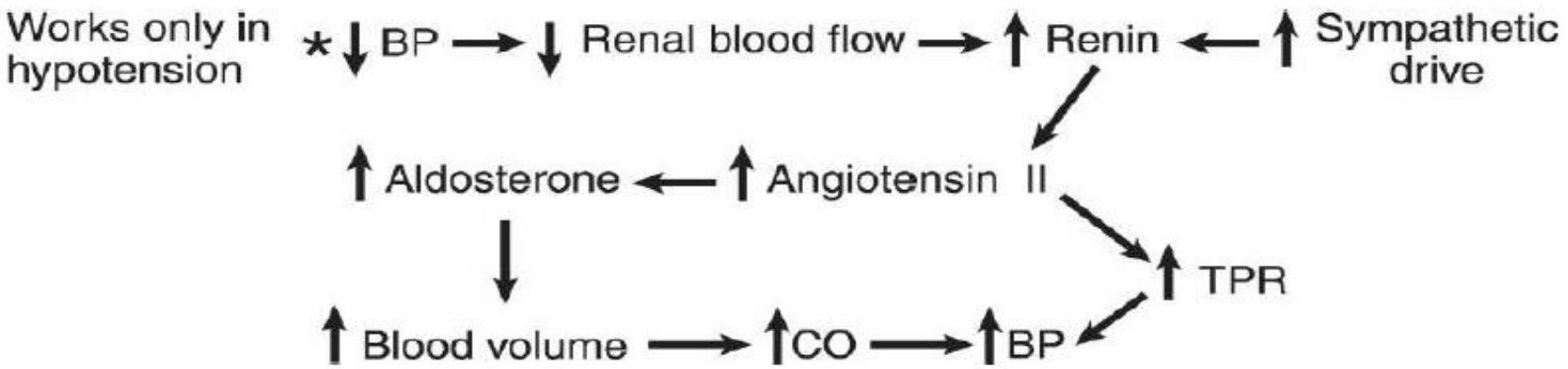


Figure II-1-3. Hormonal Feedback Loop

Thank you