

ANS PHARMACOLOGY

Objectives

- @ the end of this session students will be able to:
 - ✓ Explain different divisions of the nervous system
 - ✓ Discuss the function of ANS
 - ✓ Identify & explain drugs acting on cholinergic system
 - ✓ Identify & explain drugs acting on adrenergic system

Nervous System

```
graph TD;
    A[Nervous System] --> B[PNS: neurons outside CNS & enter or leave CNS];
    A --> C[CNS: Brain & Spinal cord];
    B --> D[Efferent Division: motor];
    B --> E[Afferent Division: sensory];
    D --> F[ANS];
    D --> G[Somatic Nervous System];
    F --> H["✓ Sympathetic<br/>✓ Parasympathetic<br/>✓ Enteric"];
    G --> I[Controls voluntary function;<br/>skeletal muscles];
```

The diagram is a hierarchical flowchart of the Nervous System. At the top is a green box labeled 'Nervous System'. Two arrows point down from it to 'PNS: neurons outside CNS & enter or leave CNS' and 'CNS: Brain & Spinal cord'. From the PNS box, two arrows point down to 'Efferent Division: motor' and 'Afferent Division: sensory'. From the 'Efferent Division: motor' box, two arrows point down to 'ANS' and 'Somatic Nervous System'. From the 'ANS' box, a single arrow points down to a box containing '✓ Sympathetic', '✓ Parasympathetic', and '✓ Enteric'. From the 'Somatic Nervous System' box, a thick blue arrow points down to a pink box containing 'Controls voluntary function;' and 'skeletal muscles'.

PNS: neurons outside CNS & enter or leave CNS

CNS: Brain & Spinal cord

Efferent Division: motor

Afferent Division:
sensory

ANS

Somatic Nervous System

- ✓ Sympathetic
- ✓ Parasympathetic
- ✓ Enteric

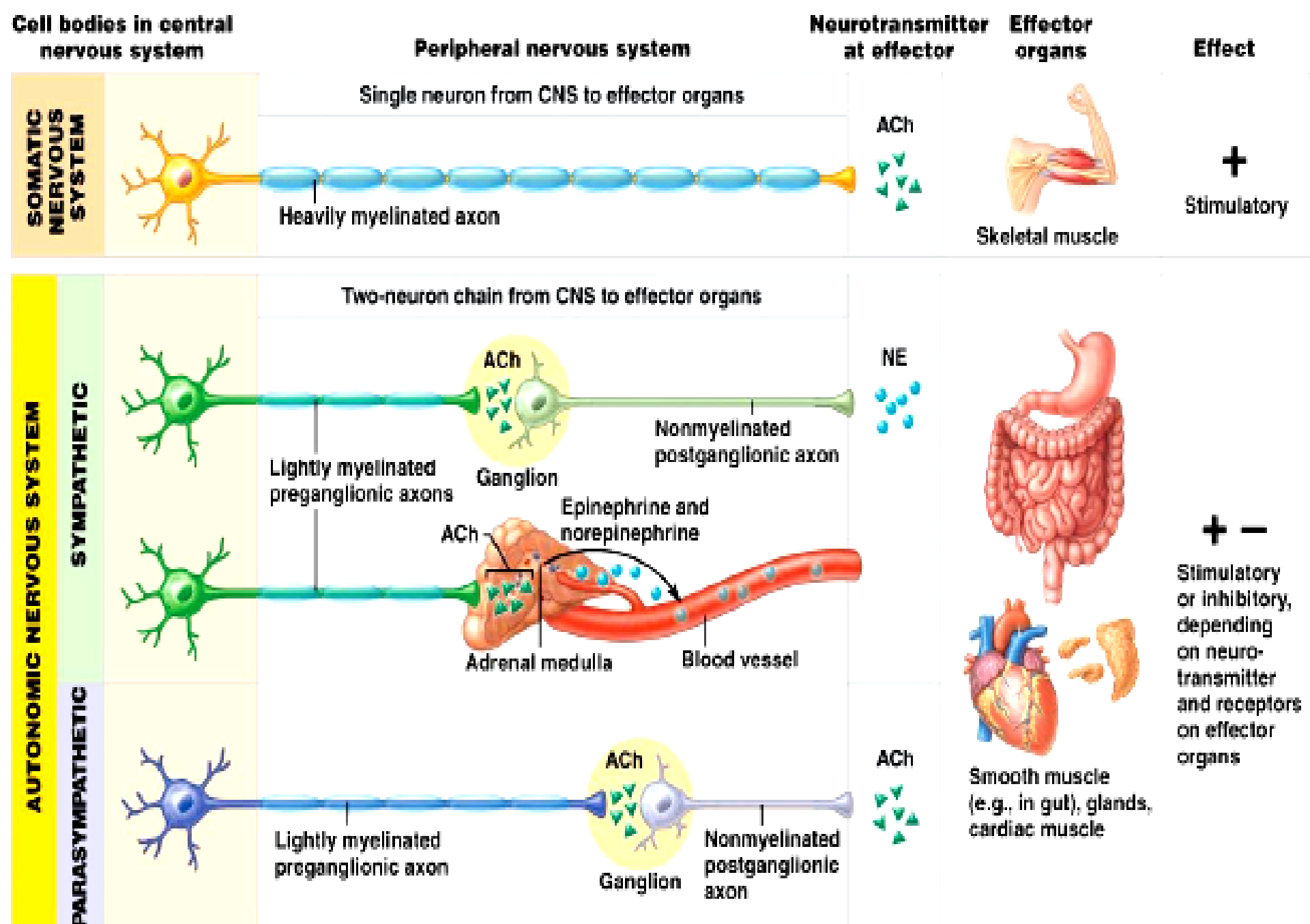
Controls voluntary function;
skeletal muscles

Autonomic Nervous System

- ✓ Largely independent (autonomous): activities are not under direct conscious control
- ✓ Concerned primarily with visceral functions: CO, blood flow distribution & digestion
- ✓ Influence prostate cancer development & progression
- ✓ Vagus nerve influences immune function & some CNS functions (seizure discharge)

Somatic Nervous System

- ✓ Concerned with consciously controlled functions:
movement, respiration & posture
- ❖ Both systems have afferent (sensory) inputs that provide information regarding the internal & external env'ts & modify motor output through reflex arcs of varying size & complexity



Parasympathicus

constricts pupils

increases saliva production

reduces the heart rate

constricts bronchia

stimulates the activity of the digestive organs

stimulates the activity of the pancreas

stimulates the gall bladder

constricts urinary bladder

stimulates erection of genitals of man and woman

Cerebrum (Brain)

cranial

cervical

thoracal

lumbal

sympa-
thetic
chain

spinal cord

sacral

Synapse

Sympathicus

dilates pupils

inhibits saliva production

dilates bronchia

raises the heart rate

inhibits the acitivity of the digestive organs

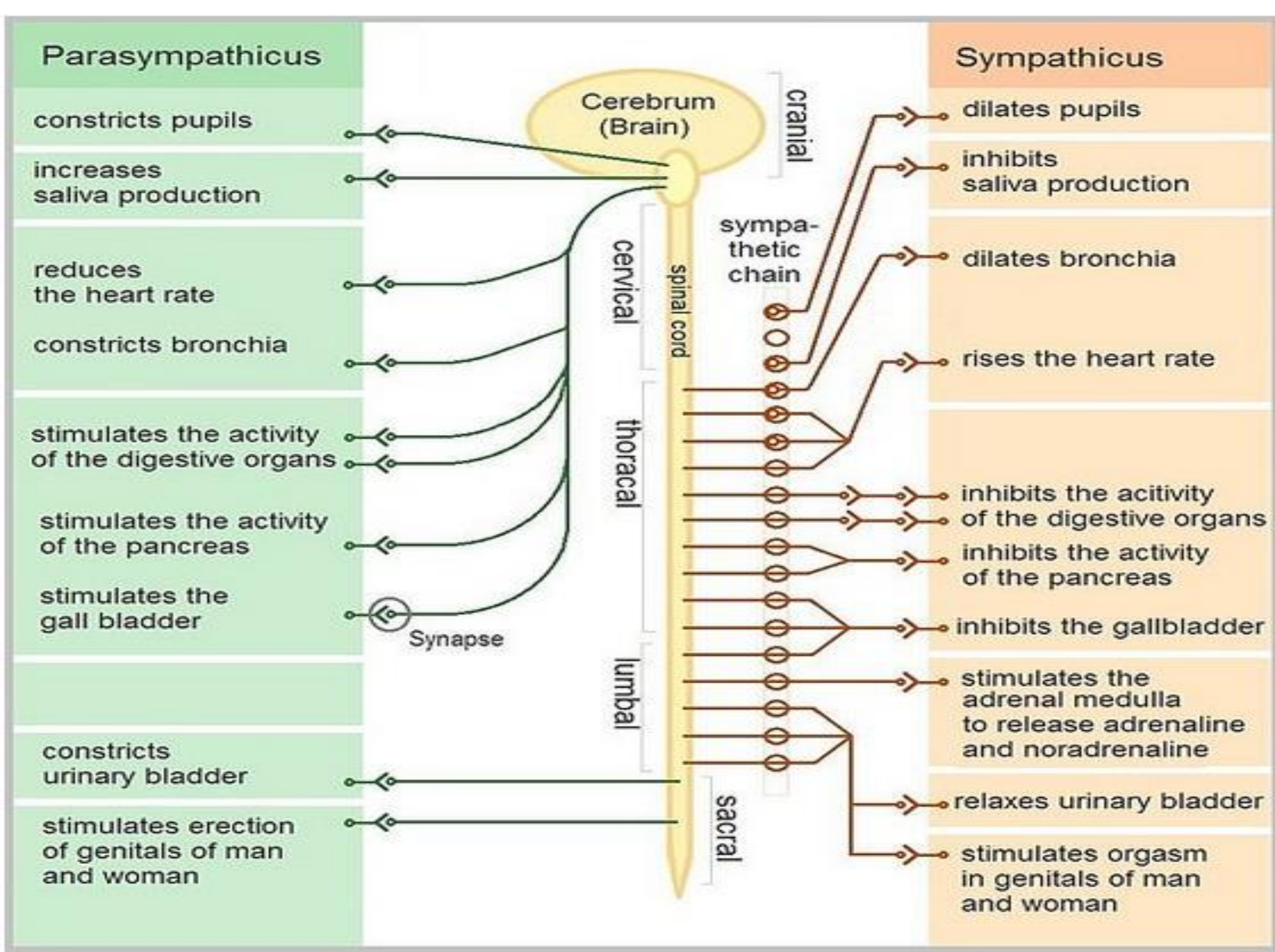
inhibits the activity of the pancreas

inhibits the gallbladder

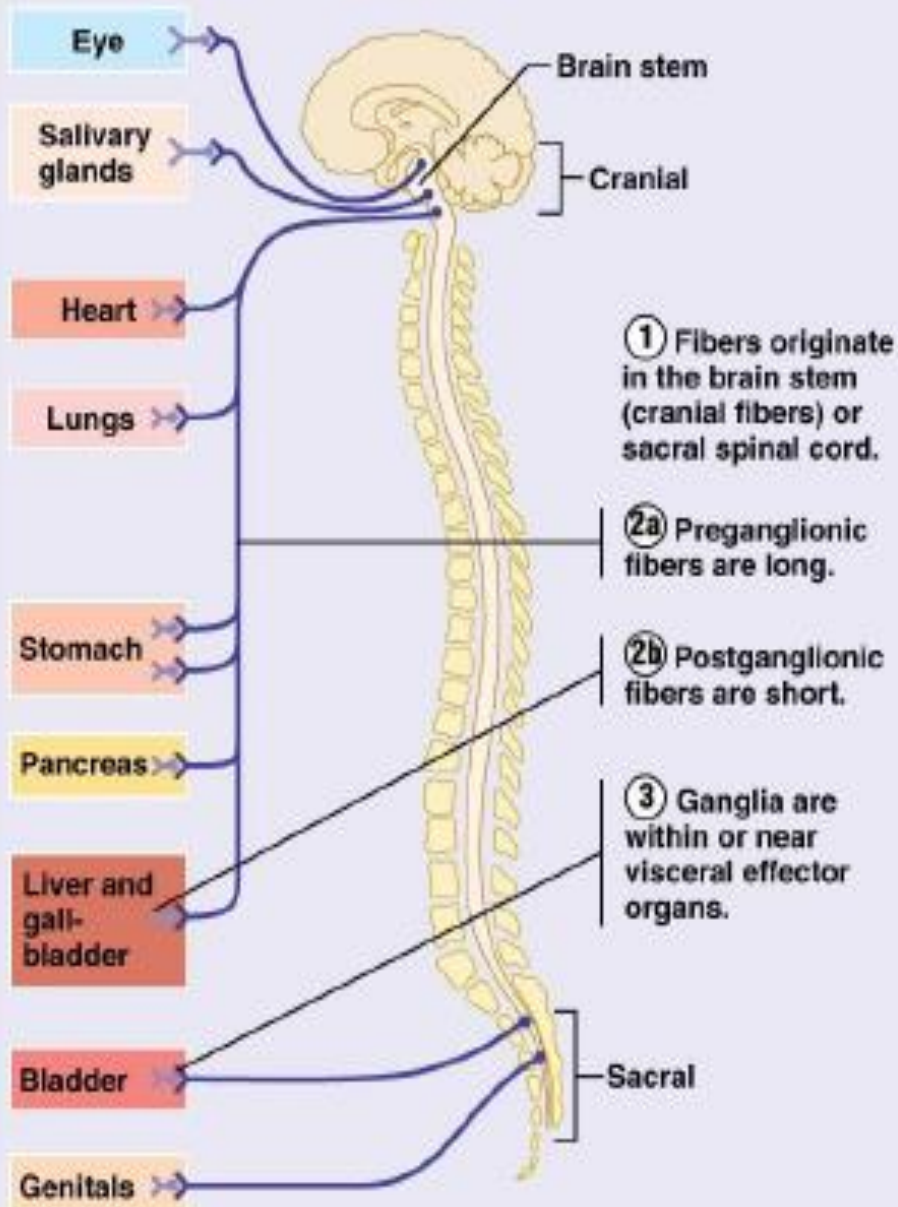
stimulates the adrenal medulla to release adrenaline and noradrenaline

relaxes urinary bladder

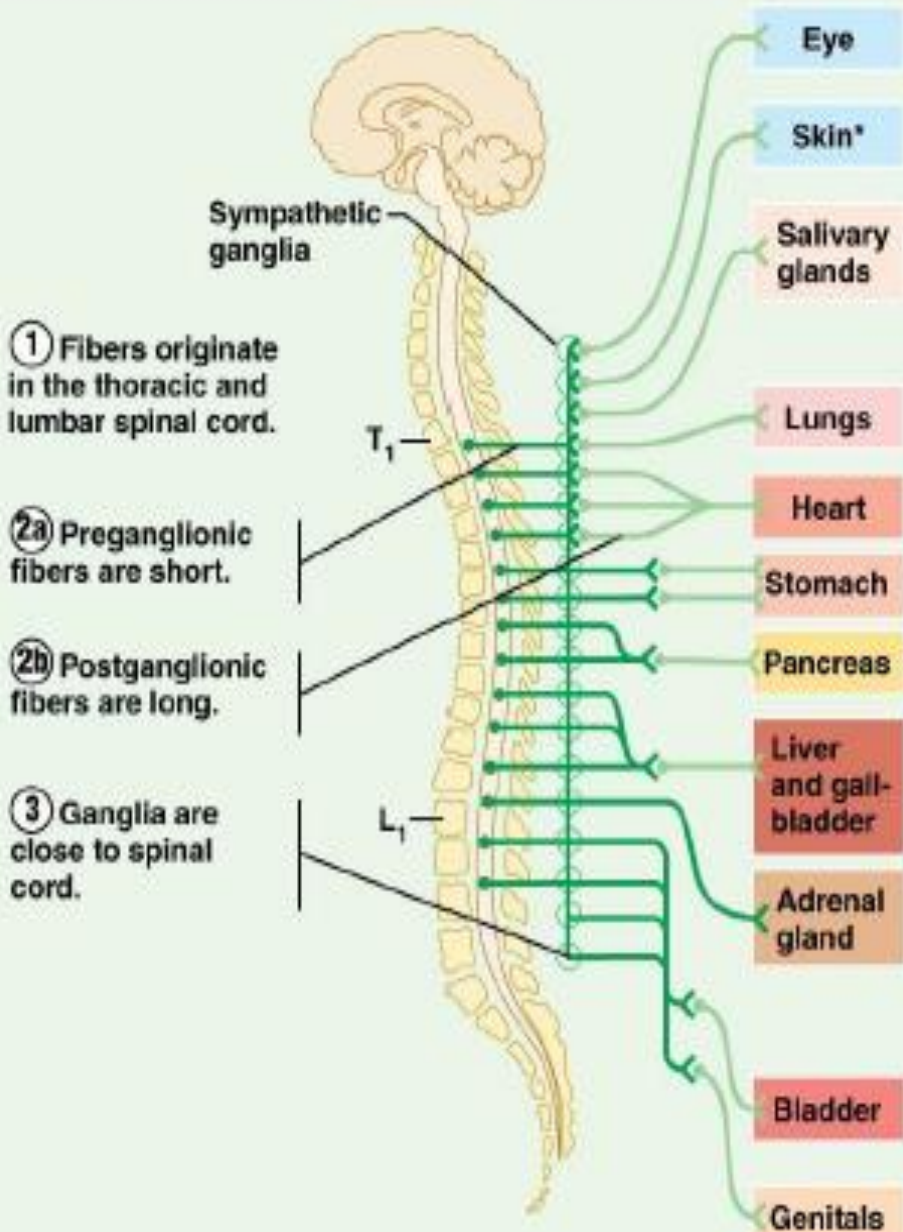
stimulates orgasm in genitals of man and woman



Parasympathetic



Sympathetic



Patterns of autonomic innervations

- **Dual innervations:** both PSNS & SNS to organ/tissue
- **Opposite action:** most of SNS functions oppose PSNS
- **Complementary actions:** SNS & PSNS supplement each other: male reproductive system

Neurotransmitter Chemistry of ANS

- ✓ Based on the primary transmitter: ACh or NE
 - Cholinergic
 - Noradrenergic or Adrenergic
- ❖ SNS fibers to the renal vasculature & kidney release DA
- ✓ A significant # of postganglionic PSNS utilize NO or peptides as the primary transmitter or cotransmitter

ANS...

Medulla

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

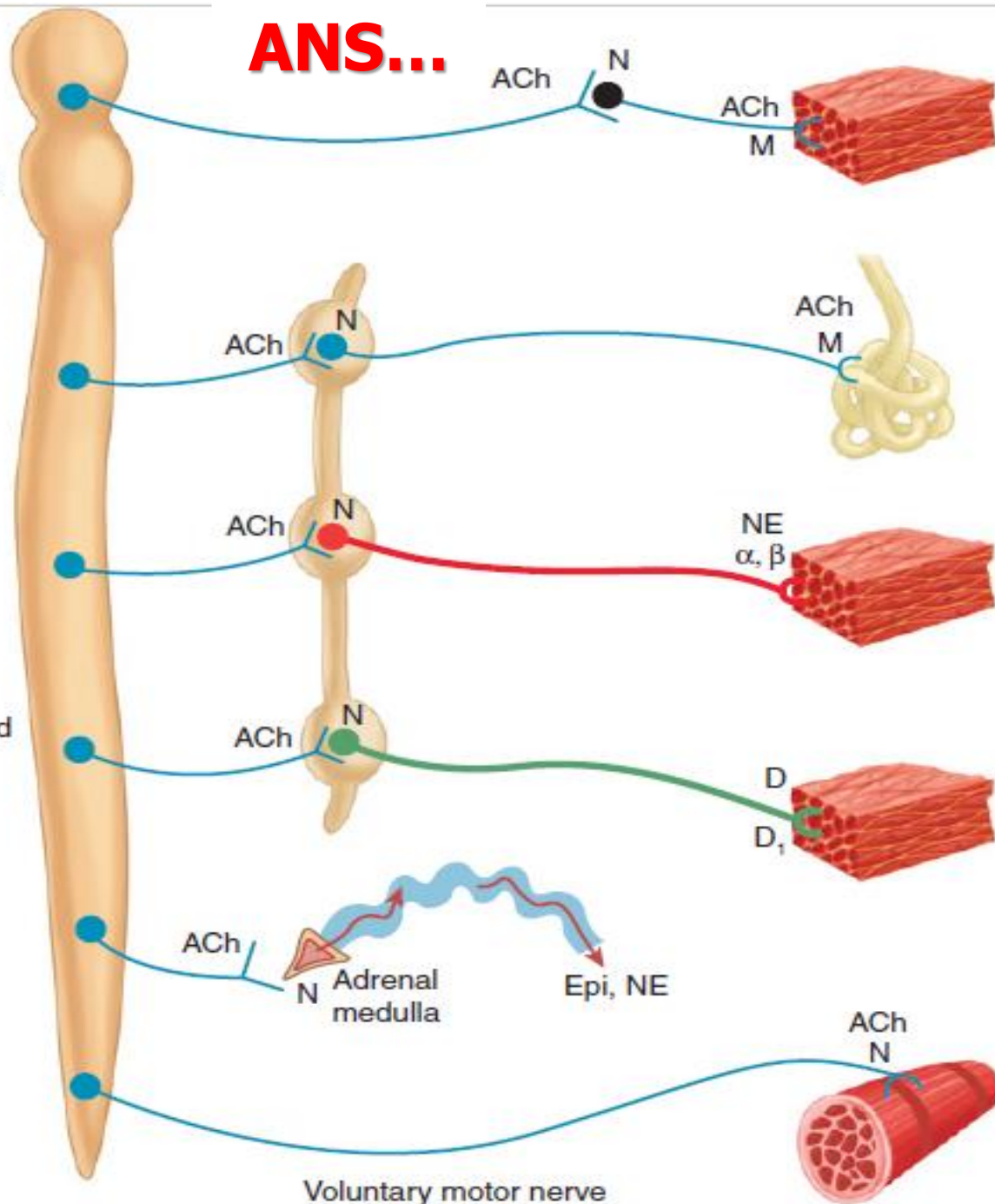
ACh
N

Somatic

Skeletal muscle

Voluntary motor nerve

Spinal cord



Co-transmitters

- ✓ Localized in the same or separate vesicles
- ✓ Include: NO, ATP, enkephalins, VIP, neuropeptide-Y, substance-P, neurotensin, somatostatin
- ✓ Main role: modulation of synaptic transmission
- ✓ Participate in feedback inhibition in the same & nearby nerve terminals
- ✓ Function as primary transmitters in other synapses

Substance	Functions
Acetylcholine (ACh)	The primary transmitter at ANS ganglia, at the somatic neuromuscular junction, and at parasympathetic postganglionic nerve endings. A primary excitatory transmitter to smooth muscle and secretory cells in the ENS. Probably also the major neuron-to-neuron ("ganglionic") transmitter in the ENS.
Adenosine triphosphate (ATP)	Acts as a transmitter or cotransmitter at many ANS-effector synapses.
Calcitonin gene-related peptide (CGRP)	Found with substance P in cardiovascular sensory nerve fibers. Present in some secretomotor ENS neurons and interneurons. A cardiac stimulant.
Cholecystikinin (CCK)	May act as a cotransmitter in some excitatory neuromuscular ENS neurons.
Dopamine	A modulatory transmitter in some ganglia and the ENS. Possibly a postganglionic sympathetic transmitter in renal blood vessels.
Enkephalin and related opioid peptides	Present in some secretomotor and interneurons in the ENS. Appear to inhibit ACh release and thereby inhibit peristalsis. May <i>stimulate</i> secretion.
Galanin	Present in secretomotor neurons; may play a role in appetite-satiety mechanisms.
GABA (γ -aminobutyric acid)	May have presynaptic effects on excitatory ENS nerve terminals. Has some relaxant effect on the gut. Probably not a major transmitter in the ENS.
Gastrin-releasing peptide (GRP)	Extremely potent excitatory transmitter to gastrin cells. Also known as mammalian bombesin.
Neuropeptide Y (NPY)	Found in many noradrenergic neurons. Present in some secretomotor neurons in the ENS and may inhibit secretion of water and electrolytes by the gut. Causes long-lasting vasoconstriction. It is also a cotransmitter in some parasympathetic postganglionic neurons.
Nitric oxide (NO)	A cotransmitter at inhibitory ENS and other neuromuscular junctions; may be especially important at sphincters. Cholinergic nerves innervating blood vessels appear to activate the synthesis of NO by vascular endothelium. NO is not stored, it is synthesized on demand by nitric oxide synthase, NOS;

Norepinephrine (NE)	The primary transmitter at most sympathetic postganglionic nerve endings.
Serotonin (5-HT)	An important transmitter or cotransmitter at excitatory neuron-to-neuron junctions in the ENS.
Substance P, related tachykinins	Substance P is an important sensory neuron transmitter in the ENS and elsewhere. Tachykinins appear to be excitatory cotransmitters with ACh at ENS neuromuscular junctions. Found with CGRP in cardiovascular sensory neurons. Substance P is a vasodilator (probably via release of nitric oxide).
Vasoactive intestinal peptide (VIP)	Excitatory secretomotor transmitter in the ENS; may also be an inhibitory ENS neuromuscular cotransmitter. A probable cotransmitter in many cholinergic neurons. A vasodilator (found in many perivascular neurons) and cardiac stimulant.

Neurotransmission

- Regardless of the type of neuron under consideration
- ✓ The fundamental steps in neurotransmission are same
- ✓ Each of these steps is a potential site for pharmacological intervention

Steps in Neurotransmission

☞ Synthesis

☞ Storage

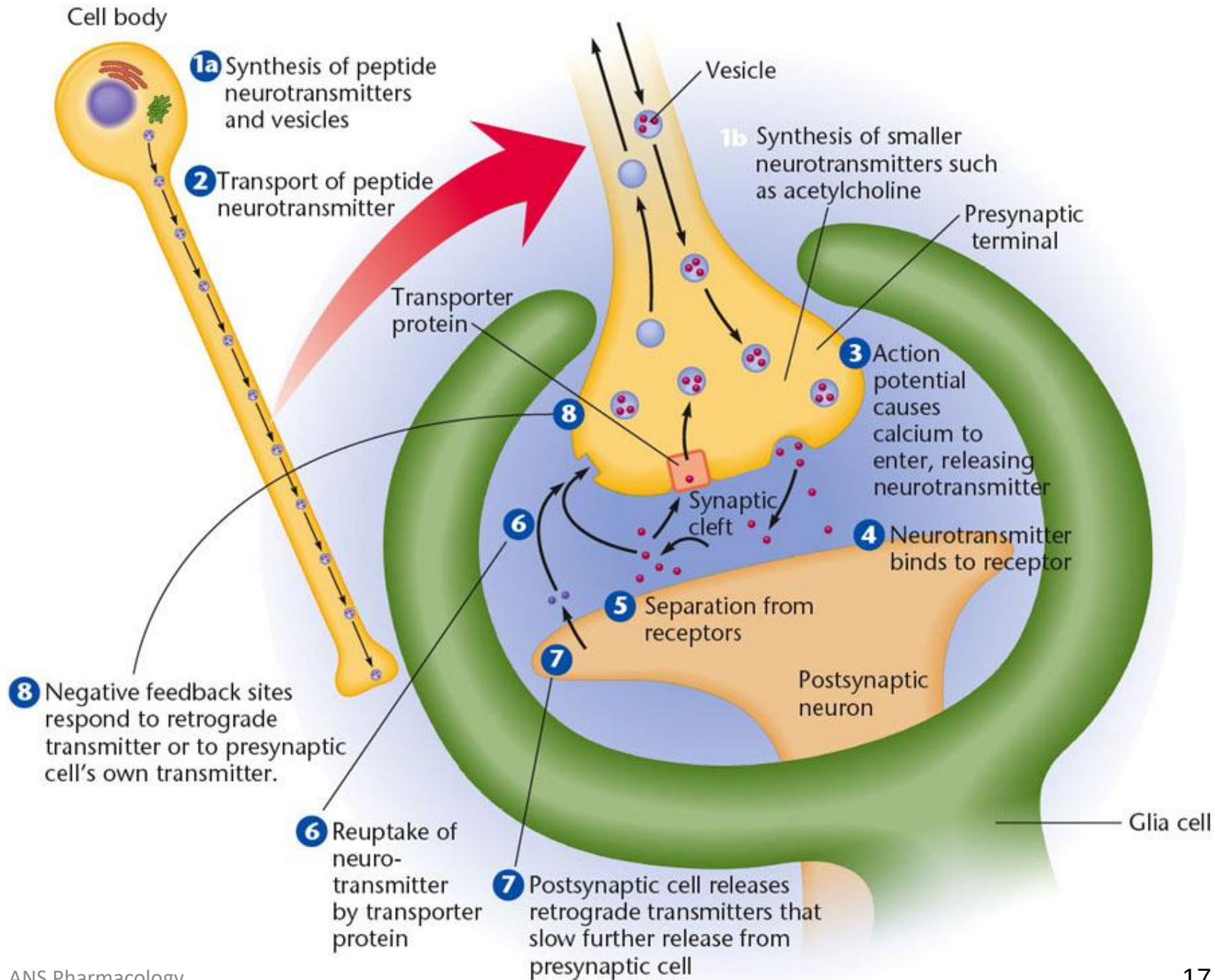
☞ Release

☞ Interaction with receptors

☞ Termination:

➤ Rapid removal: reuptake or degradation

❖ Recovery of the effector cell to the state that preceded transmitter action



Terminologies

- ⇒ Cholinergic
- ⇒ Noradrenergic or Adrenergic
- ⇒ Parasympathomimetic
- ⇒ Sympathomimetic
- ⇒ Parasympatholytic
- ⇒ Sympatholytic

■ **Cholinergic:**

- ✓ All preganglionic autonomic fibers
- ✓ Most postganglionic PSNS fibers
- ✓ Some postganglionic SNS fibers: to sweat gland
- ✓ SNS fibers to the adrenal medulla
- ✓ All somatic fibers

- **Adrenergic:**

- ✓ Most postganglionic SNS fibers

- **Dopaminergic???**

- ✓ Some postganglionic SNS fibers to the splanchnic & renal vasculature

■ Parasympathetic:

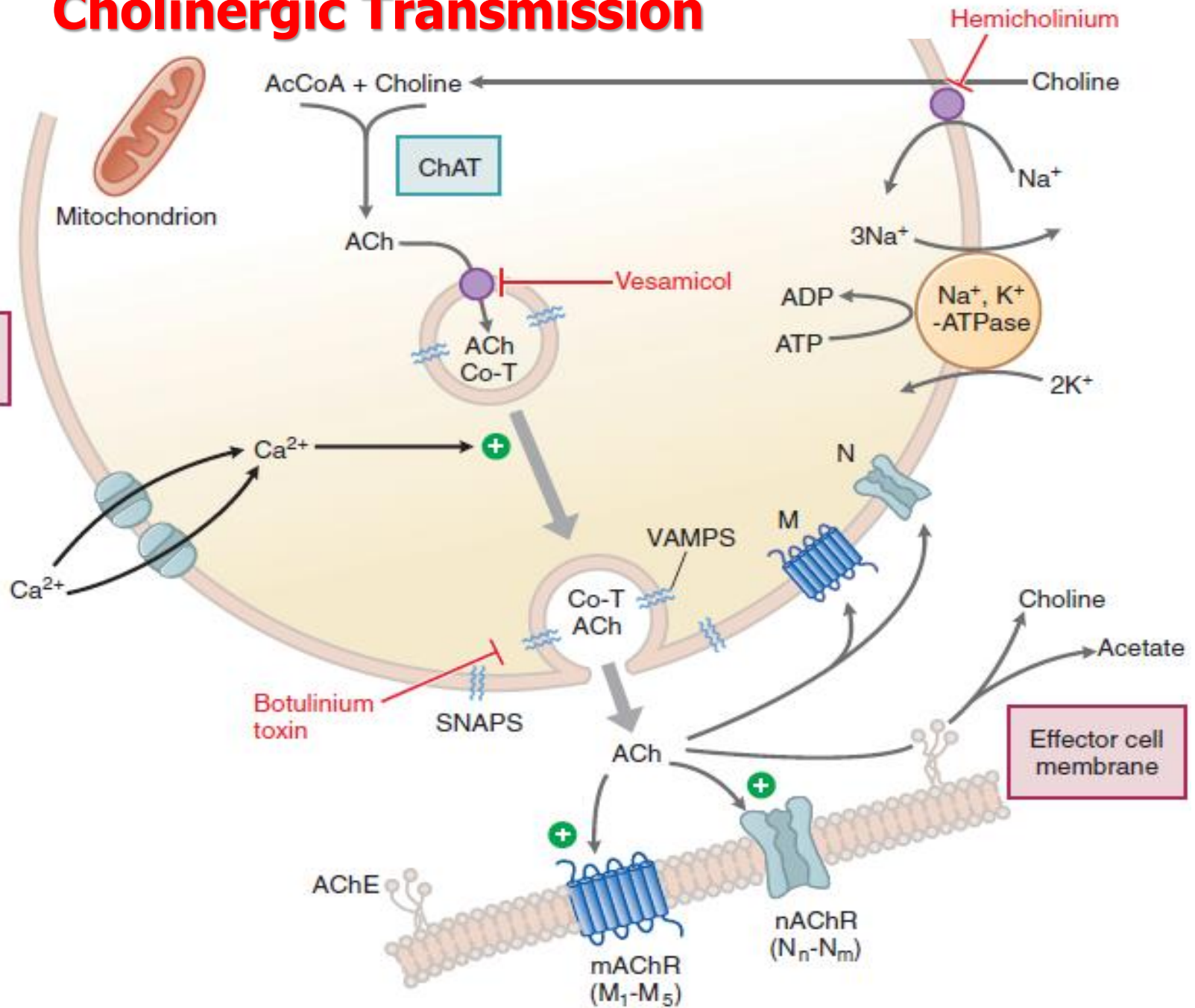
- ✓ A trophotropic one: leading to growth
- ✓ Used to rest & digest

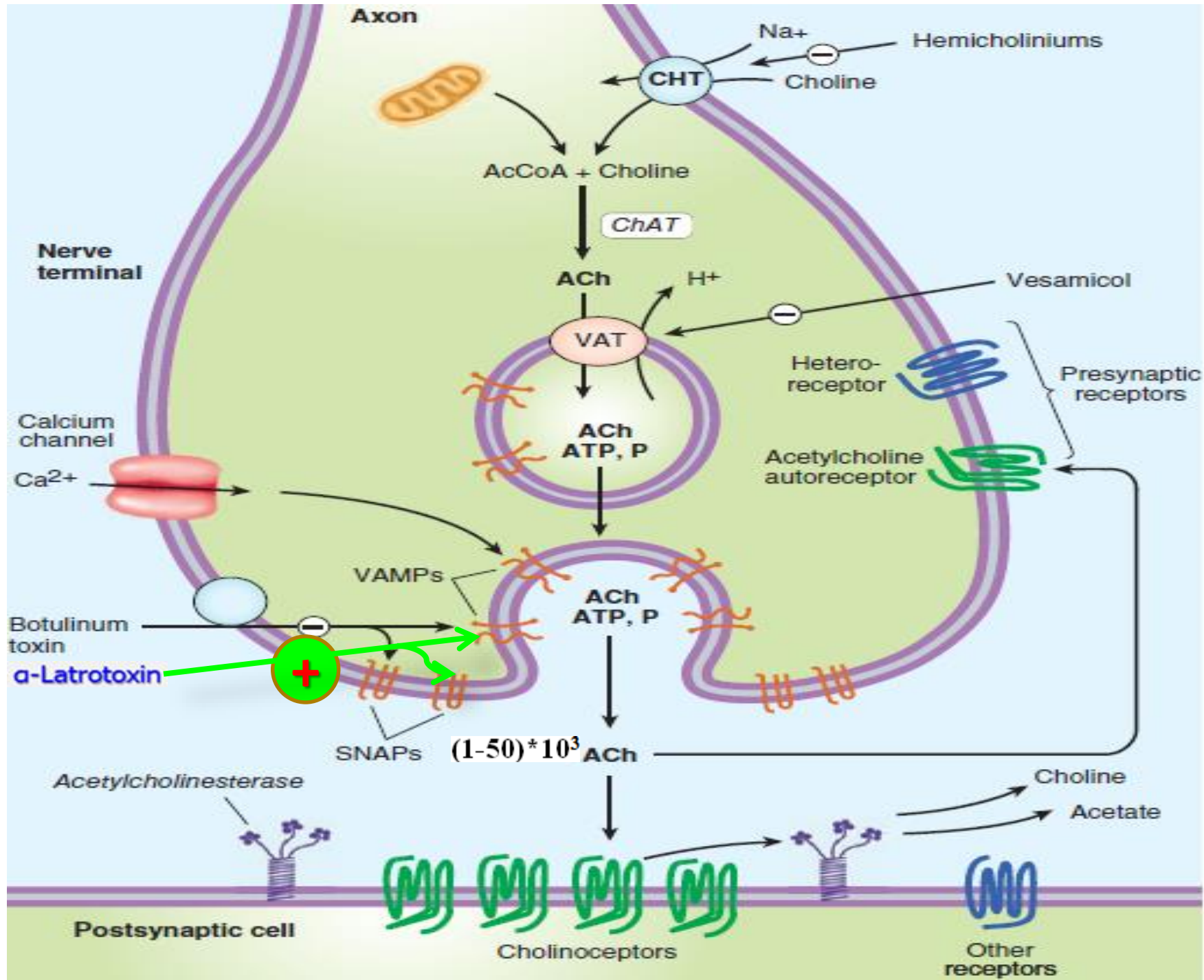
■ Sympathetic:

- ✓ An ergotropic one: leading to energy expenditure
- ✓ Activated for fight or flight
- Opposite & complementary actions
- Cooperate in the brain stem, medulla & spinal cord

Cholinergic Transmission

Cholinergic varicosity





Termination of Cholinergic Transmission

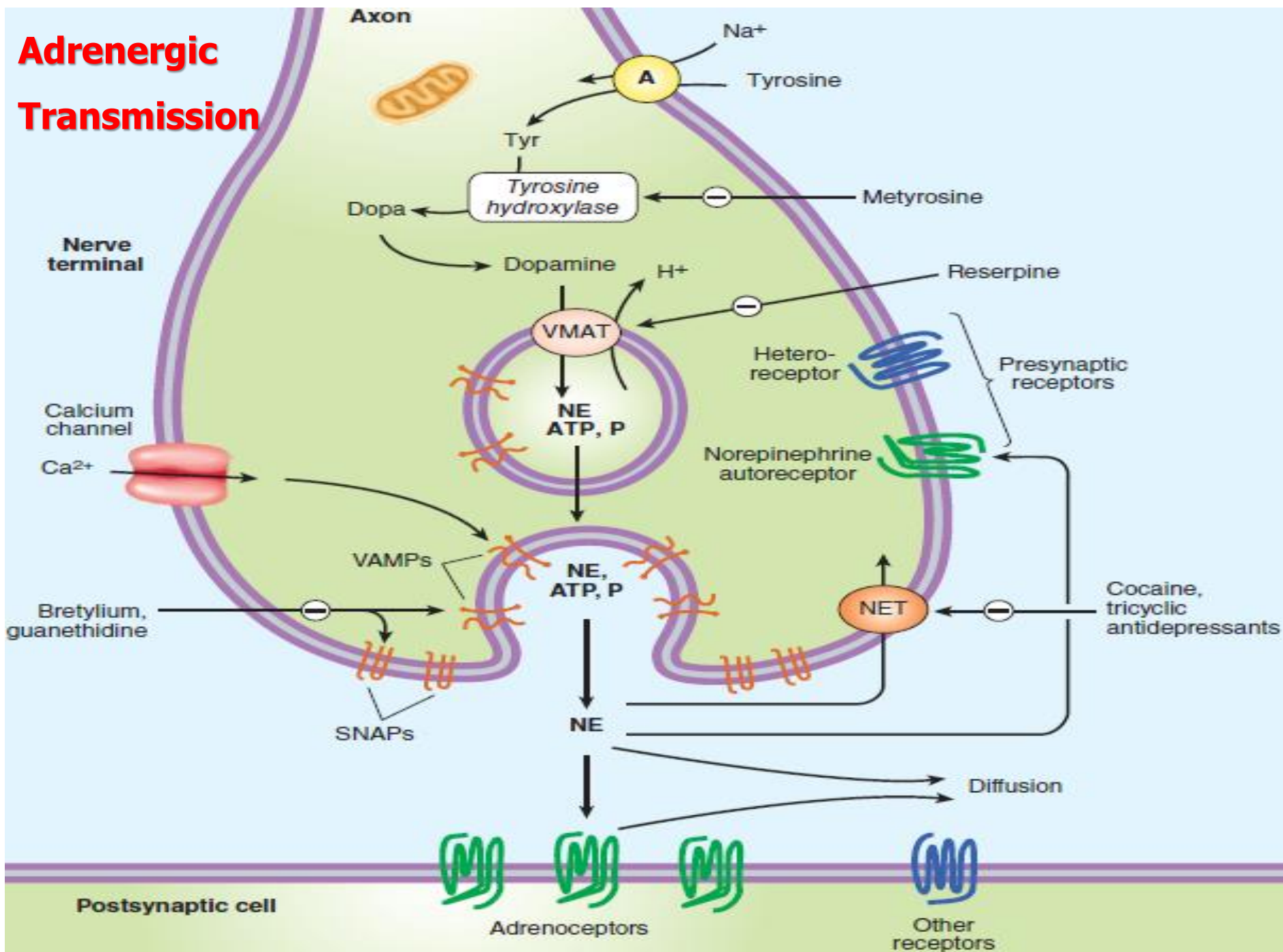
■ Cholinesterase

- ✓ Two types;
- True cholinesterase: AChE
 - ❖ Found in the chemical synapse, RBC membrane
 - ❖ Specific to Ach
 - ❖ Inhibition: important to amplify endogenous ACh

Termination...

- Pseudo-/plasma-cholinesterase: BuChE
 - ❖ Found in the plasma, liver, glia & other tissues
 - ❖ Non specific: ACh + other ester compounds
 - ❖ Not important in the physiologic termination of synaptic ACh
 - ❖ Targeting is not important

Adrenergic Transmission



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*.

4**BINDING TO RECEPTOR**

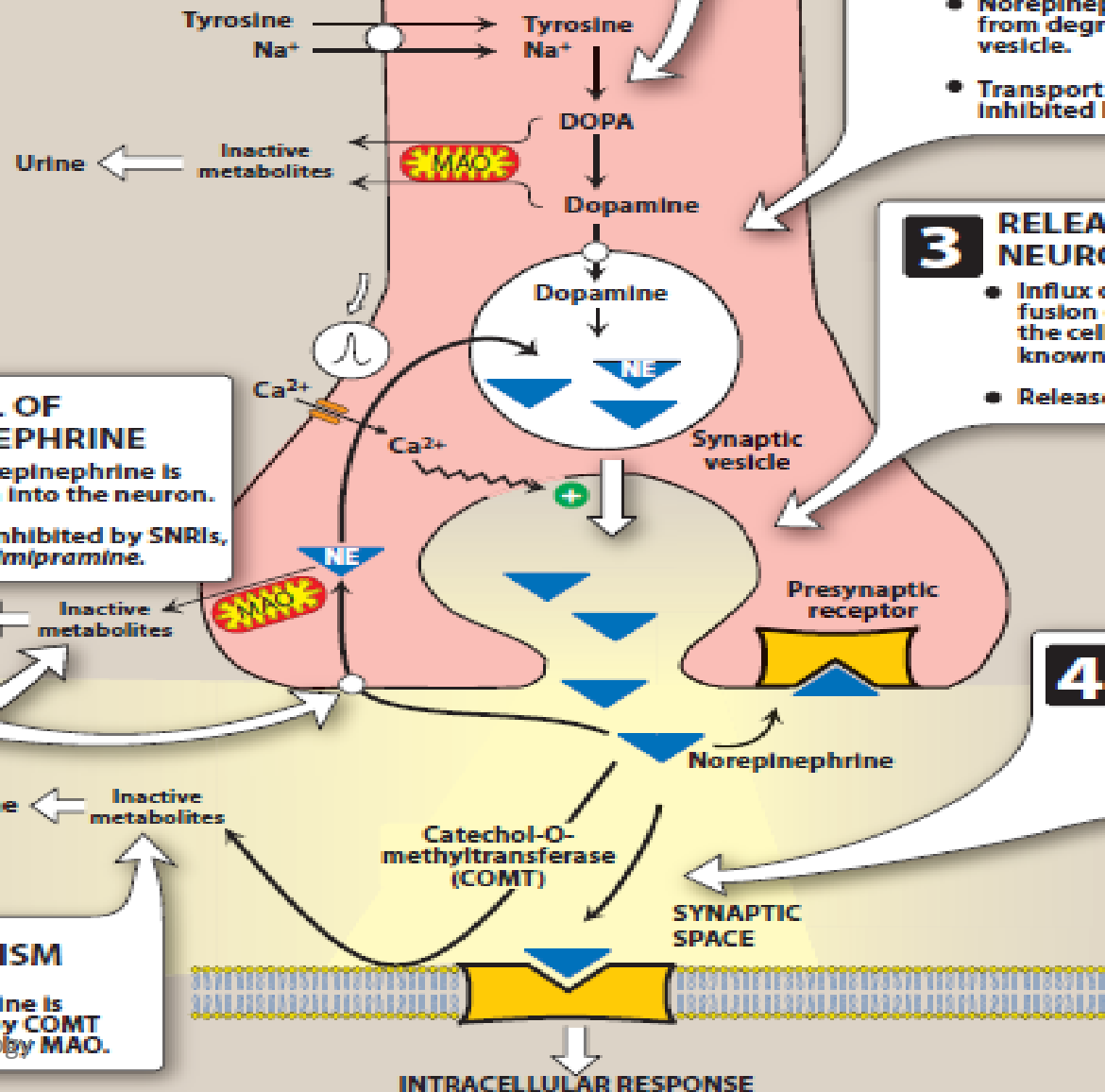
- Postsynaptic receptor is activated by the binding of neurotransmitter.

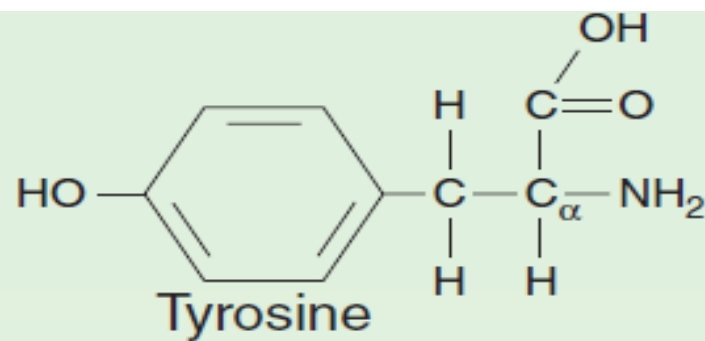
5**REMOVAL OF NOREPINEPHRINE**

- Released norepinephrine is rapidly taken into the neuron.
- Reuptake is inhibited by SNRIs, cocaine, and imipramine.

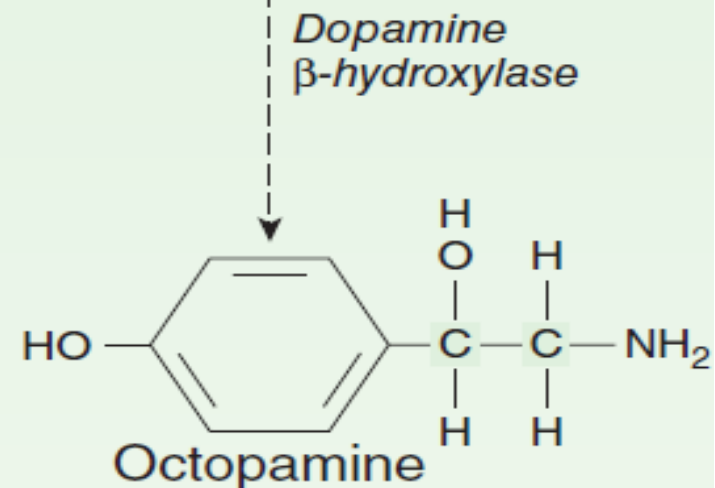
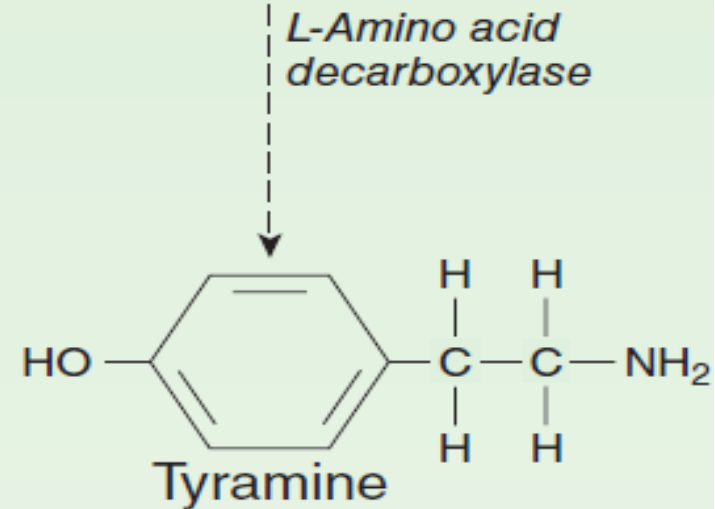
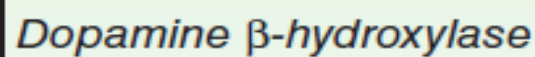
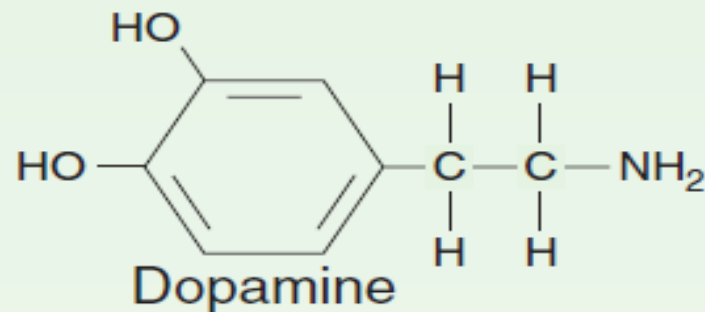
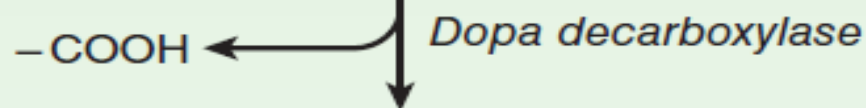
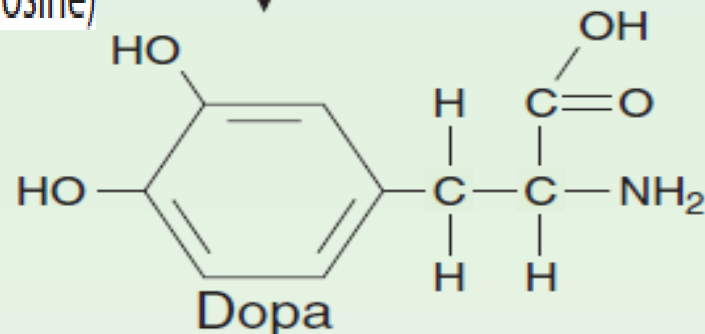
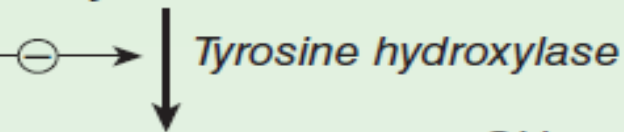
6**METABOLISM**

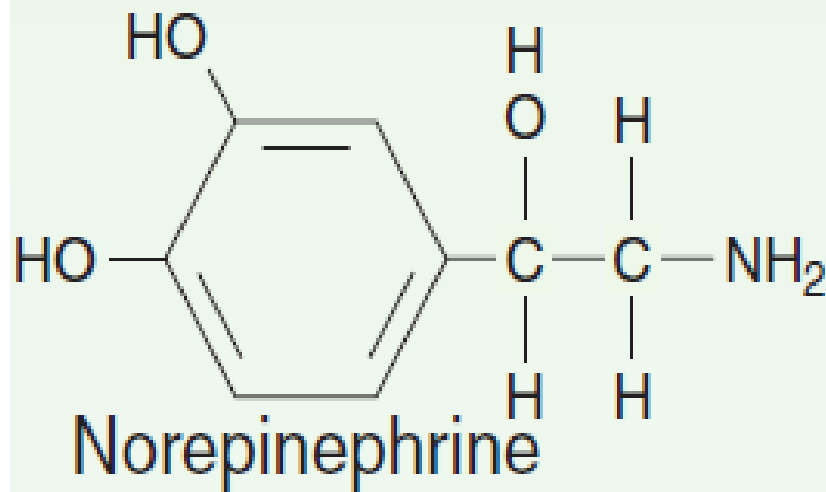
- Norepinephrine is methylated by COMT and oxidized by MAO.





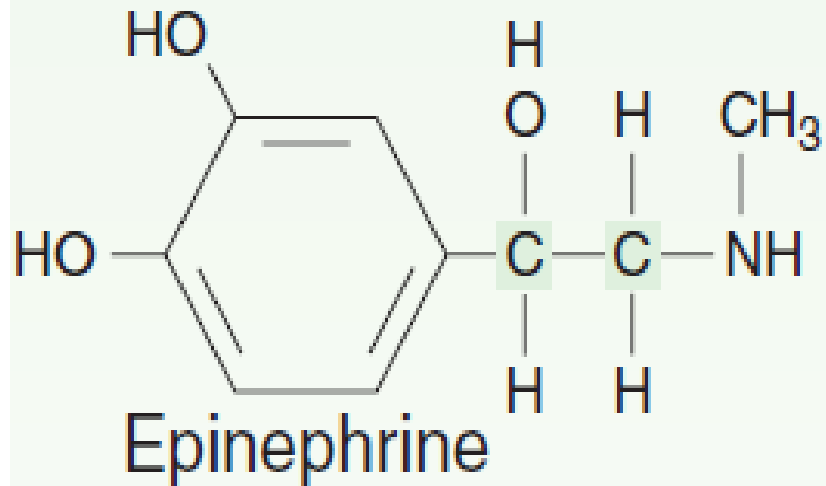
Metyrosine
(α -methyltyrosine)





*Hydroxylase
(from liver)*

Phenylethanolamine-N-methyltransferase

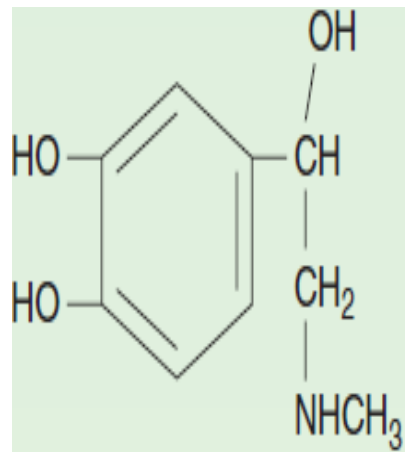


Termination of Adrenergic Transmission

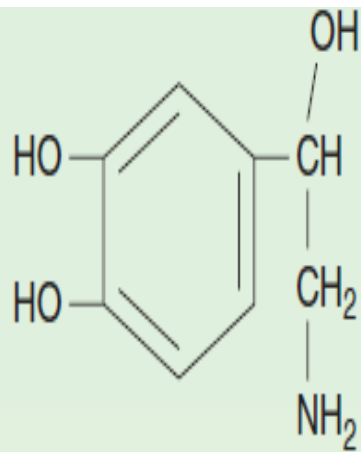
- Results from two processes:
 - ✓ **Reuptake:** into the nerve terminal, glia or other cells
 - ✓ Simple diffusion away from the receptor site with eventual **metabolism** in the plasma or liver
- ❖ Metabolism is not the 1^o mechanism @ physiologic NE

Termination...

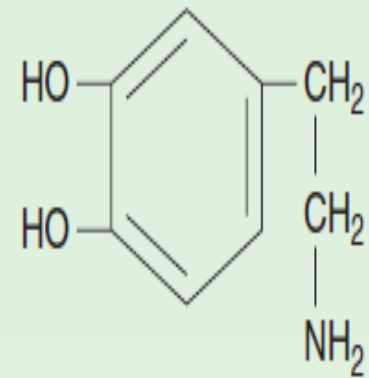
- ✓ NE & E can be metabolized by several enzymes
- ✓ MAO in the mitochondria of the nerve terminal,
 - Have high activity: significant turnover of NE even in the resting terminal
- ✓ Excretion of metabolites: via urine
- ❖ An estimate of catecholamine turnover can be made by measuring total metabolites (VMA & metanephrines) in a 24-hr urine sample



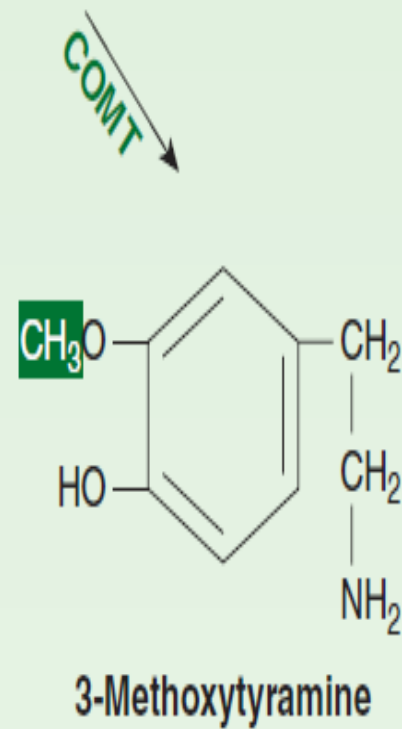
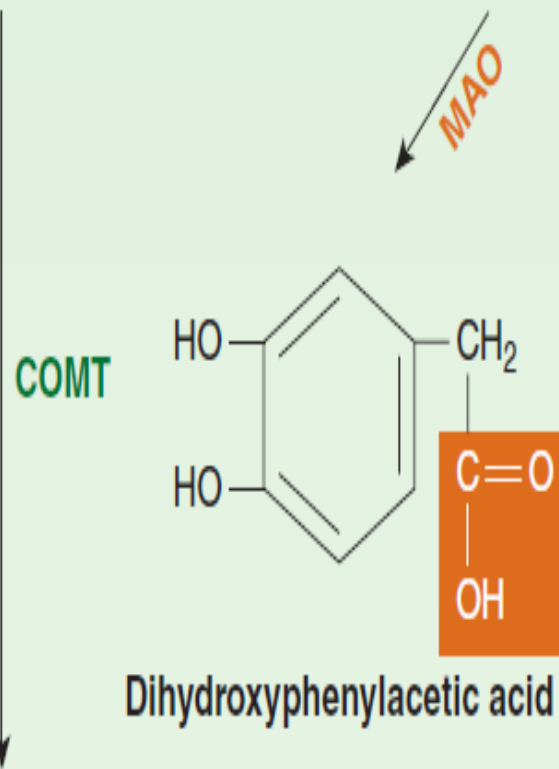
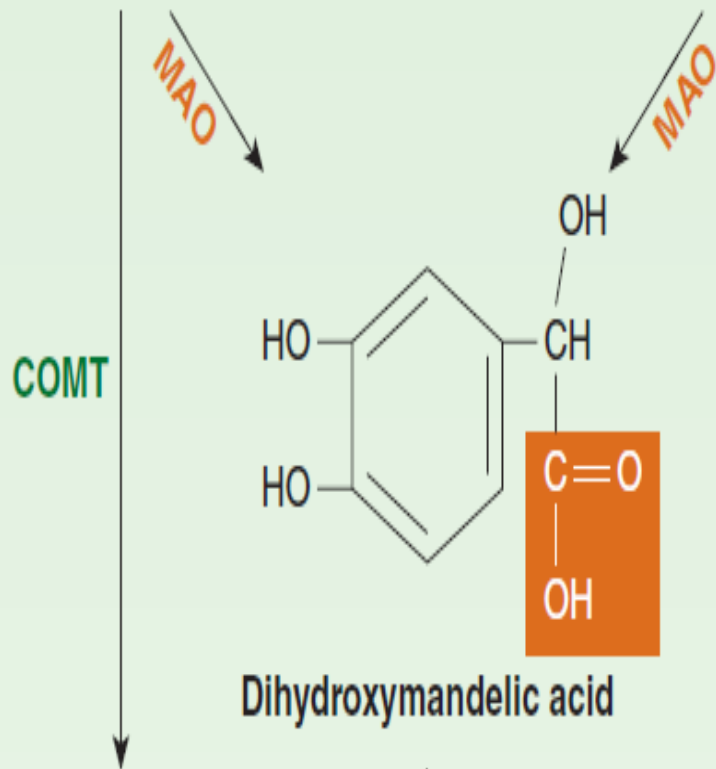
Epinephrine

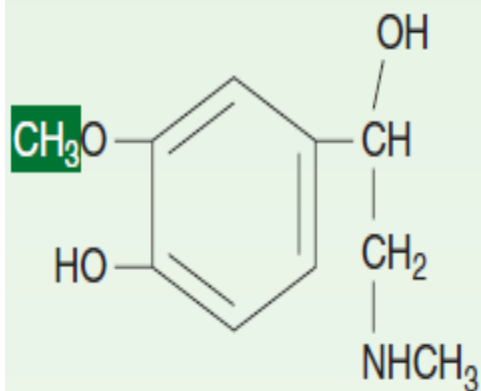


Norepinephrine



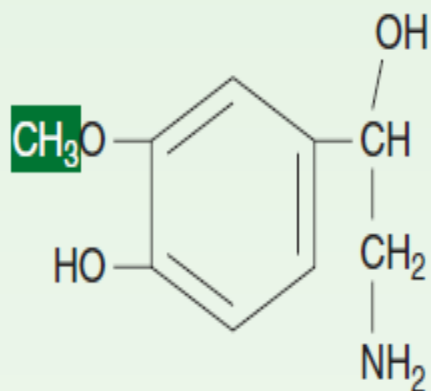
Dopamine





Metanephrine

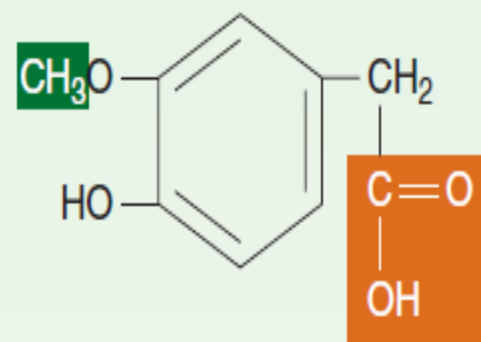
COMT



Normetanephrine

COMT

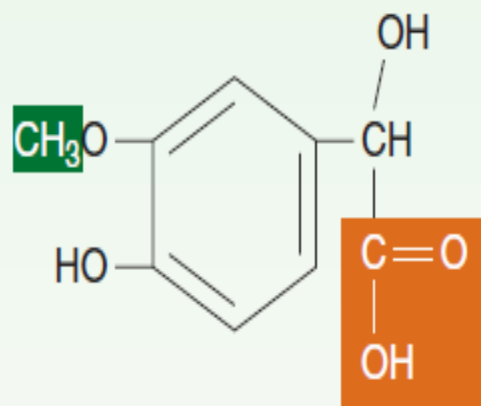
MAO



Homovanillic acid

MAO

MAO



3-Methoxy-4-hydroxy-mandelic acid (VMA)

Receptors of ANS

✓ **Cholinoceptors:** stimulated by ACh

➤ Muscarinic: M_1 - M_5

➤ Nicotinic: N_N , N_M

❖ Named after the alkaloids originally used in their identification: muscarine & nicotine

❖ ACh was later identified as the physiologic transmitter at both muscarinic & nicotinic receptors, both receptors were recognized as cholinoreceptor subtypes

Receptors...

- **Adrenoceptors:** named after the nerves that usually innervate them
- ✓ Types: on the basis of both agonist & antagonist selectivity & on genomic grounds
 - α -adrenoceptor
 - β -adrenoceptor
 - Dopamine-receptors: two D_1 like: D_1 & D_5 & three D_2 like: D_2 , D_3 & D_4

Major Autonomic Receptor Types

Receptor Name	Typical Locations	Result of Ligand Binding
Cholinoceptors		
Muscarinic M ₁	CNS neurons, sympathetic postganglionic neurons, some presynaptic sites	Formation of IP ₃ and DAG, increased intracellular calcium
Muscarinic M ₂	Myocardium, smooth muscle, some presynaptic sites; CNS neurons	Opening of potassium channels, inhibition of adenyl cyclase
Muscarinic M ₃	Exocrine glands, vessels (smooth muscle and endothelium); CNS neurons	Like M ₁ receptor-ligand binding
Muscarinic M ₄	CNS neurons; possibly vagal nerve endings	Like M ₂ receptor-ligand binding
Muscarinic M ₅	Vascular endothelium, especially cerebral vessels; CNS neurons	Like M ₁ receptor-ligand binding
Nicotinic N _N	Postganglionic neurons, some presynaptic cholinergic terminals; pentameric receptors typically contain α and β type subunits only	Opening of Na ⁺ , K ⁺ channels, depolarization
Nicotinic N _M	Skeletal muscle neuromuscular end plates; receptors typically contain two α 1 and β 1 type subunits in addition to γ and δ subunits	Opening of Na ⁺ , K ⁺ channels, depolarization

Receptor Name	Typical Locations	Result of Ligand Binding
Adrenoceptors		
Alpha ₁	Postsynaptic effector cells, especially smooth muscle	Formation of IP ₃ and DAG, increased intracellular calcium
Alpha ₂	Presynaptic adrenergic nerve terminals, platelets, lipocytes, smooth muscle	Inhibition of adenylyl cyclase, decreased cAMP
Beta ₁	Postsynaptic effector cells, especially heart, lipocytes, brain; presynaptic adrenergic and cholinergic nerve terminals, juxtaglomerular apparatus of renal tubules, ciliary body epithelium	Stimulation of adenylyl cyclase, increased cAMP
Beta ₂	Postsynaptic effector cells, especially smooth muscle and cardiac muscle	Stimulation of adenylyl cyclase and increased cAMP. Activates cardiac G _i under some conditions.
Beta ₃	Postsynaptic effector cells, especially lipocytes; heart	Stimulation of adenylyl cyclase and increased cAMP ¹
Dopamine receptors		
D ₁ (DA ₁), D ₅	Brain; effector tissues, especially smooth muscle of the renal vascular bed	Stimulation of adenylyl cyclase and increased cAMP
D ₂ (DA ₂)	Brain; effector tissues, especially smooth muscle; presynaptic nerve terminals	Inhibition of adenylyl cyclase; increased potassium conductance
D ₃	Brain	Inhibition of adenylyl cyclase
D ₄	Brain, cardiovascular system	Inhibition of adenylyl cyclase

Nonadrenergic, Noncholinergic (NANC) Neurons

- ✓ Nerve fibers that do not show the histochemical characteristics of either cholinergic or adrenergic fibers
- ✓ Found in the autonomic effector tissues (gut, airways, bladder) & ENS
- ✓ Are both motor & sensory fibers
- ✓ Transmitters: peptides (most), NOS & purines
- ✓ Capsaicin can cause the release of transmitter (especially substance P) from such neurons, & if given in high doses, destruction of the neuron

- ✓ ENS contains NANC neurons, cholinergic & adrenergic fibers
- Enteric NANC neurons in the intestine contain:
 - ❖ NOS, CGRP, CCK, 5-HT, VIP, dynorphin, enkephalins, gastrin-releasing peptide, neuropeptide Y, somatostatin, substance P
 - ❖ Some contain as many as five d/t transmitters

- ✓ NANC sensory fibers are probably termed **sensory-efferent or sensory local effector fibers** b/c, when activated by a sensory input,
- They are capable of releasing transmitter peptides from;
 - ❖ The sensory ending itself,
 - ❖ Local axon branches &
 - ❖ Collaterals that terminate in the autonomic ganglia
- ✓ These peptides are potent agonists in many autonomic effector tissues

Functional Organization of Autonomic Activity

- ✓ Autonomic function is integrated & regulated at many levels,
 - From the CNS to the effector cells
- ✓ Regulation: negative feedback (mostly) & several other mechanisms

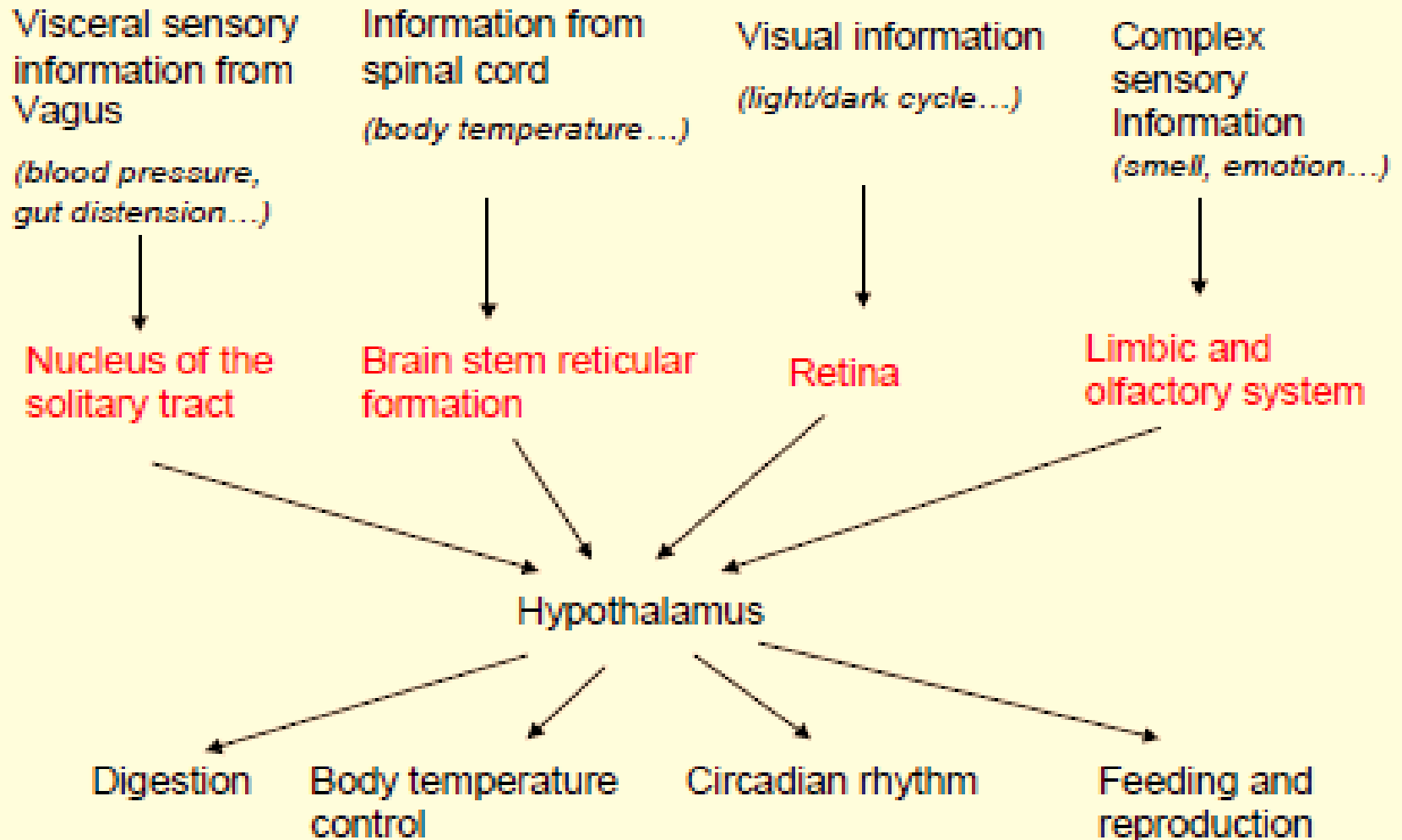
■ Central Integration

✓ At the highest level:

➤ Midbrain & medulla, ANS & the endocrine system are integrated with each other, with sensory input & with information from higher CNS centers, including the cerebral cortex

Central integration...

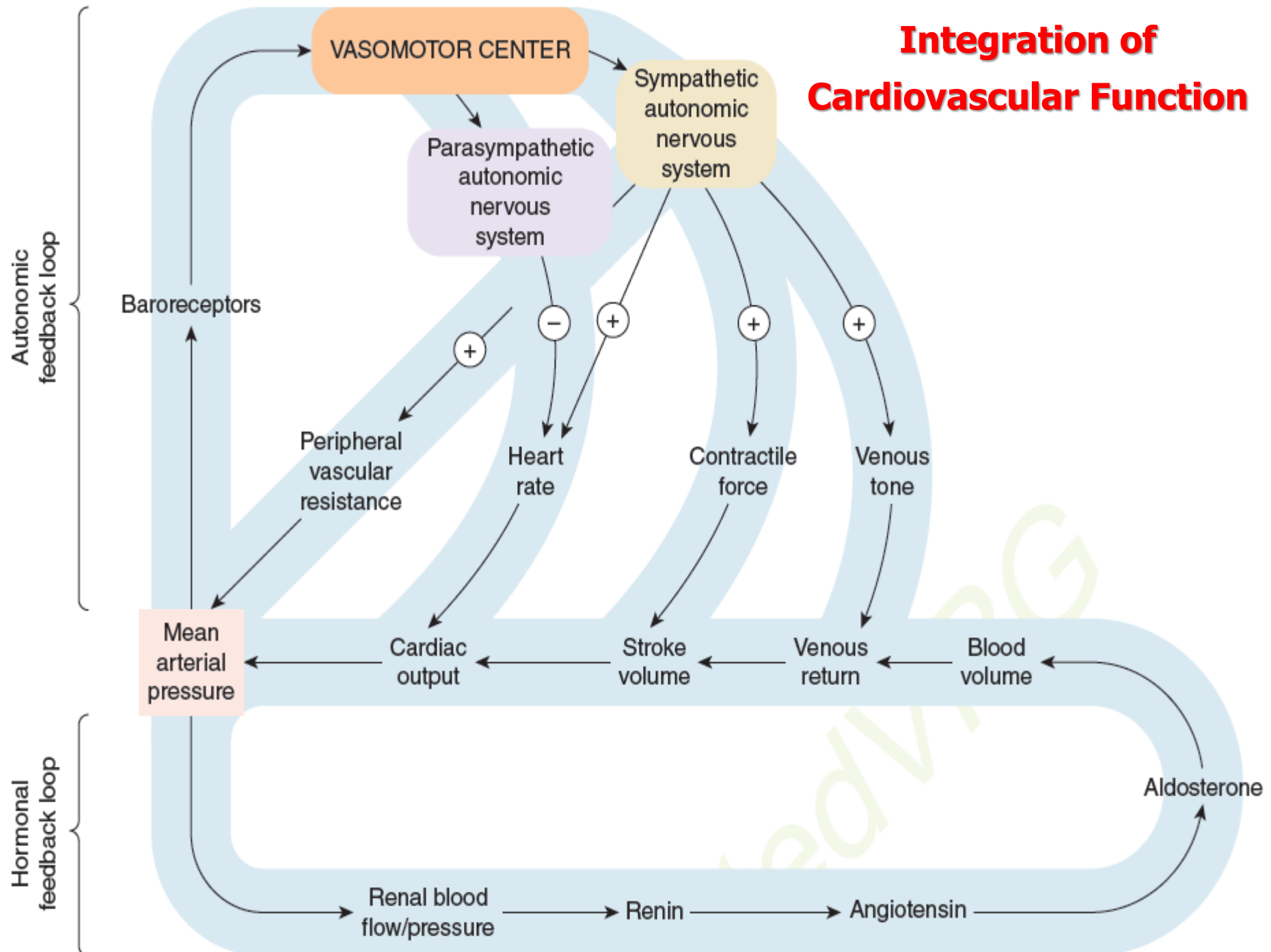
The hypothalamus receives inputs from:



- For some organs, sensory fibers associated with the PSNS exert reflex control over motor outflow in the SNS
- ✓ The sensory carotid sinus baroreceptor fibers in the CN-IX have a major influence on SNS outflow from the vasomotor center

- ✓ PSNS sensory fibers in the wall of the urinary bladder significantly influence SNS inhibitory outflow to the bladder
- ✓ Within ENS, sensory fibers from the wall of the gut synapse on both preganglionic & postganglionic motor neurons that control intestinal smooth muscle & secretory cells

Integration of Cardiovascular Function



Regulation of Autonomic Function

- ❑ **Presynaptic Regulation:** probably occurs in all nerve fibers
 - **Autoreceptors:** presynaptic receptors that respond to the primary transmitter released by the nerve ending
 - Usually inhibitory (**-ve feedback**): α_2 in NA neurons
 - ❖ But, β receptors on NA fibers & nAChR of somatic motor fibers are excitatory

■ Heteroreceptors

- ✓ Found at the nerve terminals
- ✓ Respond to many other s/cs released from other nerve terminals that synapse with the nerve ending
- ✓ Ligands for these receptors may diffuse to the receptors from the blood or from nearby tissues
- Some vagal fibers in the myocardium synapse on sympathetic NA nerve terminals & inhibit NE release

Autoreceptor, heteroreceptor, and modulatory effects on nerve terminals in peripheral synapses

Transmitter/Modulator	Receptor Type	Neuron Terminals Where Found
Inhibitory effects		
Acetylcholine	M ₂ , M ₁	Adrenergic, enteric nervous system
Norepinephrine	Alpha ₂	Adrenergic
Dopamine	D ₂ ; less evidence for D ₁	Adrenergic
Serotonin (5-HT)	5-HT ₁ , 5-HT ₂ , 5-HT ₃	Cholinergic preganglionic
ATP, ADP	P2Y	Adrenergic autonomic and ENS cholinergic neurons
Adenosine	A ₁	Adrenergic autonomic and ENS cholinergic neurons
Histamine	H ₃ , possibly H ₂	H ₃ type identified on CNS adrenergic and serotonergic neurons
Enkephalin	Delta (also mu, kappa)	Adrenergic, ENS cholinergic
Neuropeptide Y	Y ₁ , Y ₂ (NPY)	Adrenergic, some cholinergic
Prostaglandin E ₁ , E ₂	EP ₃	Adrenergic
Excitatory effects		
Epinephrine	Beta ₂	Adrenergic, somatic motor cholinergic
Acetylcholine	N _M	Somatic motor cholinergic
Angiotensin II	AT ₁	Adrenergic

■ Postsynaptic Regulation

- ✓ Can be considered from two perspectives:
- Modulation by previous activity at the primary receptor
- ❖ Up- or down-regulate receptor # or desensitize receptors
- ❖ Known to occur in response to ↓ed or ↑ed activation
- ❖ Well documented in several receptor-effector systems

✓ Up-regulation: denervation supersensitivity

- ❖ In skeletal muscle, nicotinic receptors are normally restricted to the end plate regions underlying somatic motor nerve terminals
- ❖ Surgical or traumatic denervation results in marked proliferation of nicotinic cholinceptors over all parts of the fiber, including areas not previously associated with any motor nerve junctions

✓ Up regulation: pharmacologic supersensitivity

- Occurs in autonomic effector tissues;
- ❖ After administration of drugs that deplete transmitter stores & prevent activation of the postsynaptic receptors for a sufficient period of time
- ❖ Prolonged administration of large doses of reserpine, can cause ↑ed sensitivity of the smooth muscle & cardiac muscle effector cells served by the depleted sympathetic fibers

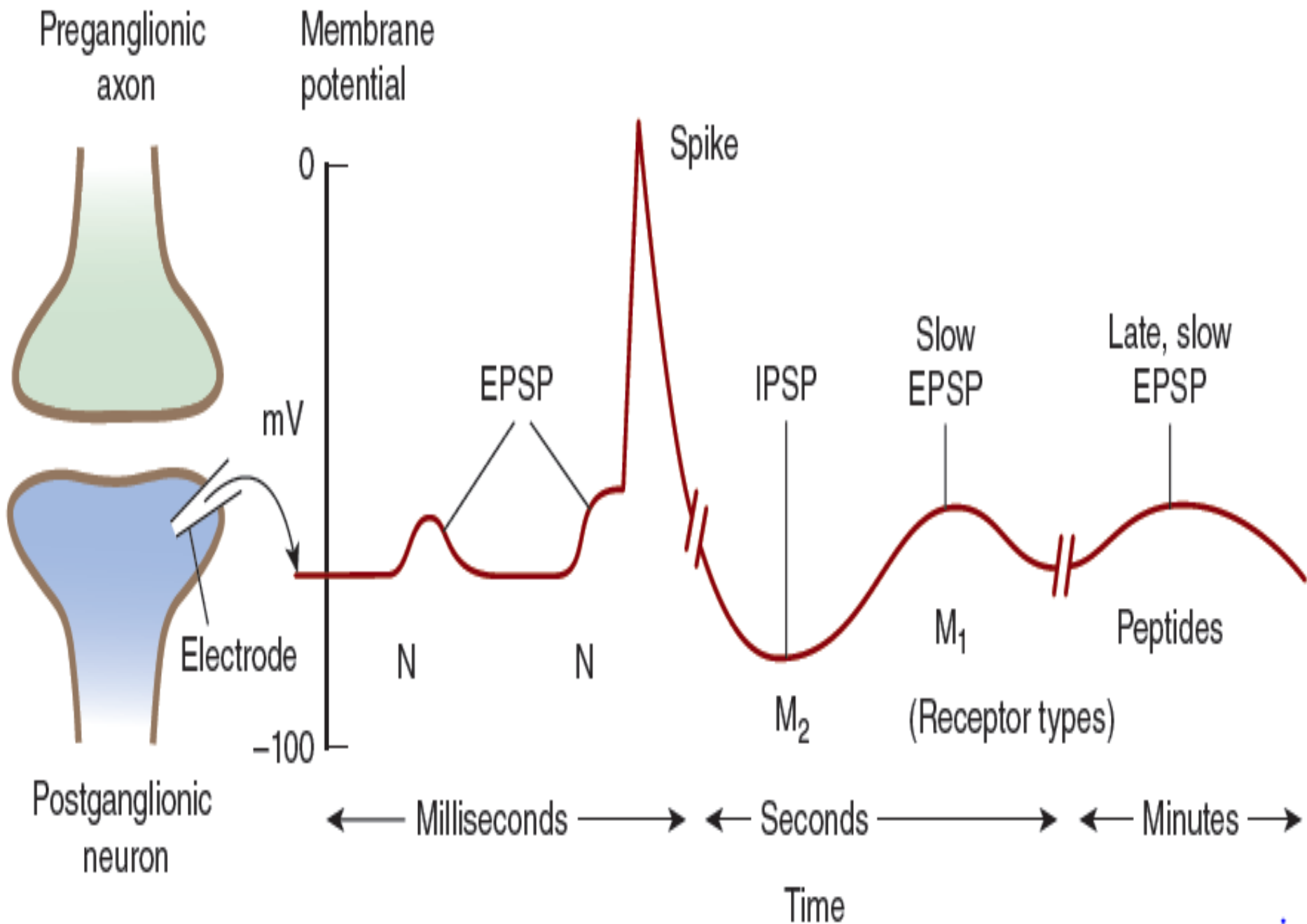
■ Modulation by other simultaneous events:

- ✓ Involves modulation of the primary transmitter-receptor event by events evoked by the same or other transmitters acting on d/t postsynaptic receptors

❖ Ganglionic transmission

- ✓ The postganglionic cells are activated (depolarized) as a result of binding of an appropriate ligand to N_N AChR
- ✓ The resulting fast EPSP evokes a propagated action potential if threshold is reached
- ✓ This is often followed by a small & slowly developing but longer-lasting hyperpolarizing after potential – a slow IPSP

- ✓ This hyperpolarization involves opening of K^+ channels by M_2 -R
- ✓ The IPSP is followed by a small, slow excitatory postsynaptic potential caused by closure of K^+ channels linked to M_1 -R
- ✓ Finally, a late, very slow EPSP may be evoked by peptides released from other fibers
- ✓ These slow potentials serve to modulate the responsiveness of the postsynaptic cell to subsequent primary excitatory presynaptic nerve activity

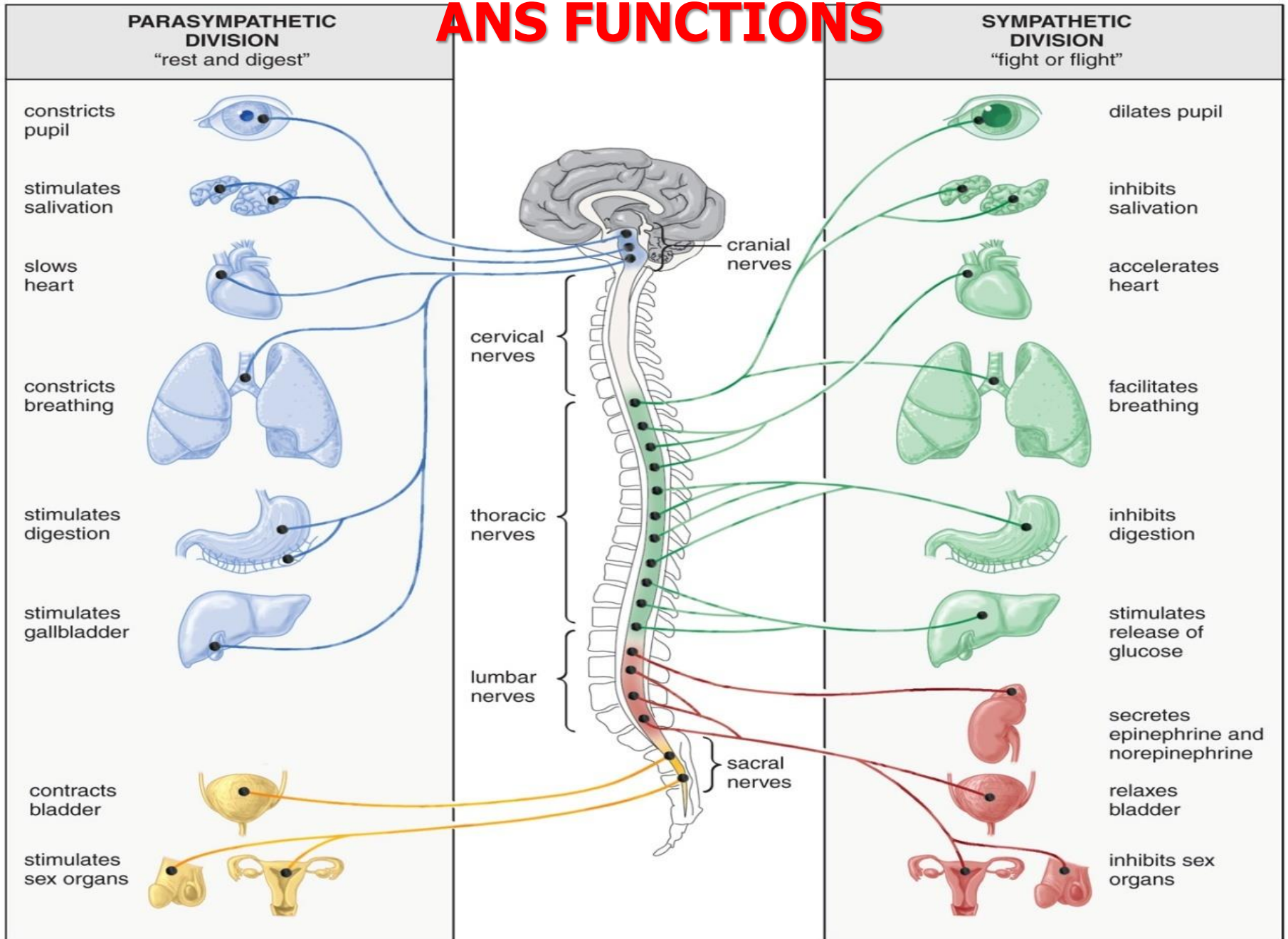


Steps in autonomic transmission: Effects of drugs.

Process Affected	Drug Example	Site	Action
Action potential propagation	Local anesthetics, tetrodotoxin, ¹ saxitoxin ²	Nerve axons	Block voltage-gated sodium channels; block conduction
Transmitter synthesis	Hemicholiniums	Cholinergic nerve terminals: membrane	Block uptake of choline and slow synthesis
	α -Methyltyrosine (metyrosine)	Adrenergic nerve terminals and adrenal medulla: cytoplasm	Inhibits tyrosine hydroxylase and blocks synthesis of catecholamines
Transmitter storage	Vesamicol	Cholinergic terminals: VAT on vesicles	Prevents storage, depletes
	Reserpine	Adrenergic terminals: VMAT on vesicles	Prevents storage, depletes
Transmitter release	Many ³	Nerve terminal membrane receptors	Modulate release
	ω -Conotoxin GVIA ⁴	Nerve terminal calcium channels	Reduces transmitter release
	Botulinum toxin	Cholinergic vesicles	Prevents release
	α -Latrotoxin ⁵	Cholinergic and adrenergic vesicles	Causes explosive transmitter release
	Tyramine, amphetamine	Adrenergic nerve terminals	Promote transmitter release
Transmitter reuptake after release	Cocaine, tricyclic antidepressants, SNRI antidepressants ⁶	Adrenergic nerve terminals, NET	Inhibit uptake; increase transmitter effect on post-synaptic receptors

Receptor activation or blockade	Norepinephrine	Receptors at adrenergic junctions	Binds α receptors; causes contraction
	Phentolamine	Receptors at adrenergic junctions	Binds α receptors; prevents activation
	Isoproterenol	Receptors at adrenergic junctions	Binds β receptors; activates adenylyl cyclase
	Propranolol	Receptors at adrenergic junctions	Binds β receptors; prevents activation
	Nicotine	Receptors at nicotinic cholinergic junctions (autonomic ganglia, neuromuscular end plates)	Binds nicotinic receptors; opens ion channel in post-synaptic membrane
	Tubocurarine	Neuromuscular end plates	Prevents activation
	Bethanechol	Receptors, parasympathetic effector cells (smooth muscle, glands)	Binds and activates muscarinic receptors
	Atropine	Receptors, parasympathetic effector cells	Binds muscarinic receptors; prevents activation
Enzymatic inactivation of transmitter	Neostigmine	Cholinergic synapses (acetylcholinesterase)	Inhibits enzyme; prolongs and intensifies transmitter action
	Tranylcypromine	Adrenergic nerve terminals (monoamine oxidase)	Inhibits enzyme; increases stored transmitter pool

ANS FUNCTIONS



Muscarinic Receptor Activation

Target		Receptor	Response
Eye	Sphincter	M ₃	Contraction—miosis
	Ciliary muscle	M ₃	Contraction—accommodation for near vision
Heart	SA node	M ₂	↓ Heart rate (HR)—negative chronotropy
	AV node	M ₂	↓ Conduction velocity—negative dromotropy No effects on ventricles, Purkinje system
Lungs	Bronchioles	M ₃	Contraction—bronchospasm
	Glands	M ₃	Secretion
GI tract	Stomach	M ₃	↑ Motility—cramps
	Glands	M ₁	Secretion
	Intestine	M ₃	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

Nicotinic Receptor Activation

Target	Receptor	Response
Adrenal medulla	N _N	Secretion of E: 80% & NE: 20%
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.

- ✓ Blood vessels solely innervated by the SNS, so stimulation of autonomic ganglia results in vasoconstriction
- ✓ Conversely, GIT is dominated by the PSNS, so ganglionic stimulation causes increased GIT motility & secretions

ANS on Heart

- ➡ Adrenergic receptors are diffuse
 - ✓ SA, atrium, AV, Purkinje fibers & generalized myocardium
- ➡ But PSNS: supply from vagus; mainly on SA & AV nodes
 - ✓ Less on atria almost none on ventricles
- Have **–ve: chronotropic & dromotropic** effect
- Have no **–ve: inotropic, bathmotropic or clinotropic** action
- ❖ Clinotropic: velocity of contraction & relaxation
- ❖ Bathmotropic: excitation of purkinje fibers

Organ System Effects of ANS

Organ	Sympathetic Activity		Parasympathetic Activity	
	Action ¹	Receptor ²	Action	Receptor ²
Eye				
Iris radial muscle	Contracts	α_1	—	—
Iris 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 ³	M ₃	—	—
Endothelium of vessels in heart, brain, viscera	—	—	Synthesizes and releases EDRF ⁴	M ₃ , M ₅ ⁵
Bronchiolar smooth muscle	Relaxes	β_2	Contracts	M ₃

Gastrointestinal tract					
Smooth muscle					
Walls	Relaxes	$\alpha_2, {}^6\beta_2$	Contracts	M_3	
Sphincters	Contracts	α_1	Relaxes	M_3	
Secretion	—	—	Increases	M_3	
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			—	—	
Eccrine	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	—	—	

Organ	Effect of Sympathetic Stimulation	Effect of Parasympathetic Stimulation
Eye		
Pupil	Dilated	Constricted
Ciliary muscle	Slight relaxation (far vision)	Constricted (near vision)
Glands	Vasoconstriction and slight secretion	Stimulation of copious secretion (containing many enzymes for enzyme-secreting glands)
Nasal		
Lacrimal		
Parotid		
Submandibular		
Gastric		
Pancreatic		
Sweat glands	Copious sweating (cholinergic)	Sweating on palms of hands
Apocrine glands	Thick, odoriferous secretion	None
Blood vessels	Most often constricted	Most often little or no effect
Heart		
Muscle	Increased rate Increased force of contraction	Slowed rate Decreased force of contraction (especially of atria)
Coronaries	Dilated (β_2); constricted (α)	Dilated
Lungs		
Bronchi	Dilated	Constricted
Blood vessels	Mildly constricted	? Dilated
Gut		
Lumen	Decreased peristalsis and tone	Increased peristalsis and tone
Sphincter	Increased tone (most times)	Relaxed (most times)
Liver	Glucose released	Slight glycogen synthesis
Gallbladder and bile ducts	Relaxed	Contracted

Kidney	Decreased urine output and increased renin secretion	None
Bladder Detrusor Trigone	Relaxed (slight) Contracted	Contracted Relaxed
Penis	Ejaculation	Erection
Systemic arterioles		
Abdominal viscera	Constricted	None
Muscle	Constricted (adrenergic α) Dilated (adrenergic β_2) Dilated (cholinergic)	None
Skin	Constricted	None
Blood		
Coagulation	Increased	None
Glucose	Increased	None
Lipids	Increased	None
Basal metabolism	Increased up to 100%	None
Adrenal medullary secretion	Increased	None
Mental activity	Increased	None
Piloerector muscles	Contracted	None
Skeletal muscle	Increased glycogenolysis Increased strength	None
Fat cells	Lipolysis	None

Drugs acting on Cholinergic System

- Cholinomimetics
 - Parasympathomimetics
- Cholinergic Blockers: anticholinergics
 - Parasympatholytics
 - Parasympathoplegics

Cholinergic Receptors

❑ Muscarinic receptors

- All are GPCRs: 3rd cytoplasmic loop coupled to G-proteins
- ✓ M₁: intramural ganglia, superficial epithelial cells & depolarization of autonomic & CNS neurons
- ✓ M₂: negative dromotropic & chronotropic on the heart
- ✓ M₃: secretion in parietal cells, stimulates smooth muscle contraction; sweat, bronchial & salivary secretions

Cholinergic Receptors

Receptor Type	Location	Coupled with	Mechanism
M ₁	Nerves, parietal cells	G _{q/11}	IP ₃ , DAG cascade
M ₂	Heart, nerves, smooth muscle	G _{i/o}	Inhibition of cAMP production, activation of K ⁺ channels
M ₃	Glands, endothelium, smooth muscle	G _{q/11}	IP ₃ , DAG cascade
M ₄	CNS	G _{i/o}	Inhibition of cAMP production
M ₅	CNS	G _{q/11}	IP ₃ , DAG cascade

Nicotinic (N_M and N_N) Receptor - (Ion channels)

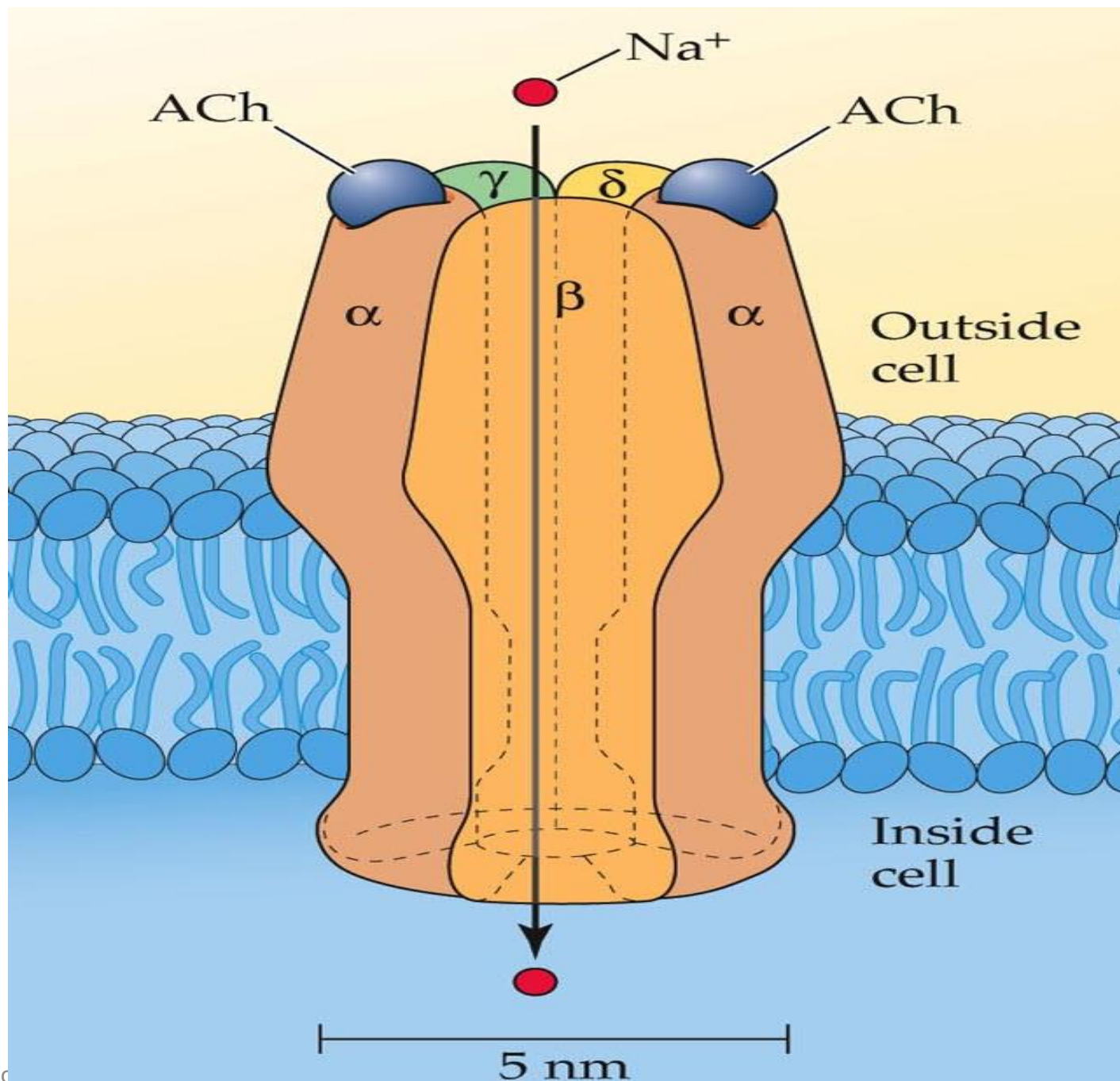
N_M (Muscle type)

- **Location:** Skeletal Muscle end plates
- **Function:** Stimulate skeletal muscle (contraction)
- **MOA:** Postsynaptic and Excitatory (increases Na^+ and K^+ permeability)
- **Agonists:** ACh, carbachol (CCh), suxamethonium
 - Selective stimulation by phenyl trimethyl ammonium (PTMA)
- **Antagonists:** tubocurarine, hexamethonium

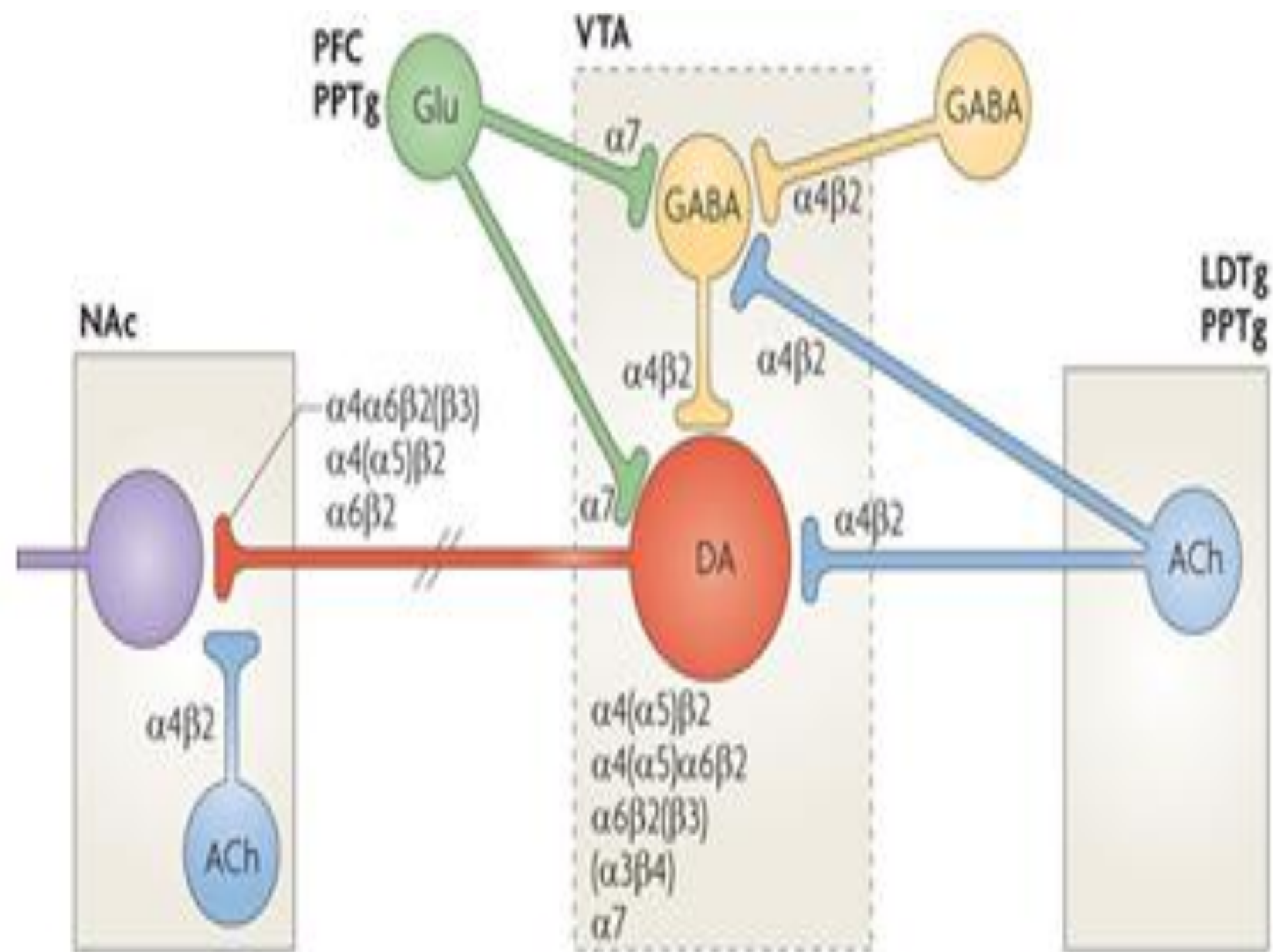
N_N (Ganglion type)

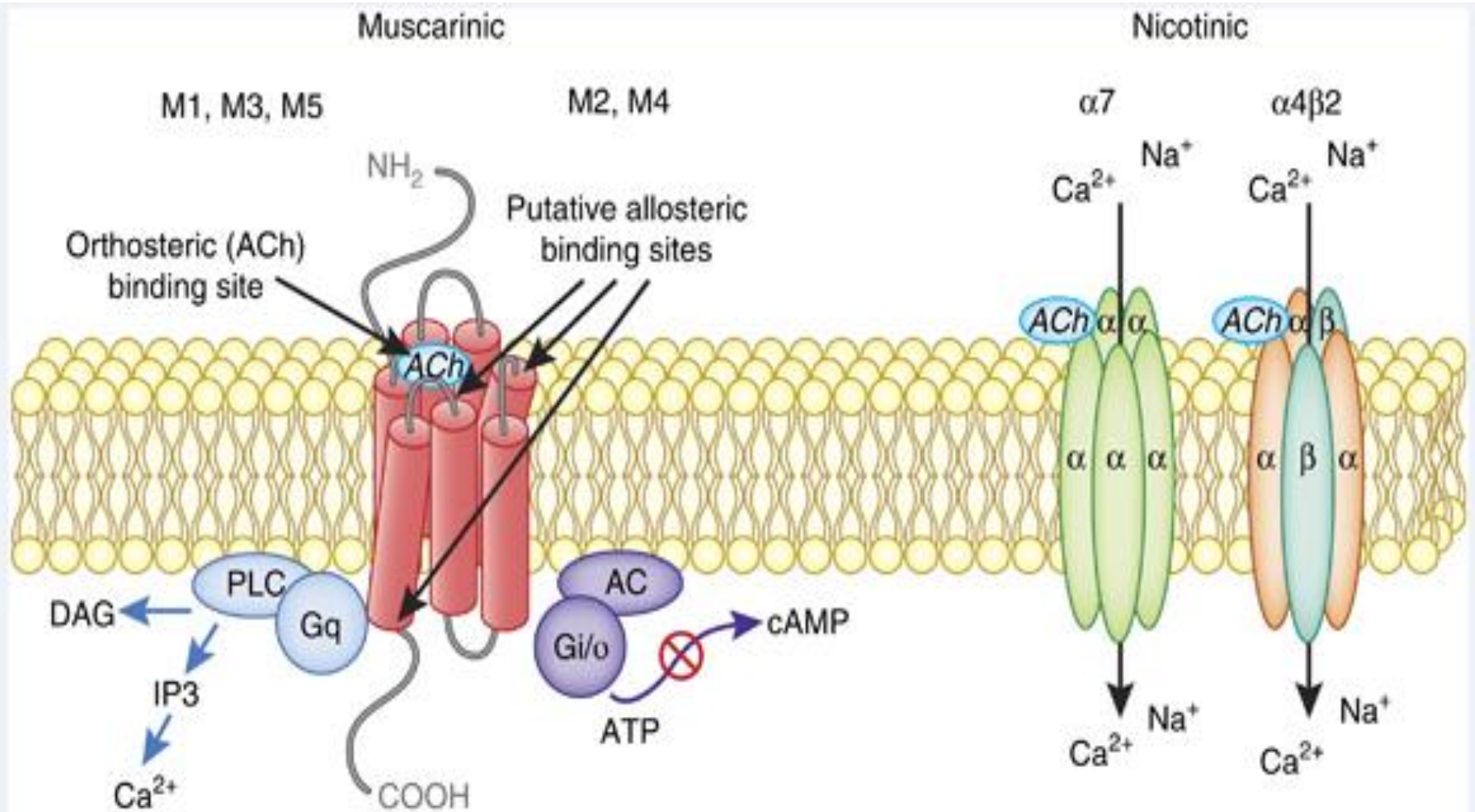
- **Location:** In autonomic ganglia of all type (ganglion type) – Sympathetic, Parasympathetic and also Adrenal Medulla
- **Function:** Depolarization and postganglionic impulse – stimulate all autonomic ganglia
- **MOA:** Excitatory – Na^+ , K^+ and Ca^{2+} channel opening
- **Agonists:** ACh, CCh, nicotine
 - Selectively stimulated by phenyl piperazinium (DMPP)
- **Antagonists:** mecamylamine, trimetaphan

Receptor Subtype	Main Synaptic Location	Membrane Response	Molecular Mechanism	Agonists	Antagonists
Skeletal Muscle (N_m) $(\alpha_1)_2\beta_1\epsilon\delta$: adult $(\alpha_1)_2\beta_1\gamma\delta$: fetal	Skeletal NMJ (postjunctional)	Excitatory; end-plate depolarization; skeletal muscle contraction	Increased cation permeability (Na^+ , K^+)	ACh Nicotine Succinylcholine	Atracurium Vecuronium d-Tubocurarine Pancuronium α -Conotoxin α -Bungarotoxin
Peripheral Neuronal (N_n) $(\alpha_3)_2(\beta_4)_3$	Autonomic ganglia; adrenal medulla	Excitatory; depolarization; firing of postganglion neuron; depolarization & secretion of catecholamines	Increased cation permeability (Na^+ , K^+)	ACh Nicotine Epibatidine Dimethylphenyl piperazinium	Trimethaphan Mecamylamine
Central Neuronal (CNS) $(\alpha_4)_2(\beta_4)_3$ $(\alpha$ -btox-insensitive) $(\alpha_7)_5$ (α -btox-sensitive)	CNS; pre-& postjunctional	Pre-& postsynaptic excitation Prejunctional control of transmitter release	Increased cation permeability (Na^+ , K^+)	Cytosine, epibatidine Anatoxin A	Mecamylamine Dihydro- β -erythrodine Erysodine Lophotoxin
			Increased permeability (Ca^{2+})	Anatoxin A	Methyllycaconitine α -Bungarotoxin α -Conotoxin ImI



- ✓ Activation of the receptor causes depolarization of the nerve cell or neuromuscular end plate membrane
- ✓ In skeletal muscle, the depolarization initiates an action potential that propagates across the muscle membrane & causes contraction
- ✓ Prolonged agonist occupancy: abolishes the effector response; 'depolarizing blockade'
- ❖ Postganglionic neuron stops firing: ganglionic effect
- ❖ Skeletal muscle relaxes: neuromuscular end plate effect





Key effectors (examples)

$\uparrow \text{PLC}\beta$
 $\uparrow [\text{Ca}^{2+}]_i$
 $\uparrow \text{MAPK}$

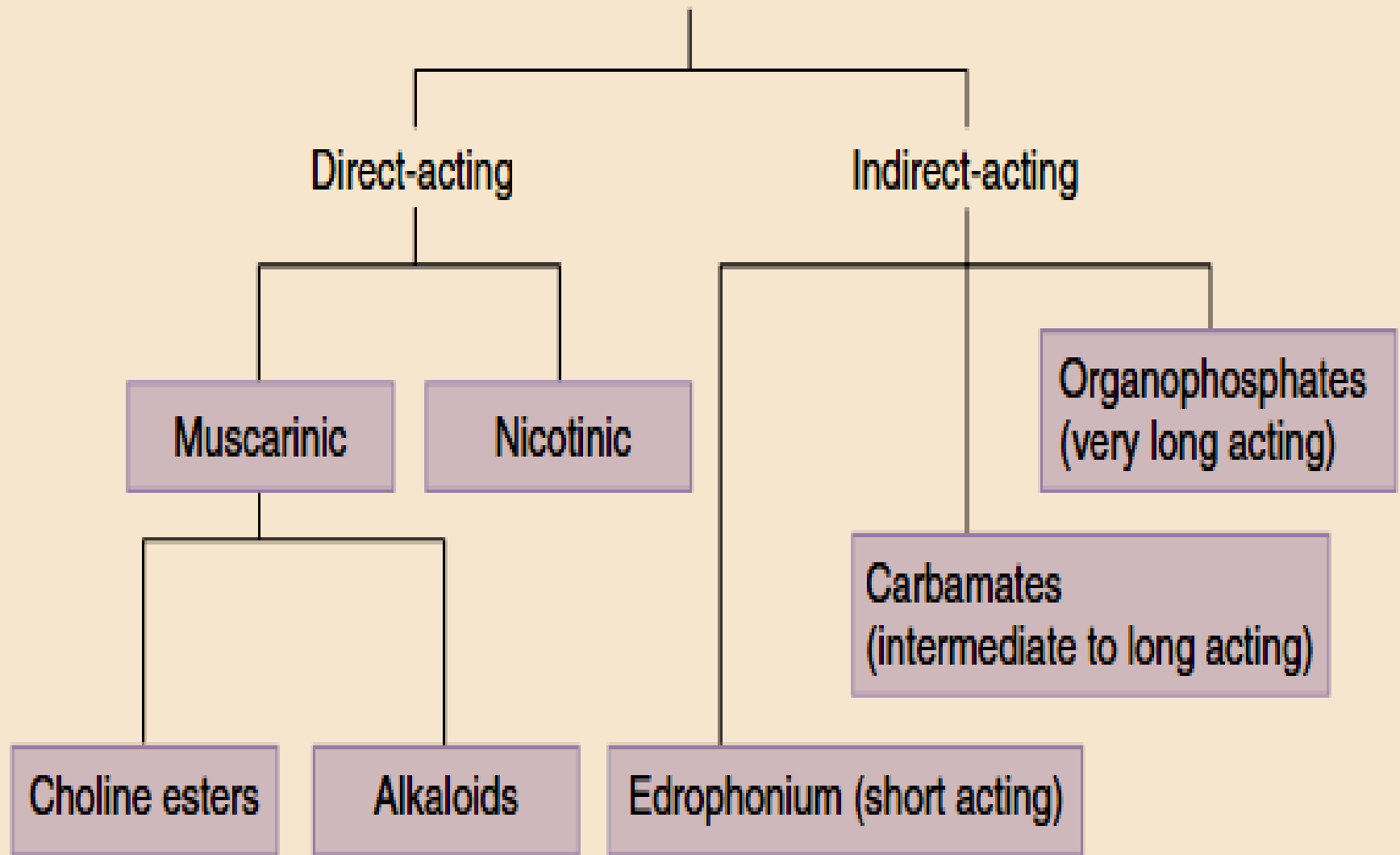
Key effectors (examples)

$\uparrow \text{AC}$
 $\uparrow \text{MAPK}$
 $\uparrow \text{GIRK ch.}$

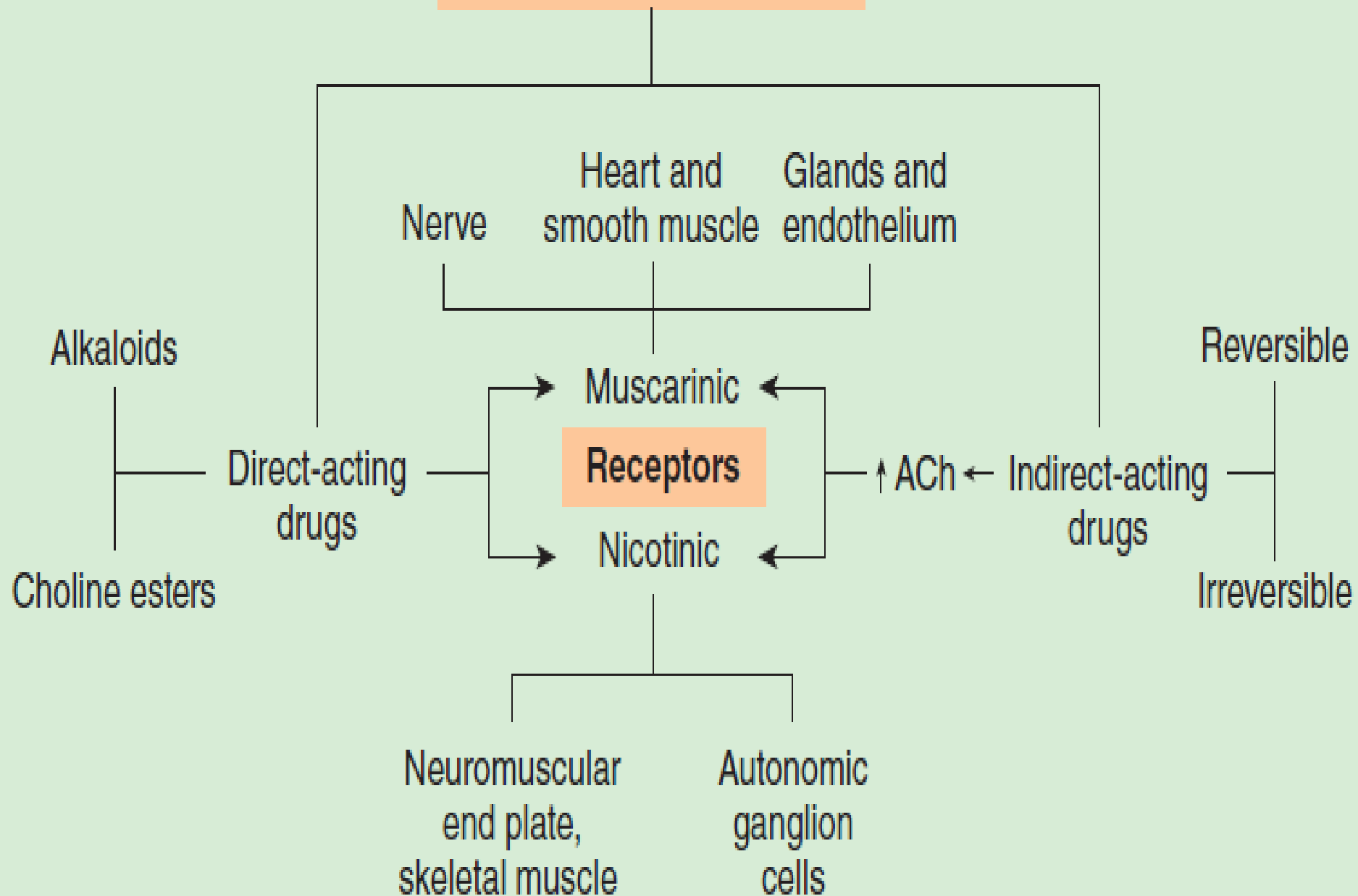
Key effectors (examples)

$\uparrow [\text{Ca}^{2+}]_i$
 $\uparrow \text{VDCC}$
 $\uparrow \text{PKC}$

Cholinomimetic (cholinergic) drugs



Cholinoceptor stimulants



Cholinomimetics

▪ Direct Acting:

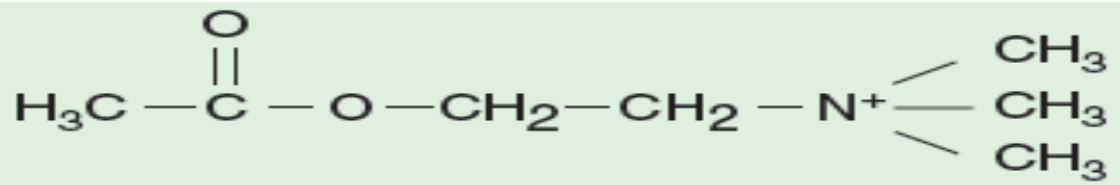
➤ Choline esters:

✓ Acetylcholine

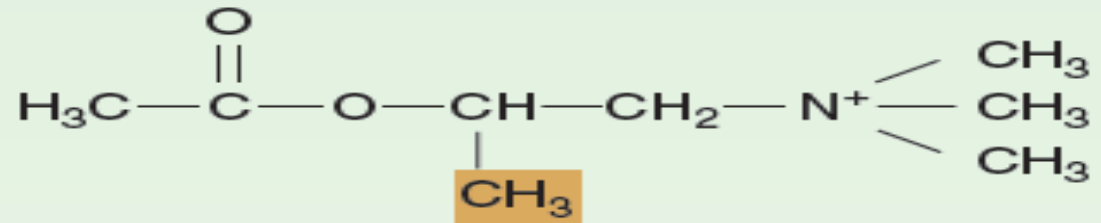
✓ Methacholine

✓ Carbachol

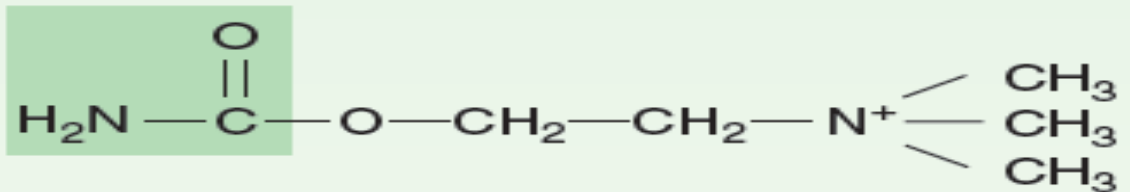
✓ Bethanechol



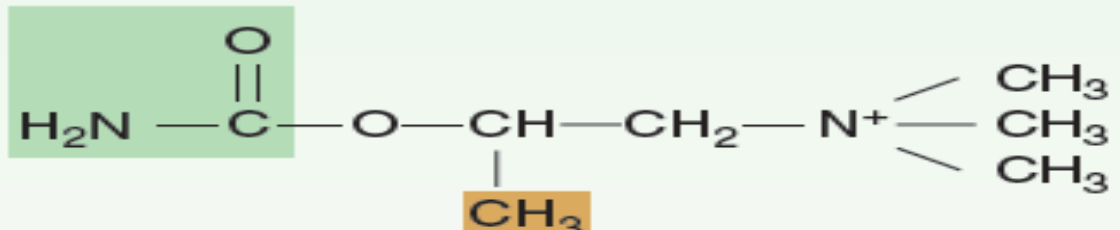
Acetylcholine



Methacholine
(acetyl-β-methylcholine)



Carbachol
(carbamoylcholine)



Bethanechol
(carbamoyl-β-methylcholine)

Cholinomimetic Alkaloids

■ Muscarinic agonists

✓ Natural alkaloids: Muscarine, Pilocarpine, Arecholine

✓ Synthetic alkaloid: Oxotramorine

■ Nicotinic agonists

✓ Natural alkaloids: Nicotine, Lobeline

✓ Synthetic alkaloids: Dimethylphenylpiperazinium(DMPP)

- **Indirectly acting:** anticholinesterases; amplifiers of Ach

- ✓ **Reversible**

- Carbamates

- ❖ Tertiary amines: Physostigmine

- ❖ Quaternary Ammonium compounds: Neostigmine,
Distigmine, Pyridostigmine, Ambenonium, Demecarium

- ❖ Alcohols: Edrophonium

- ❖ Miscellaneous: Tacrine, Donepezil, Galantamine,
Rivastigmine

- **Irreversible:** Organophosphorus compounds

- ✓ Therapeutically useful: Echothiophate

- ✓ Nerve gases: Sarin, Tabun, Soman

- Warfare & terrorism

- ✓ Insecticides:

- Parathion, Malathion, Diisopropyl Fluorophosphate: DFP,

- Tetramethyl Pyrophosphate: TMPP

- Octamethyl Pyrophosphotetraamide: OMPA

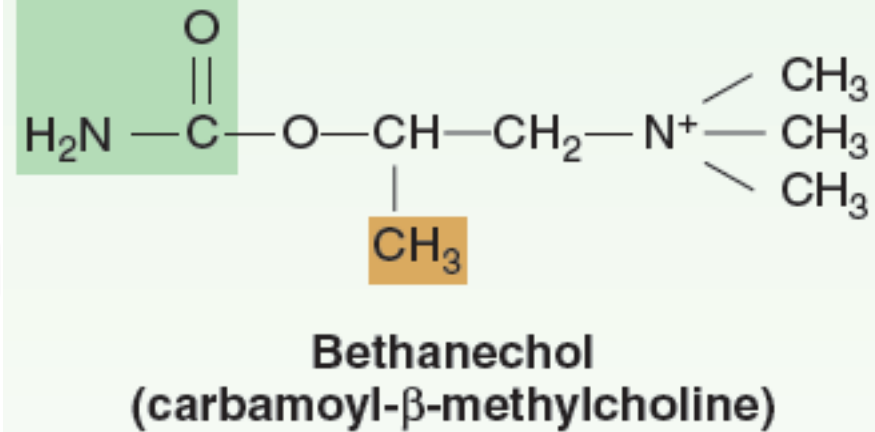
- **Acetylcholine:** not used as a drug!
- ✓ Lack of specificity for nAChRs or mAChRs
- ✓ **Ester & quaternary ammonium** salt functional groups
- **Parenterally:** hydrolysis by BChE in serum, $t_{1/2}$ - a fraction of a second
- **Orally:** rapid hydrolysis in the GIT
- ✓ Poorly absorbed: quaternary ammonium

- ✓ Choline esters: have quaternary ammonium group
- ✓ All are hydrolyzed in the GIT
- ✓ The tertiary natural cholinomimetic alkaloids (pilocarpine, nicotine, lobeline) well absorbed from most sites of adm.
- ✓ Muscarine: a quaternary amine is less completely absorbed from the GIT & too toxic
- ✓ Excretion mainly by the kidneys

Direct Cholinergic Agonists

- Differ from ACh;
- ✓ Have longer duration of action
- ✓ Effective orally & parenterally
- ✓ Relatively more selective but, still less potent than ACh

Bethanechol:



- ✓ Not hydrolyzed by AChE d carbamic acid
- ✓ Has strong muscarinic activity
- ✓ No or little nicotinic actions: β -methyl group
- ✓ Major actions: on the smooth muscle of bladder & GIT

■ **Uses:**

✓ **Urinary retention**

- 10-50 mg PO TID/QID
- Some patients may require doses of 50-100 mg PO BID
- Take 1 hour AC or 2 hours PC

✓ **GERD: off-label**

- 25 mg PO QID, take 1 hr AC or 2 hrs PC

Carbachol: Miostat^R

- ✓ Has both muscarinic & nicotinic actions
- ✓ A carbamate ester: more resistant toward acid-base or AChE-catalyzed hydrolysis → long DOA
- ✓ Has more pronounced effect in the GIT & CVS:
 - Stimulates & then depress b/c of ganglion stimulation activity

✓ Glaucoma

- 1-2 gtt instilled into conjunctival sac three times daily

✓ As a miotic during ocular surgery

- 0.5 mL instilled into the anterior chamber before or after securing sutures

✓ Dosage forms & strengths

- Intraocular solution: 0.01%

- Topical solution: 1.5% & 3%

Methacholine: Provocholine^R

- ✓ Metabolism: by AChE but @ a slower rate
- ✓ DOA: intermediate b/n ACh & Carbachol
- ✓ Acts on mAChRs, little on nAChRs; β -Me group
- ✓ Actions on CVS are more marked
- ✓ Use: Dx of asthma/bronchial hypersensitivity; inhalation
- ✓ S/E: bradycardia, hypotension

Properties of choline esters

Choline Ester	Susceptibility to Cholinesterase	Muscarinic Action	Nicotinic Action
Acetylcholine chloride	++++	+++	+++
Methacholine chloride	+	++++	None
Carbachol chloride	Negligible	++	+++
Bethanechol chloride	Negligible	++	None

Effects of direct-acting cholinceptor stimulants

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, veins	Dilation (via EDRF). Constriction (high-dose direct effect)

NO



Lung

Bronchial muscle	Contraction (bronchoconstriction)
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
--	-----------

Cholinomimetic alkaloids

- **Pilocarpine:** tablet: 5mg, 7.5mg

- Xerostomia: radiation-induced

- ❖ 5mg PO q8hr; may titrate up to 10mg PO q8hr; not to exceed 30 mg/day

- Xerostomia: Sjogren's syndrome associated

- ❖ 5 mg PO q6hr

- Onset: 20'

- Duration: 3-5 hr (single dose), >10hr (multiple dose)

- **Pilocarpine:** ophthalmic solution: 1%, 2%, 4%, gel: 4%
- ✓ Solution: 1-2 gtt up to q6hr; adjust conc. & frequency
- ✓ Gel: 0.5-inch ribbon in lower conjunctival sac of affected eye(s) qhs
- ✓ Onset: 10-30 min (miosis); 1hr (IOP)
- ✓ Duration: 4-8hr (miosis); 4-12hr (IOP)
- Counteract mydriatic effects of sympathomimetic agents
- (Off-label): solution; 1gtt of 1% solution in affected eye

- **Cevimeline:** capsule

- ✓ Synthetic: quinuclidine derivative of ACh

- ✓ M3-selective: lacrimal & salivary glands

- ❖ Increases salivation:

- ✓ Sjögren syndrome-associated xerostomia: 30mg PO q8hr

- Muscarine & Arecoline: not clinically used due to toxicity

- **Nicotine:** gum; 2mg, 4mg
- ✓ Rx: smoking cessation
- Weeks 1-6: 1 piece of gum q1-2hr; ches at least 9 pieces per day during the 1st 6 wks to ↑chances of quitting
- Weeks 7-9: 1 piece of gum q2-4hr
- Weeks 10-12: 1 piece of gum q4-8hr
- <25 cigarettes/day: initiate with 2 mg
- ≥25 cigarettes/day: initiate with 4 mg
- ❖ For strong/frequent craving: may use 2nd piece within 1hr

- **Varenicline:** tablet; 0.5 mg, 1 mg
- ✓ Selective partial agonist at $\alpha 4\beta 2$ nAChR
- ✓ Used exclusively for smoking cessation
- Set a date to stop smoking & begin Varenicline 1wk before this date OR
- The patient can begin Varenicline & then quit smoking b/n days 8 & 35 of treatment
- ❖ Quit smoking date regimen: refer

Pilocarpine



- ✓ Obtained from *Pilocarpus microphyllus* & *Pilocarpus japorandi*
- ✓ A tertiary amine hence, can cross the cornea of the eye & BBB easily
- ✓ Pure muscarinic agonist
- ✓ Compared with ACh & its derivatives, it is far less potent
- ✓ Not affected by cholinesterase

Pilocarpine...

- ➔ Actions: rapid miosis & accommodation for near vision
- ➔ Therapeutic use: Rx of glaucoma
- ✓ DOC in the emergency lowering of IOP (glaucoma) as a result of ↑drainage of aqueous humor
- ➔ ADE: enters brain & cause CNS disturbances, sweating & salivation
- ➔ Action lasts up to 1 day
- ➔ Available as 0.5-4% eye drops

Indirect Cholinergic Agonists

- Classified in to three chemical groups:
 - ✓ Simple alcohols bearing a quaternary ammonium group:
edrophonium
 - ✓ Carbamic acid esters of alcohols having quaternary or tertiary ammonium groups (carbamates: neostigmine)
 - ✓ Organic derivatives of phosphoric acid (organophosphates: echothiophate)

■ **MOA:**

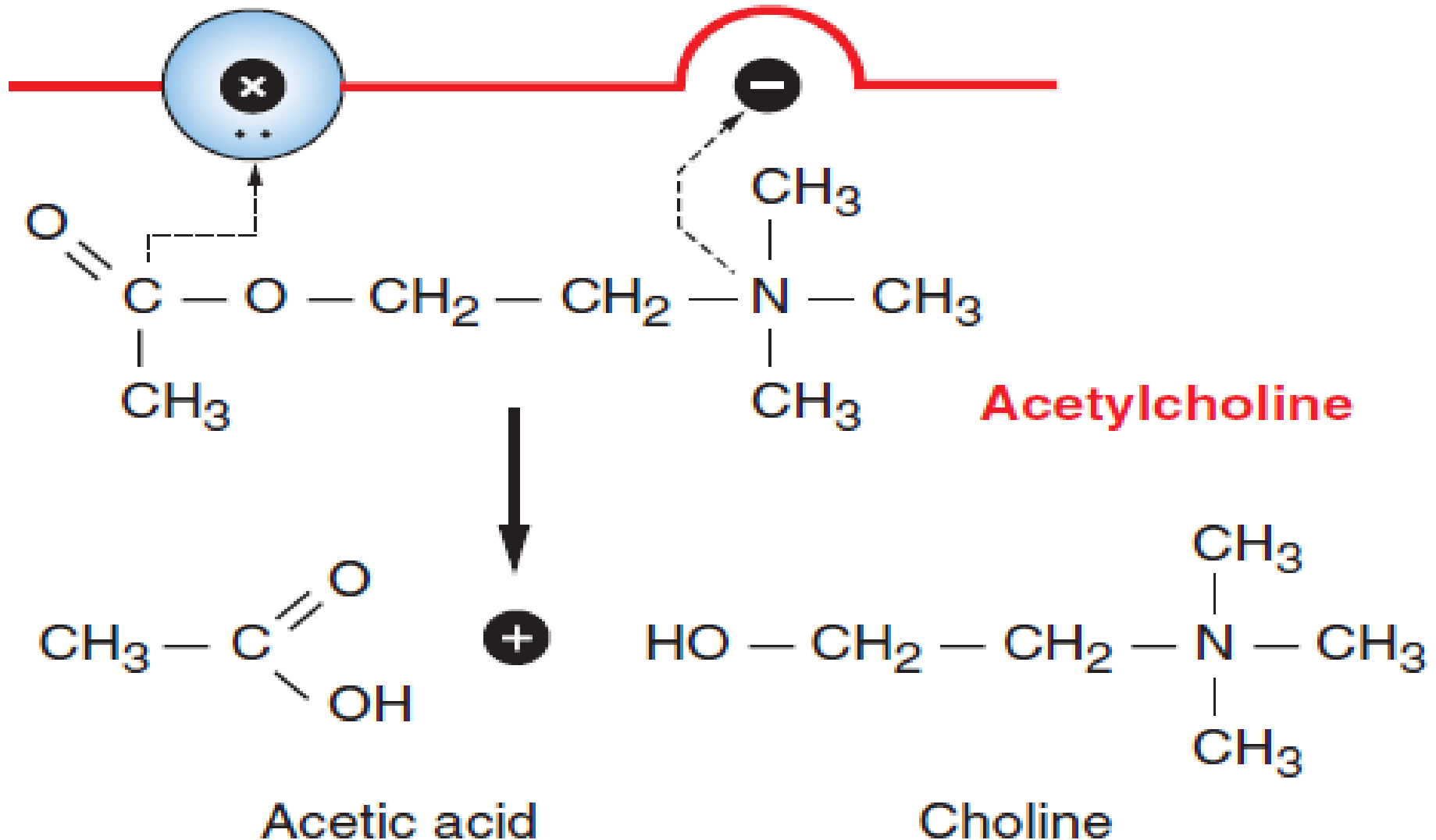
- ✓ Inhibit AChE: protect ACh from hydrolysis
- Results in accumulation of ACh in the synaptic cleft
- Provoke response at all cholinergic receptors: mAChRs & nAChRs of ANS, NMJ & brain
- ✓ ACh interacts with AChE at two sites: the N^+ of choline (ionic bond) binds to the anionic site & the acetyl ester binds to the esteratic site (serine residue)

- ✓ As ACh is hydrolyzed, the serine-OH side chain is acetylated & free choline is released
- ✓ Acetyl-serine is hydrolyzed to serine & acetate: this hydrolysis takes a half life of 100-150 microseconds

Acetylcholinesterase

Esteratic
site

Anionic
site



▪ **Quaternary Alcohols: Edrophonium**

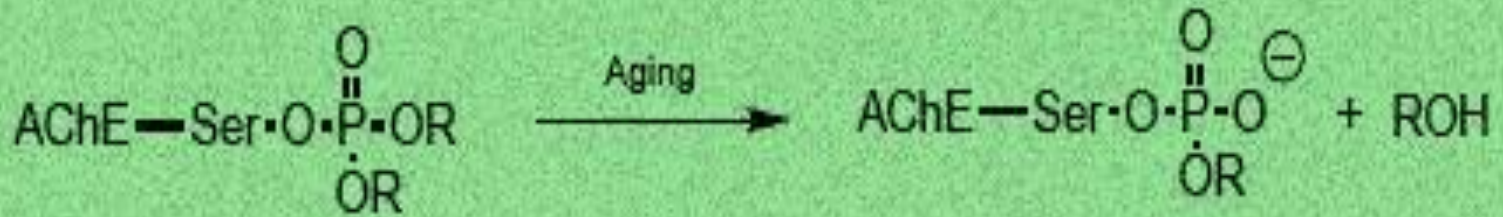
- ✓ Reversible binding: electrostatic & H-bonds to the active site, thus preventing access of ACh
- Enzyme-inhibitor complex short-lived: 2-10 minutes

▪ **Carbamate Esters: Neostigmine & Physostigmine**

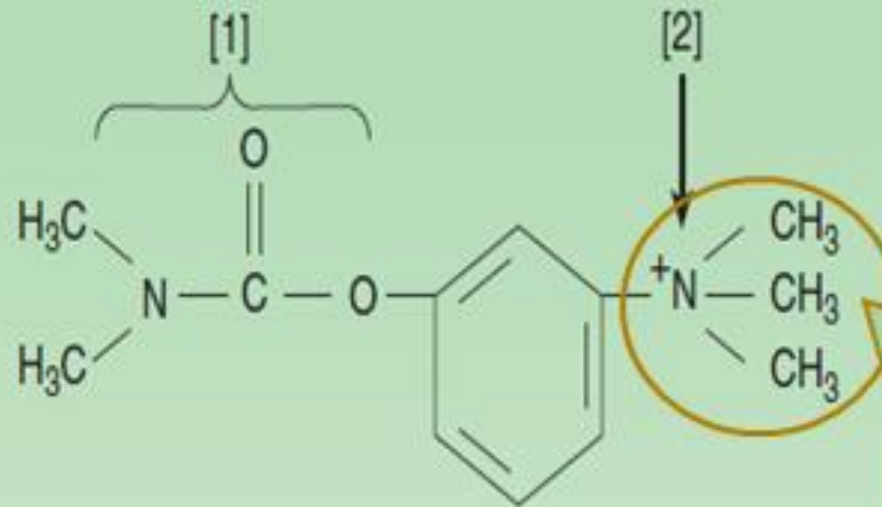
- ✓ Undergo a two-step hydrolysis as ACh
- Covalent binding: carbomylated enzyme
- Resistant to hydration: prolonged (1/2 - 6 hrs)

■ Organic

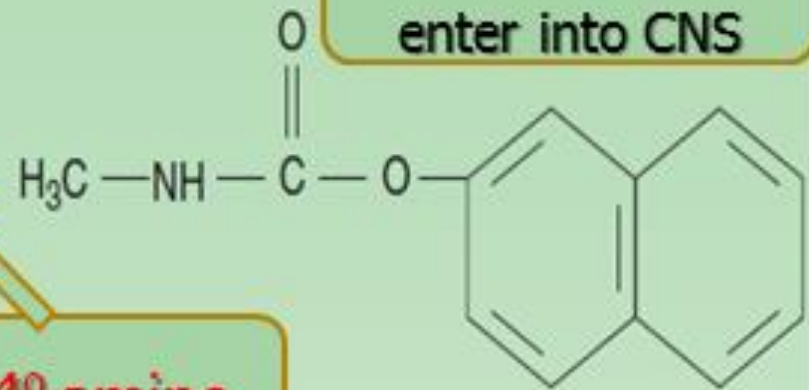
✓ Covalent



- ✓ Phosphorylated enzyme: extremely stable & hydrolyzes in water at a very slow rate (hundreds of hours)
- ✓ Phosphorylated enzyme => aging
 - Involves the breaking of one of the oxygen-phosphorus bonds of the inhibitor & further strengthens the phosphorus-enzyme bond: 10' for Soman, 48 hrs: VX



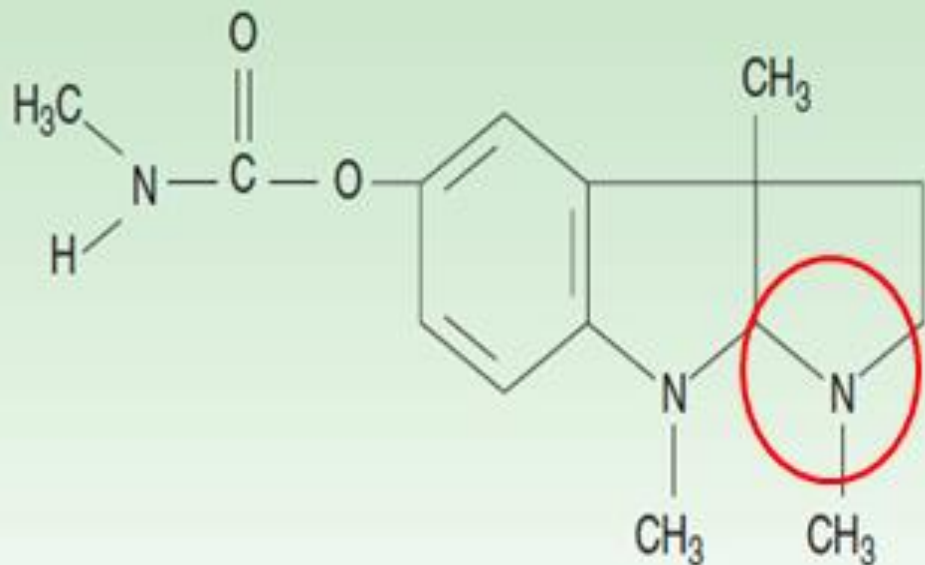
Neostigmine



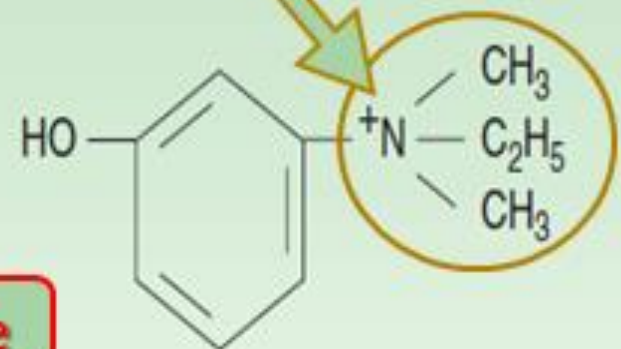
Highly lipophilic:
enter into CNS

4⁰ amine

Carbaryl



Physostigmine



Edrophonium

3⁰ amine

Physostigmine

- ✓ A carbamic acid ester found naturally in plants
- ✓ A tertiary amine: more lipophilic
- ✓ Can diffuse across the BBB
- ✓ Inhibits AChE by acting as a substrate & carbamylating the enzyme
- ✓ AChE is carbamylated at a slow rate, but physostigmine has exceptionally high affinity for the catalytic site of the enzyme

Additional actions:

- ✓ Neostigmine, physostigmine & demecarium also have direct agonist action at skeletal muscle nAChRs
- ✓ Duration of action: 2-4 hours

👉 Therapeutic use:

- ✓ ↑intestinal & bladder motility (in atony of either organ)
- ✓ For the Rx of glaucoma: Pilocarpine is more effective
- ✓ Rx of overdose of anticholinergic drugs: atropine, phenothiazine & TCAs

👉 Adverse effects:

- ✓ Effect on CNS may lead to convulsions with high doses
- ✓ Bradycardia and fall in CO
- ✓ Paralysis of skeletal muscle (rare with therapeutic doses)

Neostigmine: Prostigmin

- ✓ A quaternary amine: more polar
- Absorbed poorly from GIT
- Does not enter to CNS
- ✓ It's effect on skeletal muscle is > that of physostigmine
- ✓ Directly stimulates nAChR at the motor end plate

Pyridostigmine & Ambenonium

- ✓ Lack CNS activity: quaternary amines
- ✓ Similar to neostigmine but slower onset & longer DOA
- ✓ Used in the **chronic** management of myasthenia gravis
- ✓ Duration of action 3-6 hours

Edrophonium

- ✓ Similar to neostigmine except;
- It is more rapidly absorbed & has a short duration of action of 10-20 minutes (prototype short-acting agent)
- ✓ A quaternary amine & for the Dx of myasthenia gravis
- ✓ Used to differentiate myasthenia gravis from cholinergic crisis
- ✓ Excess drug may provoke cholinergic crisis
- ✓ Antidote = Atropine

Tacrine, Donepezil, Rivastigmine & Galantamine

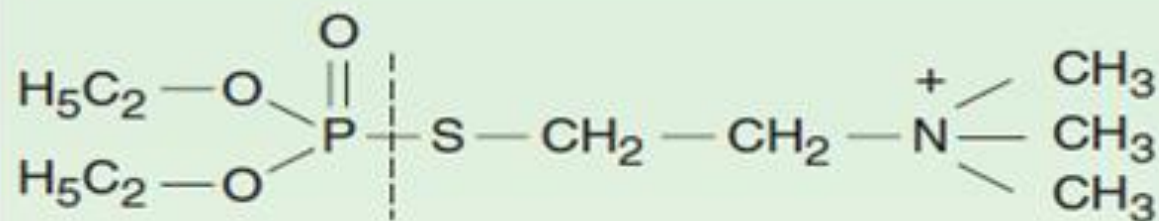
- ✓ For Alzheimer's disease
- ✓ Neuropathology: NFTs, amyloid plaques & loss of ACh neurons in meynert's nucleus => cognitive dysfunction
- Tacrine is hepatotoxic & replaced by;
- Donepezil: QD- long $t_{1/2}$
- Galantamine & Rivastigmine

Irreversible Anticholinesterases

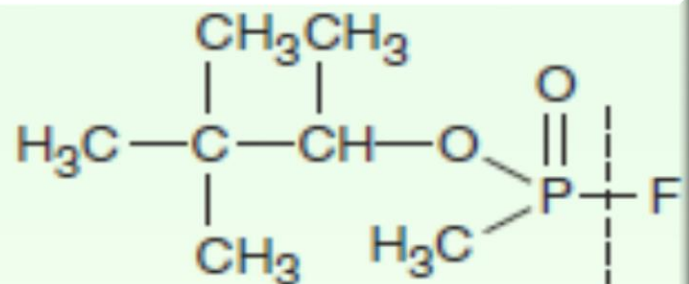
- ☞ They form phosphate esters with the enzyme
- ☞ Bind covalently to AChE which is extremely stable
- ☞ Leads to long lasting ↑ in ACh action
- ☞ The rate of hydrolysis of the phosphorylated enzyme is much slower (hrs) than that of the carbamylated enzyme

Organophosphates

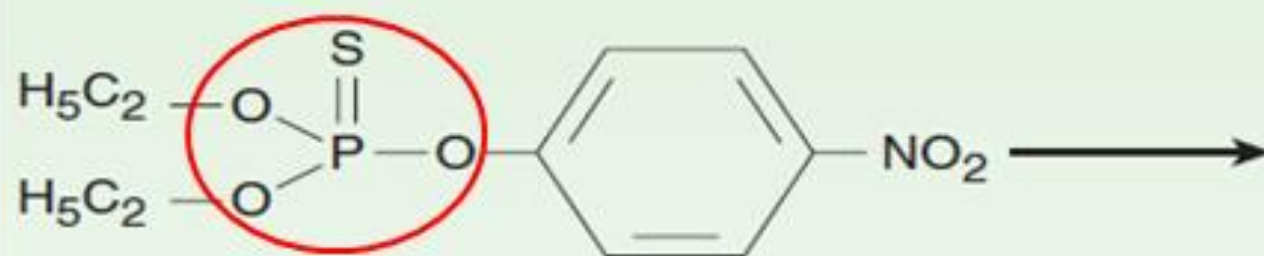
- ✓ Highly lipid-soluble liquids, except echothiophate (polar)
- ✓ Relatively less stable than the carbamates when dissolved in water & thus have a limited $t_{1/2}$ in the env't
- ✓ Echothiophate is highly polar & more stable than others
- ✓ When prepared in aqueous solution for ophthalmic use, it retains activity for weeks: longer DOA
- ✓ Thiophosphate insecticides (parathion, malathion...) are quite lipid-soluble & are rapidly absorbed by all routes
- ✓ CNS toxicity except echothiophate



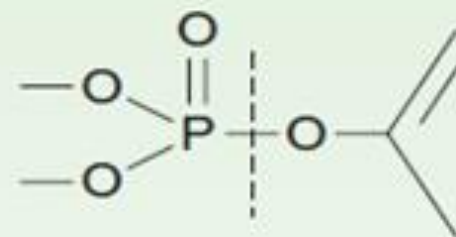
Echothiophate



Soman

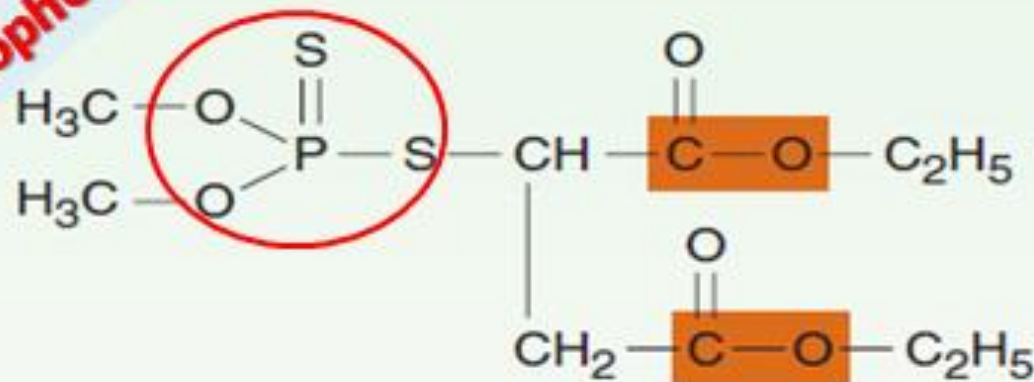


Parathion

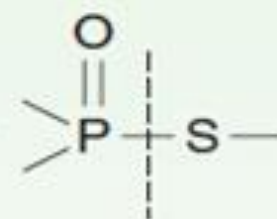


Paraoxon

Thiophosphates

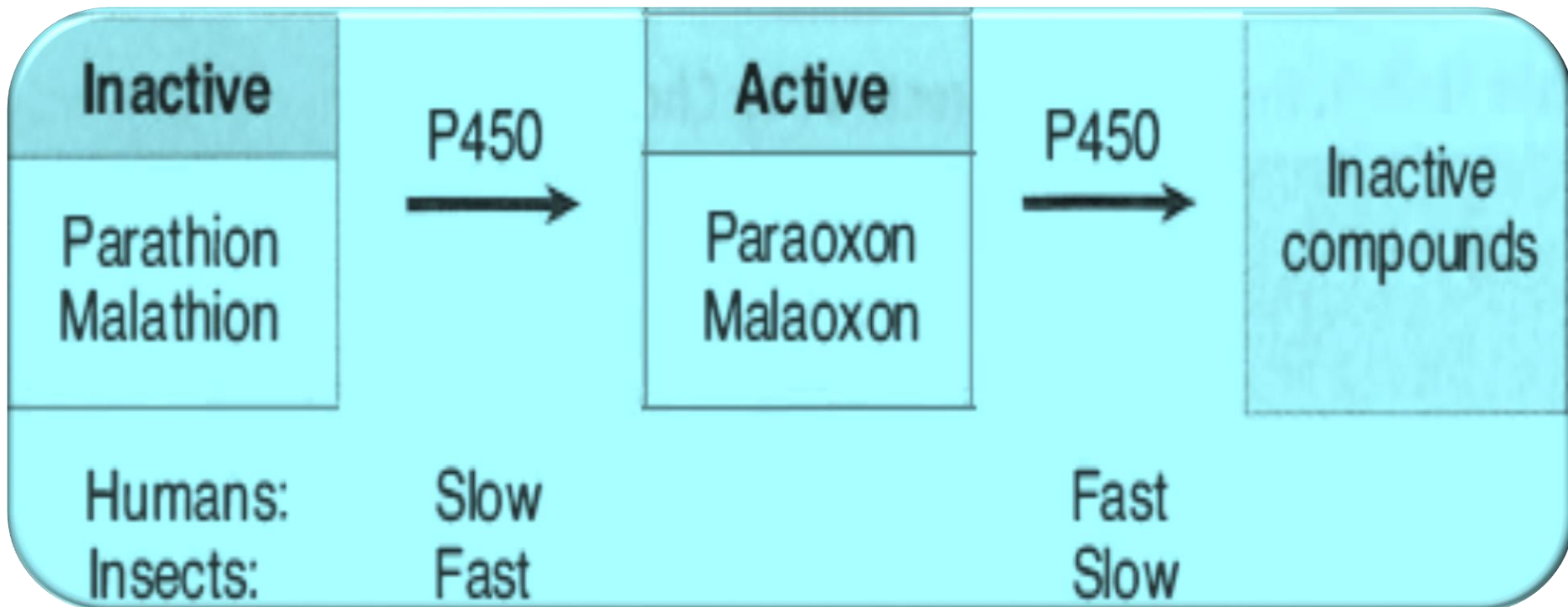


Malathion



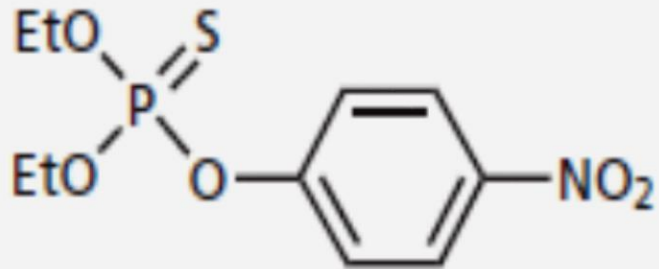
Malaoxon

- Insecticidal AChEIs: extremely lipophilic & have high vapor pressure



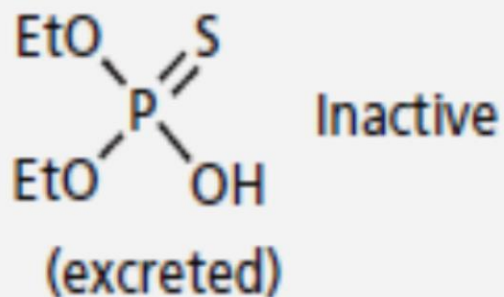
- ✓ Selectivity towards insects
- ✓ Parathion- not detoxified effectively- dangerous

Mammals



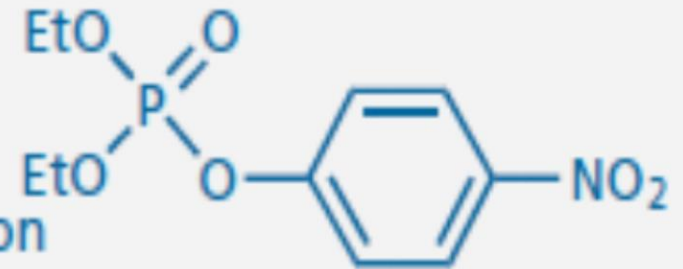
Parathion
(inactive prodrug)

Mammalian
metabolism



Insects

Insect
oxidative
desulphurization



Active drug

Phosphorylates enzyme

Death

Irreversible anticholinesterases ...

■ Effects:

- ♠ Initially: miosis, salivation, sweating, vomiting, diarrhea and bronchial constriction, followed by involvement of nervous systems
- ♠ Cause persistent depolarization of muscle end plates resulting in blockade of neuromuscular transmission + weakness and paralysis
- ♠ Respiratory paralysis (central as well as peripheral)
- ♠ Death is generally due to respiratory failure

Classic Clue

**AChE inhibitor poisoning:
“Dumbbeelss”**

Diarrhea

Urination

Miosis

Bradycardia

Bronchoconstriction

Emesis

Excitation (CNS/muscle)

Lacrimation

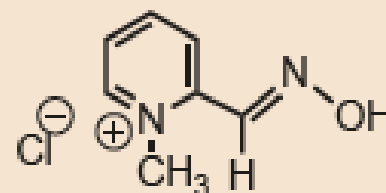
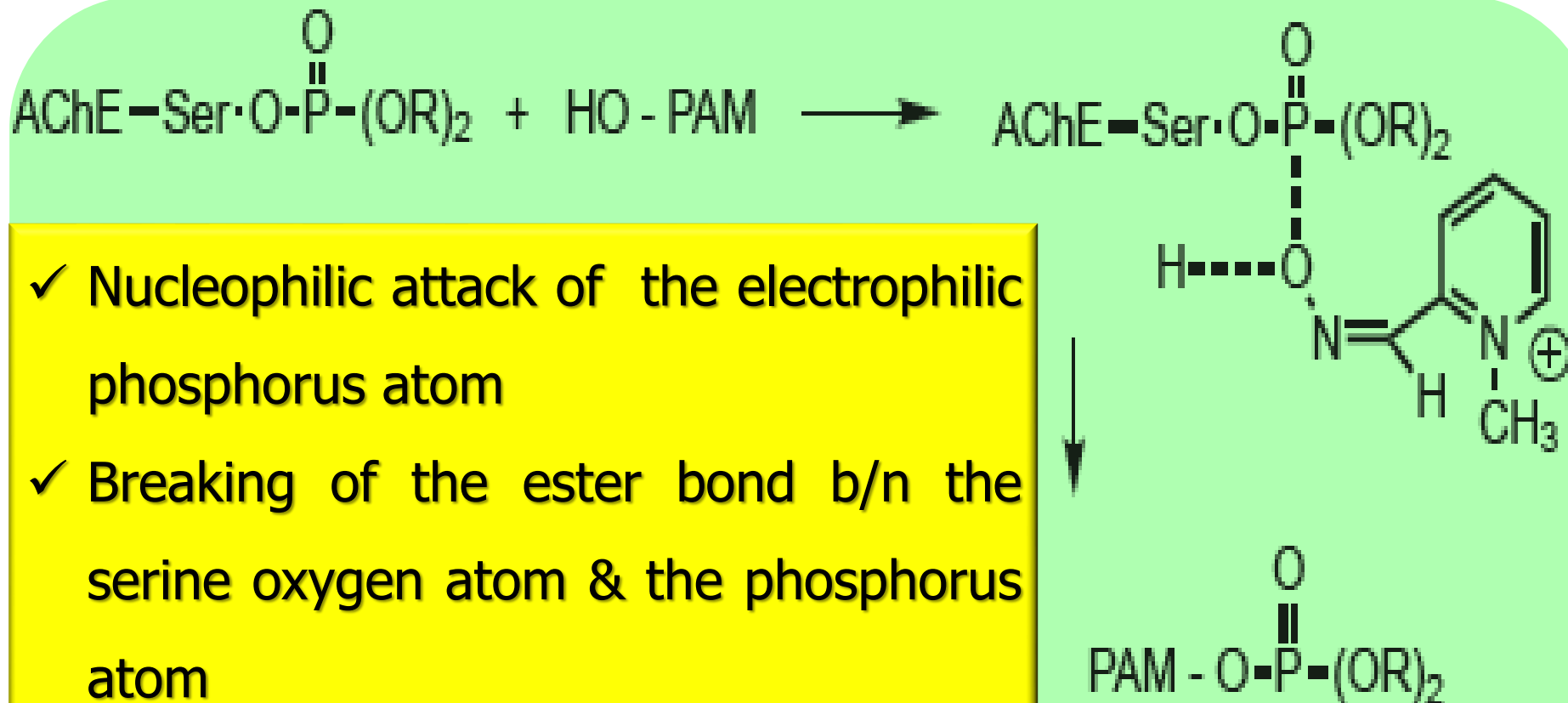
Salivation

Sweating

Treatment

- ✓ Maintenance of respiration
- ✓ **Atropine** parenterally in large doses
- ✓ Pralidoxime chloride (2-PAM, or 2-pyridine aldoxime methyl chloride) effective as an antidote for poisoning by phosphate ester AChEIs

Reactivation of AChE with 2-PAM



Pralidoxime chloride (2-PAM)

Pralidoxime: IV,IM,SC

- ✓ Must be given within a short period of time after enzyme phosphorylation
- ✓ Little rxn is likely if given 36 hours after exposure
- ✓ Unable to penetrate into the CNS, not useful in treating the CNS effects of organophosphates
- ✓ Pro-2-PAM is a prodrug of pralidoxime which avoids this problem
- ✓ As a tertiary amine it can pass through the BBB and is oxidized to pralidoxime once it has entered the CNS

Clinical Use of Cholinomimetics

■ Glaucoma:

- ✓ Muscarinic stimulants: pilocarpine
- ✓ ChEIs: Physostigmine, echothiophate
- Decrease intraocular pressure by;
 - Contraction of the ciliary body => outflow of aq. humor &
 - Diminishing the rate of aqueous humor secretion
- ❖ Pilocarpine DOC in the emergency lowering of IOP

➡ Action lasts up to 1 day

➡ Available as 0.5-4% eye drops

✓ ADE: CNS disturbances, sweating & salivation

✓ Replaced by prostaglandin derivatives & topical β blockers

- **Accommodative esotropia:**

- ✓ Strabismus caused by hypermetropic accommodative error in young children
- Dx & Rx: cholinomimetics (pilocarpine)
- Dosage is similar to or higher than for glaucoma

- Postoperative ileus/ paralytic ileus
- ✓ Atony or paralysis of the stomach or bowel following surgical manipulation
- Bethanechol: 10-25 mg PO TID/QID
- ❖ Cholinergic crisis if it is given IV or IM
- Neostigmine: 0.5-1 mg SC or 15 mg PO

- Congenital megacolon
- Atony of the bladder:
 - Bethanechol: 5 mg SC repeated in 30'
 - Neostigmine: 0.5-1 mg SC or 15 mg PO

■ Dry mouth:

- ✓ Pilocarpine used to increase salivary secretion
- ✓ Cevimeline, a quinuclidine derivative of ACh, is a new direct-acting muscarinic agonist used for the treatment of dry mouth associated with Sjögren's syndrome and that caused by radiation damage of the salivary glands

■ Myasthenia gravis:

- ✓ Antibodies are produced against the main immunogenic region found on $\alpha 1$ subunits of the nicotinic receptor-channel complex
- ✓ Antibodies are detected in 85% of myasthenic patients
- ✓ The antibodies reduce nicotinic receptor function by;

- Cross-linking receptors: stimulates their internalization & degradation;
- Causing lysis of the postsynaptic membrane;
- Binding to the nicotinic receptor & inhibiting function
- ✓ **Rx:** Pyridostigmine or Neostigmine
- Duration of action 2-4 hours
- ✓ **Dx:** Edrophonium 2 mg IV, if no rxn after 45 sec.
additional 8 mg may be injected

- Reversal of pharmacologic paralysis after surgery:
- ✓ Neuromuscular blockage as adjunct to surgical anesthesia (e.g. pancuronium) is reversed by;
- Neostigmine & Edrophonium: given IV/IM
- Snake venoms: curare like effect
- ✓ Rx: Neostigmine nasal spray to prevent respiratory arrest
- Antimuscarinic drug poisoning: atropine, TCA over dose
- ✓ Rx: Physostigmine, b/c can cross BBB

- Treatment of Alzheimer's disease:
 - ✓ Neuropathology: NFTs, amyloid plaques & loss of ACh neurons in meynert's nucleus => cognitive dysfunction
 - ✓ Donepezil (qd, long $t_{1/2}$), Galantamine, Rivastigmine
 - ✓ Tacrine: hepatotoxic, replaced by the above drugs

■ Side effects:

✓ Sweating

✓ Salivation

✓ Flushing

✓ ↓BP

✓ Abdominal pain, nausea, diarrhea

✓ Bronchospasm

Properties of Indirect-acting Cholinomimetics

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

Group, Drug	Uses	Approximate Duration of Action
Alcohols		
Edrophonium	Myasthenia gravis, ileus, arrhythmias	5–15 minutes
Carbamates and related agents		
Neostigmine	Myasthenia gravis, ileus	0.5–4 hours
Pyridostigmine	Myasthenia gravis	4–6 hours
Physostigmine	Glaucoma	0.5–2 hours
Organophosphates		
Echothiophate	Glaucoma	100 hours

Cholinergic antagonists: Parasympatholytics

- Cholinergic blockers or anti-cholinergic drugs
- Bind to cholinceptors but do not trigger the usual receptor mediated intracellular effects
- Anti-muscarinic agents
- Anti-nicotinic agents:
 - ❖ Ganglionic blockers
 - ❖ Neuromuscular blocking drugs

AUTONOMIC

SOMATIC

Sympathetic innervation
of adrenal medulla

Sympathetic

Parasympathetic

No ganglia

Preganglionic
neuron

Ganglionic
transmitter

Acetylcholine

Acetylcholine

Acetylcholine

Nicotinic
receptor

Nicotinic
receptor

Nicotinic
receptor

Sites of action
of ganglionic
blockers

Adrenal medulla

Postganglionic
neurons

Neuroeffector
transmitter

Epinephrine and
norepinephrine
released into the blood

Norepinephrine

Acetylcholine

Site of
action
of neuro-
muscular
blockers

Acetylcholine

Adrenergic
receptor

Adrenergic
receptor

Muscarinic
receptor

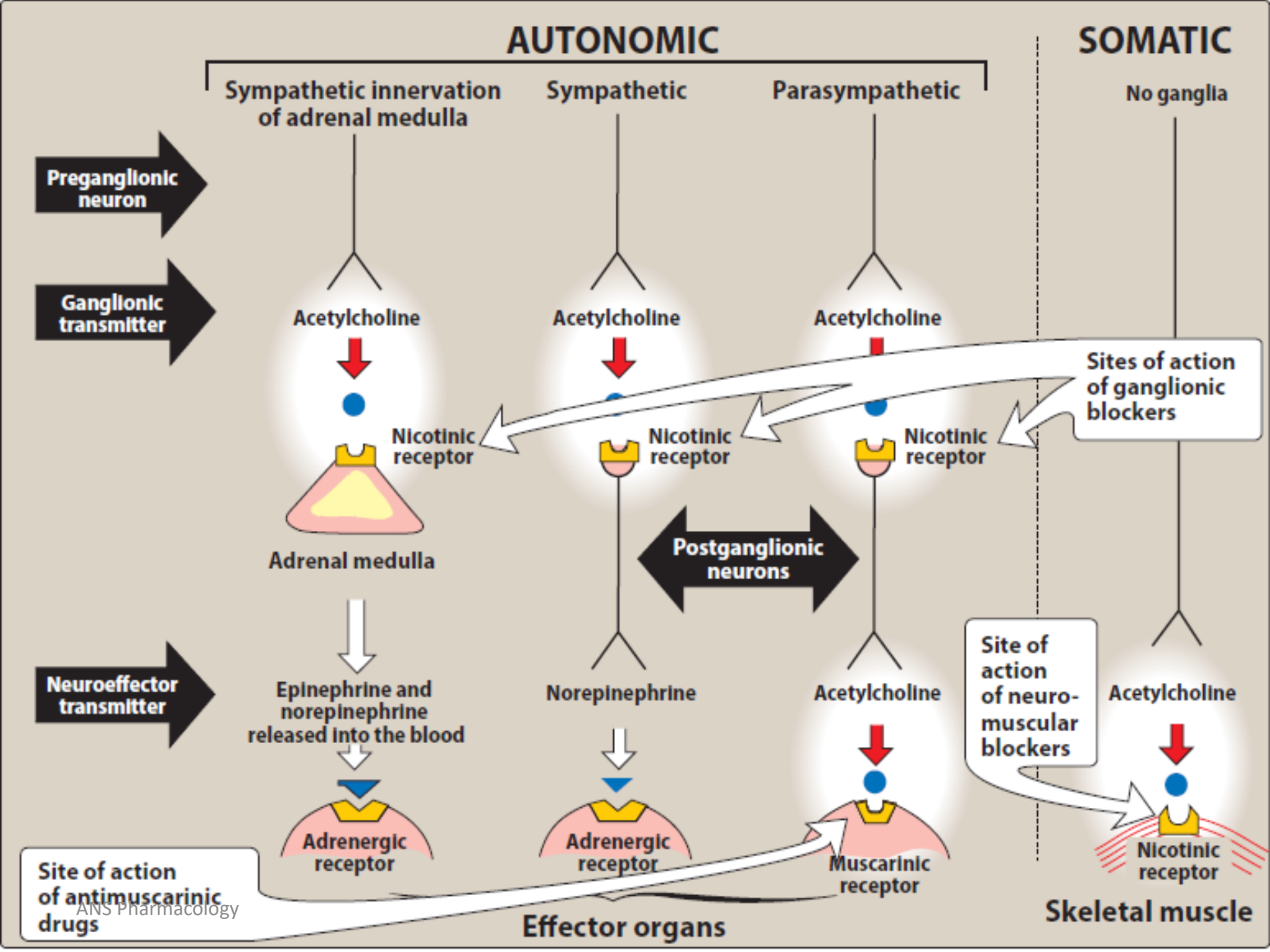
Nicotinic
receptor

Site of action
of antimuscarinic
drugs

Effector organs

Skeletal muscle

ANS Pharmacology



Antimuscarinic agents

- ✓ Block mAChRs but do not block nAChRs
- No action at skeletal NMJ or autonomic ganglia
- **Classification:**
 - ✓ **Natural alkaloids:** atropine, hyoscine (scopolamine)
 - ✓ **Semi-synthetics:** homatropine, atropine methonitrate, hyoscine butyl bromide, ipratropium bromide, tiotropium bromide
 - ✓ **Synthetics:** cyclopentolate, tropicamide, pirenzepine, telenzepine, biperiden, benztropine

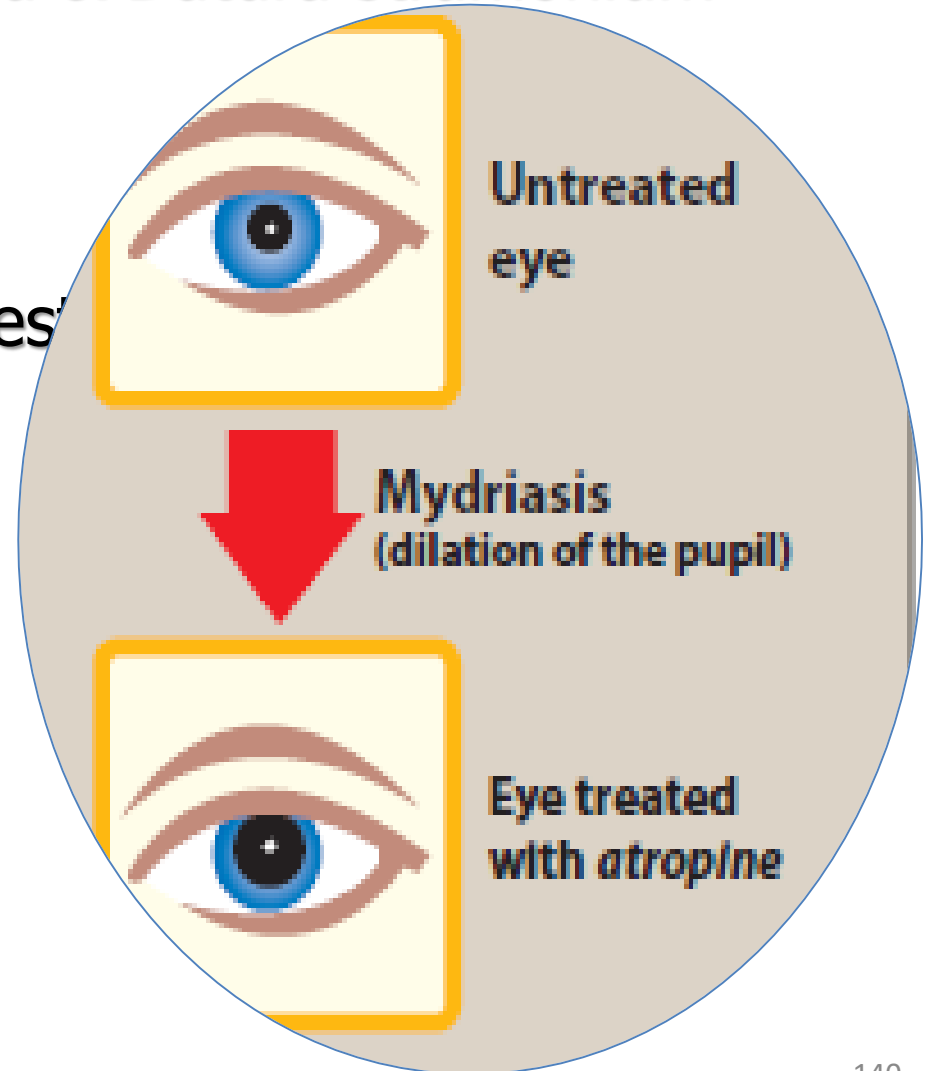
Atropine/hyoscyamine: prototype

✓ Source: *Atropa belladonna* & *Datura stramonium*

✓ High affinity for mAChRs

✓ A tertiary amine alkaloid ester

CNS



Actions of Atropine

- **Eye:**
 - ✓ Persistent mydriasis: dilation of the pupil
 - ✓ Cycloplegia: inability to focus for near vision
 - ✓ Raise in IOP: C/I in glaucoma
- **GI:** antispasmodic; reduce activity of GIT
- **Urinary system:** reduce hypermotility of the urinary bladder

■ CVS:

- ✓ At low dose decrease heart rate (bradycardia)
- Blockade of the M1 presynaptic receptors
- ✓ At high-dose increase heart rate (tachycardia)
- Blocking the M2 at SA node & AV node

■ Secretions:

- ✓ Block salivary glands (dry mouth, xerostomia) & sweat glands

Atropine effects in order of increasing dose:

- ✓ Decreased secretions (salivary, bronchiolar, sweat)
- ✓ Mydriasis & cycloplegia
- ✓ Hyperthermia (with resulting vasodilation)
- ✓ Tachycardia
- ✓ Sedation
- ✓ Urinary retention and constipation
- ✓ Behavioral: excitation and hallucinations

PK of Atropine

- ✓ Relatively lipid soluble & readily crosses membrane barriers (tertiary amine)
- ✓ Well distributed into the CNS and other organs
- ✓ Eliminated partially by metabolism in the liver and partially by renal excretion
- ✓ The elimination half-life is approximately 2 h
- ✓ DOA is 4-8 h except in the eye, where effects last for 72 h or longer

Therapeutic uses of atropine

- ✓ **Ophthalmic:** for Dx (measurement of refractive errors)
- ✓ **Antispasmodic agent:** to relax GIT and urinary bladder
- ✓ **As antidote** for cholinergic agonists
- Over dose of organophosphates & some type of mushroom poisoning
- ✓ **Anti-secretory agent:** to block secretion in the upper and lower respiratory tracts prior to surgery
- ✓ **Cardiovascular:** the drug is used to treat bradycardia of varying etiologies

Adverse Effects

- ✓ Dry mouth
- ✓ Blurred vision
- ✓ Tachycardia
- ✓ Constipation...

Tropicamide & Cyclopentolate

- ✓ Used as ophthalmic solutions for mydriasis & cycloplegia
- ✓ Their duration of action is shorter than that of atropine
 - Atropine: 5-6 days,
 - Scopolamine: 3-7 days,
 - Homatropine: 12-24 hours,
 - Cyclopentolate: 3-6 hours,
 - Tropicamide: 15-60 min

Benztropine & Trihexyphenidyl

- ✓ Adjunct with other antiparkinsonian agents to treat
 - Parkinson's disease &
 - Parkinsonian syndromes: antipsychotic induced extrapyramidal symptoms

Hyoscine (Scopolamine)

- ✓ An alkaloid obtained from *Hyoscyamus niger*
- ✓ Scopolamine is L-hyoscine (more active than D-hyoscine)
- ✓ Produces peripheral effects similar to those of atropine
- ✓ Has greater action on the CNS: tertiary amine
- ✓ Unlike atropine, CNS effects are observed at therapeutic doses
- ✓ Longer duration of action in comparison to atropine

■ Therapeutic use:

- ✓ Anti motion sickness agent, antispasmodic
- Much more effective prophylactically than for treating motion sickness once it occurs
- ❖ It also has the unusual effect of blocking short-term memory

Scopolamine...

- ✓ Produces sedation, but at higher doses: excitement
- ✓ May produce euphoria: susceptible to abuse
- ✓ The amnesic action of scopolamine makes it an important adjunct drug in anesthetic procedures
- ♠ Pk & adverse effects: similar to atropine
- ♠ Hyoscine butyl bromide vs Hyoscine hydro bromide????

Propantheline

- ✓ Has been the most popular anticholinergic used for peptic ulcer and gastritis
- It reduce gastric secretion
- Action lasts 6-8 hours
- Available as 15 mg tab

Clidinium

- ✓ Anticholinergic agent
- Elicits antispasmodic & antisecretory effects on GIT
- ✓ Used in combination with benzodiazepines for nervous dyspepsia, gastritis, irritable colon, peptic ulcer etc
- ✓ Librax: clidinium bromide + cholorodiazepoxide (2.5 mg + 5 mg)

Ipratropium/Tiotropium Bromide, Aclidinium

- 💡 Ipratropium (IH): a quaternary derivative of atropine
- ✓ Rx of asthma in patients who are unable to take adrenergic agonists
- 💡 Also beneficial in the management of COPD
- 💡 Because of its **positive charge**:
 - ✓ Does not enter the systemic circulation or the CNS
 - ✓ Thus, only to the pulmonary system
- 💡 **Tiotropium**: QD; Ipratropium: up to QID
- 💡 Aclidinium: newer long acting antimuscarinic: LAMA
- Used with LABAs in COPD

Darifenacin, Fesoterodine, Oxybutynin, Solifenacin, Tolterodine & Trospium chloride

- ✓ These synthetic atropine-like drugs are used to treat overactive bladder
- By blocking mAChRs in the bladder, intravesical pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced

Antimuscarinics...

Target	Effect	Use	Drug
Glands	↓secretion	PUD	Pirenzepine, Telenzepine
Eye	Mydriasis	Ophthalmic examination	Atropine, Tropicamide, Cyclopentolate
Urinary bladder	↓ tone with constriction	Urinary frequency	Tolferodine, Darifenacin, Fesoterodine
GI smooth muscle	↓ motility with tone	Hyper motility	Hyoscine
CNS	Block all muscarinic	Motion sickness Parkinsonism	Hyoscine Benztropine
Respiratory	Relaxation	Asthma	Ipratropium, Tiotropium, Aclidinium

Drugs Acting on Autonomic Ganglia: Ganglion Blockers

- ♠ Act on the nicotinic receptor
- ♠ Show no selectivity: acts on autonomic ganglia
- ✓ They block the entire output of ANS at the nAChR
- ✓ Response: complex & unpredictable, making impossible to have selective actions
- Prevent baroreceptor reflex changes in heart rate
- ✓ Therapeutic use: rare, due to toxicities
- Mecamylamine is used in hypertension rarely
- ✓ Often serve as tools for experimental pharmacology

Characteristics of ganglion blocking Agents

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

Classes of Ganglionic Blockers

- Competitive blockers

- ✓ Hexamethonium

- ✓ Pentolinium

- ✓ Mecamylamine - amelioration of Tourette's syndrome

- ✓ Pempidine

- ✓ Trimethaphan

■ Persistent Depolarizing blockers

- ✓ Nicotine (large dose)
- ✓ Anticholinesterases (large dose)
- ✓ Varenicline: selective partial agonist at $\alpha 4\beta 2$ nAChR
- Used exclusively for smoking cessation

Nicotine

- ➡ A natural liquid alkaloid obtained from *Nicotiana glauca*
- ➡ Small doses of nicotine activate nAChRs
- ➡ Large doses inhibit the receptor by exerting persistent depolarization
- ➡ Effects result from its action on
 - ✓ The adrenal medulla
 - ✓ The autonomic ganglia
 - ✓ The neuromuscular junction and on the CNS

Nicotine...

👉 In small doses:

- ✓ **Rise in BP:** b/c of the release of catecholamines from the adrenal medulla & sympathetic ganglia, leading to increase HR & vasoconstriction
- ✓ **Increase secretion of glands:** b/c of PSNS stimulation
- ✓ **Contraction of skeletal muscle:** b/c of its action on NMJ
- ✓ **Excitation:** because of its action on the CNS

☞ Higher doses:

- ✓ **BP falls** because of ganglionic blockade
- ✓ Activity both in GI tract & bladder musculature ceases
- ✓ Currently not used: except in smoking cessation

Stimulatory effects of Nicotine

Nicotine

Dopamine

Pleasure, appetite suppression

Norepinephrine

Arousal, appetite suppression

Acetylcholine

Arousal, cognitive enhancement

Glutamate

Learning, memory enhancement

Nicotine

Serotonin

Mood modulation, appetite suppression

β -Endorphin

Reduction of anxiety and tension

GABA

Reduction of anxiety and tension

Adverse effects

- ↳ Interrupt sympathetic control of venous tone,
- ✓ They cause marked venous pooling
- Postural hypotension
- Dry mouth, blurred vision, constipation & severe sexual dysfunction
- ↳ So, rarely used

Neuromuscular blockers: skeletal muscle relaxants

- Block cholinergic transmission b/n motor nerve endings & the nAChRs on the neuromuscular endplate of skeletal muscle
- Structural analogue of ACh & act either as **antagonists** (non-depolarizing type) or **agonists** (depolarizing type)
- Useful clinically during surgery to produce complete muscle relaxation

Neuromuscular blocking drugs...

- Non depolarizing blockers

(competitive)

- ✓ D-Tubocurarine, Metocurine

- ✓ Atracurium (cisatracurium)

- ✓ Vecuronium, Pancuronium

- ✓ Rocuronium, Mivacurium

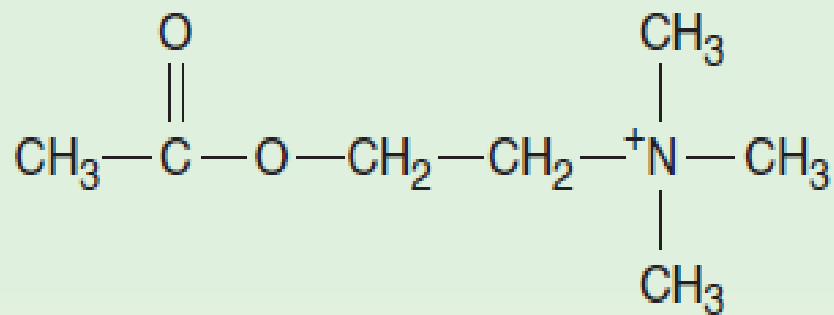
- ✓ Pipecuronium, Gantacurium

- Depolarizing blockers

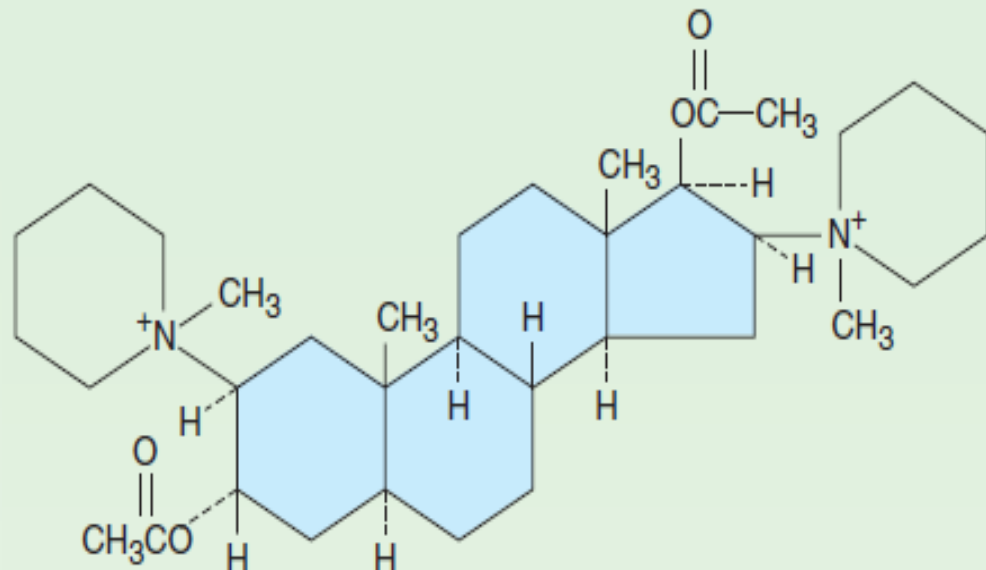
- ✓ Suxamethonium

(succinylcholine)

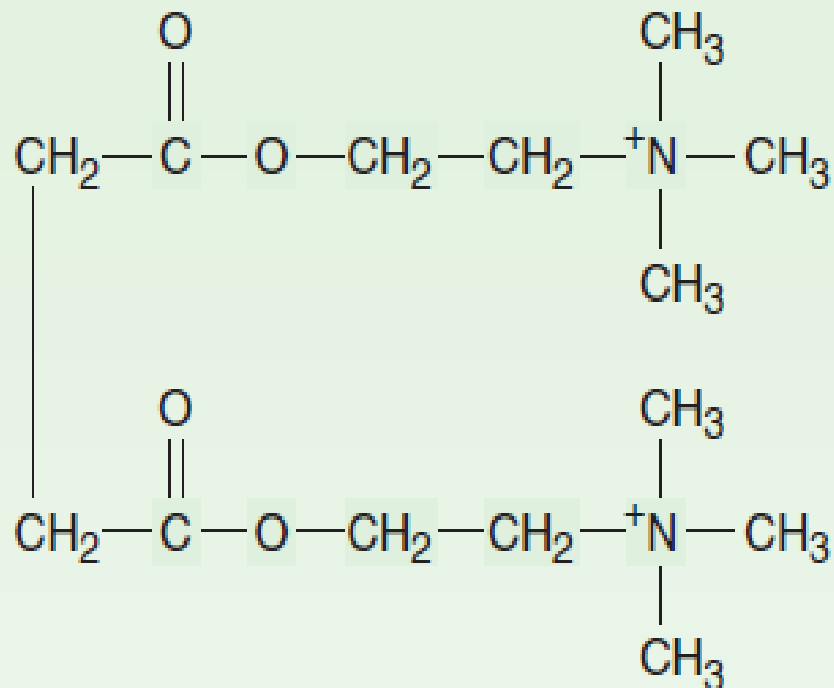
- ✓ Decamethonium



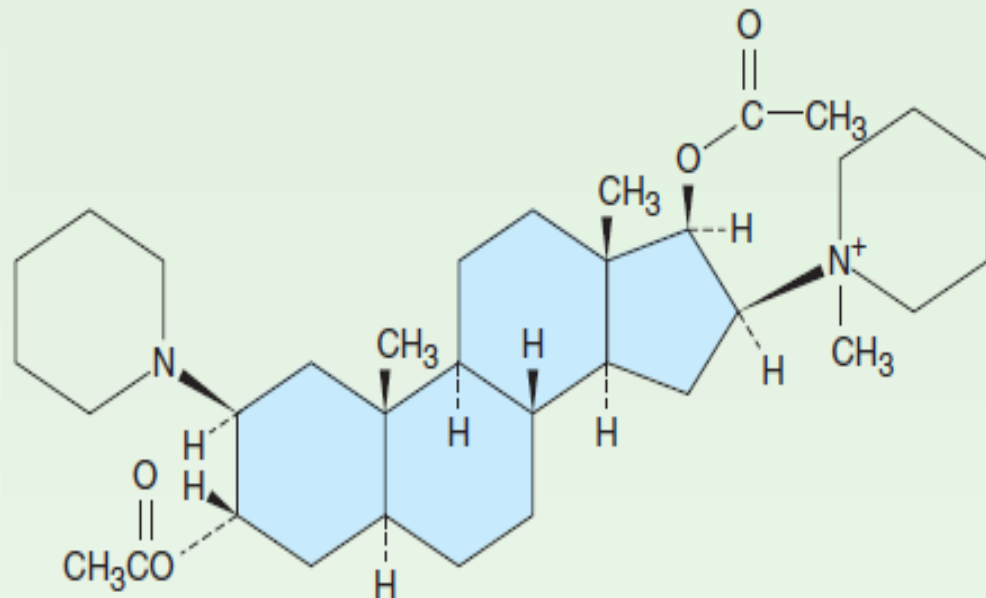
Acetylcholine



Pancuronium

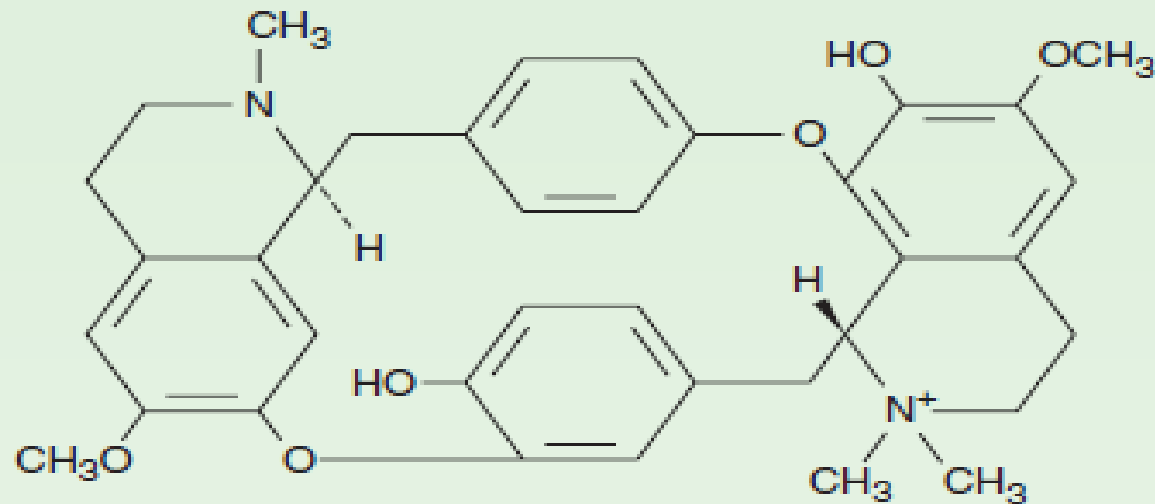


Succinylcholine

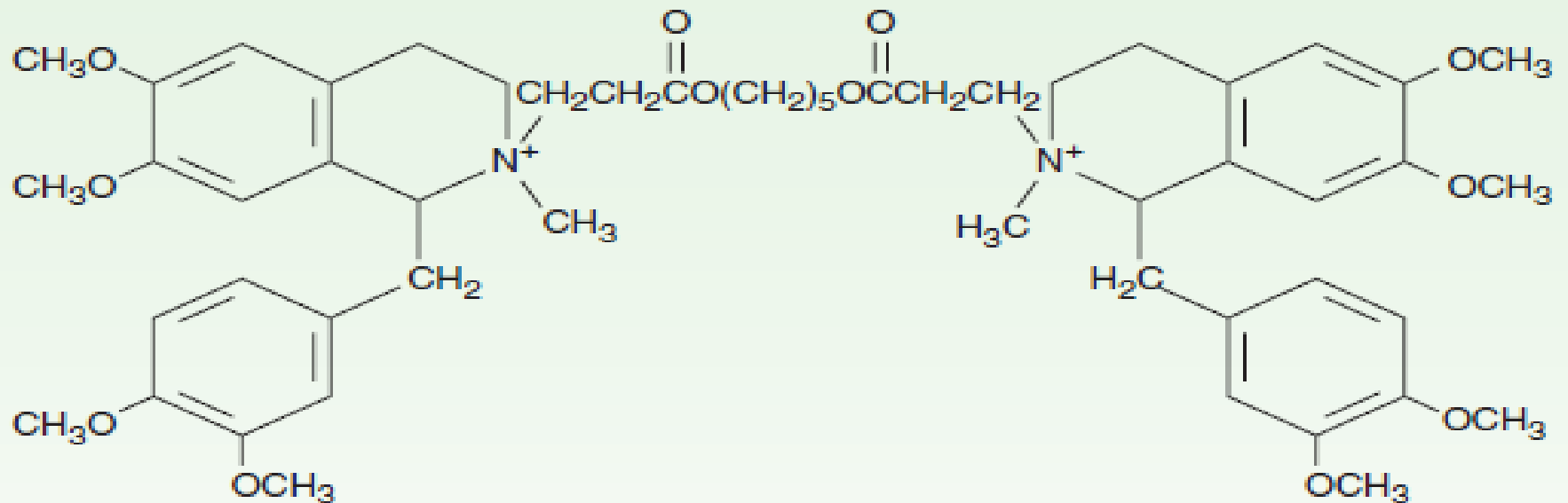


Vecuronium

Isoquinolines



Tubocurarine



Atracurium

Non-depolarizing (competitive) blockers

- ➔ The first drug was curare, native hunters of the Amazon in south America used to paralyze animals
- ➔ Tubocurarine was ultimately purified and introduced into clinical practice
- ➔ Pancuronium, atracurium, vecuronium, and several newer drugs are shorter-acting nondepolarizing blockers

▪ Mechanism of action

- ➔ At low doses: competitively block ACh at nAChR
- ✓ Prevent depolarization of the muscle causing flaccid paralysis that lasts 30-60 minutes (longer in large doses)
- ✓ Their action can be overcome by increasing the concentration of ACh in the synapse
- ChEIs: neostigmine or edrophonium

↪ At high doses:

- ✓ Can block the ion channels of the motor endplate
- ✓ This leads to further weakening of neuromuscular transmission, thereby reducing the ability of cholinesterase inhibitors to reverse the actions of the non-depolarizing blockers

👉 Action:

- ➡ All muscles are not equally sensitive to be blocked
- ✓ Face & eye paralyzed first (rapidly contracting muscles) followed by fingers there after, limb, neck & trunk muscles; then intercostal muscles and finally diaphragm
- ✓ Recovery is in the reverse manner

👉 Therapeutic uses:

- ✓ Adjuvant drug in anesthesia during surgery to relax skeletal muscle

➡ PK

- ✓ ROA: IV for all neuromuscular blockers
- Since they are 4⁰ amines uptake is minimal after PO
- ✓ Termination is through redistribution (not metabolized)
- ✓ Most drugs excreted primarily unchanged in urine
- ➡ S/E: safe (minimal)

▪ **Drug interactions:**

- ✓ General anesthetics: isoflurane, increase the action of nondepolarizing agents;
- Reduce the dose of NMJ blockers
- ✓ Aminoglycosides: inhibit presynaptic ACh release & potentiate the effect of nondepolarizing NMJ blockers

Depolarizing agents: Succinylcholine

⇒ MOA:

- ✓ Binds to the nAChR & acts like ACh to depolarize the junction
- ✓ Persist at high concentration in the synaptic cleft
- ✓ Remain attached to the receptor for a relatively long time
- ✓ Renders the receptor incapable of transmitting further impulses

Depolarizing agents...

- Phase-I block: depolarizing
 - ✓ First cause the opening of sodium channel
 - ✓ Results in depolarization of the receptor
 - ✓ This leads to a transient twitching of the muscle (fasciculations)

■ Phase-II block: desensitizing

- ✓ With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked
- ✓ But, receptor is desensitized to the effect of Ach
- ✓ This causes a resistance to depolarization & flaccid paralysis
- ✓ Channel block may become more important than agonist action at the receptor

- **Action:**

- ➔ As with the competitive blockers, the respiratory muscles are paralyzed last
- ➔ Succinylcholine initially produces brief muscle fasciculations that cause muscle soreness
- ➔ The duration of action of succinylcholine is extremely short, due to rapid hydrolysis by BuChE

Action...

→ However, succinylcholine that gets to the NMJ is not metabolized by AChE, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes)

Depolarizing agents ...

Therapeutic uses: Succinylcholine

- ➡ Onset: rapid; useful when rapid endotracheal intubation is required during the induction of anesthesia (a rapid action is essential if aspiration of gastric contents is to be avoided during intubation)
- ➡ It is also used during electroconvulsive shock treatment

■ Pharmacokinetics:

- ✓ ROA: Succinylcholine is injected IV
- ✓ DOA: brief b/c redistribution & rapid hydrolysis by BuChE
- Sometimes given by continuous infusion to maintain a longer duration of effect
- ✓ Drug effects rapidly disappear upon discontinuation

Nondepolarizing Agent	Duration of Action	Ganglion Blockade	Histamine Release	Cardiac Muscarinic Receptors	Comments
Tubocurarine ^a	Long	+	++	—	Prototype
Atracurium ^a	Intermediate	—	+	—	Inactivated spontaneously in plasma; laudanosine, a breakdown product, may cause seizures
Cisatracurium ^a	Intermediate	—	—	—	Less laudanosine formed than atracurium
Mivacurium ^a	Short	—	++	—	Hydrolyzed by plasma cholinesterase
Pancuronium ^b	Long	—	—	++	Increased heart rate
Vecuronium ^b	Intermediate	—	—	—	Metabolized by liver
Depolarizing Agent					
Succinylcholine	Very short	++	+	++	Hydrolyzed by cholinesterase; malignant hyperthermia is a rare, potentially fatal complication

- S/E:

- ✓ Hyperthermia: halothane + succinylcholine

- Rx: Dantrolene; RYR1 antagonist

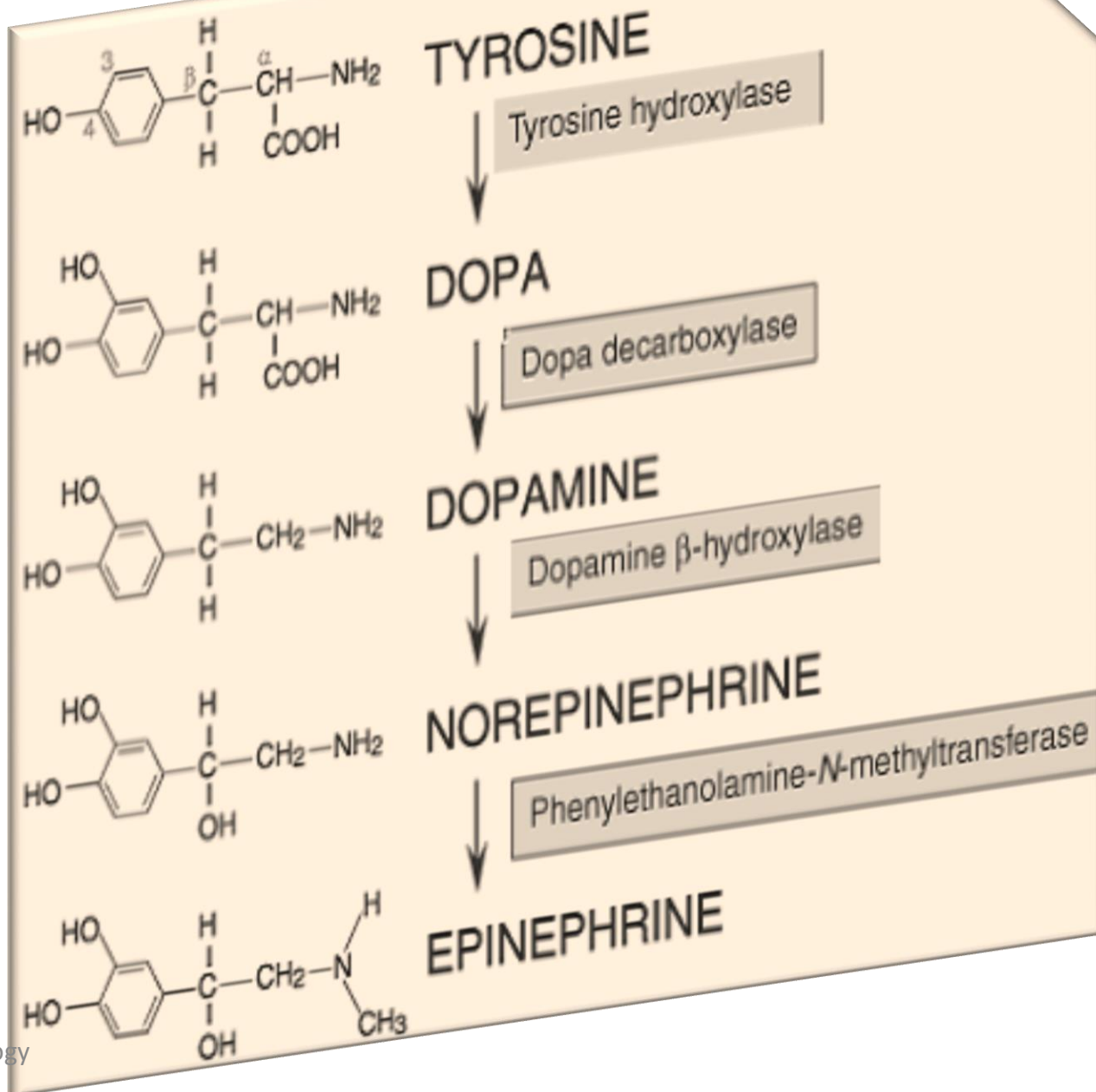
- ✓ Apnea: in plasma ChE deficient patients

- ✓ Hyperkalemia: increases K^+ release from intracellular stores

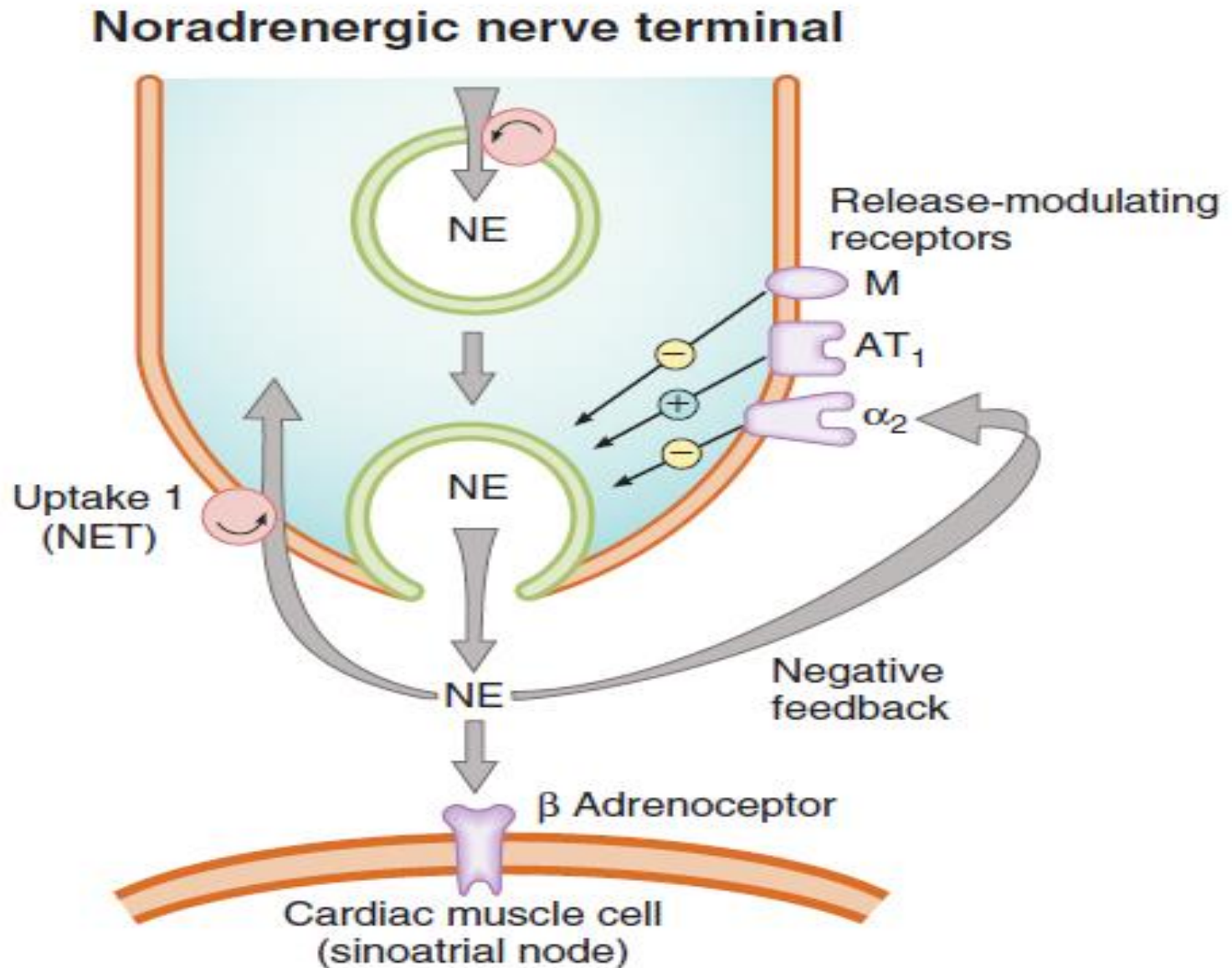
- ✓ Aminoglycosides: potentiate the effect of NMJ blocker

Drugs acting on Adrenergic System

- The adrenergic neuron release NE in CNS & SNS
 - Ultimately SNS effects mediated by NE
 - Receptors: presynaptic or postsynaptic
- In response to stimuli: stress, the adrenal medulla releases E, & transported in the blood to target tissues
- E acts as a hormone, whereas NE acts as a NT



Modulation of NE release



Receptor	Agonist	Antagonist	G Protein	Effects
α_1 type	Phenylephrine	Prazosin	G_q	$\uparrow$ IP3, DAG common to all
α_{1A}		Tamsulosin		
α_{1B}				
α_{1D}				
α_2 type	Clonidine	Yohimbine	G_i	$\downarrow$ cAMP common to all
α_{2A}	Oxymetazoline			
α_{2B}		Prazosin		
α_{2C}		Prazosin		
β type	Isoproterenol	Propranolol	G_s	$\uparrow$ cAMP common to all
β_1	Dobutamine	Betaxolol		
β_2	Albuterol	Butoxamine	G_s, G_q	
β_3	Mirabegron			
Dopamine type	Dopamine			
D_1	Fenoldopam		G_s	$\uparrow$ cAMP
D_2	Bromocriptine		G_i	$\downarrow$ cAMP
D_3			G_i	$\downarrow$ cAMP
D_4		Clozapine	G_i	$\downarrow$ cAMP
D_5			G_s	$\uparrow$ cAMP

⇒ α_1 -receptors:

- ✓ Present on the smooth muscles
- Mediate constriction of smooth muscle

⇒ α_2 -receptors:

- Located primarily on pre-synaptic nerve endings
- Postsynaptically: β -cell of the pancreas

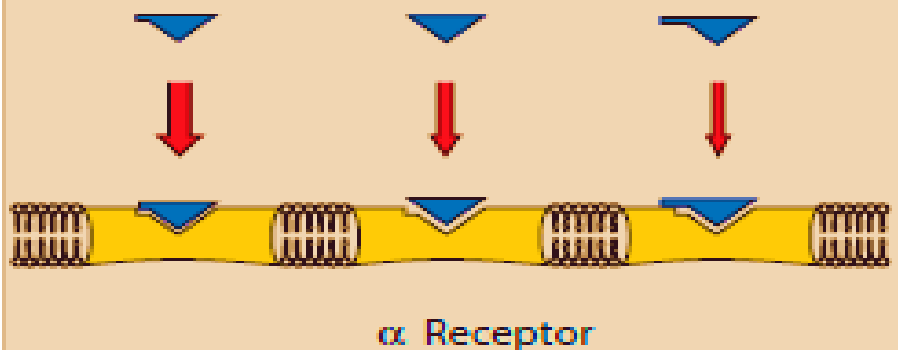
⇒ β -Adrenoceptors:

- ✓ β_1 : heart, kidney
- ✓ β_2 : liver, pancreas, smooth muscles of; bronchi, uterus, blood vessels of skeletal muscle
- ✓ β_3 (modified β_1): adipose tissue (lipolysis), detrusor muscle of bladder (relaxation), several tissues (unclear role)

Relative Receptor Affinities	
Alpha agonists	
Phenylephrine, methoxamine	$\alpha_1 > \alpha_2 >>>> \beta$
Clonidine, methylnorepinephrine	$\alpha_2 > \alpha_1 >>>> \beta$
Mixed alpha and beta agonists	
Norepinephrine	$\alpha_1 = \alpha_2; \beta_1 >> \beta_2$
Epinephrine	$\alpha_1 = \alpha_2; \beta_1 = \beta_2$
Beta agonists	
Dobutamine ¹	$\beta_1 > \beta_2 >>>> \alpha$
Isoproterenol	$\beta_1 = \beta_2 >>>> \alpha$
Albuterol, terbutaline, metaproterenol, ritodrine	$\beta_2 >> \beta_1 >>>> \alpha$
Dopamine agonists	
Dopamine	$D_1 = D_2 >> \beta >> \alpha$
Fenoldopam	$D_1 >> D_2$

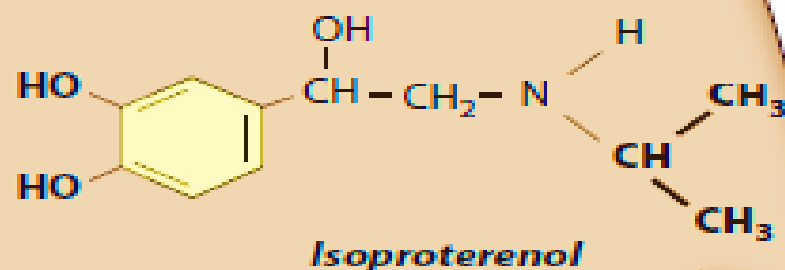
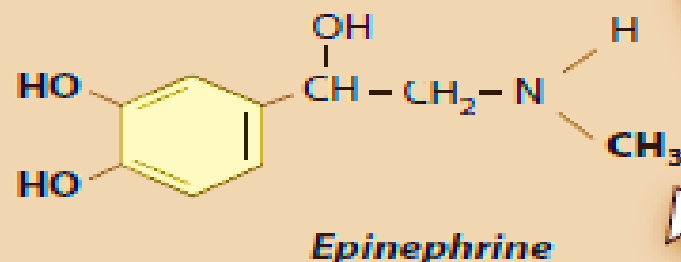
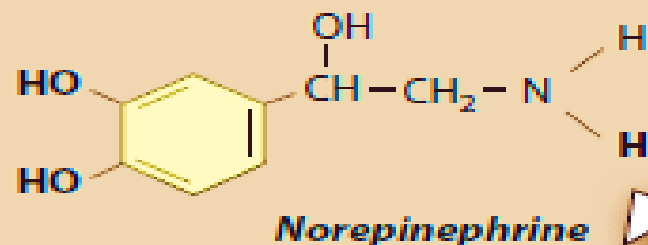
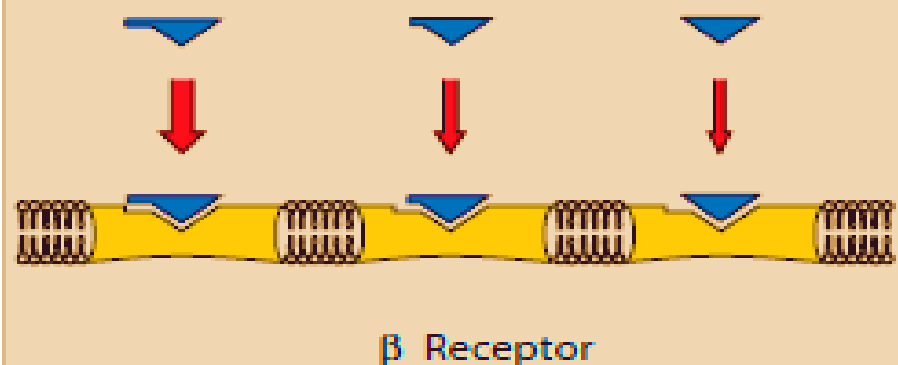
A α -Adrenoceptors

Epinephrine Norepinephrine Isoproterenol



B β -Adrenoceptors

Isoproterenol Epinephrine Norepinephrine



Affinity for β receptors increases as group on the amine nitrogen gets larger.

Distribution of Receptors

- Adrenergically innervated organs & tissues tend to have a predominance of one type of receptors
- Vasculature of skeletal muscle have both α_1 & β_2 receptors, but β_2 predominate
- Other tissues may have one type of receptors exclusively, with particular no significant number of others
- Heart: predominantly β_1

Receptor

Response

α_1

Eye—radial (dilator) muscle

Contraction—mydriasis

Arterioles (skin, viscera)

Contraction— $\uparrow$ TPR— $\uparrow$ diastolic pressure,
 $\uparrow$ afterload

Veins

Contraction— $\uparrow$ venous return— $\uparrow$ preload

Bladder trigone and sphincter
and prostatic urethra

Contraction—urinary retention

Male sex organs

Vas deferens—ejaculation

Liver

$\uparrow$ glycogenolysis

Kidney

$\downarrow$ renin release

α_2

Prejunctional nerve terminals

$\downarrow$ transmitter release and NE synthesis

Platelets

Aggregation

Pancreas

$\downarrow$ insulin secretion

Receptor

Response

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)

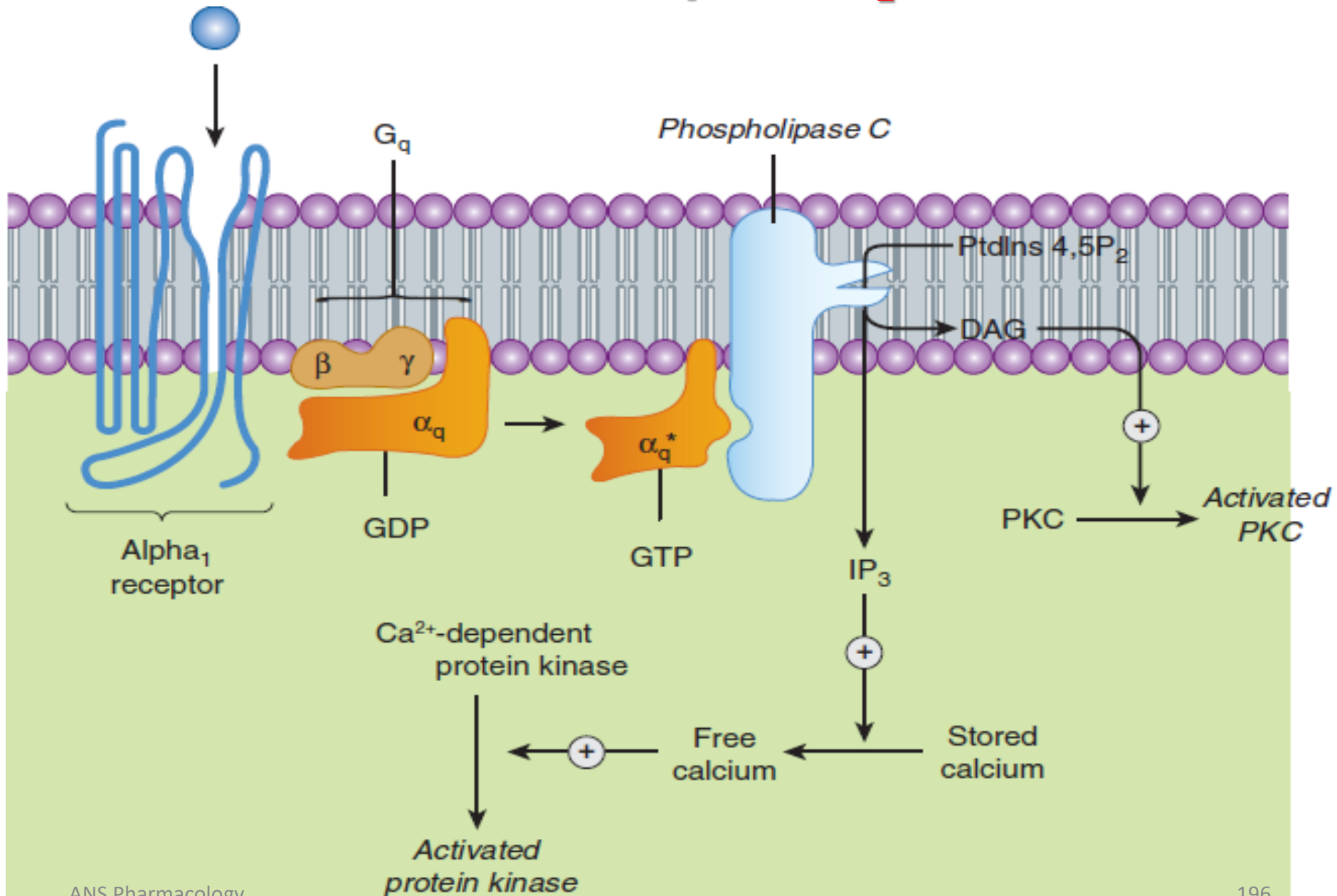
Liver

↑ glycogenolysis

Pancreas

↑ insulin secretion

Adrenoceptors: α_1



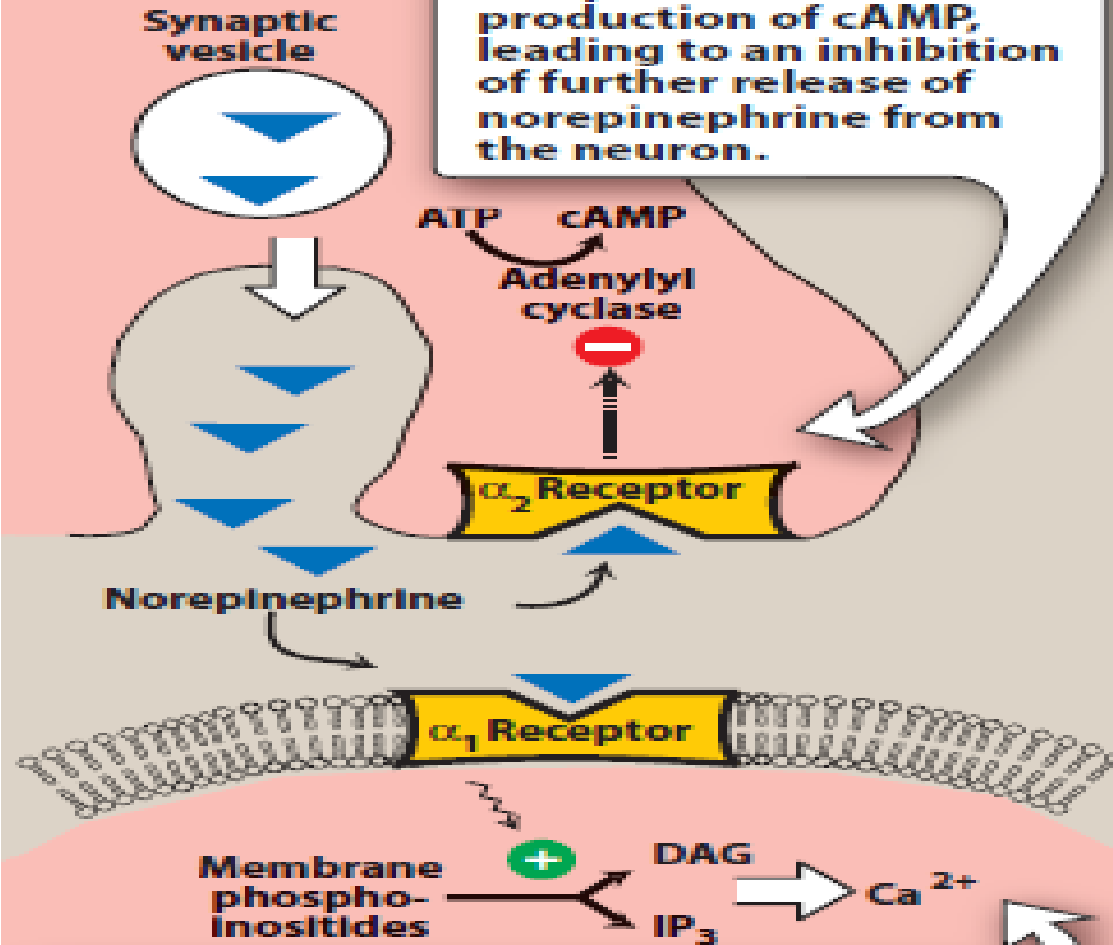
- α_1 receptors activate signal transduction pathways that stimulate tyrosine kinases
- ✓ They have been found to activate mitogen-activated kinases (MAP kinases) & polyphosphoinositol-3-kinase (PI-3-kinase)
- ✓ These pathways may have importance for the α_1 mediated stimulation of cell growth & proliferation through the regulation of gene expression

Adrenoceptors: α_2

- ✓ Direct effect on vascular smooth muscle: contraction
- ✓ NE/E stimulation of α_2 engages $G_{i/o}$ classes of G-protein
- ✓ $G_{i/o}$ inhibits adenylyl cyclase thus decreasing cAMP levels
- ✓ $G_{i/o}$ increases Ca^{2+} influx
- ✓ Decrease in cAMP allows calcium-calmodulin stimulation of MLCK activity, causing contraction

α_2 Receptors

Activation of the receptor decreases production of cAMP, leading to an inhibition of further release of norepinephrine from the neuron.



α_1 Receptors

Activation of the receptor increases production of DAG and IP_3 , leading to an increase in intracellular calcium ions.

✓ Pre-synaptic α_2 :
indirectly cause
vasodilation

➡ β -Adrenoceptors:

➡ Differ in their location & sensitivity to E & NE:

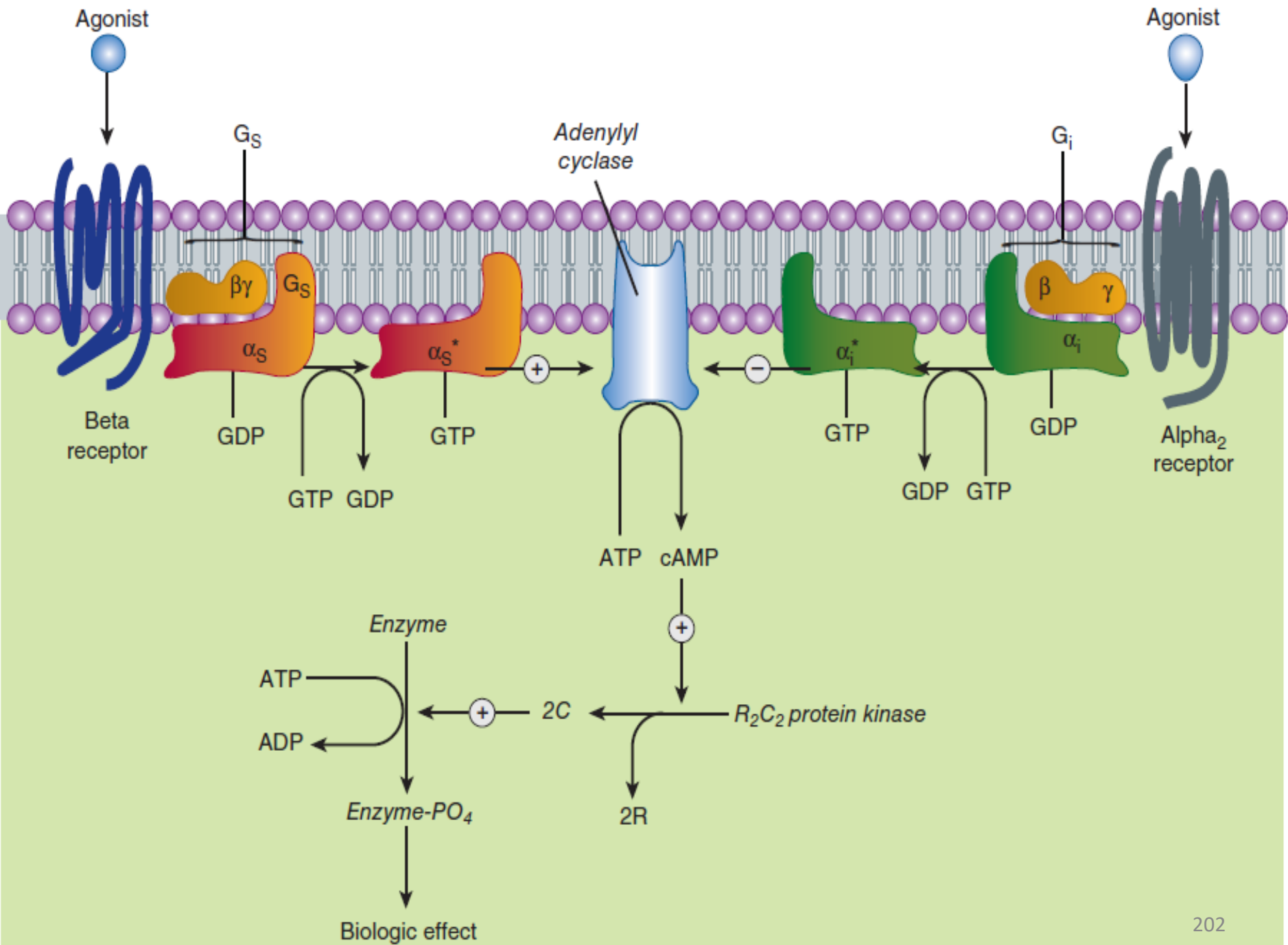
➤ β_1 myocardium: E $\approx$ NE

➤ β_2 smooth muscle: essentially no affinity for NE

❖ β_3 is a lower affinity receptor compared with β_1 & β_2 but
is more resistant to desensitization

❖ Selective agonists are being developed for the Rx of
obesity, DM, HF...

- ↪ All three β adrenoceptors function through a major class of signal transducer: G-proteins
- ↪ G-proteins couple β adrenoceptors to adenylyl cyclase:
- ↪ β agonists increase intracellular cAMP levels => PKA activity, which in turn regulate downstream effectors



☞ β_1 :

- ✓ G_s : activation of adenylyl cyclase & increased cAMP levels
- ✓ Activates PKA, which directly phosphorylates proteins essential for cardiac muscle contraction
- ✓ Positive inotropic & chronotropic effects on the heart; speeds conduction across the AV node

☞ β_2 :

- ✓ G_s : activation of adenylyl cyclase & increased cAMP levels
- ✓ Relaxes vascular, bronchial, GI & genitourinary smooth muscle
- ✓ Stimulates the uptake of potassium into skeletal muscle
- ✓ Stimulates glycogenolysis & gluconeogenesis in the liver

☞ β_3 :

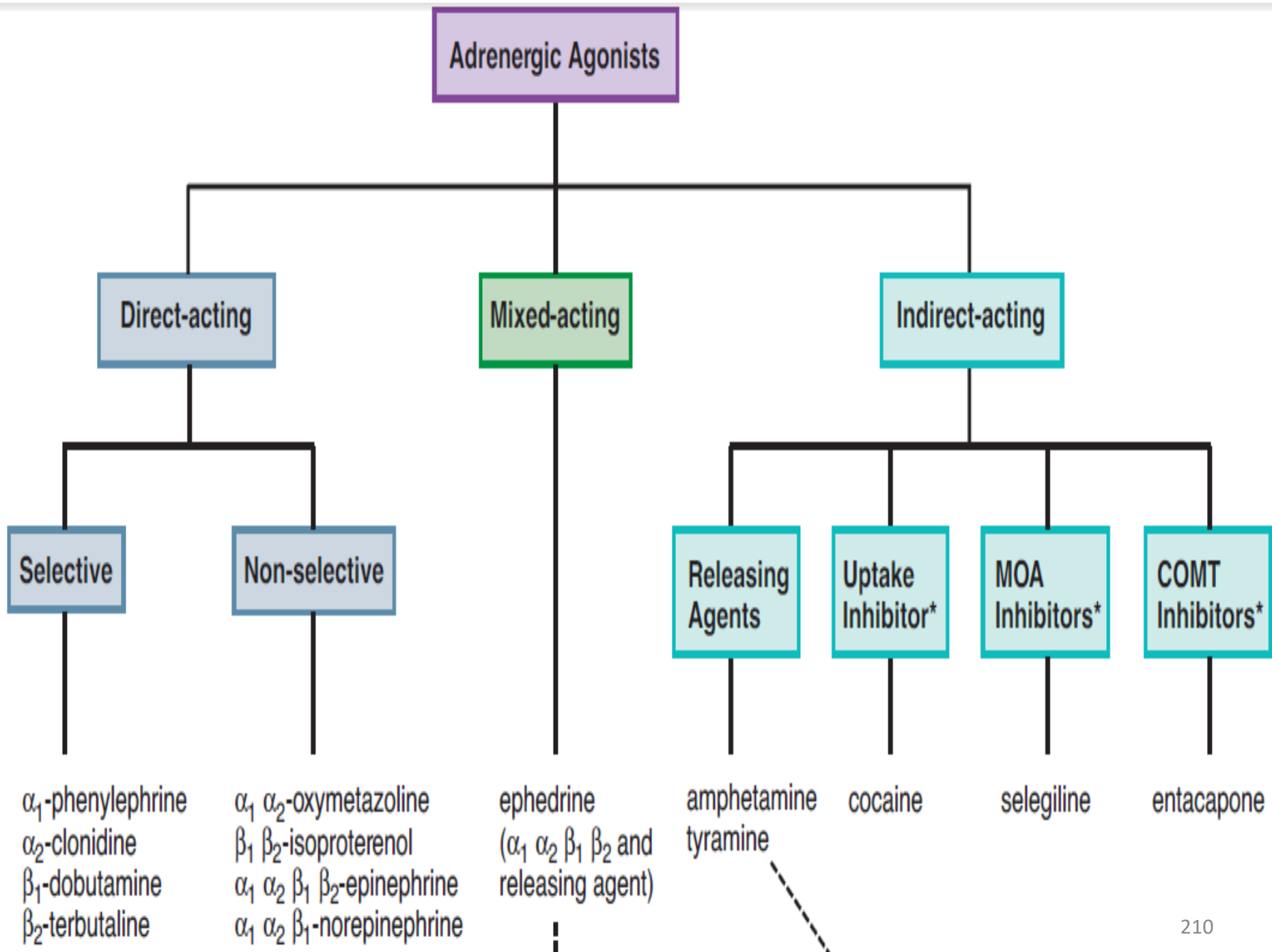
- ✓ Coupled to G_s : stimulates adenylate cyclase & increases cAMP levels
- ✓ Activates PKA which stimulates the lipase activity i.e. another context-specific effectors
- ✓ Adipose tissue: lipolysis

- ✓ β_1 , β_2 & β_3 : all activate G_s which stimulates adenylyl cyclase and increases cAMP levels => activates PKA
- ✓ Outcome depends on what PKA phosphorylates:
 - Troponin in cardiac muscle (contraction);
 - MLCK or K^+ channels in smooth muscle (relaxation);
 - Lipase in adipose tissue-lipolysis

Adrenoceptor Agonists & Sympathomimetic Drugs

- Traditionally, drugs that mimic the actions of E or NE:
sympathomimetic drugs
- ✓ Based on MOA & spectrum of receptors they activate;
 - Direct agonists: directly interact with & activate
adrenoceptors; E, NE
 - Indirect agonists: enhance the actions of endogenous
catecholamines
 - Mixed agonists

- Indirect agonists: have either of two d/t mechanisms;
 - ✓ Displace stored catecholamines from the adrenergic nerve ending: tyramine or
 - ✓ Decrease the clearance of released NE either by;
 - Inhibiting reuptake: cocaine, TCAs
 - Prevent enzymatic metabolism: MAOIs, COMTIs



Direct Acting Sympathomimetics

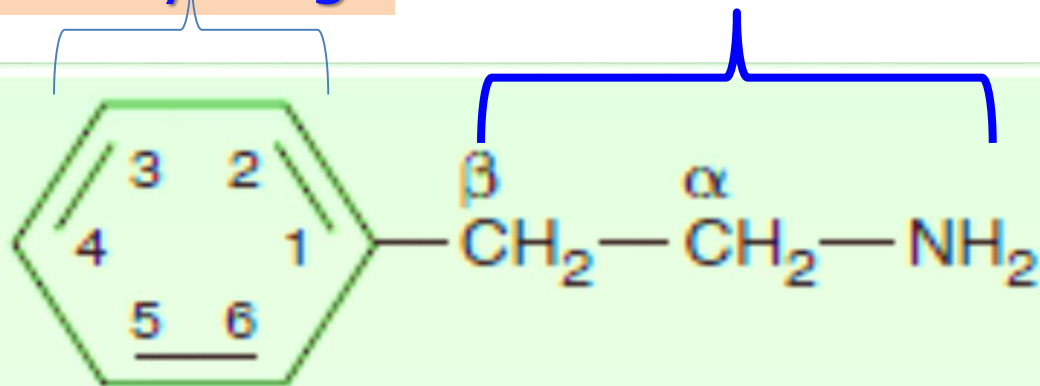
- ♠ Act on adrenergic receptors
- ♠ Based on their chemical structure;
 - Catecholamines
 - Non-catecholamines

Catecholamines

- Derivatives of β -phenyl ethylamine
- When 3,4-OH is added to phenyl ring → catechol ring
- Hence, catechol ethyl amine → catecholamines

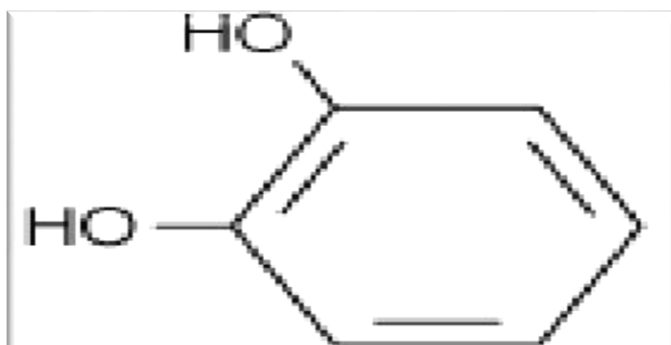
Phenyl ring

Ethyl amine



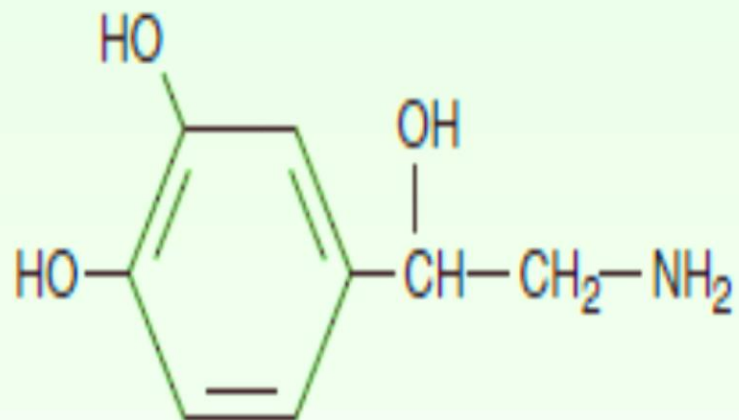
Phenylethylamine

ANS Pharmacology

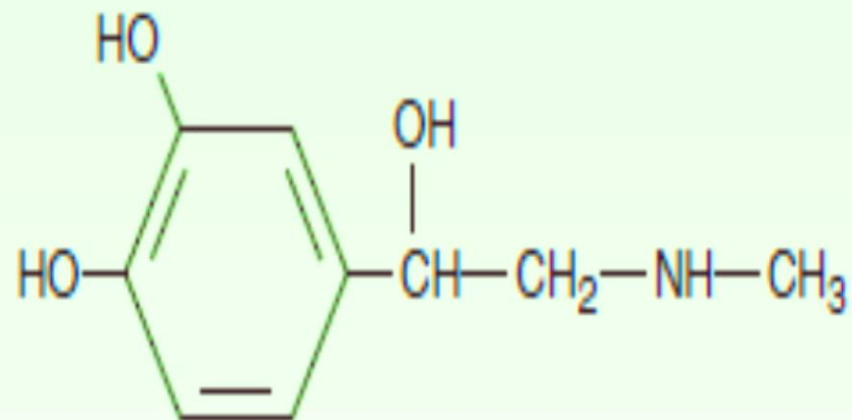


Catechol

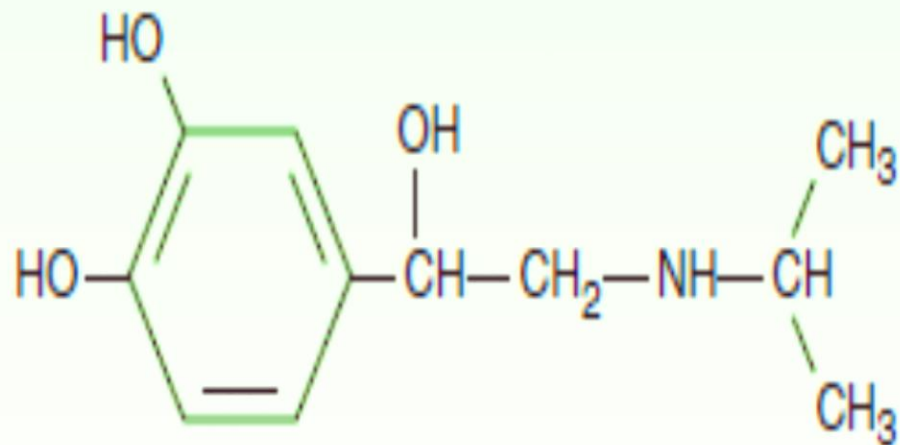
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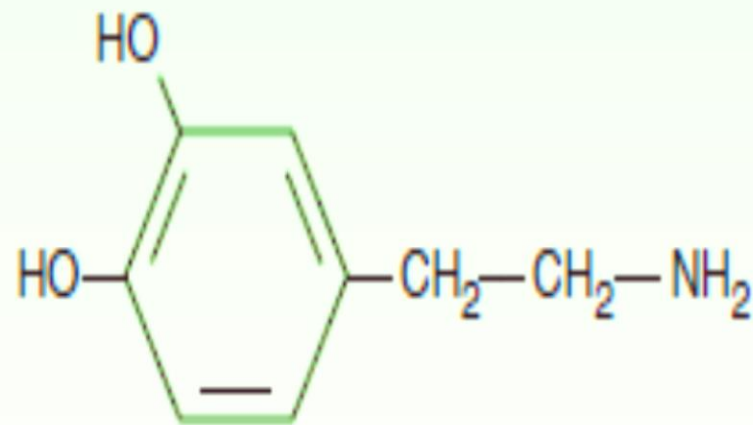
Norepinephrine



Epinephrine



Isoproterenol



Dopamine

■ Substitution on the Benzene Ring

- ➡ Maximal α & β activity is found with catecholamines
- Drugs with 3,4-OH groups
- ✓ 3,4-OH is important for receptor binding
- Amphetamine & ephedrine has no OH hence work indirectly

- ↳ Catecholamines are not active orally
- Inactivation by gut & liver COMT
- ➔ Absence of one or both-OH groups on the phenyl ring
- Increases oral bioavailability & duration of action
- ↳ Furthermore, absence of ring-OH groups;
- Increase CNS distribution

■ Substitution on the Amino group

- Increasing the size of alkyl substituents on the amino group tends to increase β -receptor activity
- NE < E < isoproterenol: at β_2 & the reverse for α receptors
- β_2 selective agonists generally require a large amino substituent group

■ Substitution at the α carbon

- ☑ Block oxidation by MAO & prolong the action of drugs:
non-catecholamines
- ☑ Methylation at α carbon; there will be steric hindrance for
MAO not to attack α carbon
- ☑ Methylation; more non-polar
- ☑ Intrinsic activity depends on ethyl group

Catecholamines

- They share the following properties:
 - ➡ High potency: by activating α or β receptors
 - ➡ Rapid inactivation: metabolized by MAO & COMT
 - ✓ Have a brief DOA when given parenterally & ineffective orally due to inactivation
 - ➡ Poor penetration into CNS: polar
 - ✓ Nevertheless have some clinical effects that are attributed to the action of CNS

Non – catecholamines

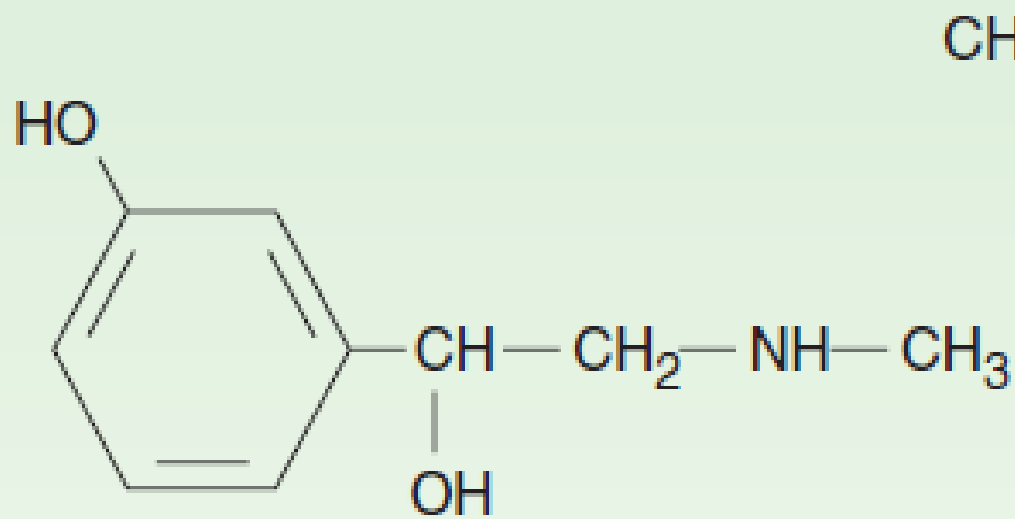
➡ Lack 3,4-OH groups: have longer half lives because:

✓ Not metabolized by COMT & MAO

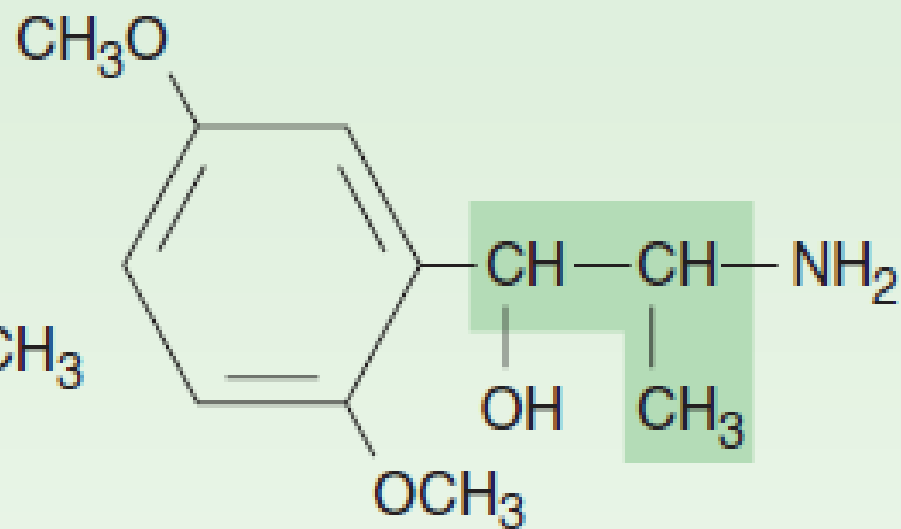
✓ Permits greater access to CNS

✓ Better selectivity

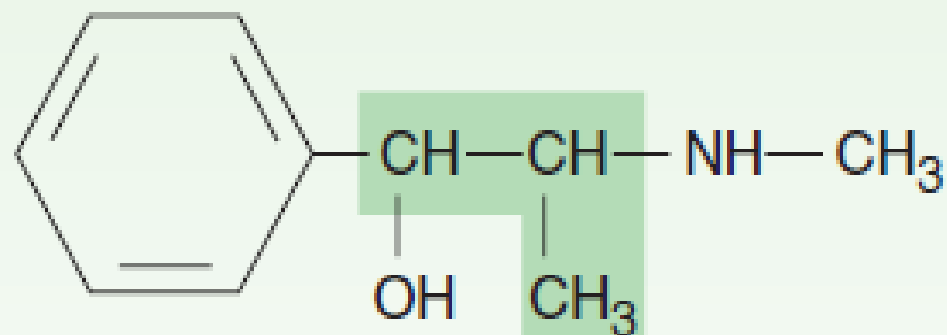
❖ Phenylephrine & Ephedrine



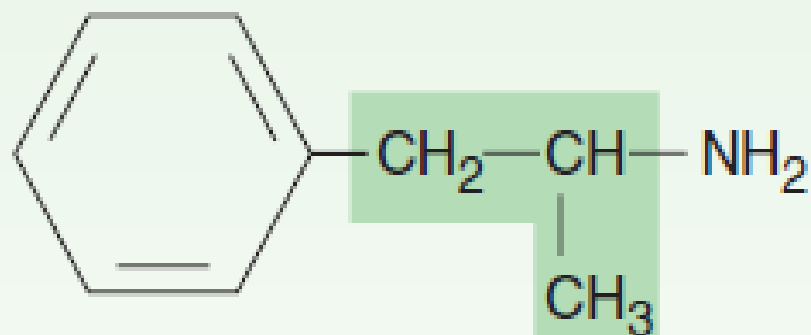
Phenylephrine



Methoxamine



Ephedrine



Amphetamine

Direct acting sympathomimetics

→ Based on their relative receptor selectivity:

① Mixed α & β agonists:

✓ NE: $\alpha_1 = \alpha_2 \gg \beta_1 \gg \gg \gg \beta_2$

✓ E: $\alpha_1 = \alpha_2$; $\beta_1 = \beta_2$

② β agonists:

✓ Dobutamine, prenalterol: $\beta_1 > \beta_2 \gg \gg \gg \alpha$

✓ Isoproterenol: $\beta_1 = \beta_2 \gg \gg \gg \alpha$

✓ Terbutaline, albuterol, salbutamol, metaproterenol,
ritodrine, nylidrine, isoxuprine: $\beta_2 \gg \beta_1$

③ α agonists

- ✓ Phenylephrine, methoxamine, metharaminol: $\alpha_1 \gg \alpha_2$
- ✓ Xylomthazoline, oxymethazoline, naphazoline: $\alpha_1 \gg \alpha_2$
- ✓ Clonidine, α -methyldopa, guanfacine, guanabenze: $\alpha_2 \gg \alpha_1$

④ Dopamine agonists

- ✓ Dopamine: $D_1 = D_2 \gg \beta \gg \alpha$
- ✓ Fenoldopam: $D_1 \gg D_2$

Adrenaline: Epinephrine

- ✓ In the adrenal medulla, NE is methylated to yield E
- ✓ Stored in chromaffin cells along with NE
- ✓ Adrenal medulla releases: $\approx 80\%$ E & 20% NE directly into the circulation
- ✓ Epinephrine interacts with α & β receptors
- ✓ At low dose, β mediated vasodilation, whereas at high dose, α mediated vasoconstriction

Epinephrine on CVS: TPR

- ✚ Constricts arterioles in the skin, mucous membranes (α), & it dilates vessels to the liver & skeletal muscle (β_2)
- ✚ β_1 are more sensitive than α_1 to Epinephrine
- ✚ Hence extreme low dose $\rightarrow$ Less TPR (β_2) $\rightarrow$ less DBP
- ✓ Moderate dose $\rightarrow$ TPR remains same $\rightarrow$ constant DBP
- ✓ Too high dose $\rightarrow$ TPR increased (α_1) $\rightarrow$ increases DBP
- ✓ SBP-increased at all doses (even at low reflex tachycardia + (β_1) (at high doses)

- ➡ E activates β_1 on the kidney to cause renin release
- ➡ Renin, an enzyme involved in the production of Ag-II
- ➡ The cumulative effect is an increase in
- ✓ SBP coupled with a slight decrease in DBP due to β_2 mediated vasodilation in the skeletal muscle vascular bed

Adrenaline: Epinephrine

Low Dose

- β_1 : $\uparrow$ HR, $\uparrow$ SV, $\uparrow$ CO, $\uparrow$ pulse pressure
- β_2 : $\downarrow$ TPR, $\downarrow$ BP

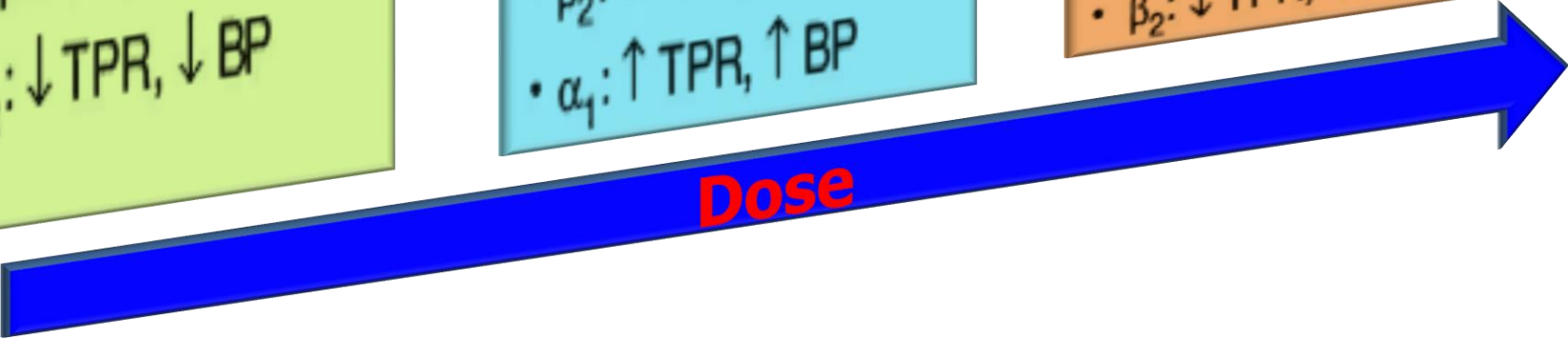
Medium Dose

- β_1 : $\uparrow$ HR, $\uparrow$ SV, $\uparrow$ CO, $\uparrow$ pulse pressure
- β_2 : $\downarrow$ TPR, $\downarrow$ BP
- α_1 : $\uparrow$ TPR, $\uparrow$ BP

High Dose

- α_1 : $\uparrow$ TPR, $\uparrow$ BP
- Potential reflex bradycardia
- β_1 : $\uparrow$ HR, $\uparrow$ SV, $\uparrow$ CO, $\uparrow$ pulse pressure
- β_2 : $\downarrow$ TPR, $\downarrow$ BP

Dose



Adrenaline: Epinephrine

- Actions on target organs
- ✓ BP: potent vasopressor; rise in SBP & DBP
- ✓ Heart:
 - Direct myocardial stimulation: +ve inotropic
 - Increased heart rate: +ve chronotropic
 - Increased conduction: +ve dromotropic

✓ Respiratory system

- Bronchodilation: β_2
- Inhibits the release of inflammatory mediators such as histamines from mast cells

✓ Hyperglycemia

- Increased glycogenolysis in liver: β_2
- Increased release of glucagon: β_2
- Decreased release of insulin: α_2

✓ Lipolysis: β_3

PKs

- ROA: IV, IM, SC
- Rapid onset but short duration
- Metabolism: MAO-A (GIT), COMT
- Excretion: via urine
- Aqueous solutions are very unstable, it oxidizes readily when exposed to light so, it is stored in amber or yellow color containers

▪ **Therapeutic uses**

- ➔ In anaphylactic shock: due to its effect on the CVS & bronchial muscles
- ➔ In acute attack of bronchial asthma
- ➔ Prolong the duration of action of local anesthetics
- ➔ Rx of complete heart block & sudden cardiac arrest (β_1) (Dopamine)
- ➔ To stop bleeding from superficial blood vessels
- ➔ Open angle glaucoma: promotes an increase in the outflow of aqueous humor, but **C/I in closed angle**

▪ Side effects

➡ Restlessness, anxiety, sweating, palpitation

✓ Severe adverse effects:

➡ Sudden rise in BP, cerebral hemorrhage, precipitation of angina pectoris, cardiac arrhythmias, etc

✓ Contraindication (CI)

⊗ Severe HTN, arrhythmias, CAD

Noradrenaline: NE

- ✓ Stimulates α receptors & has less pronounced effect on β_1 but it lacks β_2 activity

- α_1 : $\uparrow$ TPR, $\uparrow$ BP
- β_1 : $\uparrow$ HR, $\uparrow$ SV, $\uparrow$ CO, $\uparrow$ pulse pressure
- Potential reflex bradycardia
- No effect on β_2

- ☞ Causes greater vasoconstriction than E: no vasodilation via β_2
- ☞ Weak β_2 = not used in Rx of asthma or anaphylaxis

■ Baroreceptor reflex:

- ↳ NE increases BP, & this stimulates the baroreceptors, inducing a rise in vagal activity
- ✓ Produces a reflex bradycardia
- ✓ Counteract the local actions of NE on the heart
- ✓ Does not affect the positive inotropic effects of the drug????

▪ **Therapeutic uses**

- Rx of hypotensive states (shock): IV infusion
- Never use in asthma

▪ **Side-effects**

- ➔ Reflex bradycardia
- ➔ It can cause tissue necrosis: extravasation

Isoproterenol

- ↳ Stimulates both β_1 & β_2
- ↳ Non-selective: rarely used
- ↳ Its action on α receptors is insignificant
- ↳ Increases heart rate, contractility, & cardiac output
- ↳ Dilates arterioles of skeletal muscle (β_2) => decreased peripheral resistance
- ↳ May be useful in AV block

Selective α_1 -agonists

■ Vasopressor agents

♠ Methoxamine

♠ Metaraminol

♠ Phenylephrine

♠ Midodrine

■ Ophthalmic decongestants & mydriatics

➡ Phenylephrine

➡ Naphazoline

➡ Tetrahydrozoline

■ Nasal decongestants

➡ Naphazoline

➡ Xylometazoline

➡ Oxymetazoline

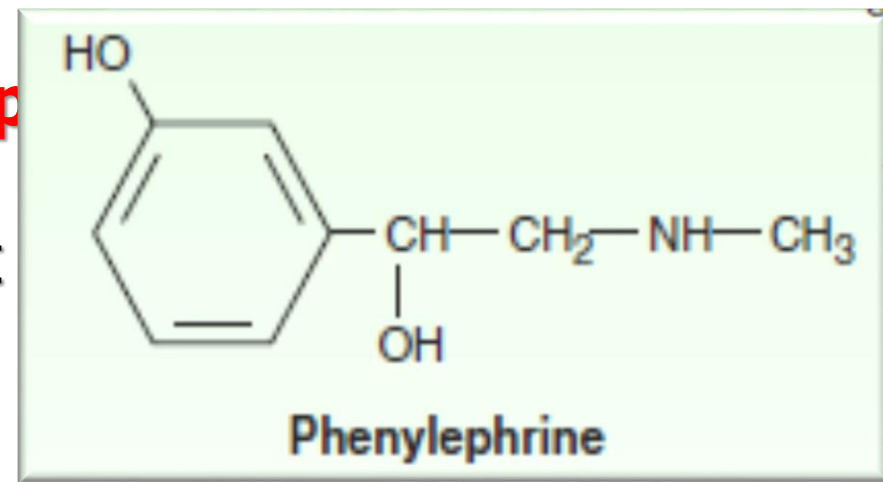
➡ Phenylephrine

➡ Phenylpropanol amine

➡ Propylhexedrine

Phenyleph

- ➔ Selective α_1 receptor agonist
- ➔ Raises both SBP & DBP
- ➔ Activates β receptors only at much higher concentrations
- ➔ Not inactivated by COMT: longer DOA
- ➔ Action-effective mydriatic and vasoconstrictor
- ➔ Use: Rx of glaucoma, as decongestant
- ➔ Raise the blood pressure: followed by reflex bradycardia



Midodrine

- ✓ A prodrug hydrolyzed to desglymidodrine, a selective α_1 -receptor agonist
- ✓ $C_{\max}$ of desglymidodrine is achieved about 1 hr after PO midodrine
- ✓ **Use:** primarily for the Rx of orthostatic hypotension, typically due to impaired ANS function
- May cause hypertension when the subject is supine

▪ **Oxymetazoline**

➡ Direct-acting α -agonist: stimulates both α_1 & α_2

✓ **Use:**

- short-term decongestants (nasal spray)
- ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, and contact lenses.
- It causes vasoconstriction which decreases congestion

⊗ **Adverse effects:**

- Nervousness, headache, trouble sleeping
- Rebound congestion & dependence with long-term use

α_2 -selective Agonists

- ✓ Act mainly in CNS: used as antihypertensive
- ✓ Activation of presynaptic α_2 inhibits release of NE by -ve feedback => fall in BP
- Clonidine, Apraclonidine
- Alpha-methyldopa
- Guanfacine, Guanabenz

Methyldopa

▪ MOA:

- ✓ α -methyldopa is the substrate for Dopa-decarboxylase & converted to α -methyl dopamine & α -methyl norepinephrine
- ✓ α -methyl norepinephrine is powerful stimulator of α_2 & hence decrease release of NE

■ **MOA...**

- ✓ Decrease sympathetic out flow ($\downarrow$ HR & contractility, veins dilate ($\downarrow$ EDV) = $\downarrow$ SBP)
 - ✓ Artery dilate ($\downarrow$ TPR = $\downarrow$ DBP)
 - ✓ JGA ($\downarrow$ renin, less Ag II) = less salt & water retention, veins & artery dilated
-
- **Use:** mainly for management of HTN in pregnancy

■ Side effects:

- ✓ Sedation: interfere with ascending reticular formation in the brain stem
- ✓ Dry mouth (xerostomia)
- ✓ Impotence: ↓ sympathetic out flow
- ✓ Positive coombs test & hepatitis (reversible)

- ✓ Dizziness & vertigo: vein dilation => less cerebral perfusion (vestibular nuclei)
- ✓ Salt & water retention: as a compensatory mechanism
- Less blood flow to kidney due to drop in perfusion pressure ↓GFR → slow flow through tubules → more reabsorption
- ❖ Hence better in combination with diuretics
- ✓ Don't stop abruptly (due to over expression of receptors): super sensitivity; rebound hypertension

Clonidine

- ➔ Central α_2 agonist → inhibition of sympathetic vasomotor centers → decreasing sympathetic outflow to the periphery → reduced TPR & BP
- ➔ Overdose stimulates peripheral postsynaptic α_1 adrenoceptors & cause hypertension by vasoconstriction
- ➔ Use: treatment of systemic hypertension
- ✓ Low dose Clonidine (50-100 μ g/dl) is used in migraine prophylaxis and menopausal flushing

▪ **Adverse effects:**

- ➔ Dry mouth, sedation, sexual dysfunction, bradycardia
- ➔ Withdrawal syndrome (rebound hypertension) follows abrupt discontinuation of long-term therapy with clonidine in some hypertensive patients
- ➔ TCAs antagonize antihypertensive action & increase rebound hypertension of abrupt withdrawal

Newer α_2 -agonists

- **Moxonidine, Rilmenidine**
 - ✓ Additionally act on imidazoline receptors
 - ✓ Have fewer CNS side effects
 - ✓ Available for the treatment of HTN
- **Dexmedetomidine:** primarily for sedation in an intensive care setting or before anesthesia
 - ✓ It also reduces the requirements for opioids in pain control
- **Tizanidine:** structurally related to clonidine
 - ✓ Used as a centrally acting muscle relaxant
 - ✓ Increases presynaptic inhibition of motor neurons

β-Adrenergic agonists

↳ β1-agonists:

✓ Dopamine

✓ Dobutamine: synthetic analogue of dopamine

✓ Prenalterol: a partial agonist

↳ Increase cardiac output with less reflex tachycardia as compared with nonselective β agonists: isoproterenol

↳ Limitation: tolerance with prolonged use

Dopamine

- ↪ Principally a NT in CNS, also acts in the PNS
- ↪ Main receptors: D₁ (PNS) & D₂ (CNS)
- ↪ D₁ found mainly in renal & splanchnic blood vessels
- 1-5µg/kg/min IV (low dose): increase RBF & urine output => D₁
- 5-15µg/kg/min IV (medium dose): increase RBF & CO, HR, contractility of the heart => β₁

➤ 20-50µg/kg/min IV (high dose): increase BP; may not have benefit (reno protective effect lost): α1

❖ Increase infusion by 1-4µg/kg/min @ 10-30' intervals

■ Use

👍 DOC for cardiogenic & septic shock: continuous infusion

👍 Rx of refractory CHF

■ PKs:

↳ Onset: rapid (5')

↳ DOA: $t_{1/2}$: 2'; short (<10')

↳ Distribution: does not cross BBB

↳ Metabolism: in liver, plasma, kidney by MAO & COMT

↳ Excreted in the urine as metabolite (80%)

Dobutamine

- ⇒ Stimulates β_1 on heart $\Rightarrow$ $\uparrow$ contractility
- ⇒ Minimal action on α & β_2
- ⇒ Net effect is $\uparrow$ ed CO, with decreased SVR with or without a small reduction in BP
- ⇒ Used to $\uparrow$ CO in acute heart failure with out severe hypotension
- ⇒ For inotropic support after cardiac surgery
- ⇒ Does not significantly elevate oxygen demands of the myocardium

■ PKs:

- ↪ On set: 1-10', DOA: $t_{1/2}$: 2'; short (10');
 - ↪ Metabolism: in liver & tissues by COMT; 3-O-Me-dobutamine (inactive)
 - ↪ Excretion: in urine as glucuronide conjugate
- ## ■ Side effects: tachycardia, palpitation, mild hypertension
- 👉 Should be used with caution in atrial fibrillation, because it increases AV conduction

Fenoldopam

- ⇒ Agonist of peripheral dopamine D1 receptors
- ⇒ A rapid-acting vasodilator to treat severe hypertension
- ✓ Acting on coronary arteries, kidney arterioles & mesenteric arteries
- ⇒ PK: ROA; IV infusion
- ⇒ Undergoes extensive first-pass metabolism, $t_{1/2}$: 10'
- ⇒ SE: headache, flushing, dizziness, nausea, vomiting, & tachycardia (due to vasodilation)

Use of selective β_2 agonists

- ➡ Rx of bronchial asthma: bronchodilators
 - ✓ Metaproterenol, Salbutamol (Albuterol), Terbutaline, Pibuterol, Bitolterol, Formoterol, Salmeterol
- ➡ As uterine relaxant & peripheral vasodilator: Ritodrine, Nylidrine, Isoxuprine
- ✓ Suppress premature labor
- ➡ Main difference is in their PK profiles for all β_2 agonists

Metaproterenol

- ➔ Belong to the structural class of resorcinol bronchodilators
- ✓ Have OH groups at 3 & 5 rather than at 3rd & 4th positions
- ✓ So, it is resistant to metabolism by COMT
- ➔ Available in IH & PO dosage forms
- ➔ Less β_2 selective, compared to albuterol & terbutaline
- ✓ More prone to cause cardiac stimulation
- **Use:**
- **In the** long term Rx of obstructive airway disease &
- ✓ **Acute** bronchospasm

Terbutaline

- ➡ Is short-acting β_2 agonist: SABA
- ➡ Belongs to resorcinol bronchodilators
- ✓ Resistant to COMT
- ➡ Effective in PO, SC or IH routes
- ✓ Onset: rapid from IH & SC
- ➡ Uses:
- ✓ Long term treatment of obstructive airway disease
- ✓ Treatment of acute bronchospasm
- ✓ Emergency treatment of status asthmaticus

Albuterol (salbutamol)

- ➡ SABA DOC for the Rx of acute asthma symptoms
- ➡ ROA: IH or PO
- ➡ Indications: as terbutaline
- ➡ PO: albuterol has the potential to delay preterm labor

Formoterol

- ➡ Is long acting, β_2 selective agonist: LABA
- ➡ It is highly lipophilic, stored in adipocytes
- ✓ Responsible for sustained action
- ➡ An alternative to salmeterol for Rx of nocturnal asthma

Salmeterol

- ➡ Partial agonist
- ➡ At least 50 times more β_2 selective than albuterol
- ➡ Highly lipophilic & has sustained action
- ➡ Long duration of action: >12hours
- ➡ Has slow onset of action
- ✓ Not suitable monotherapy for acute attacks of asthma

- ➡ Due to its sustained duration of action;
- ✓ DOC for Rx of nocturnal asthma
- ✓ Shouldn't be used more than BID
- ✓ Shouldn't be used for to treat acute asthma
- ➡ Metabolized by CYP3A4 to α -OH-salmeterol
- ➡ Excretion: through feces

Ritodrine

- ↪ Selective β_2 agonist, developed specifically for use as uterine relaxant
- ↪ Absorption: 30% after PO
- ↪ Excretion: 90% via urine as inactive conjugate
- ↪ Uses: given IV in selected pts to arrest premature labor

Adverse effects of β 2 selective adrenomimetics

- ➔ Tremor, feeling of restlessness, apprehension & anxiety
- ➔ Tachycardia, which may result from
 - ✓ β 1 stimulation
 - ✓ Reflex response to peripheral vasodilation
- ➔ Cardiac arrhythmias or myocardial ischemia
 - ✓ Less likely to in pts without pre-existing cardiac disease
 - ✓ High risk of occurrence in pts with underlying CAD or pre-existing arrhythmia

- ➔ Pulmonary edema: in women who receive ritodrine or terbutaline for preterm labor
- ➔ Larger doses of β_2 adrenomimetics may
 - ✓ Increase plasma glucose level
 - ✓ Increase lactate & free fatty acids level in plasma
 - ✓ Hypokalemia
- ☛ Note: all the ADRs are far less likely with IH than with parenteral or PO therapy

■ **Mirabegron**

- β_3 selective agonist that relaxes the detrusor smooth muscle & increases bladder capacity
- Used for pts with overactive bladder: urinary urgency & frequency
- May increase BP & should not be used in patients with uncontrolled hypertension

INDIRECT ACTING ADRENERGIC AGONISTS

▪ MOA:

- ✓ Enter the sympathetic nerve ending & displace stored catecholamines: amphetamine like or “displacers”
- ✓ Inhibit reuptake by interfering with the action of NET
- ✓ MAO & COMT inhibitors

▪ **Releasing agents**

- Amphetamine
- Phenmetrazine
- Methylphenidate
- Modafinil
- Tyramine

Amphetamine

- ➡ Marked central stimulatory action is often mistaken by drug abusers as its only action
- ➡ $\uparrow$ BP significantly (α -agonist action) on vasculature as well as β -stimulatory effects on the heart
- ➡ **MOA:** primary through the cellular release of stored catecholamines: DA, NE

Effects:

- ✓ Euphoria, insomnia, suppress appetite
- ✓ Decrease the feeling of fatigue

Therapeutic use:

- ✓ Narcolepsy (tendency to fall sleep)
- ✓ Attention deficit hyperactivity disorder: ADHD
- ✓ Weight reduction

Tyramine

- ➡ Enter the nerve terminal & displace stored catecholamine
- ➡ Clinically not useful, but it is important as it is found in fermented foods: aged cheese & Chianti wine
- ➡ A by-product of tyrosine metabolism
- ➡ Normally oxidized by MAO in the GIT
- ➡ If the patient is taking MAOIs: hypertensive crisis

Food	Tyramine Content of an Average Serving
Beer	4–45 mg
Broad beans, fava beans	Negligible (but contains dopamine)
Cheese, natural or aged	Nil to 130 mg (cheddar, Gruyère, and Stilton especially high)
Chicken liver	Nil to 9 mg
Chocolate	Negligible (but contains phenylethylamine)
Sausage, fermented (eg, salami, pepperoni, summer sausage)	Nil to 74 mg
Smoked or pickled fish (eg, pickled herring)	Nil to 198 mg
Wine (red)	Nil to 3 mg
Yeast (eg, dietary brewer's yeast supplements)	2–68 mg

Reuptake Inhibitors: Cocaine

- A local anesthetic with sympathomimetic action by inhibiting reuptake of catecholamines
- It readily enters the CNS and produces an amphetamine-like psychological effect
- ✓ Inhibit DA reuptake into neurons in the “pleasure centers” of the brain

Atomoxetine & Reboxetine

- ✓ Selective inhibitor of NET
- ✓ Used in the treatment of attention deficit disorders

Duloxetine & Milnacipran

- ✓ 5-HT & NE transporter blocker
- ✓ Approved for the treatment of pain in fibromyalgia

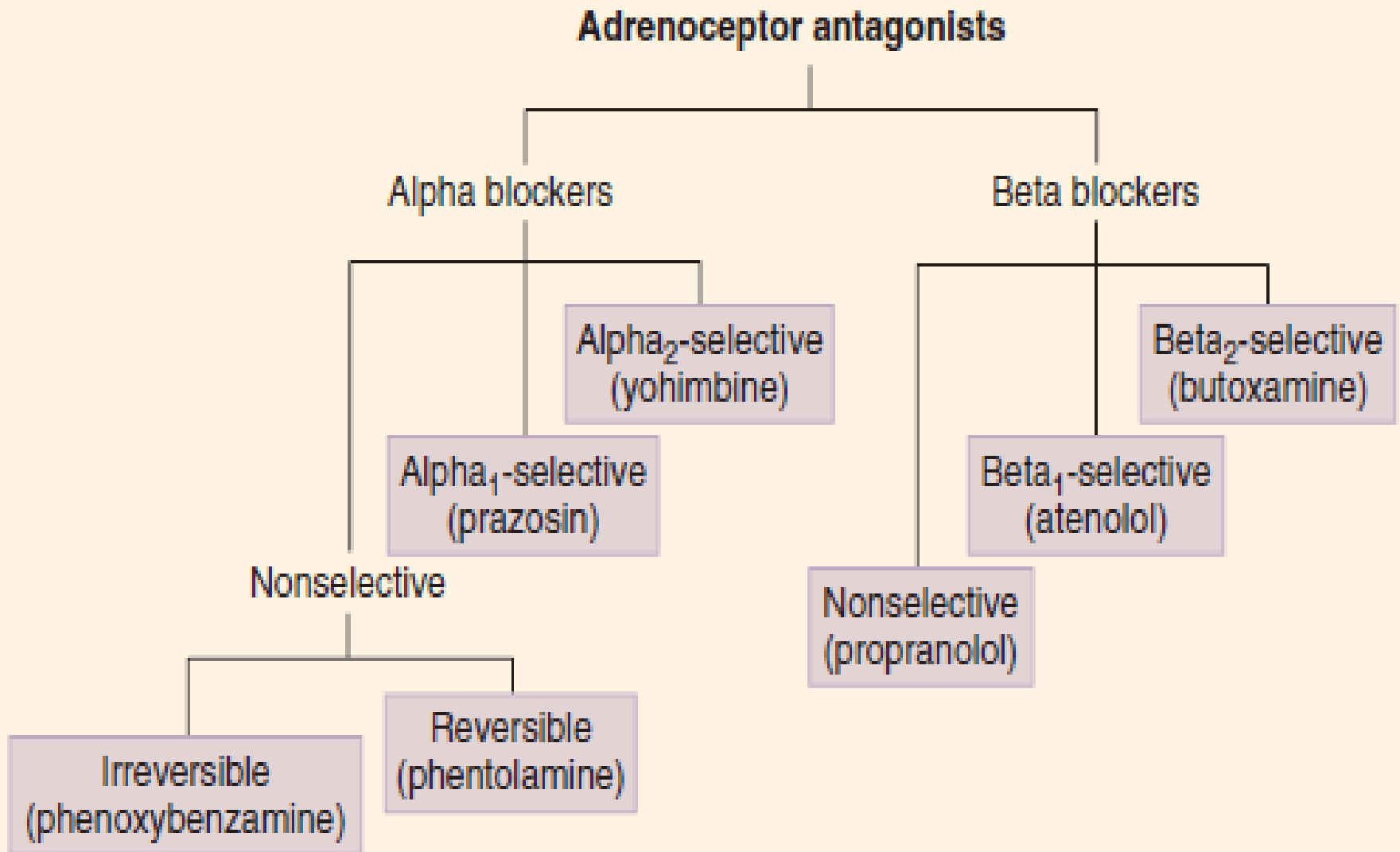
Mixed acting adrenergic agonists

▪ Ephedrine

- ☞ A plant alkaloid, is now made synthetically
- ☞ Releases stored NE from nerve endings & directly stimulate both α & β receptors
- ☞ It is not a catechol: poor substrate for COMT and MAO;
- ✓ Has a long duration of action but less potent

- ☞ Excellent absorption orally & penetrates in to CNS
- ☞ Raises BP by vasoconstriction & cardiac stimulation
- ☞ Produces bronchodilation
- ☞ Used to treat asthma, nasal congestion & to raise BP
- ☞ Clinical use is declining due to availability of better, more potent agents which cause fewer site effects

Adrenergic Antagonists: Sympatholytics



Alpha Receptor Antagonists

```
graph TD; A[Alpha Receptor Antagonists] --> B[Non-selective]; A --> C["α1-selective"]; A --> D["α2-selective"];
```

Non-selective

- phenoxybenzamine
- phentolamine

α₁-selective

- prazosin
- terazosin
- doxazosin
- alfuzosin
- tamsulosin
- indoramin
- urapidil
- bunazosin

α₂-selective

- yohimbine

Alpha-receptor blockers

- **Non competitive antagonists: irreversible**

- ✓ Form stable (covalent) bonds with α receptors & their effects can persist for days or even weeks

- Phenoxybenzamine: $\alpha_1 > \alpha_2$

- ✓ **Reversible, competitive antagonists:**

- ✓ Persists only for a few hours

- Phentolamine: $\alpha_1 = \alpha_2$

- Prazosin, Terazosin, doxazosin: α_1 - selective

Selective α_1 -antagonists:

- ➡ Prazosin, terazosin, doxazosin, tamsulosin
- ➡ Are highly selective for α_1 receptors: relaxation of both arteries & veins
- ✓ Leads to fall in EDV & TPR (lowered preload & after load)
- ✓ Exhibit greater clinical utility than non-selective blockers

- ☞ They generally differ in their pharmacokinetics
- ☞ Well absorbed after PO, highly bound to plasma proteins
- ☞ Metabolized in the liver & excreted in the feces & urine
- ☞ Except tamsulosin, others are non-selective among α_1 subtypes: α_{1A} , α_{1B} , α_{1D}
- ✓ Tamsulosin-more on α_{1A} (prostate & bladder) less on α_{1B} (blood vessels) $\Rightarrow$ least effect on BP
- ✓ Improves urine flow

■ Therapeutic uses

- 👍 Rx of essential hypertension
- 👍 CHF: b/c reduce both preload & after load
- 👍 BPH owing to
 - ✓ Relaxation of smooth muscles in the bladder neck, prostate capsule & prostatic urethra
 - ✓ Rapidly improve urine flow

■ Side effects

- 👉 1st dose phenomenon: major SE
- ✓ Postural hypotension & syncope: after 30-90' of 1st dose
- Minimized by limiting initial dose & gradually increasing the dose
- 👉 Headache, dizziness, asthenia (loss of strength)
- 👉 Tamsulosin may cause impaired ejaculation
- ✓ Doesn't produce orthostatic hypotension @ therapeutic dose unlike the other α_1 -blockers:
- Due to its selective effect on α_{1A} receptors

■ Prazosin

- ✓ Extensively metabolized
- ✓ Only about 50% BA
- ✓ Half-life: about 3 hours

■ Terazosin

- ✓ High bioavailability
- ✓ A small fraction is excreted
- ✓ Half-life: 9-12 hours
- ✓ For hypertension & BPH

■ Doxazosin

- ✓ Extensively metabolized
- ✓ Moderate BA
- ✓ Longer half-life ~22 hrs
- ✓ For HTN & BPH

■ Alfuzosin

- ✓ BA~60%
- ✓ Approved for use in BPH
- ✓ May increase risk of QT

Selective α_2 -antagonists

- **Mirtazapine:** used as antidepressant
- **Yohimbine:** is an alkaloid obtained from plants
- ✓ Readily enters to CNS
- ✓ Competitive α_2 -selective antagonist: $\uparrow$ SNS, $\uparrow$ BP & HR
- Produces opposite effects to clonidine
- **Therapeutic uses:**
 - Rx of erectile dysfunction in men
 - Not widely used due to availability of effective agents

Non-selective α -blockers: block α_1 & α_2

✓ Phenoxybenzamine, Phentolamine, Tolazoline

▪ **Phenoxybenzamine**

☞ Is a haloalkylamine that blocks both α_1 & α_2 irreversibly

☞ Major effect is vasodilation: α blocking in blood vessels

➤ Causes reduced TPR: α_1 & α_2 blockade

➤ ↑ed CO: due to reflex sympathetic stimulation

☞ Tachycardia:

- ✓ Reflex to hypotension, ↑ release of NE/EP due to blockage of presynaptic α_2A adrenoceptors
- In addition to antagonism of α -receptor, it can
- ✓ Blocks H1, mAChRs & 5-HT & inhibits uptake of NE
- ✓ Half life: < 24 hrs but,
- ☞ DOA maintained for days: due to irreversible inactivation of α -receptors

▪ **Therapeutic uses:**

- ☞ Rx of pheochromocytoma
- ☞ Rx of BPH: to reduce obstructive symptoms only

▪ **Adverse effects:**

- ✓ Reflex tachycardia
- ✓ Postural hypotension
- ✓ Inhibit ejaculation

■ **Phentolamine & tolazoline**

- ✓ Are competitive antagonists at α adrenoceptors
- ✓ Antagonism is reversible, have short duration of action
- ✓ Tolazoline is less potent than phentolamine

■ **Action:**

- ✓ $\downarrow$ BP by blocking α -receptors (α_1 & α_2B)
- ✓ Reflex $\uparrow$ HR, $\uparrow$ CO
- Vasodilation $\rightarrow \downarrow$ BP $\rightarrow$ reflex excitement on heart
- Block presynaptic α_{2A} $\rightarrow \uparrow$ release of NE/EP $\rightarrow$ activate β_1

▪ **Therapeutic uses:**

- ✓ BPH, Pheochromocytoma
- ✓ Hypertensive emergencies
- ✓ Local vasoconstrictor excess

▪ **Side effects:**

- ✓ Postural hypotension, reflex tachycardia
- ✓ GI stimulation: abdominal pain, nausea, PUD

➤ **Stimulate cholinergic & histaminergic receptors**

Beta Receptor Antagonists

Non-selective (First Generation)

- nadolol
- penbutolol
- pindolol
- propranolol
- timolol
- sotalol
- levobunolol
- metipranolol

β_1 -selective (Second Generation)

- acebutolol
- atenolol
- bisoprolol
- esmolol
- metoprolol

Non-selective (Third Generation)

- carteolol
- carvedilol*
- bucindolol
- labetalol*

β_1 -selective (Third Generation)

- betaxolol
- celiprolol
- nebivolol

Esmolol: shortest half life, 10'

Drugs marked by * also block α_1

β -blockers

① Cardio selectivity: β_1

✓ Less effect on vasculature, bronchioles, uterus, & metabolism

✓ Safer in asthma, DM, peripheral vascular diseases

② Combined α_1 & β blocking activity: **Lab**etalol & carvedilol

✓ Use in CHF (carvedilol) & in HTN emergencies (labetalol)

③ K^+ channel & β -blocking activity: Sotalol

④ Intrinsic activity & membrane stabilizing activity

✓ May be considered as partial antagonists

👍 Less bradycardia (β_1)

👍 Slight vasodilation or bronchodilation (β_2)

👍 Minimal change in plasma lipids (β_2)

👉 Acebutolol, carteolol, celiprolol, pindolol, penbutolol

Pharmacological actions of β -blockers

① Heart: β_1

- ✓ ↓Automaticity & AV-conduction
- ✓ ↓myocardial contraction & ↓HR
- Over all effect on the CVS: ↓ BP
- ✓ ↓Automaticity & conduction: Rx of arrhythmia
- ✓ ↓In O_2 demand in pts with CAD; angina & MI

② CNS/Neurological: sedation with Propranolol, Carvedilol

③ Liver: β_2

✓ Decrease glycogenolysis, increase LDLs, TGs

✓ Aggravate hypoglycemia in DM pts treated with insulin or oral hypoglycemic agents

✓ β_1 selective blockers are less likely to produce hypoglycemic effects

④ Respiratory system: bronchoconstriction

- ✓ Little effect on pulmonary functions of normal individuals
- ✓ Cause life-threatening bronchospasm in pts with COPD
- ✓ β_1 selective blockers or those with intrinsic sympathomimetic activity are less likely than propranolol to cause severe bronchoconstriction

- ⑤ Eye (β_2): $\downarrow$ IOP by reducing production of aq. humor
- ⑥ Adipose tissue
 - ✓ Non selective β blockers reduce lipolysis
 - ✓ Reduce HDL, increase LDL & increase triglycerides
- ⑦ Kidney (β_1): reduce renin release
- ⑧ Blood vessels in skeletal muscle (β_2): vasoconstriction

General therapeutic uses of B-blockers

- Rx of HTN: labetalol, atenolol, metoprolol, propranolol, timolol
- ✓ B/c they ↓CO, ↓sympathetic outflow from the CNS & ↓rennin release from kidneys
- ✓ Usually used in combination with diuretics or vasodilators

↪ In IHD:

✓ In the treatment of angina pectoris

↪ Propranolol, metoprolol, atenolol

✓ Contractility & HR $\Rightarrow$ $\downarrow$ work load $\Rightarrow$ $\downarrow$ myocardial oxygen demand

✓ Prevention of myocardial infarction

- ➡ In Rx of cardiac arrhythmias: class II: propranolol, acebutolol, Esmolol
- ✓ Decrease automaticity and AV node conduction velocity
- ➡ In treatment of glaucoma: Betaxolol, levobunolol, timolol
- ✓ Timolol is applied topically to treat glaucoma
- ✓ They do not affect accommodation & pupillary reactions

- In hyperthyroidism: propranolol
- ✓ Reduce symptoms of sympathetic over activity caused by the excess thyroxin
- In pheochromocytoma: Propranolol together with α_1 -blockers
- Anxiety: to ↓ sympathetic manifestations (propranolol)
- Migraine headache (propranolol)
- ✓ Blockade of cranial beta receptors reduce vasodilation

Adverse effects of β -blockers

- ☛ CVS: bradycardia, hypotension, AV block
- ✓ More pronounced with β_1 selectives
- ☛ Bronchoconstriction
- ☛ Hypoglycemia, affect lipid profile
- ☛ Muscle pain & fatigue, sleep disturbances, nightmares
- ☛ Impaired sexual activity
- ☛ Reduce peripheral blood flow $\Rightarrow$ cold extremities
- ✓ Produced by non-selective blockers

Contraindications to β -blockers

- ✗ Heart failure, bradycardia, slow AV-node conduction
- ✗ Asthma & COPD
- ✗ Diabetes mellitus, hypothyroidism
- ✗ Combination with Ca^{2+} -channel blockers
- ✗ Some general anesthetics- cardiac depression

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
<i>Propranolol</i>	β_1, β_2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
<i>Nadolol</i> <i>Pindolol</i> ¹	β_1, β_2	Hypertension
<i>Timolol</i>	β_1, β_2	Glaucoma, hypertension
<i>Atenolol</i> <i>Bisoprolol</i> ² <i>Esmolol</i> <i>Metoprolol</i> ²	β_1	Hypertension Angina Myocardial infarction
<i>Acebutolol</i> ¹	β_1	Hypertension
<i>Nebivolol</i>	β_1 , NO ↑	Hypertension
<i>Carvedilol</i> ² <i>Labetalol</i>	$\alpha_1, \beta_1, \beta_2$	Hypertension

Characteristics of some beta blockers

Drugs	β_1 -Selective	ISA	Sedation	Blood Lipids
Acebutolol	+	++	+	-
Atenolol	+	-	-	↑↑
Metoprolol	+	-	+	↑↑
Pindolol	--	++	+	-
Propranolol	-	-	+++	↑↑
Timolol	-	-	++	↑↑

ISA=intrinsic sympathetic activity

	Selectivity	Partial Agonist Activity	Local Anesthetic Action	Lipid Solubility	Elimination Half-life	Approximate Bioavailability
Acebutolol	β_1	Yes	Yes	Low	3–4 hours	50
Atenolol	β_1	No	No	Low	6–9 hours	40
Betaxolol	β_1	No	Slight	Low	14–22 hours	90
Bisoprolol	β_1	No	No	Low	9–12 hours	80
Carteolol	None	Yes	No	Low	6 hours	85
Carvedilol ¹	None	No	No	Moderate	7–10 hours	25–35
Celiprolol	β_1	Yes	No	Low	4–5 hours	70
Esmolol	β_1	No	No	Low	10 minutes	0
Labetalol ¹	None	Yes	Yes	Low	5 hours	30
Metoprolol	β_1	No	Yes	Moderate	3–4 hours	50
Nadolol	None	No	No	Low	14–24 hours	33
Nebivolol	β_1	γ^2	No	Low	11–30 hours	12–96
Penbutolol	None	Yes	No	High	5 hours	>90
Pindolol	None	Yes	Yes	Moderate	3–4 hours	90
Propranolol	None	No	Yes	High	3.5–6 hours	30 ³
Sotalol	None	No	No	Low	12 hours	90
Timolol	None	No	No	Moderate	4–5 hours	50

¹Carvedilol and labetalol also cause α_1 -adrenoceptor blockade.

² β_1 agonist
ANS Pharmacology

³Bioavailability is dose-dependent.

- **β_2 - selective antagonists**

↳ Butoxamine

✓ Clinical use???

Drugs Affecting Neurotransmitter Release or Uptake

▪ Reserpine

- ✓ Blocks the Mg^{2+} /ATP dependent transport of biogenic amines (NE, DA, 5-HT) from cytoplasm in to storage vesicles
- ✓ Deplete NE from the adrenergic nerve terminal stores
- ✓ Impaired general function of Symp.
- ✓ Slow onset and long duration of action

■ **Guanethidine**

- ✓ Blocks release of the stored NE as well as displaces NE from storage vesicles
- ✓ Gradual depletion of NE in nerve endings (except in CNS)
- ✓ Orthostatic hypotension, male sexual dysfunction, supersensitivity to NE due to depletion (hypertension crisis in patient with pheochromocytoma)