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Programme: M.Sc., Biomedical Science

Course Title : Pharmacology and Toxicology
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Unit-2
Pharmacology of ANS - Part 2

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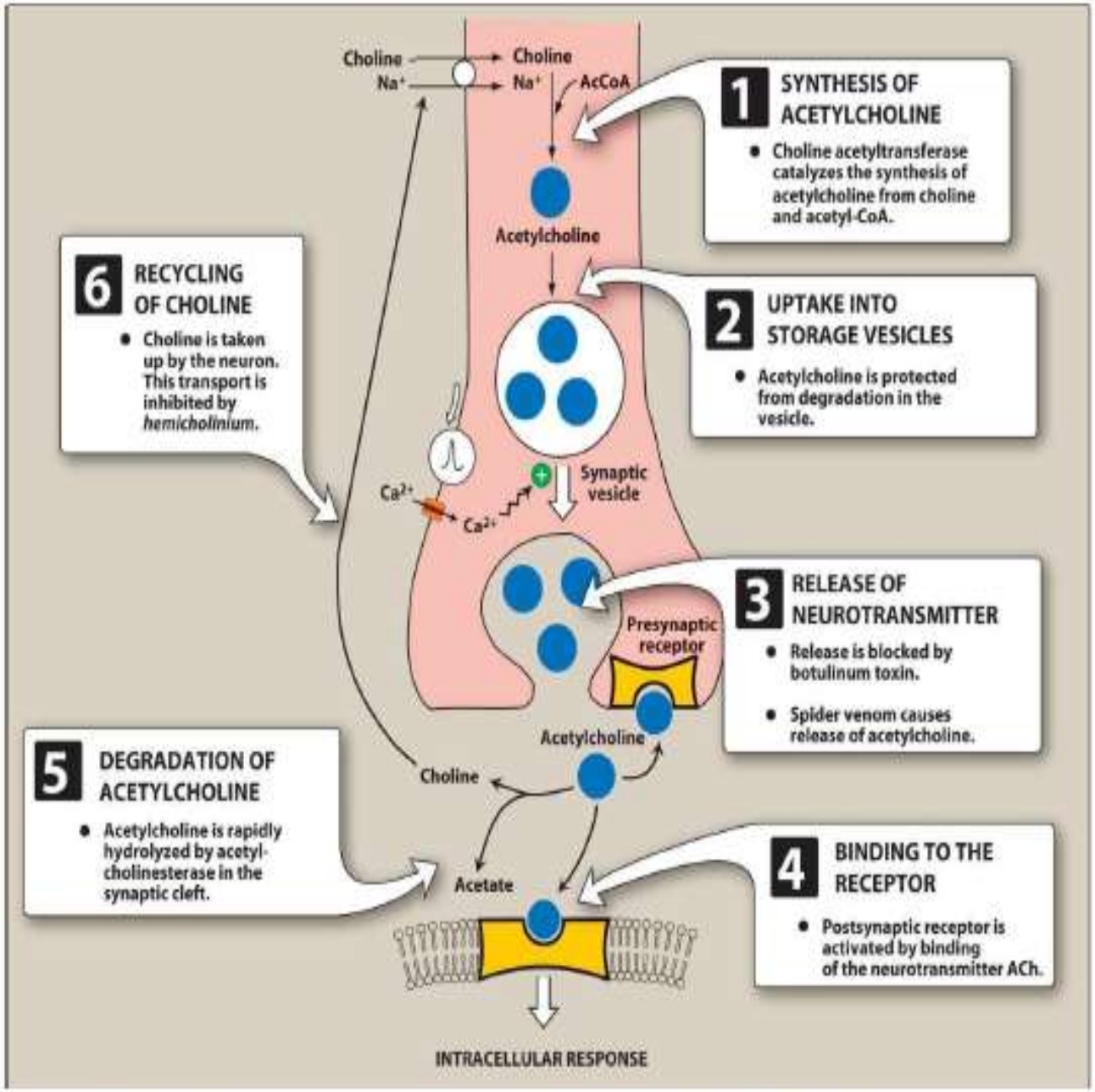
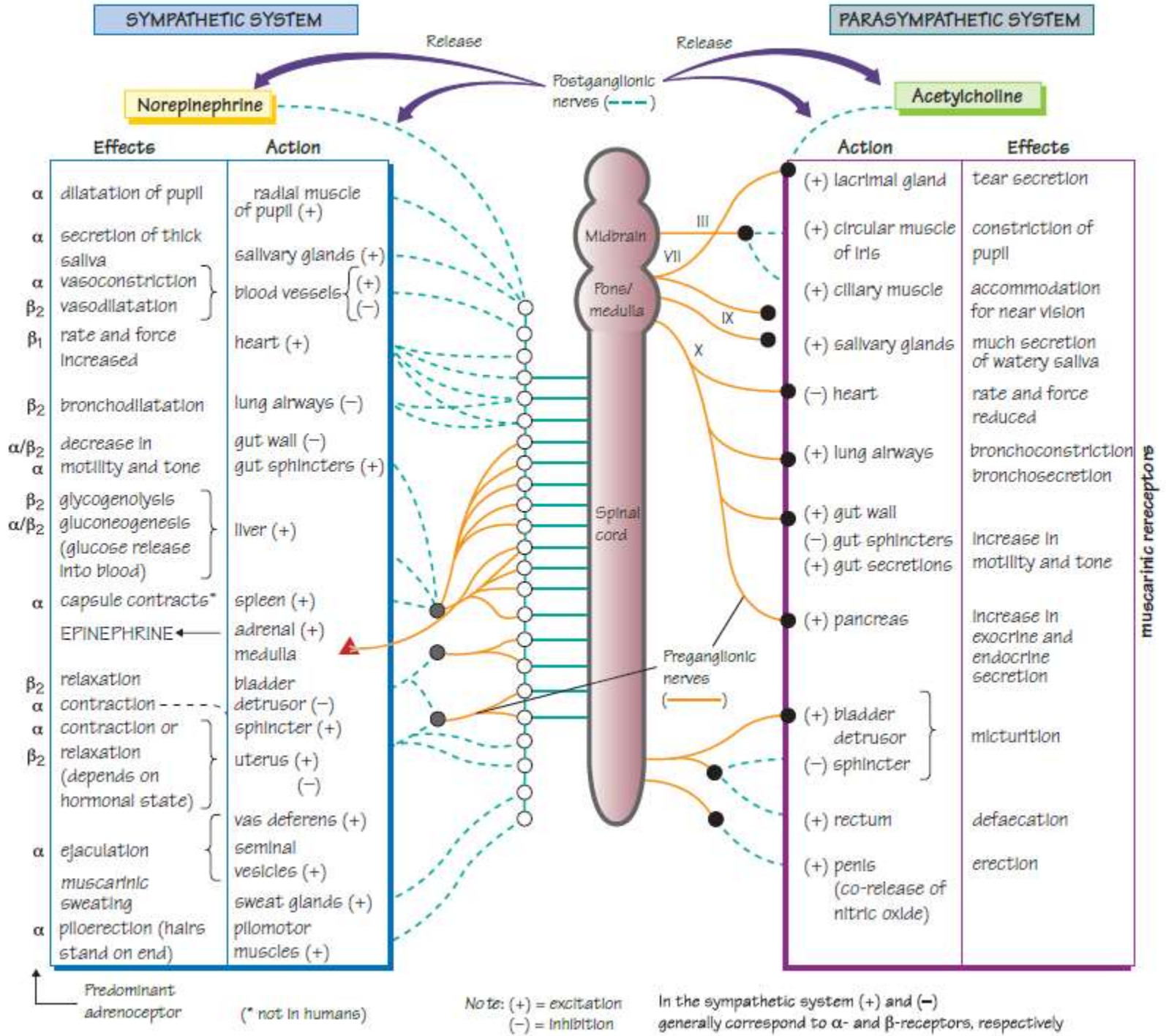
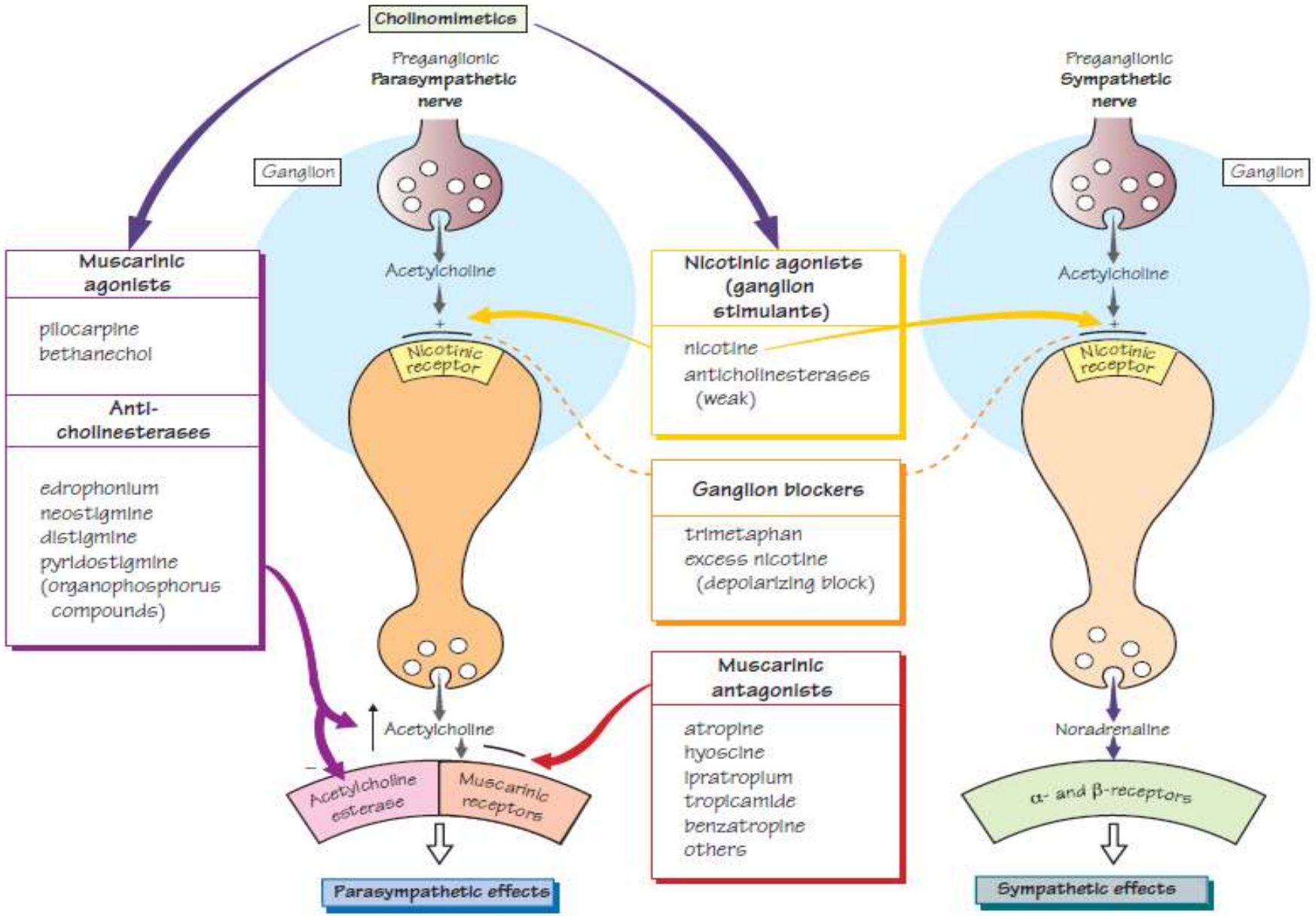


Figure 4.3 Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.


SYMPATHETIC SYSTEM
PARASYMPATHETIC SYSTEM
Release
Release
Postganglionic nerves (– – –)
Norepinephrine
Acetylcholine
Effects
Action
Action
Effects
α dilatation of pupil
radial muscle of pupil (+)
α secretion of thick saliva
salivary glands (+)
α vasoconstriction
β2 vasodilatation
blood vessels (+) (–)
β1 rate and force increased
heart (+)
β2 bronchodilatation
lung airways (–)
α/β2 decrease in
α motility and tone
gut wall (–)
gut sphincters (+)
β2 glycogenolysis
α/β2 gluconeogenesis (glucose release into blood)
liver (+)
α capsule contracts*
spleen (+)
EPINEPHRINE
adrenal (+) medulla
β2 relaxation
α contraction
bladder detrusor (–)
α contraction or
β2 relaxation (depends on hormonal state)
sphincter (+)
uterus (+) (–)
vas deferens (+)
α ejaculation
seminal vesicles (+)
muscarinic sweating
sweat glands (+)
α piloerection (hairs stand on end)
pilomotor muscles (+)
Midbrain
Pons/ medulla
Spinal cord
III
VII
IX
X
Preganglionic nerves (——)
(+) lacrimal gland
tear secretion
(+) circular muscle of iris
constriction of pupil
(+) ciliary muscle
accommodation for near vision
(+) salivary glands
much secretion of watery saliva
(–) heart
rate and force reduced
(+) lung airways
bronchoconstriction
bronchosecretion
(+) gut wall
(–) gut sphincters
(+) gut secretions
increase in motility and tone
(+) pancreas
increase in exocrine and endocrine secretion
(+) bladder detrusor
(–) sphincter
micturition
(+) rectum
defaecation
(+) penis (co-release of nitric oxide)
erection
muscarinic rereceptors
Predominant adrenoceptor
(* not in humans)
Note: (+) = excitation
(–) = inhibition
In the sympathetic system (+) and (–) generally correspond to α- and β-receptors, respectively

8 Autonomic drugs acting at cholinergic synapses



(Cholinomimetic, Parasympathomimetic)

- These are drugs which produce actions similar to that of ACh, either by directly interacting with cholinergic receptors (cholinergic agonists) or by increasing availability of Ach.

CHOLINERGIC AGONISTS

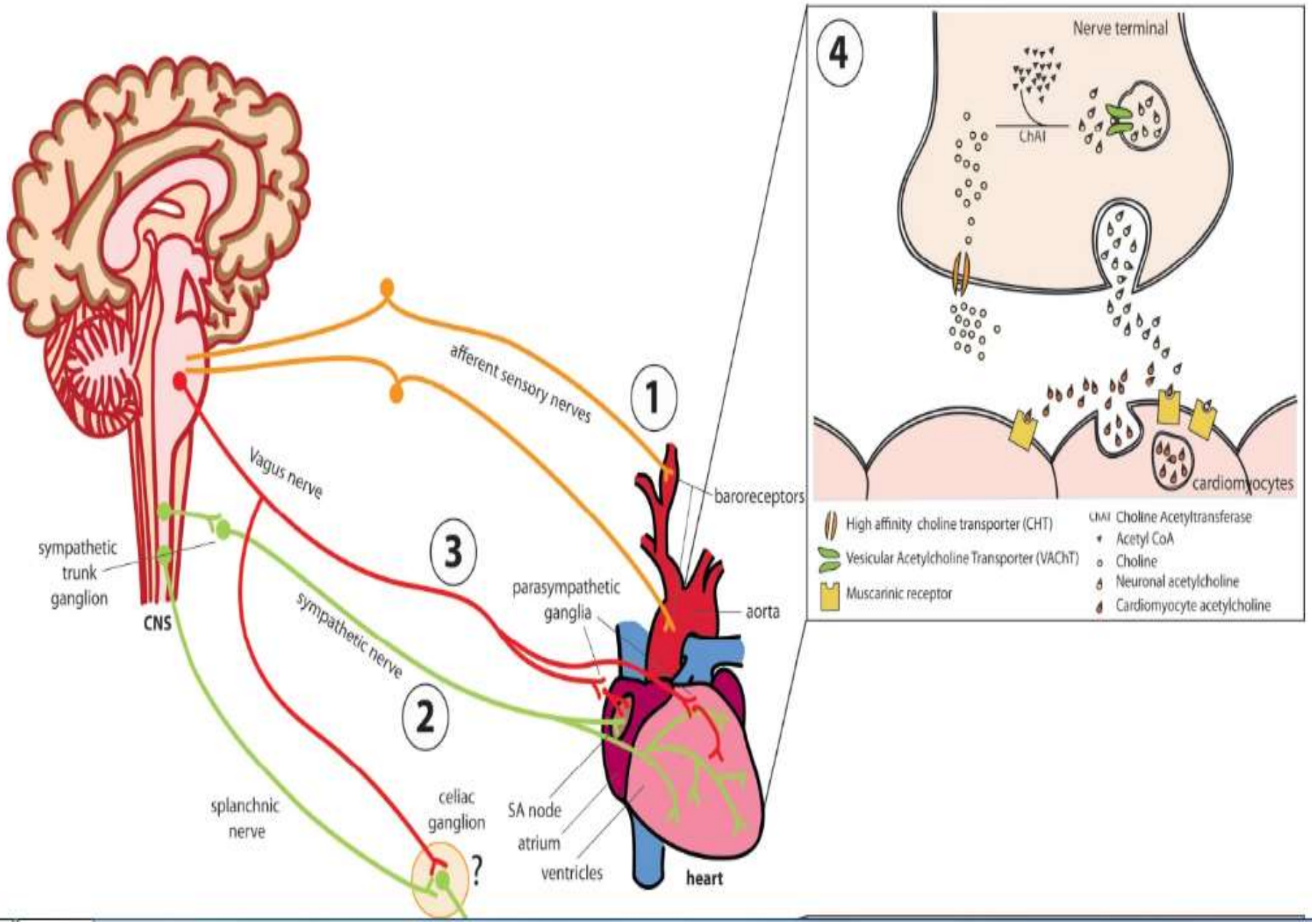
- Choline esters
- Acetylcholine
- Methacholine
- Carbachol
- Bethanechol

Alkaloids

- Muscarine
- Pilocarpine
- Arecoline

A. Muscarinic

- **1. Heart :** ACh hyperpolarizes the SA nodal cells and decreases the **rate of diastolic depolarization**. As a result, rate of impulse generation is reduced **bradycardia or even cardiac arrest** may occur.
- At the A-V node and His-Purkinje fibres refractory period (RP) is increased and conduction is slowed:
- Due to nonuniform vagal innervation, the intensity of effect on RP and conduction of different atrial fibres varies inducing in homogeneity and predisposing to **atrial fibrillation or flutter.**
- Ventricular contractility is also decreased but the effect is not marked.
- The cardiac **muscarinic receptors are of the M2 subtype.**


afferent sensory nerves
1
baroreceptors
Vagus nerve
3
sympathetic trunk ganglion
CNS
parasympathetic ganglia
aorta
sympathetic nerve
2
splanchnic nerve
celiac ganglion
?
SA node
atrium
ventricles
heart
4
Nerve terminal
ChAT
cardiomyocytes
High affinity choline transporter (CHT)
Vesicular Acetylcholine Transporter (VAChT)
Muscarinic receptor
ChAT Choline Acetyltransferase
Acetyl CoA
Choline
Neuronal acetylcholine
Cardiomyocyte acetylcholine

2. Blood vessels

- All blood vessels are dilated, though only few (skin of face, neck, salivary glands) receive cholinergic innervation.
- Fall in BP and flushing, especially in the blush area occurs.
- **Muscarinic (M3) receptors** are present on vascular endothelial cells: vasodilatation is primarily mediated through the release of an endothelium dependent relaxing factor **(EDRF) which is nitric oxide (NO).**
- It may also be due to inhibitory action of ACh on NA release from tonically active vasoconstrictor nerve endings.

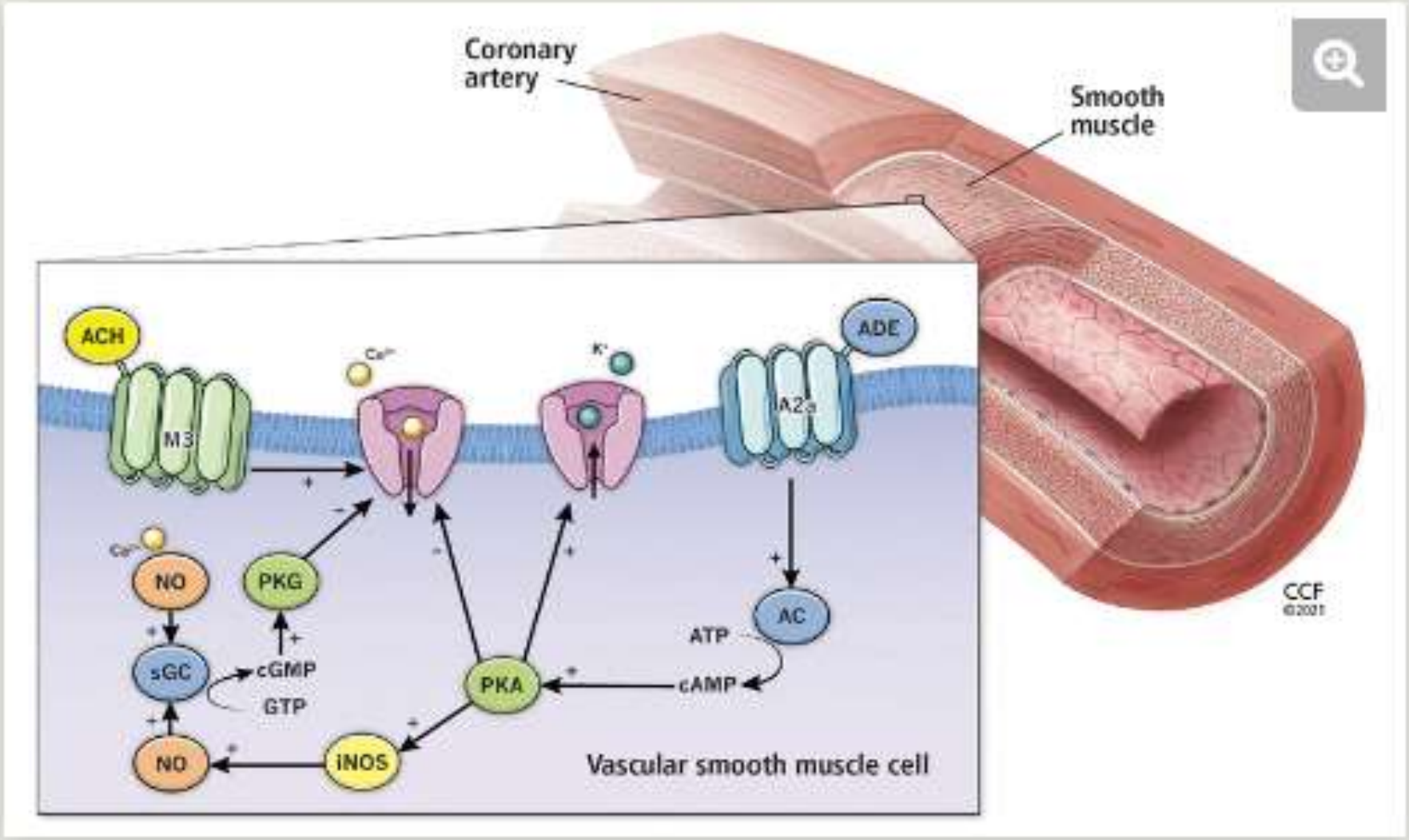


Figure 1

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The effects of acetylcholine (ACH) and adenosine (ADE) on the smooth muscle of the coronary vasculature. ACH binds to the muscarinic receptor (M3), stimulating the release of calcium (Ca^{2+}) into the vascular smooth muscle cell, which drives nitric oxide (NO) formation for vasodilation and also drives contraction for vasoconstriction. ADE stimulates the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), leading to inhibition of calcium influx and induction of nitric oxide formation, both of which result in vasodilation.

Smooth muscle

- Smooth muscle in most organs is contracted (mainly through **M3 receptors**).
- Tone and **peristalsis in the gastrointestinal tract is increased** and sphincters relax abdominal cramps and evacuation of bowel.
- **Peristalsis in Ureter is increased**. The detrusor muscle contracts while the bladder trigone and sphincter relaxes - voiding of bladder.
- **Bronchial muscles constrict, asthmatics** are highly sensitive- dyspnoea, precipitation of an attack of bronchial asthma.

Glands

- Secretion from all parasympathetically innervated glands is increased **via M3 and some M2 receptors:** sweating, salivation, lacrimation, tracheobronchial and gastric secretion.
- The effect on pancreatic and intestinal glands is not marked.
- Secretion of milk and bile is not affected

Eye

- Contraction of circular muscle of iris- miosis.
- Contraction of ciliary muscle -spasm of accommodation, increased outflow facility, reduction in intraocular tension (especially in glaucomatous patients)

B. Nicotinic

- Autonomic ganglia : **Both sympathetic and parasympathetic ganglia are stimulated**.
- This effect is manifested at higher doses.
- High dose of ACh given after atropine causes **tachycardia and rise in BP** due to stimulation of sympathetic ganglia and release of catecholamines

Skeletal muscles

- **Iontophoretic application of ACh to muscle endplate causes contraction of the fibre**.
- Intraarterial injection of high dose can cause twitching and fasciculations, but i. v. injection is generally without any effect (due to rapid hydrolysis of ACh).

CNS

- ACh injected i.v. does not penetrate blood-brain barrier and no central effects are seen.
- Direct injection into the brain, or other cholinergic drugs which enter brain, produce a complex pattern of **stimulation followed by depression**

Uses

- Choline esters are rarely, if ever, clinically used.
- ACh is not used because of evanescent and nonselective action.
- Methacholine was occasionally used to terminate paroxysmal supraventricular tachycardia but is obsolete now.
- Bethanechol has been used in postoperative postpartum nonobstructive urinary retention, neurogenic bladder, congenital megacolon and gastroesophageal reflux.
- Side effects are prominent: belching, colic, involuntary urination/ defecation, flushing, sweating, fall in BP, bronchospasm.

CHOLINOMIMETIC ALKALOIDS

- **Pilocarpine:** It is obtained from the leaves of ***Pilocarpus microphyllus*** and other species.
- It has prominent muscarinic actions and also stimulates ganglia-mainly through ganglionic muscarinic receptors.

Pilocarpine

- Sweating, salivation and increases other secretions as well.
- The cardiovascular effects are complex. Small doses generally cause fall in BP (muscarinic), but higher doses elicit rise in BP and tachycardia which is probably due to ganglionic stimulation (through ganglionic muscarinic receptors).
- Applied to the eye, it penetrates cornea and promptly causes miosis, ciliary muscle contraction and fall in intraocular tension lasting 4-8 hours.

- Pilocarpine is used only in the eye as 0.5—4% drops.
- It is a third-line drug in open angle glaucoma.
- An initial stinging sensation in the eye and painful spasm of accommodation are frequent side effects.
- Other uses as a miotic are to counteract mydriatics after they have been used for testing refraction and to prevent/break adhesions of iris with lens or cornea by alternating it with mydriatics

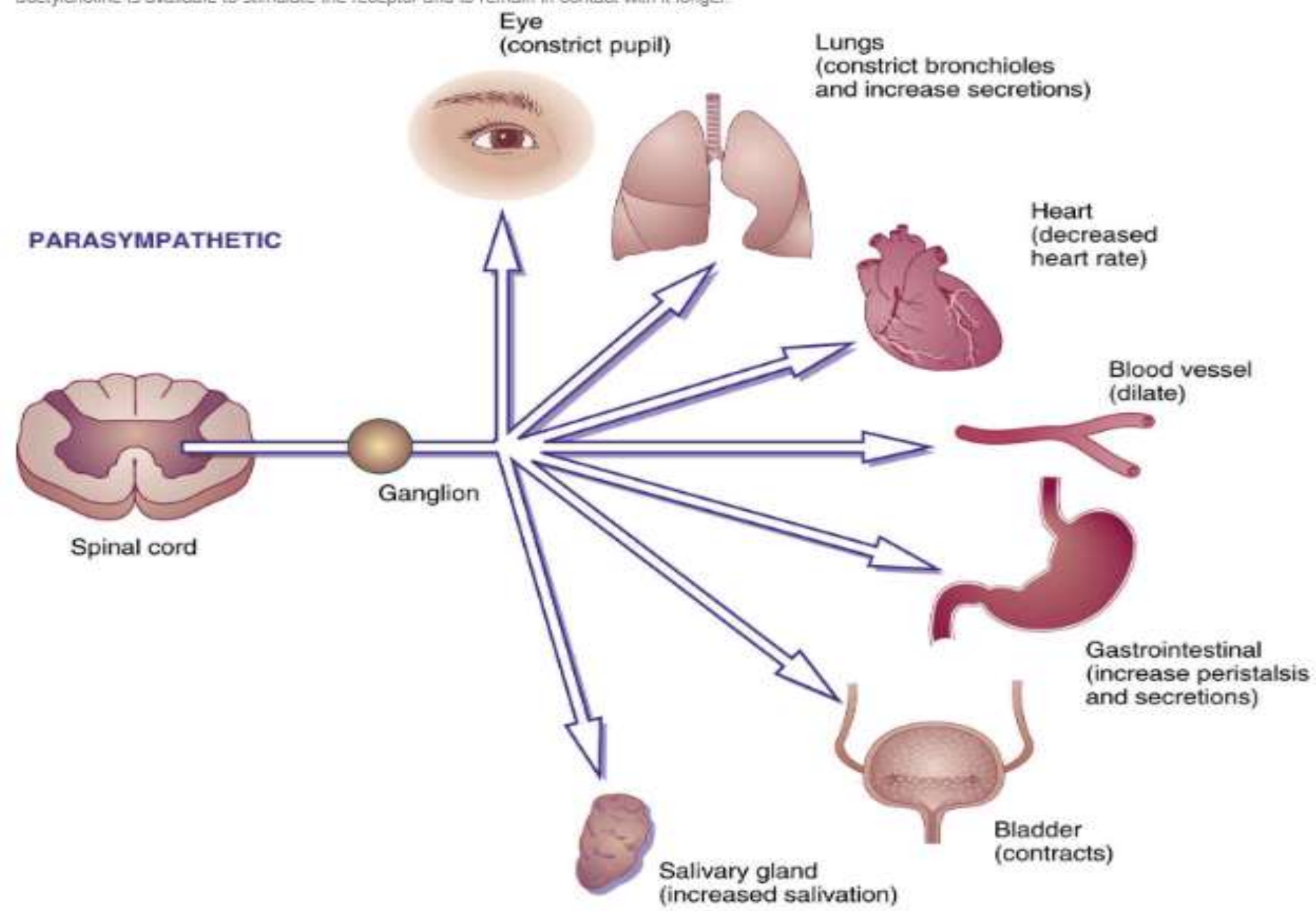


FIG. 16.1 Parasympathetic responses. Stimulation of the parasympathetic nervous system or use of parasympathomimetic drugs will cause the pupils to constrict, bronchioles to constrict and bronchial secretions to increase, heart rate to decrease, blood vessels to dilate, peristalsis and gastric secretions to increase, the bladder muscle to contract, and salivary glands to increase salivation.

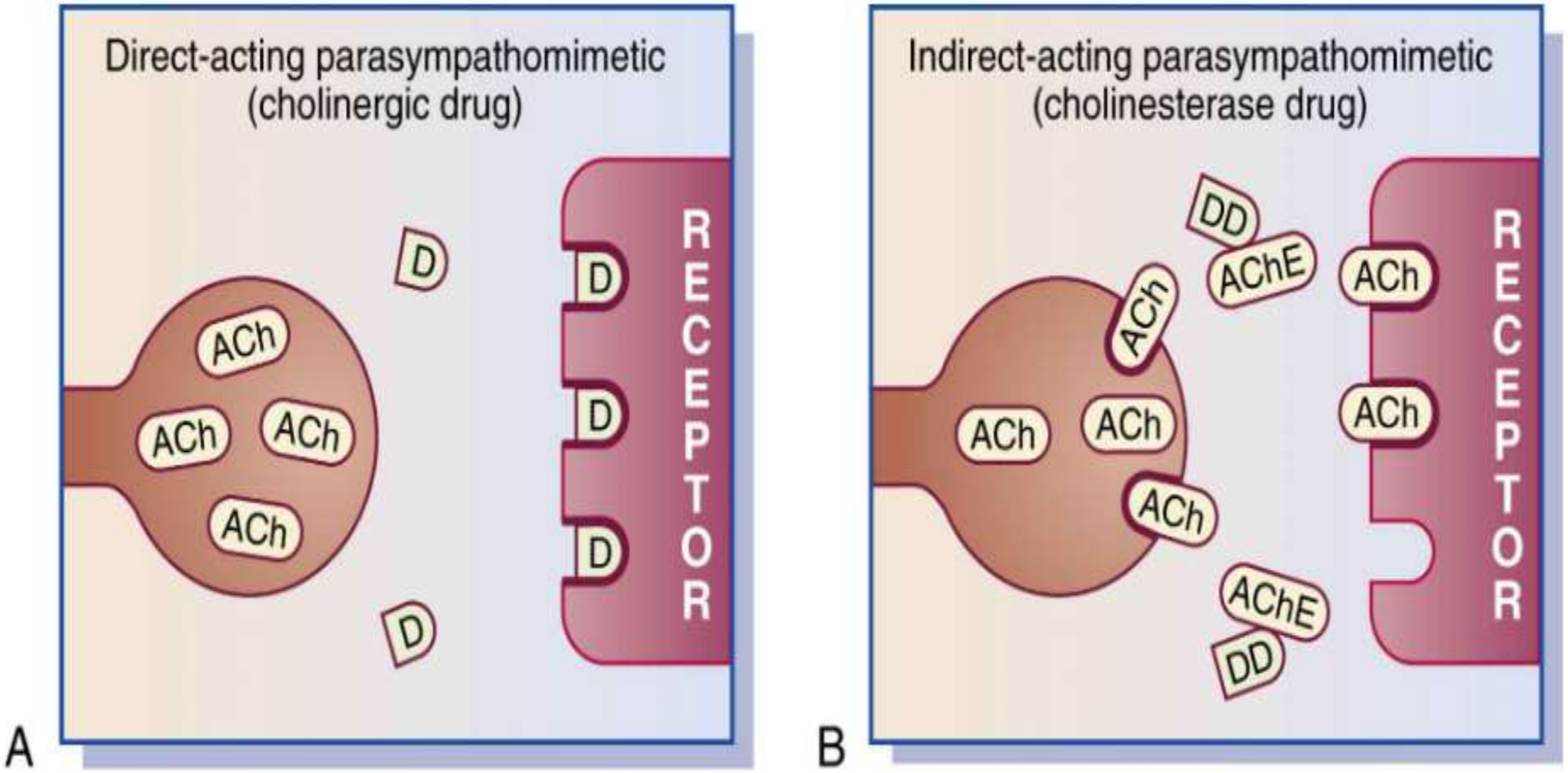


FIG. 16.2 A, Direct-acting parasympathomimetic (cholinergic agonist). Cholinergic agonists resemble acetylcholine and act directly on the receptor. B, Indirect-acting parasympathomimetic (cholinesterase inhibitor). Cholinesterase inhibitors inactivate the enzyme acetylcholinesterase (cholinesterase), thus permitting acetylcholine to react to the receptor. ACh, Acetylcholine; AChE, acetylcholinesterase or cholinesterase; D, cholinergic agonist; DD, cholinesterase inhibitor (anticholinesterase).

Adrenergic neurons

- Adrenergic neurons release norepinephrine as the primary neurotransmitter.
- These neurons are found in the CNS and in the sympathetic nervous system, where they serve as **links between ganglia and the effector organs**.
- Adrenergic drugs act on adrenergic receptors, located either **presynaptically on the neuron** or **postsynaptically** on the effector organ

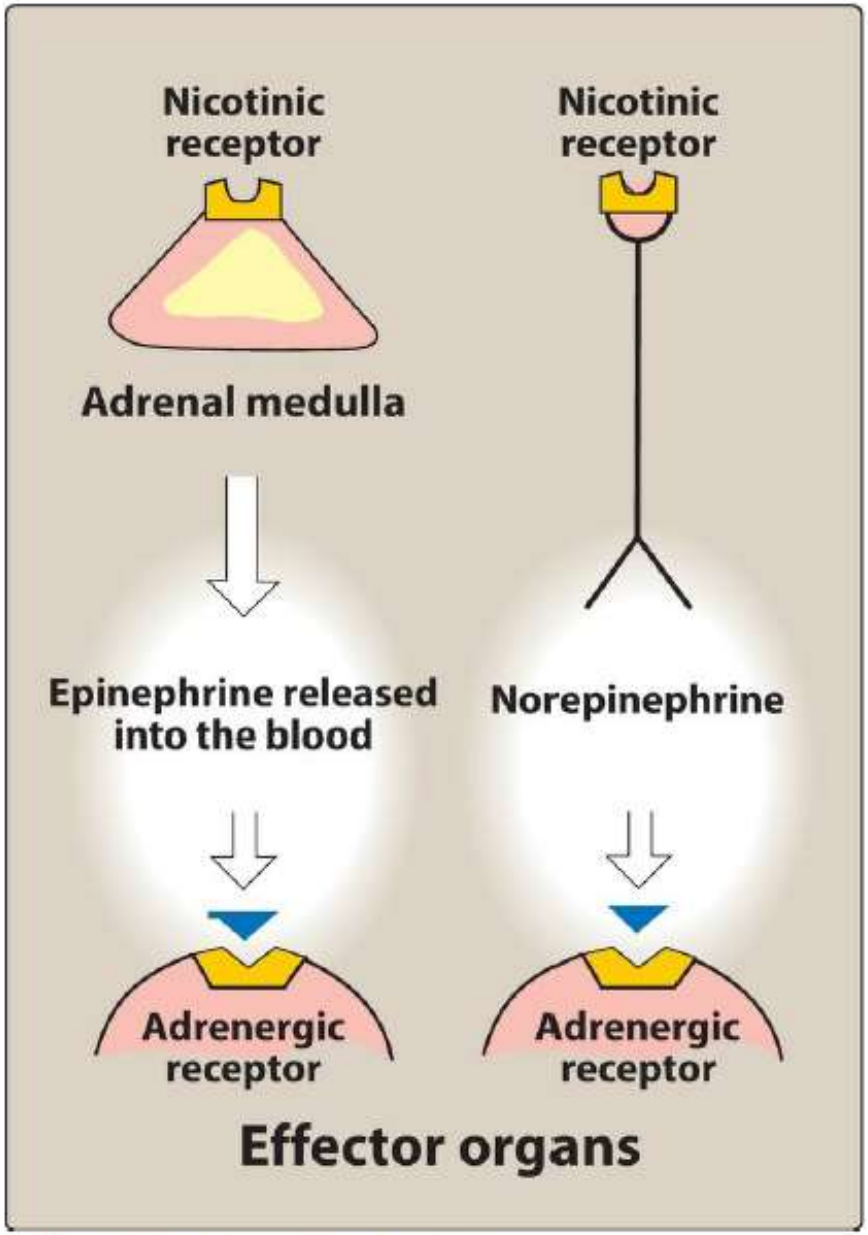


Figure 6.2 Sites of actions of adrenergic agonists.

Adrenoceptors

- ***α-receptors*** *mediate excitatory* effects of sympathomimetic amines,
- Their inhibitory effects are generally mediated by ***β-receptors***

  (exceptions are the smooth muscle of the **gut, for which α-stimulation is inhibitory,** and the **heart, for which β-stimulation is excitatory**).
- Responses mediated by **α- and β-receptors** can be distinguished by:
- (i) phentolamine and propranolol, which *selectively block α- and β-receptors, respectively;* and
- (ii) the relative potencies, on different tissues, of norepinephrine (NE), epinephrine (E) and isoprenaline (I).
- The order of potency is NE > E > I where excitatory (α) responses are examined, but for inhibitory (β) responses this order is reversed (I >> E > NE).

β-Adrenoceptors

- **BA are not homogeneous. Norepinephrine** is an effective stimulant of cardiac β-receptors, but has little or no action on the β-receptors mediating vasodilatation.
- On the basis of the type of differential sensitivity they exhibit to drugs, β-receptors- two types:
- β1 (heart, intestinal smooth muscle)
- B2 (bronchial, vascular and uterine smooth muscle).

α-Adrenoceptors

- **AA are divided into two classes, originally depending** on whether their location is postsynaptic (α1) or presynaptic (α2).
- **Stimulation of the presynaptic α2-receptors** by synaptically released norepinephrine reduces further transmitter release (negative feedback).
- Postsynaptic α2-receptors occur in a few tissues, e.g. Brain, vascular smooth muscle (but mainly α1).

ADRENERGIC TRANSMISSION

Adrenergic (more precisely 'Noradrenergic‘) transmission is restricted to the sympathetic division of the ANS

Endogenous catecholamines

There are three closely related (CAs).

Noradrenaline (NA)

It acts as transmitter at postganglionic sympathetic sites (except sweat glands, hair follicles and some vasodilator fibres) and in certain areas of brain.

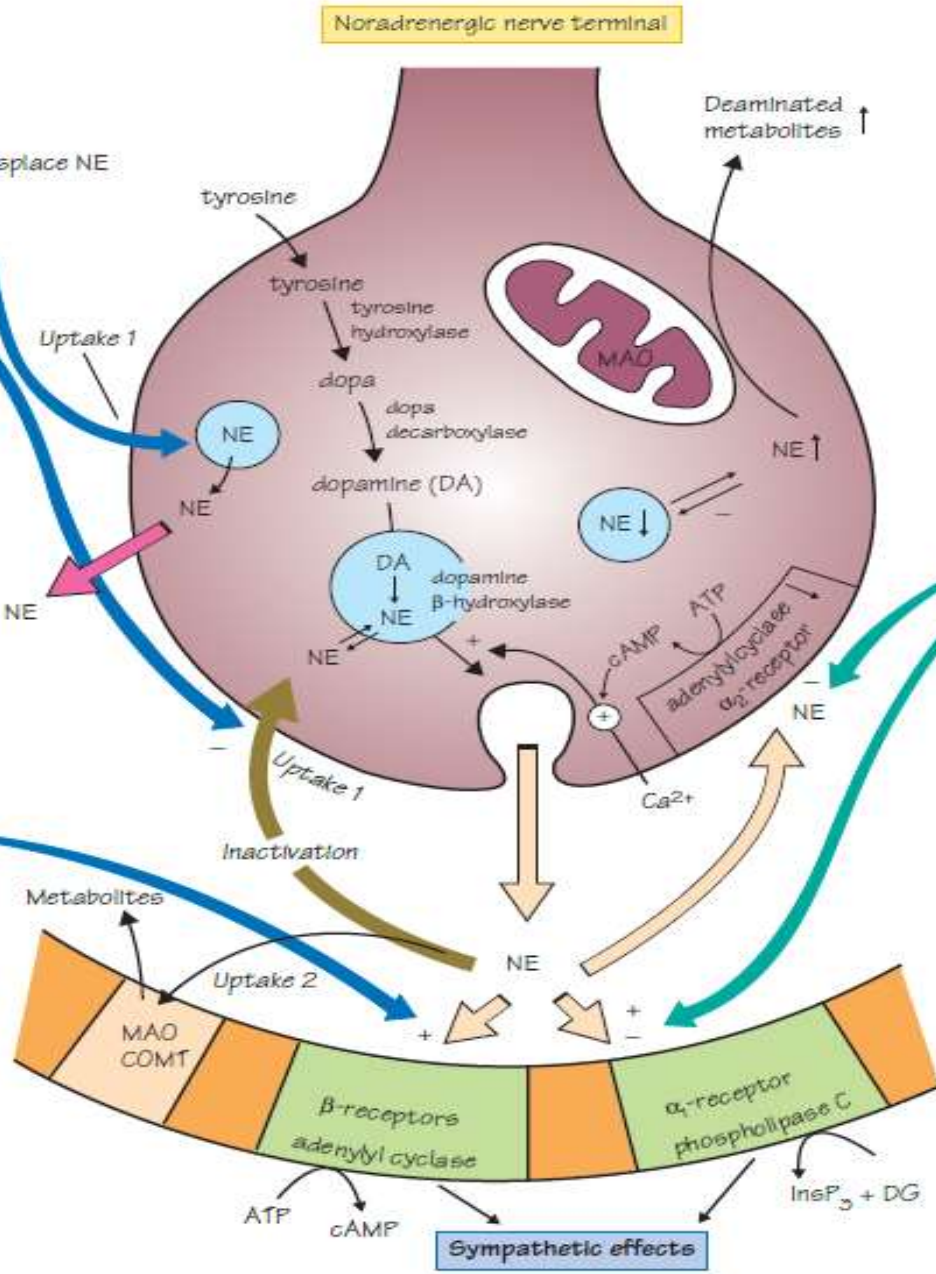
Adrenaline (Adr)

It is secreted by adrenal medulla and may have a transmitter role in the brain.

Dopamine (DA)

It is a major transmitter in basal ganglia, limbic system, CTZ, anterior pituitary, etc. and in a limited manner in the periphery

9 Drugs acting on the sympathetic system



Sympathomimetics

Indirectly acting
- *ephedrine*
- *amfetamine*
- *(tyramine)*
- *cocaine*

Directly acting

α-AGONISTS

α_1/α_2
- *norepinephrine*
- *epinephrine*

α_2
- *clonidine*
- *α-methyl-norepinephrine*

α_1
- *phenylephrine*
- *metaraminol*

β-AGONISTS

β_1/β_2
- *epinephrine*
- *isoprenaline*

β_2
- *salbutamol*
- *terbutaline*

β_1
- *norepinephrine*
- *dobutamine*

Adrenoceptor antagonists

α-BLOCKERS

α_1/α_2
- *phenoxybenzamine*
- *phentolamine*

α_1
- *prazosin*

β-BLOCKERS

β_1/β_2
- *propranolol* †
- *nadolol* ††
- *timolol* †
- *oxprenolol* †*
- *pindolol**
- *carvedilol*

β_1 (cardioselective)
- *metoprolol* †
- *atenolol* ††
- *acebutolol**

* Partial agonist activity
† Most lipid soluble
†† Least lipid soluble

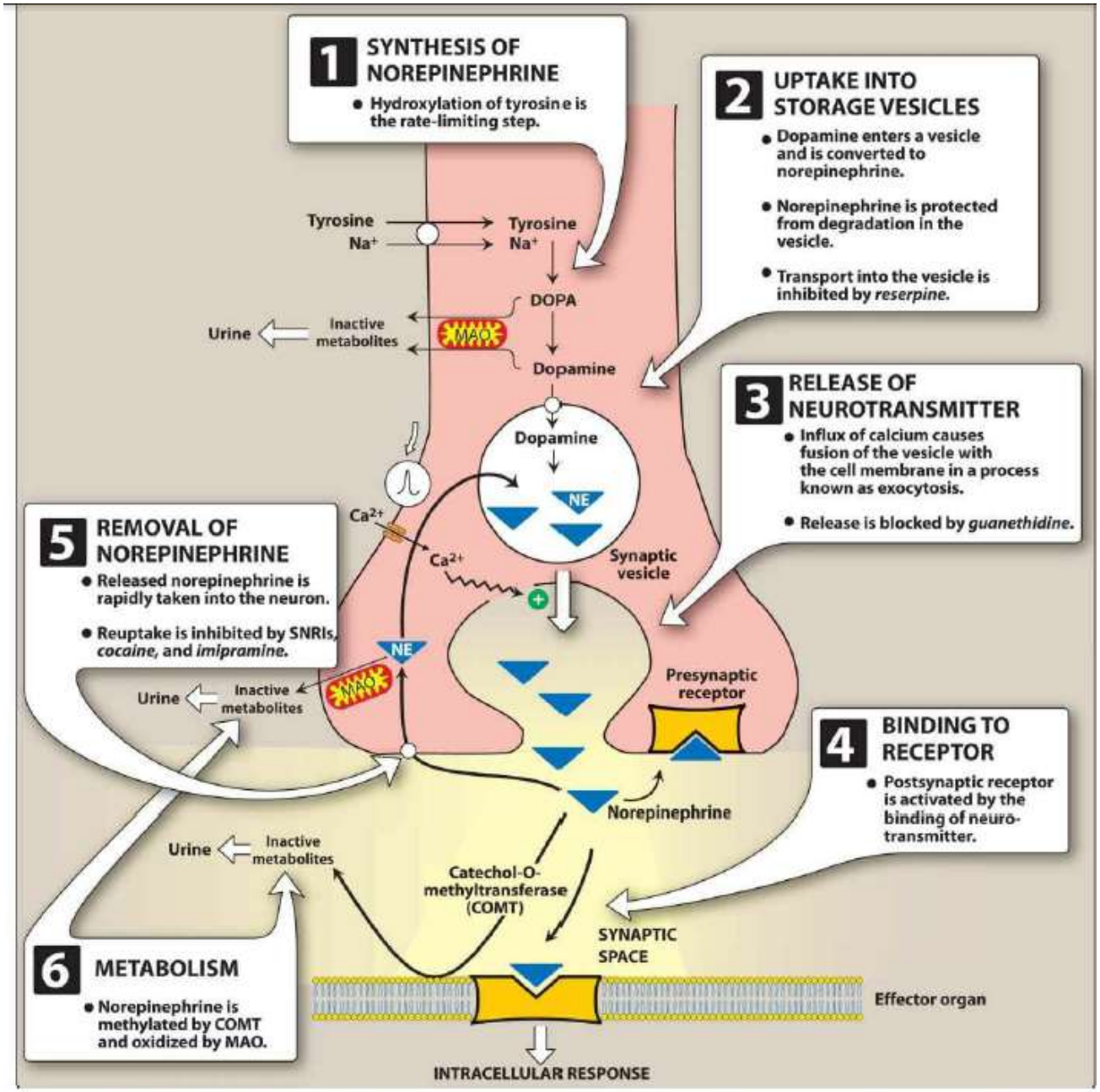


Figure 6.3 Synthesis and release of norepinephrine from the adrenergic neuron. DOPA = dihydroxyphenylalanine; MAO = monoamine oxidase; NE = norepinephrine; SNRI = serotonin–norepinephrine reuptake inhibitor.

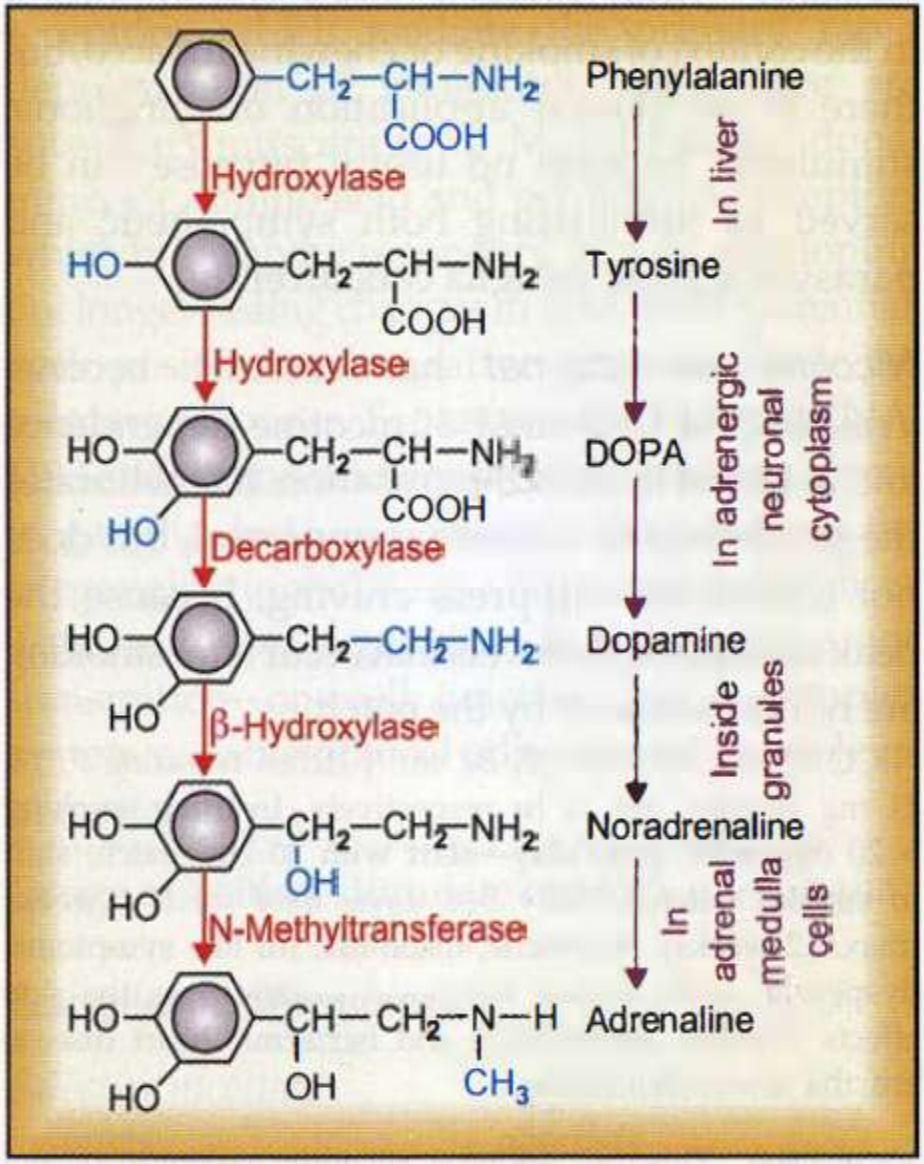


Fig. 9.1: Steps in the synthesis of catecholamines

Synthesis of CAs Catecholamines

- CAs are synthesized from the amino acid phenylalanine
- Tyrosine hydroxylase is the rate limiting enzyme and its inhibition by a methyl-p-tyrosine results in depletion of CAs;
- This can be used in pheochromocytoma before surgery and in inoperable cases.
- All enzymes of CA synthesis are rather nonspecific and can act on closely related substrates,
- **Dopa decarboxylase** from 5-HT from 5-hydroxytryptophan
- **methyl DA** from a methyl dopa.
- Synthesis of NA occurs in all adrenergic neurones, while that of Adr occurs only in the adrenal medullary cells.
- It probably requires high concentration of glucocorticoids reaching through intraadrenal portal circulation for induction of the methylating enzyme

ADRENERGIC DRUGS

- **Sympathomimetics**- These are drugs with actions similar to that of Adr or of sympathetic stimulation.
- **Direct sympathomimetics-** They act directly as agonists on **a** and/ or **b** adrenoceptors - Adr, NA, isoprenaline (Iso), phenylephrine, methoxamine, xylometazoline, salbutamol and many others.
- **Indirect sympathomimetics-** They act on adrenergic neurone to release NA, which then acts on the adrenoceptors - tyramine, amphetamine.
- **Mixed action sympathomimetics-** They act directly as well as indirectly - ephedrine, dopamine, mephentermine.

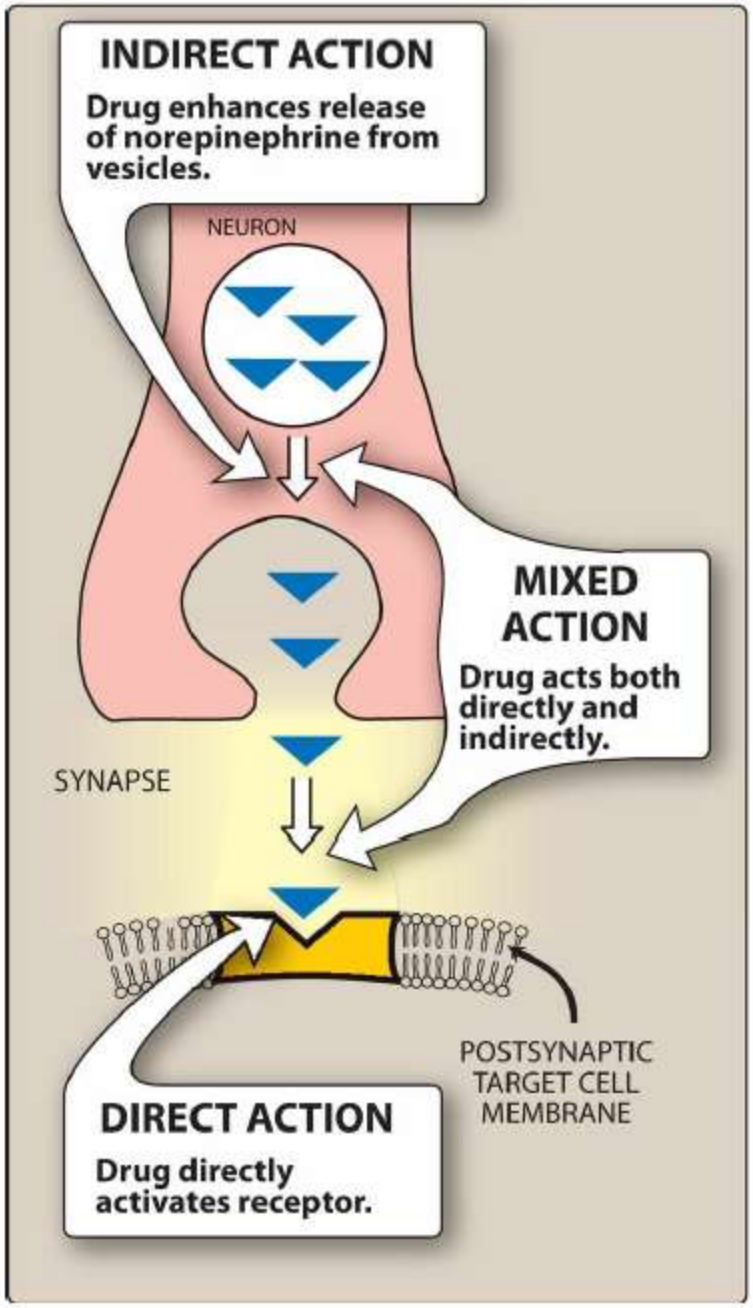


Figure 6.8 Sites of action of direct-, indirect-, and mixed-acting adrenergic agonis

Table 9.5: Adrenergic responses mediated through α and β receptors

	α actions	β actions
1.	Constriction of arterioles and veins → rise in BP ($\alpha_1 + \alpha_2$)	Dilatation of arterioles and veins → fall in BP (β_2)
2.	Heart—little action, arrhythmia at high dose (α_1)	Cardiac stimulation (β_1), ↑ rate, force and conduction velocity
3.	—	Bronchodilatation (β_2)
4.	Contraction of radial muscles of iris → mydriasis (α_1), decreased aqueous secretion	No effect on iris, slight relaxation of ciliary muscle, Enhanced aqueous secretion
5.	Intestinal relaxation, contraction of sphincters	Intestinal relaxation (β_2)
6.	Bladder trigone—contraction (α_1)	Detrusor—relaxation (β_2)
7.	Uterus—contraction (α_1)	Relaxation (β_2)
8.	Splenic capsule—contraction (α_1)	Relaxation (β_2) (slight)
9.	Neuromuscular transmission facilitated, ↑ ACh release	Active state—prolonged in fast contracting muscle, abbreviated in slow contracting muscle; tremors (β_2)
10.	Insulin secretion inhibited (α_2) (dominant)	Augmented insulin (mild) and glucagon secretion (β_2)
11.	Liver—glycogenolysis (α in some species)	Liver—glycogenolysis (β_2) → hyperglycaemia Muscle—glycogenolysis (β_2) → hyperlactacidaemia Fat—lipolysis ($\beta_1 + \beta_2 + \beta_3$) → increased blood FFA, calorigenesis
12.	—	Renin release from kidney (β_1)
13.	Male sex organs—ejaculation (α_1)	—
14.	Salivary gland—K^+ and water secretion (α_1)	Ptylin secretion
15.	—	ADH secretion from posterior pituitary (β_1)
16.	Nictitating membrane—contraction (in animals)	—

CLASSIFICATION OF ADRENERGIC DRUGS

I. Pressor agents
- Noradrenaline
- Phenylephrine
- Ephedrine
- Methoxamine
- **DOPAMINE**
- Mephentermine

II. Cardiac stimulants
- **ADRENALINE**
- Isoprenaline

Ill. Bronchodilators

Isoprenaline

SALBUTAMOL (ALBUTEROL)

Terbutaline

Dobutamine

Salmeterol

Formoterol

Bambuterol

IV. Nasal decongestants

PHENYLEPHRINE

Naphazoline

Xylometazoline

Pseudoephedrine

Oxymetazoline

Phenyl propanolamine

V. CNS stimulants

AMPHETAMINE

Methamphetamine

Dexamphetamine

VI. Anorectics

- **FENFLURAMINE**
- Dexfenfluramine
- Sibutramine

VII. Uterine relaxant and vasodilators

- Ritodrine
- **ISOXSUPRINE**
- Salbutamol
- Terbutaline

Pressor agents

- Dopamine (DA) : It is a dopamine (D1 and D2) as well as adrenergic a and b1 (but not b2) agonist.
- The D1 receptors in renal and mesenteric blood vessels are the most sensitive: i.v. infusion of low dose of DA dilates these vessels (by raising intracellular cAMP).
- This increases g.f.r. and Na+ excretion.
- Moderately high doses produce a positive inotropic (direct B1 and D1 action + that due to NA release), but little chronotropic effect on heart.
- Vasoconstriction (a1 action) occurs only when large doses are infused.

- At doses normally employed, it raises cardiac output and systolic BP with little effect on diastolic BP.
- It has practically no effect on nonvascular a and b receptors; does not penetrate blood-brain barrier-no CNS effects.
- Dopamine is used in patients of cardiogenic or septic shock and severe CHF wherein it increases BP and urine outflow.
- It is administered by i.v. infusion (0.2-1 mg/min) which is regulated by monitoring BP and rate of urine formation.
- DOP AMINE, INTROPIN,

SELECTIVE B2 STIMULANTS

- These include, **salbutamol, terbutaline, salmeterol, formoterol and ritodrine.**
- They cause **bronchodilatation, vasodilatation and uterine relaxation,** without producing significant cardiac stimulation.
- B2 selectivity is only relative.
- used in **bronchial asthma**

Other Uses

- As **uterine relaxant** to delay premature labour.
- **Ritodrine** is the preferred drug
- In **hyperkalaemic familial periodic paralysis**- B2 agonists benefit by **enhancing K +uptake into muscle** - lowering plasma K+ levels.
- The most important side effect is muscle tremor; tachycardia and arrhythmias are less likely.

Amphetamines

- Synthetic compounds- similar to Ephedrine
- Orally (4-6 hours)
- The CNS actions are more prominent;
- Maximal selectivity is exhibited by Dextroamphetamine and Methamphetamine

Central Effects

- Include alertness, increased concentration and attention span, Euphoria, talkativeness, increased work capacity.
- Fatigue is allayed.
- Athletic performance is improved temporarily followed by deterioration. **'dope test'**
- The reticular activating system is stimulated resulting in wakefulness and postponement of sleep deprivation induced physical disability.
- But this is short-lived and may be accompanied by anxiety, restlessness, tremor, dysphoria and agitation.
- Such use before examinations can only be condemned.

Amphetamines

- **Stimulate respiratory centre**, specially if it has been depressed.
- **Hunger is suppressed** as a result of inhibition of hypothalamic feeding centre.
- They also have weak **anticonvulsant, analgesic and antiemetic actions:** potentiate antiepileptics, analgesics and antimotion-sickness drugs.
- Peripheral effects on heart and BP are not significant at the usual doses (which cause only slight rise in BP), but tone of vesical sphincter is definitely increased.

Amphetamines

- Drugs of abuse and are capable of producing marked psychological but little or no physical dependence
- Toxicity - **Administration of chlorpromazine** which controls both central as well as peripheral a adrenergic effects.
- The central actions are largely mediated by release of NA in the brain.
- However, certain actions are probably due to DA and 5-HT release.
- It also inhibits neuronal uptake of DA.

Phenylephrine

- It is a selective **a1** agonist, has negligible **b** action.
- It raises BP by causing vasoconstriction.
- Topically it is used as a nasal decongestant and for producing mydriasis when cycloplegia is not required.
- Phenylephrine tends to reduce intraocular tension by constricting ciliary body blood vessels.
- It is also a frequent constituent of orally administered nasal decongestant preparations.
- Central effects are not seen with usual clinical doses.

Administration and preparations

- CAs are absorbed from the intestine but are rapidly degraded by MAO and COMT present in the intestinal wall and liver. They are thus orally inactive.

1. Adrenaline (Epinephrine)

- For systemic action, 0.2-0.5 mg s.c., i.m., action lasts 1;2 to 2 hrs.
- ADRENALINE 1 mg/ml inj.
- As local vasoconstrictor, 1 in 200,000 to 1 in 100,000 added to lidocaine; in XYLOCAINE with ADRENALINE: lidocaine 21.3 mg + adrenaline 0.005 mg/ml inj; 30 rnl vial.

2. Noradrenaline

- (Norepinephrine, levarterenol) 2-4].ug/min i.v. infusion; local tissue necrosis occurs if the solution extravasates; do not mix with NaHC03in the same bottle (rapid oxidation occurs); action starts declining within 5 min of discontinuing infusion.
- It is rarely used now as a pressor agent.

3. Isoprenaline

- (Isoproterenol) 20 mg sublingual, 1-2 mg i.m., 5-10].ug/ min i.v. infusion; action lasts 1-3 hrs.
- It is occasionally used to maintain idioventricular rate till pacemaker is implanted.
- For bronchial asthma, it has been superseded by selective B2 agonists.
- ISOPRIN 4 mg/2 ml inj, NEOEPININE 20 mg sublingual tablets.

Acknowledgement

- The Presentation is being used for educational and non commercial Purposes
- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.