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PHARMACOLOGY OF PERIPHERAL NERVOUS SYSTEM

Part 1: Adrenergic system

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Human nervous system

- The nervous system has 2 main parts:
 - **Central Nervous System (CNS)** is made up of the brain and spinal cord
 - **Peripheral Nervous System (PNS)** is made up of nerves that branch off from the spinal cord and extend to all parts of the body

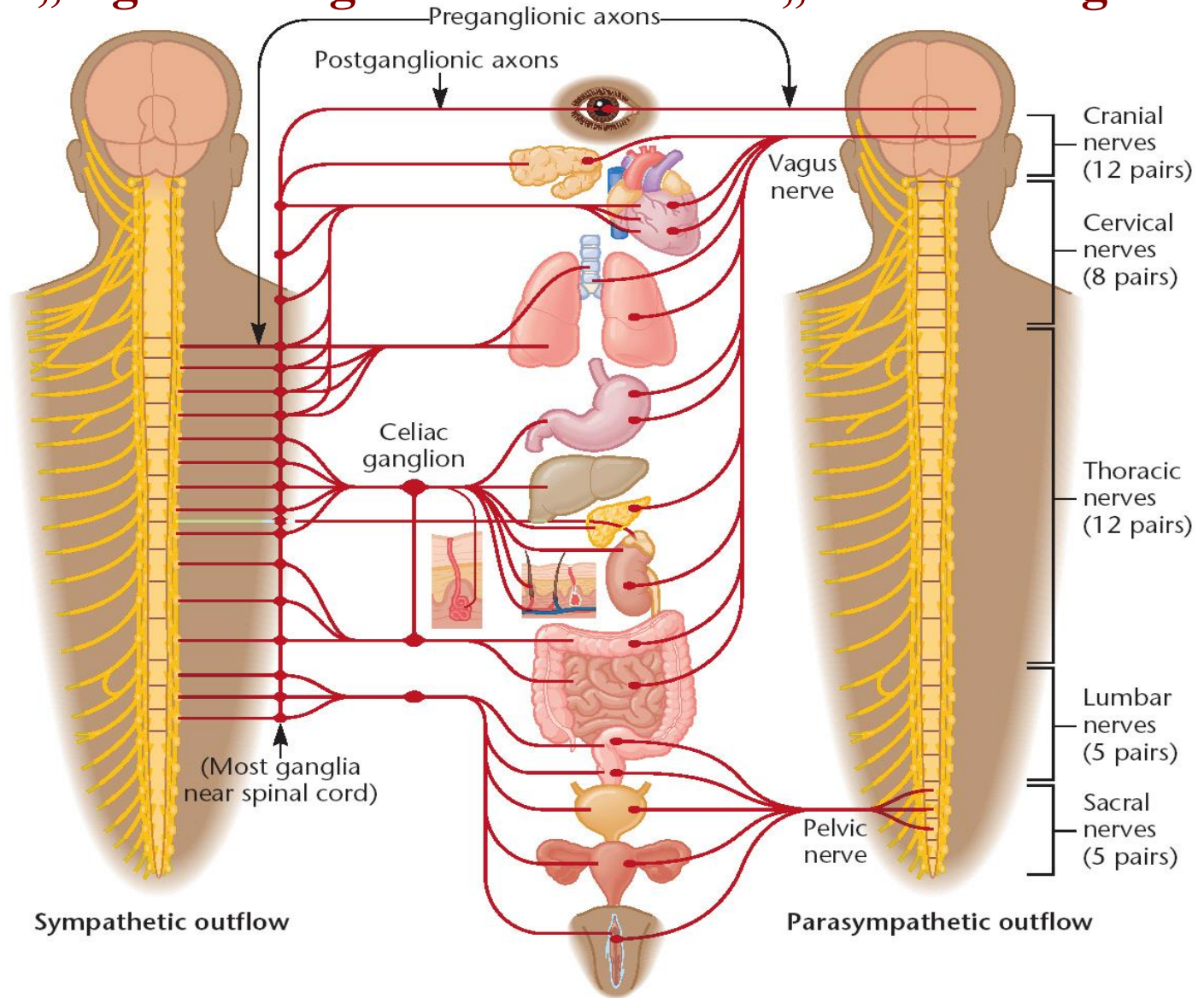
Peripheral nervous system

– Includes:

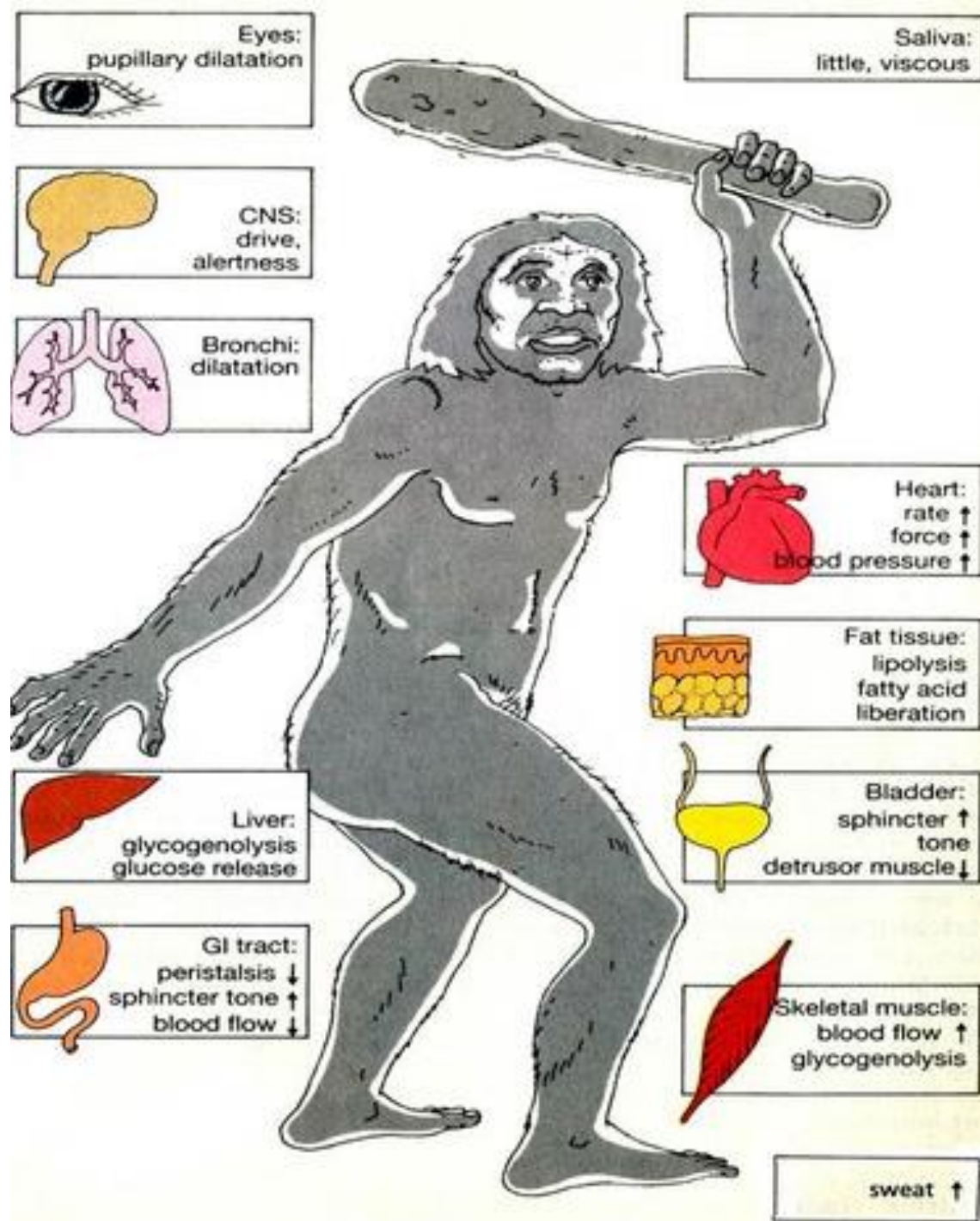
- 1) Motor neurons (mediating voluntary movement)
- 2) Autonomic nervous system:
 - **Sympathetic nervous system**
 - **Parasympathetic nervous system**
 - **Enteric nervous system** (semi-independent part of NS, whose function is to control GIT)

Sympathetic „Fight or Flight“

Parasympathetic „Rest and Digest“



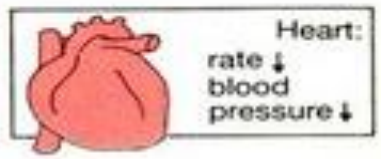
SYMPATHETIC



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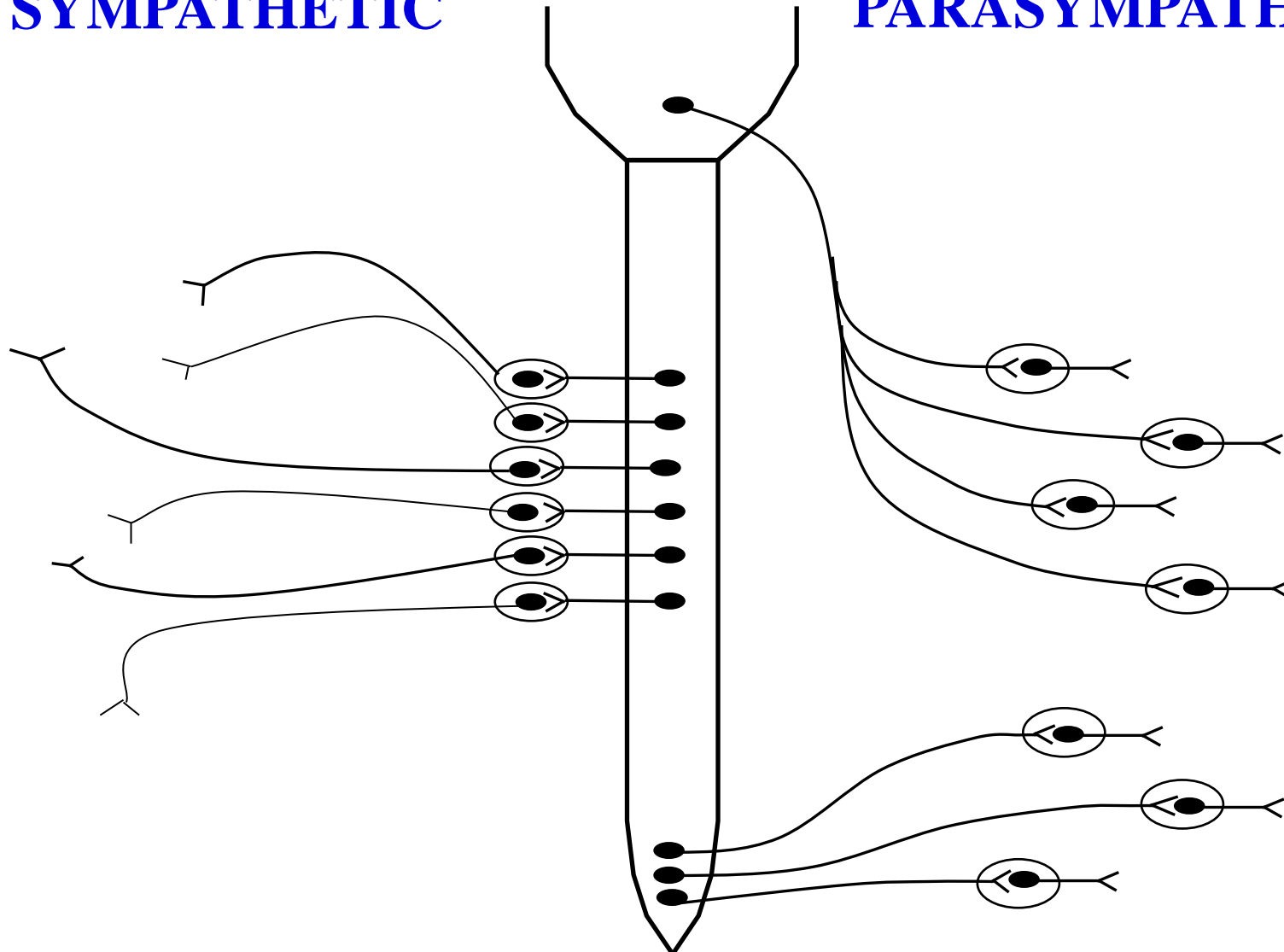
Saliva:
copious, liquid



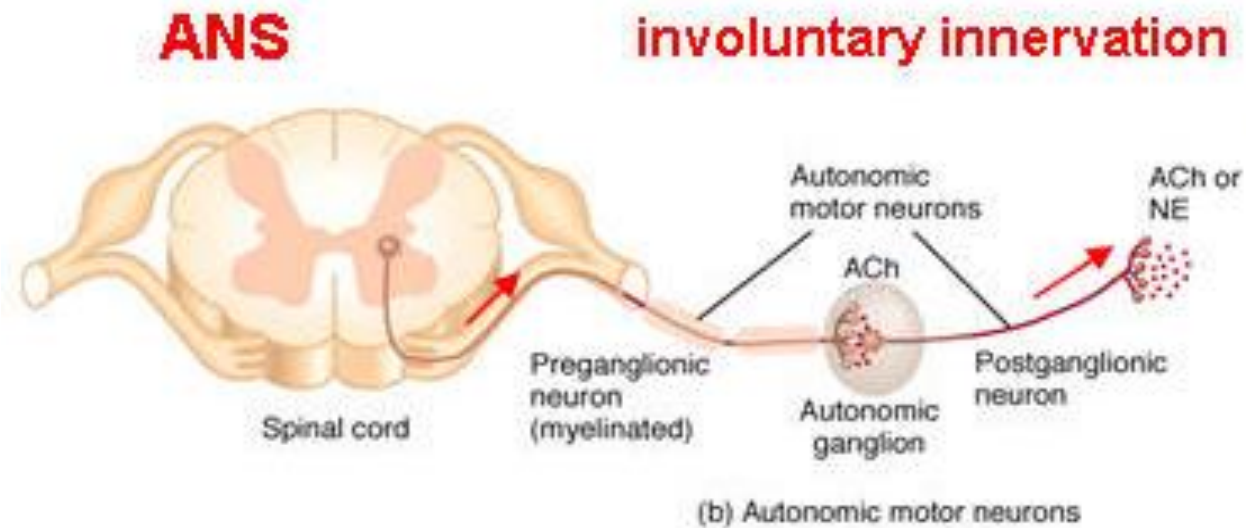
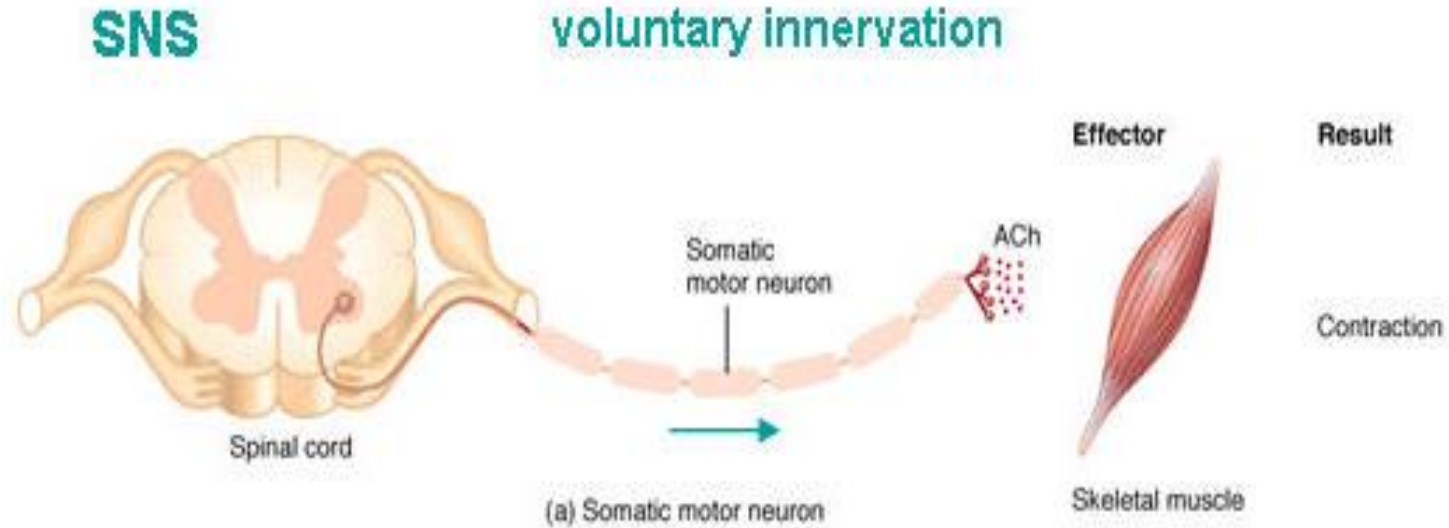
Anatomic structure of ANS

SYMPATHETIC

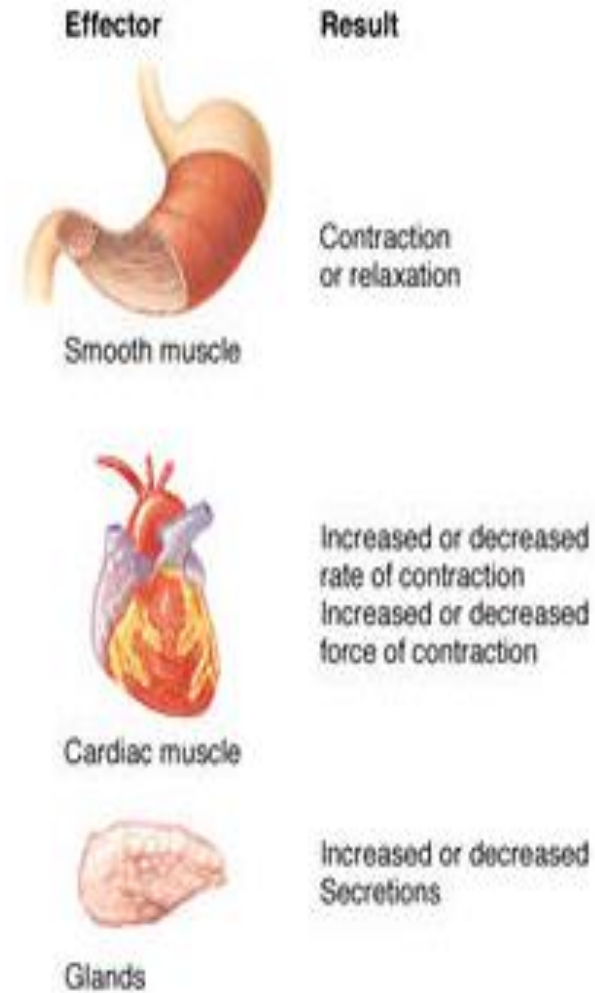
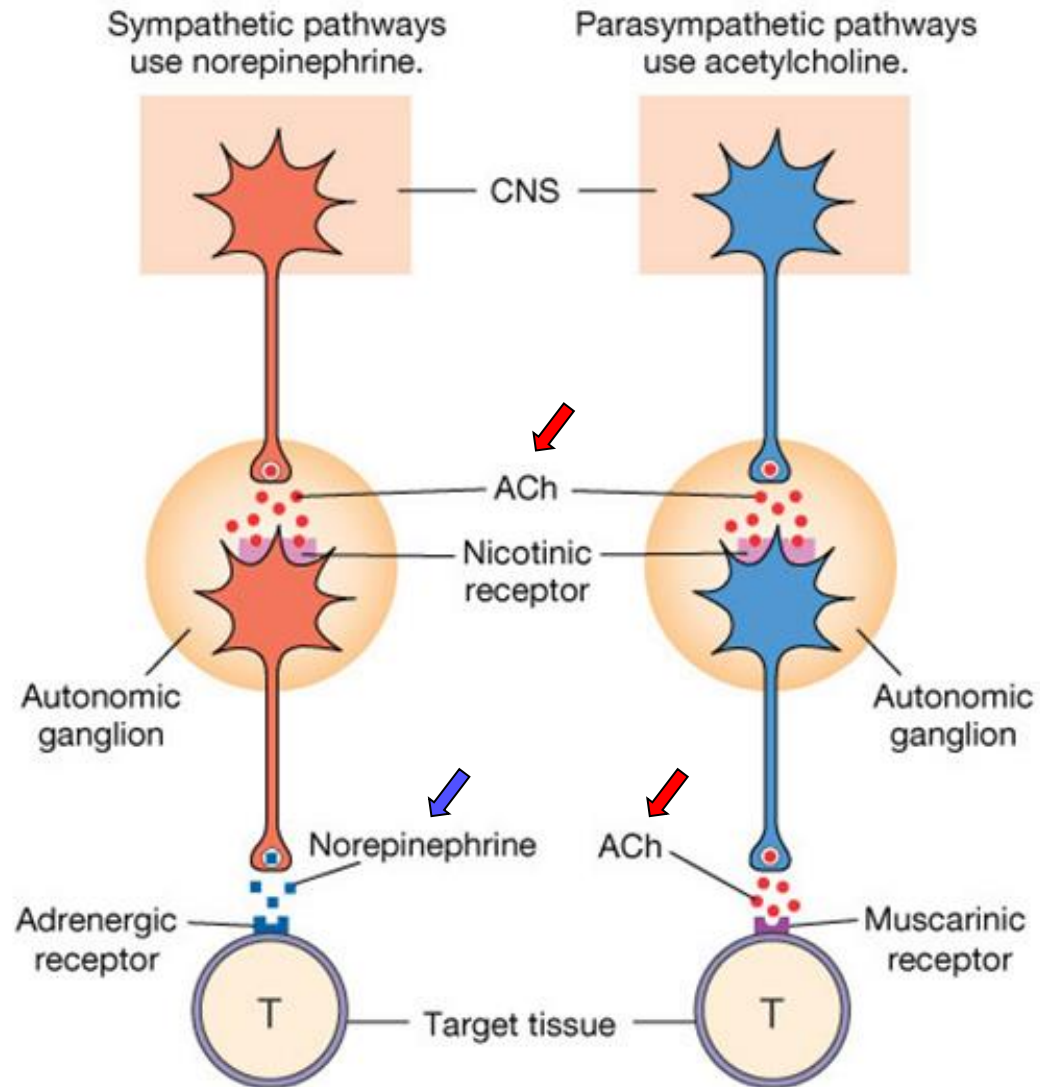
PARASYMPATHETIC



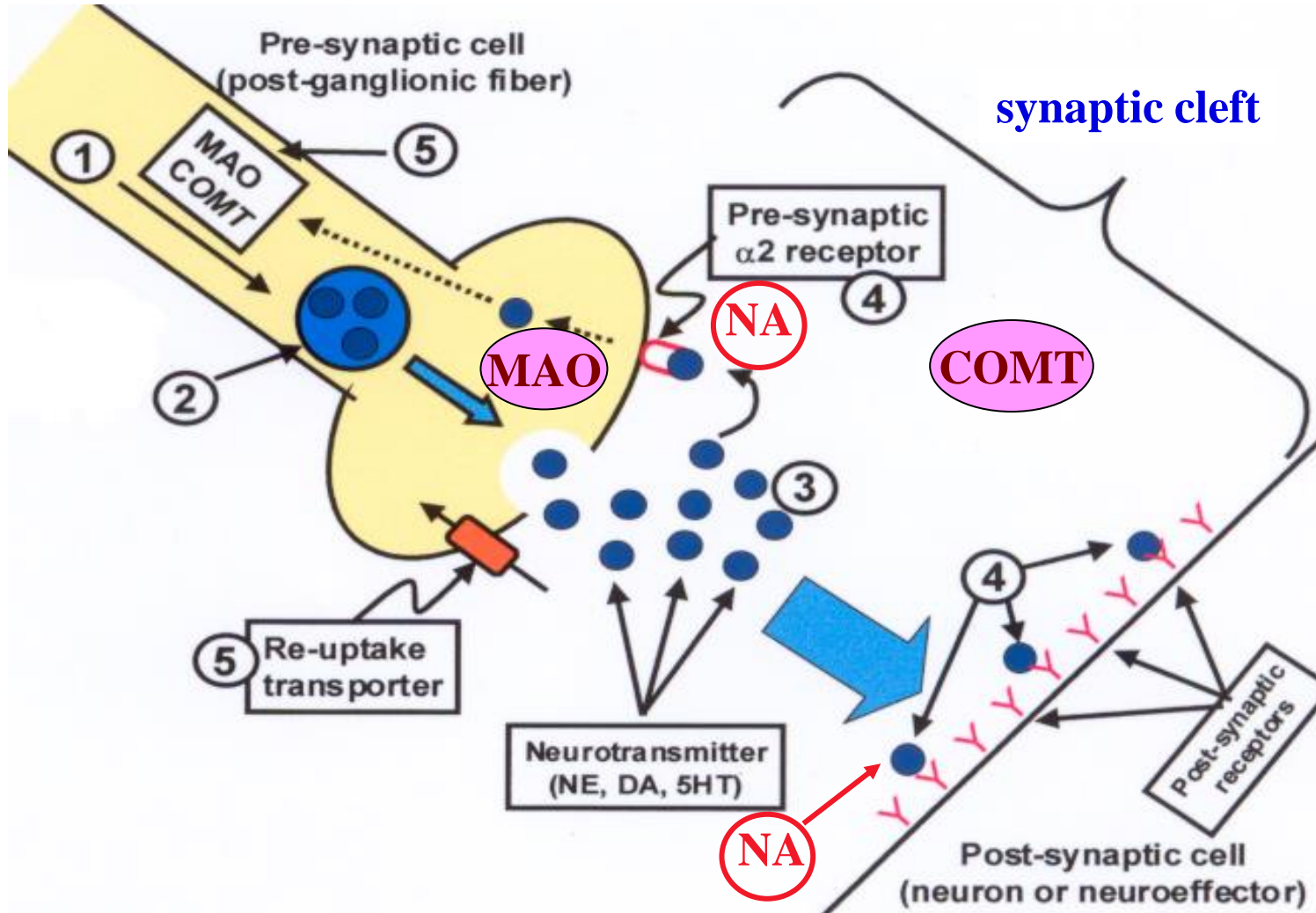
Scheme of innervation



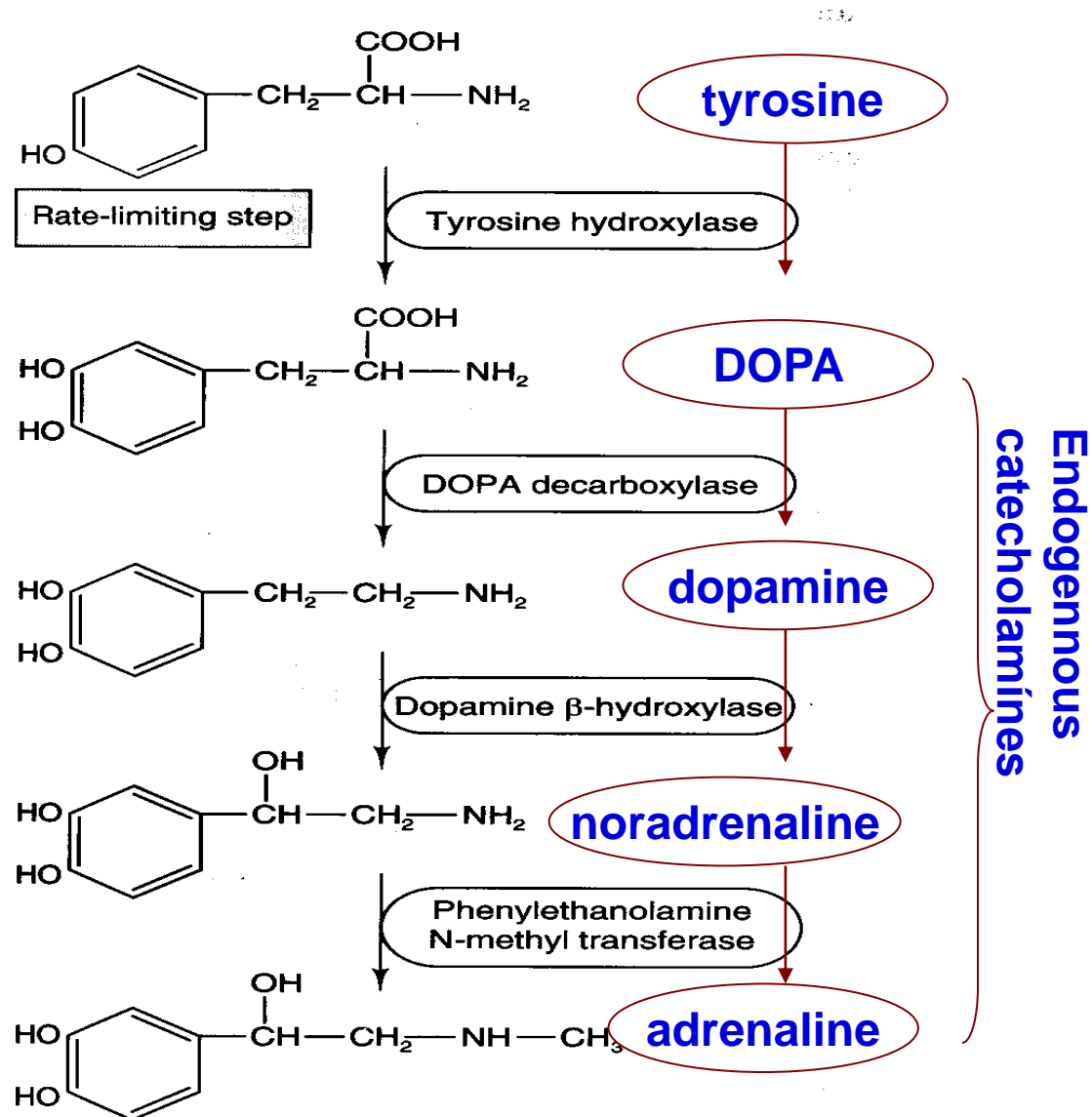
Scheme of involuntary innervation



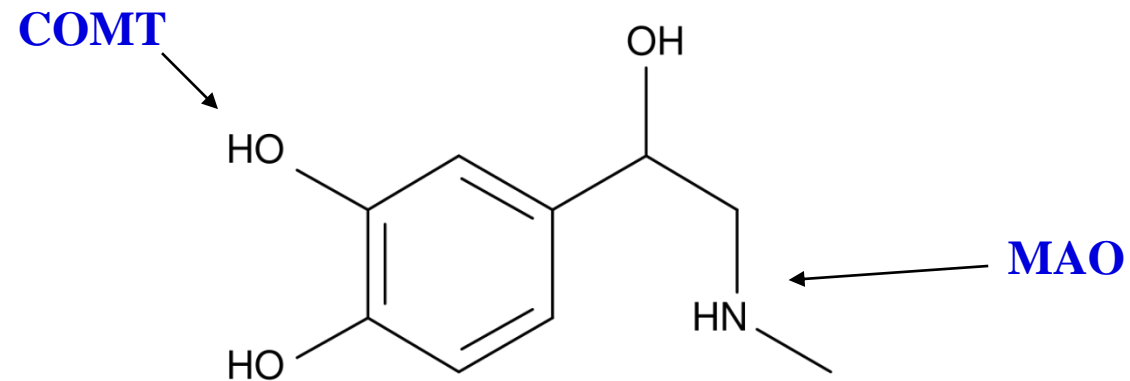
Sympathetic nerve ending



Biosynthesis of catecholamines



Metabolic biodegradation of catecholamines

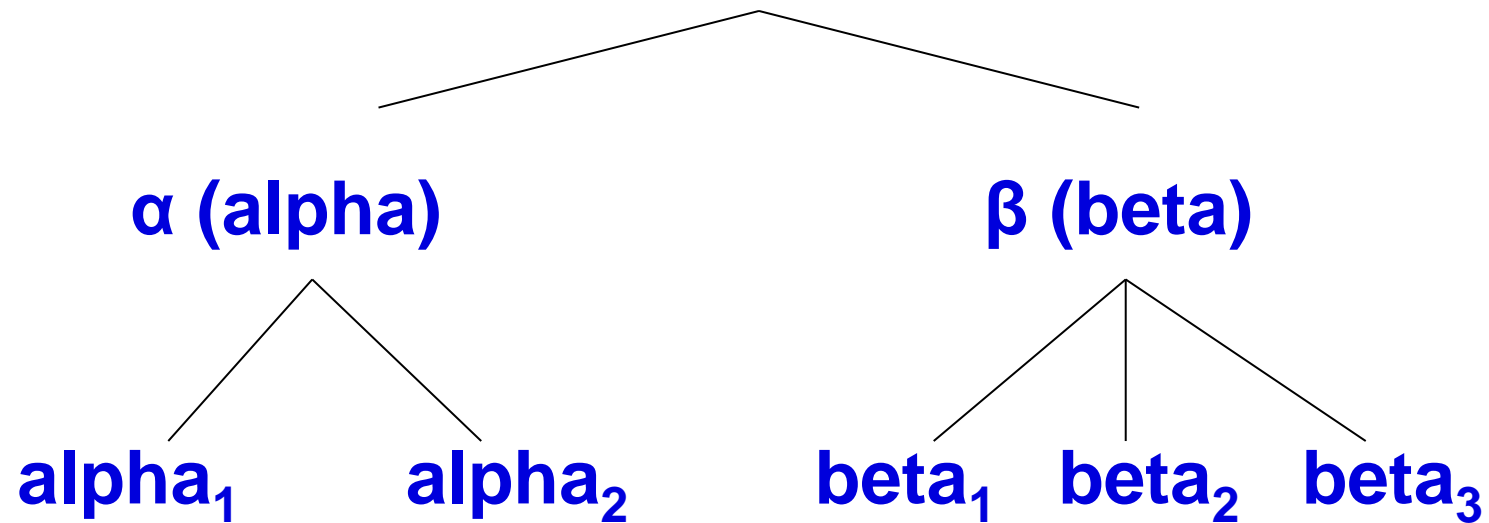


MAO ⇒ monoaminoxidase

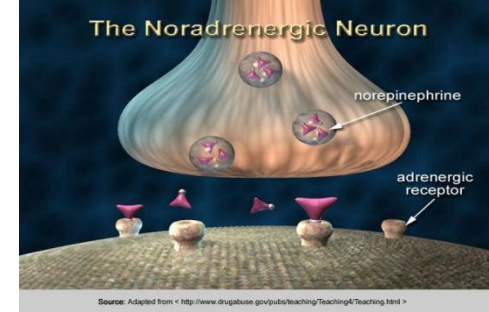
COMT ⇒ catechol-O-methyltransferase

Receptors of sympathetic nervous system

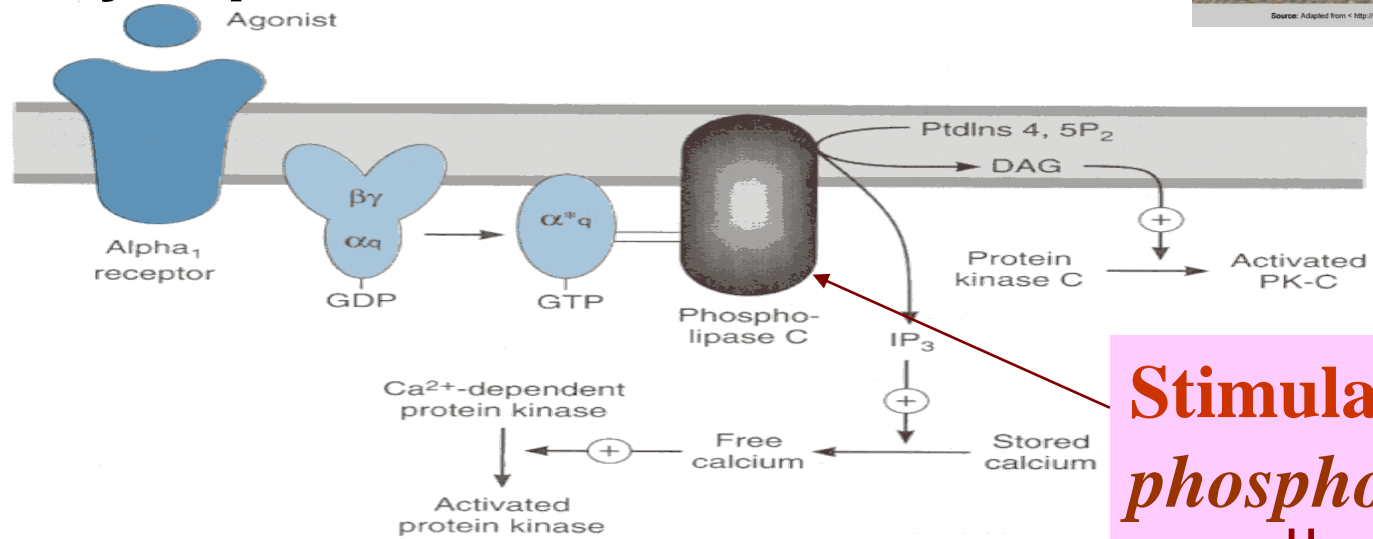
ADRENORECEPTORS



α_1 -adrenoceptors postsynaptic!!



Mechanisms of action



Stimulation of
phospholipase C

IP₃, DAG

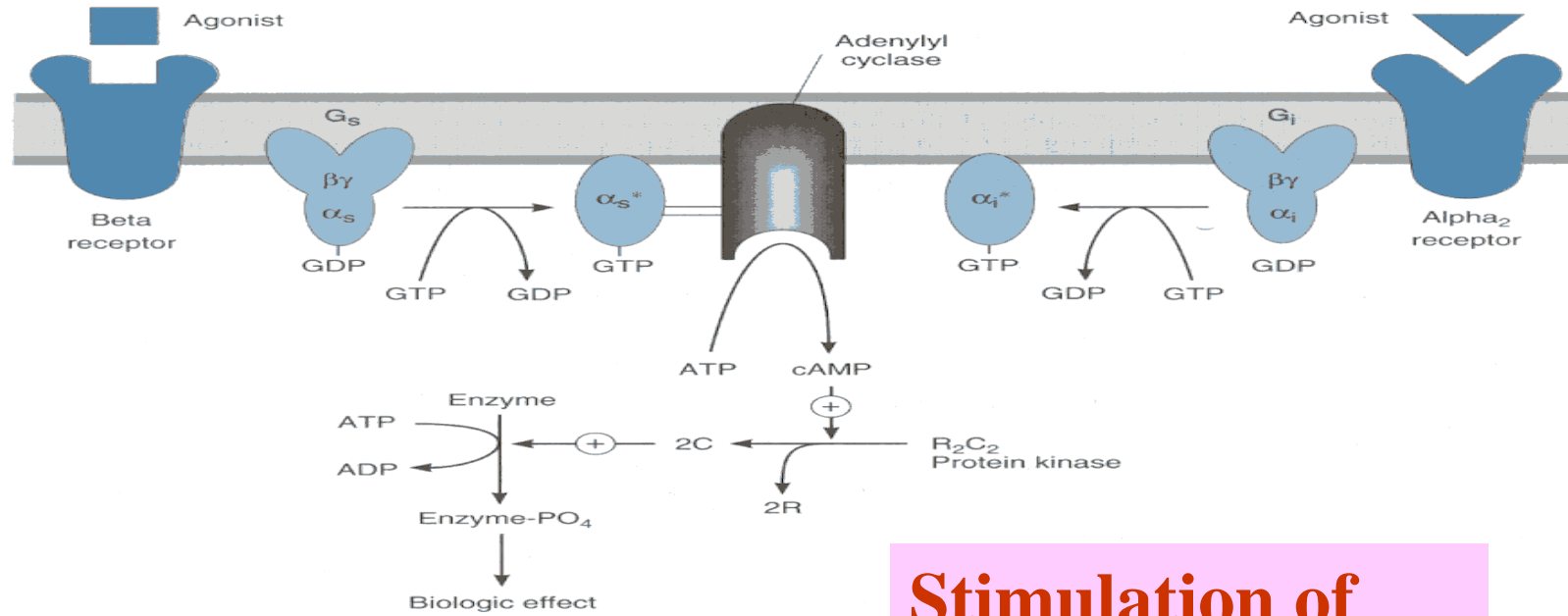
α_2 -adrenoceptors \Rightarrow
presynaptic!!

Inhibition of
adenylate cyclase

~~cAMP~~

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$\beta_{1,2}$ -adrenoceptors



**Stimulation of
adenylate cyclase
⇓
cAMP**

Alpha-adrenergic receptors

Types and location of α -ARs:

α 1-AR

– Smooth muscle

- blood vessels \rightarrow vasoconstriction
- GIT \rightarrow relaxation
- sphincters (GIT, bladder) \rightarrow contraction
- eye - iris (radial muscle) \rightarrow contraction
- liver \rightarrow glycogenolysis

α 2-AR autoreceptors \rightarrow presynaptic effect (vessels, GIT)

Beta-adrenergic receptors

Types and location of β -ARs:

β 1-AR

- Heart (β 1 \gg β 2)
 - nodal system, ventricles, juxtaglomerular apparatus

β 2-AR

- Smooth muscle
 - bronchi (β 2 \gg β 1), vessels, uterus, GIT
- Eye (ciliary muscle)
- Skeletal muscle
- Liver

β 3-AR

- gallbladder, urinary bladder, brown **adipose tissue**

Characteristics of adrenergic receptors

Receptor Type	Tissue Distribution	Mechanism of Action	Agonist Potency	Physiological Effects	Agonist	Antagonist
α_1	Vascular Smooth Muscles, Visceral smooth Muscles	Gq-protein coupled activates Phospholipase C, IP3+DAG	Epi \geq NE \gg Iso	Smooth muscle contractions, Gluconeogenesis, Vasoconstriction	Norepinephrine, Phenylephrine, Methoxamine	Doxazosin, Phentolamine, Prazosin
α_2	Pre-synaptic terminals, pancreas, platelets, Ciliary epithelium, Salivary Glands	Gi-protein coupled inhibits Adenyl cyclase	Epi \geq NE \gg Iso	Inhibits release of Neurotransmitter	Clonidine, Monoxidine	Yohimbine, Idazoxan, Tolazoline
β_1	Heart, Kidney, some pre-synaptic terminals	Gs-protein coupled activates Adenyl cyclase +PKA	Iso $>$ Epi \geq NE	Increase heart rate and Renin secretion	Isoproterenol, Norepinephrine, Dobutamine	Propranolol, Metoprolol, Atenolol
β_2	Visceral smooth muscles, Bronchioles, Liver, Skeletal Muscles	Gs-protein coupled activates Adenyl cyclase +PKA, Ca-channels	Iso $>$ Epi \gg NE	Vasodilation, Bronchodilation, Inhibits insulin secretion	Isoproterenol, Salbutamol, Salmeterol, Albuterol, Formoterol, Terbutaline, Levalbuterol	Propranolol, ICI-118,551, Nadolol, Butoxamine
β_3	Adipose Tissue	Gs-protein coupled activates Adenyl cyclase +PKA	Iso = NE $>$ Epi	Increase lipolysis	Isoproterenol, Amibegron, Solabegron	SR59230A

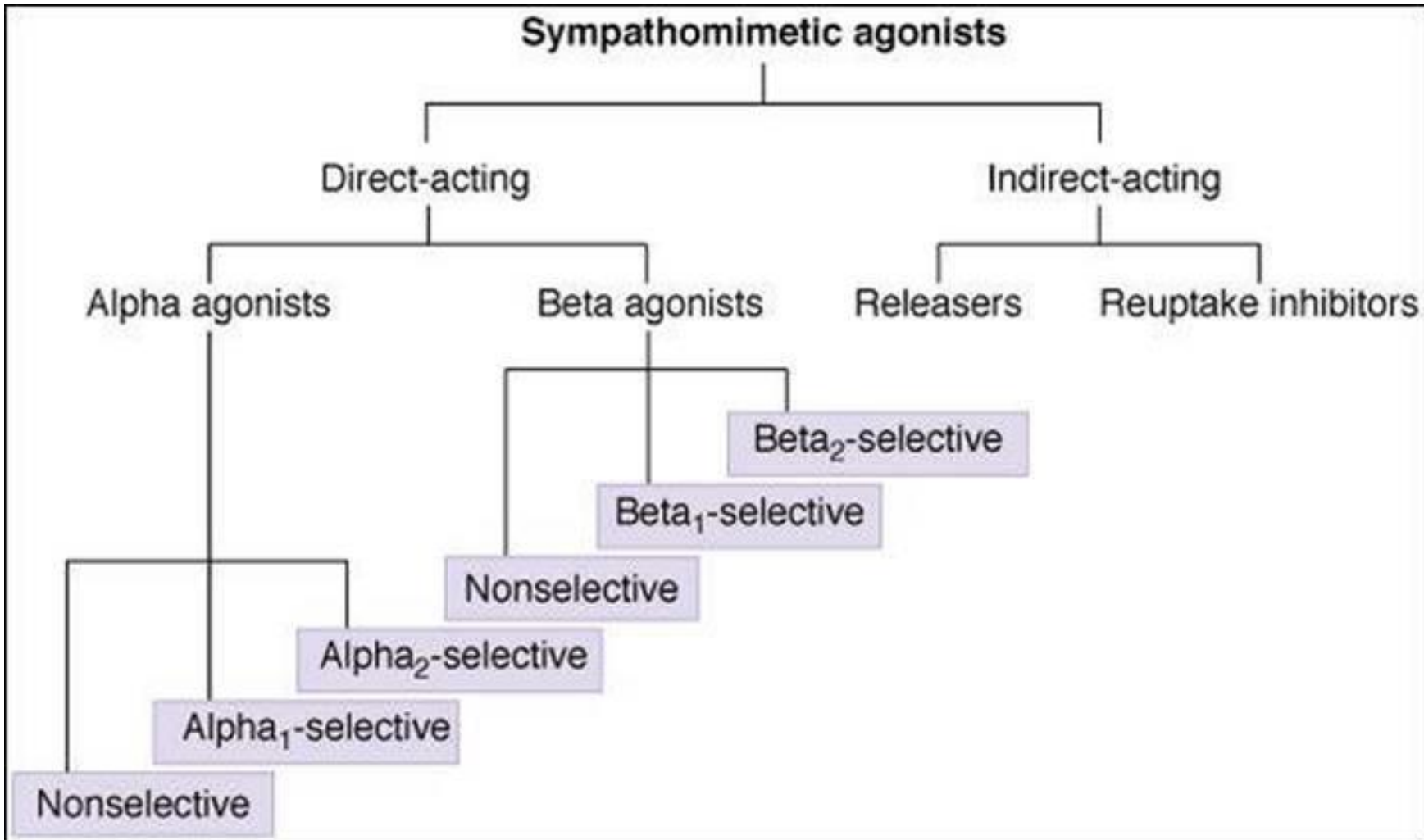
NE: Norepinephrine, Epi: Epinephrine and Iso: Isoproterenol

Classification of drugs affecting adrenergic system

Drugs:

- Direct α and β -adrenoceptor **agonists** (non-selective/selective)
- Indirectly acting **sympathomimetics** (increase NA activity)
- Direct α and β -adrenoceptor (β -blockers) **antagonists**
- Indirectly acting **sympatholytics** (affect NA uptake or storage)

Sympathomimetics



Non-selective Sympathomimetics

1) Catecholamines

- **Noradrenaline (norepinephrine):** $\alpha > \beta_1 > \beta_2$, **I:** local use (+ LA), mainly states of shock and hypotension
- **Adrenaline (epinephrine):** acts more strongly on β_2 -rec, **I:** cardiac arrest, peripheral circulatory failure, anaphylaxis, endotoxic shock, bronchospasm, local decongestion
- **Dopamine: I:** acute renal and splanchnic circulatory disorders, shock and heart failure

Non-selective Sympathomimetics

- Effects of **dopamine** depend on dose:
 - Lowest doses: renal → on **D-rec** → vasodilation in the renal and splanchnic circulation → improves kidney blood flow; used in shock and blood redistribution
 - Medium doses (2-10 µg/kg/min): on **β1-rec** → stimulation of cardiac activity (increase in sysBP, positive ino- and chronotropic effect)
 - Higher doses: pressor → also **α1-rec** → vasoconstriction including renal vessels, increase in blood pressure

Non-selective Sympathomimetics

2) Ephedrine and pseudoephedrine

Indirectly acting sympathomimetics (mainly increase endogenous neurotransmitters)

- ***Ephedrine*** or ***amphetamine*** and its derivatives: *MDMA* (ecstasy/Molly) or *methamphetamine* (Meth) - Accumulated by uptake (presynaptic) and displace NA from vesicles, allowing it to escape
- *Cocaine* a **TCA** (prevent the reuptake of neurotransmitters)
- *iMAO* (***A-moclobemide***, ***B-selegiline***), *iCOMT* (block the biodegradation of neurotransmitters)

Selective Sympathomimetics – β_1

Dobutamine

- Chemically related to dopamine, but its effect is dominant on β_1 -rec
- It has an inotropic effect without much effect on heart rate
- It is given as an infusion

I: heart failure, shock and diagnostic stress tests

SE: hypertension, angina pectoris, arrhythmia

Selective Sympathomimetics – β_2

Therapeutic use: effect on β_2 -rec of the uterus and respiratory tract:

– Tocolytics (arrest of labor and relaxation of uterine smooth muscle)

- ***hexoprenaline and ritodrine***

– Antiasthmatics

- SABA: ***salbutamol, hexoprenaline, fenoterol***

- RABA: ***formoterol*** + SABA

- LABA: ***salmeterol, formoterol, clenbuterol***

- ultra LABA: ***indacaterol***

SE: through β_2 -rec = tachyarrhythmias, ischemia, skeletal muscle tremor

Selective Sympathomimetics – β_3

Therapeutic use: effect on β_3 -rec of the bladder → allows greater fulfillment of the bladder → extends the period when the patient does not feel the urge to urinate

- *mirabegron*

I: treatment of overactive bladder

SE: tachycardia, increase in blood pressure, urinary tract infections

Selective Sympathomimetics – α_1

Therapeutic use: effect on α_1 -rec in blood vessels (vasoconstriction), urinary tract (stronger sphincter contractions and urinary retention), in the eye (mydriasis); and especially mucous membranes (decongestion):

- *naphazoline, oxymetazoline, xylometazoline, tetrazyline*

I: treatment of rhinitis, swelling of the nasal mucosa and conjunctivitis

SE: during long-term therapy - swelling and subsequent atrophy of the nasal mucosa

Selective Sympathomimetics – α_2

Therapeutic use: effect on α_2 -rec in CNS leads to induction of negative feed back \rightarrow reduction in activity of SNS \rightarrow antihypertensive drug

- ***clonidine, α -methyldopa***

I: α -methyldopa is drug of choice in hypertension in pregnancy

SE: drowsiness, dizziness, weakness, headache, orthostatic hypotension; nausea, vomiting

Sympatholytics – β blockers

Therapeutic use: effect on cardiac activity (negatively chrono, ino, dromo, bathmotropic), reduce renin excretion, reduce intraocular pressure

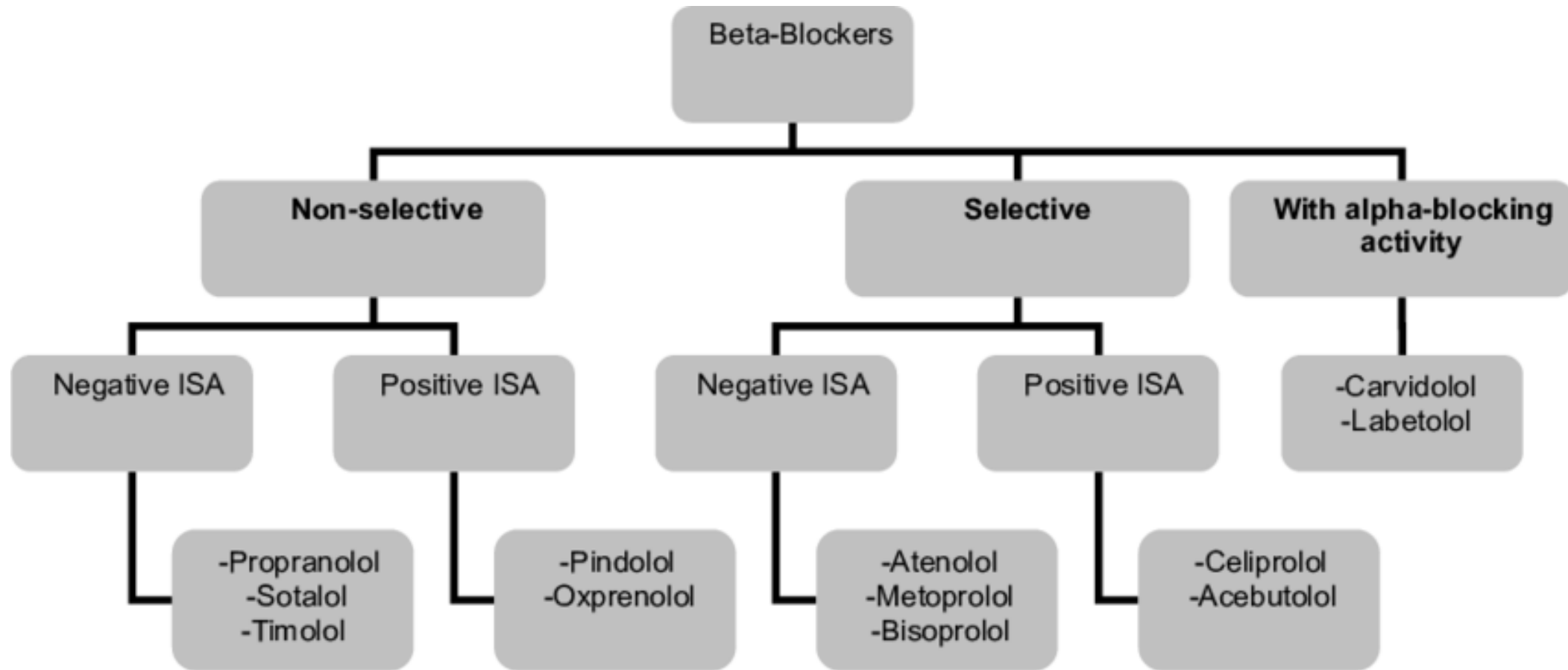
The main effect is the cardioprotection:

- ***antiischemic effect*** (reduction of cardiac output)
- ***antiarrhythmic effect*** (increase in fibrillation threshold)
- ***bradycardic effect*** (improved coronary flow)

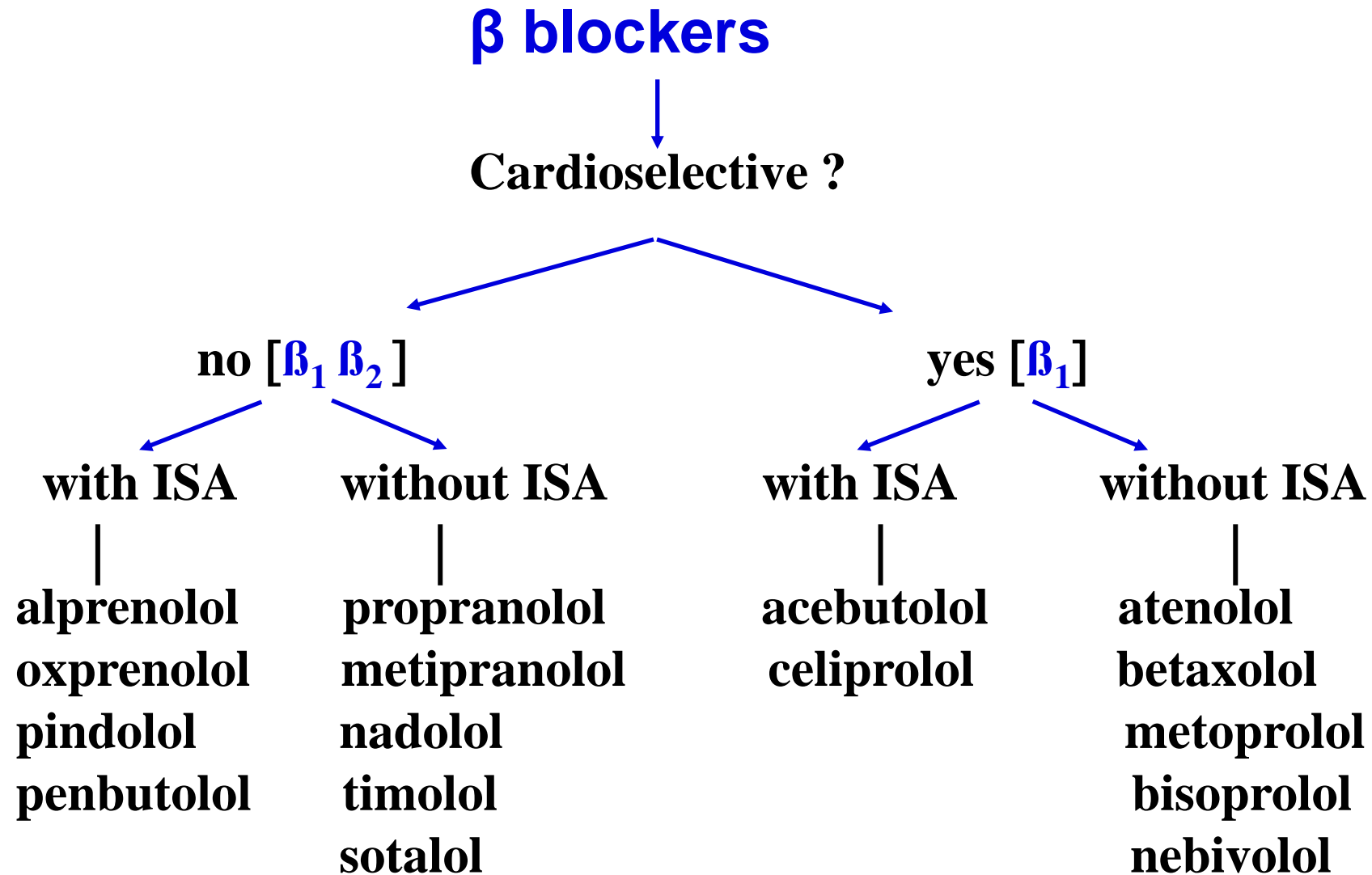
I: hypertension, arrhythmia, coronary heart disease, glaucoma and tremor

SE: bradycardia, bronchospasm, sedation; worsening of glucose intolerance, increase in TG and decrease in HDL; rebound phenomenon

Classification of β blockers



Classification of β blockers



Indications of β blockers

– Cardiovascular system:

- ischemic heart disease (angina pectoris, acute MI and prevention after MI)
- arrhythmias
- arterial hypertension
- chronic heart failure
- cardiomyopathy (dilatation and hypertrophic)

– CNS:

- anxiety, tremor, narcolepsy

– Endocrine system:

- thyrotoxicosis, pheochromocytome

– Ophthalmology:

- glaucoma

Sympatholytics – α

Ergot alkaloids with complex effects (on α - and D-rec, uterine muscle, and with 5-HT effects)

Therapeutic use:

Vasodilating effect

- ***dihydroergotamine, dihydroergocristine, dihydroergotoxin***

I: disorders of central and peripheral blood circulation, migraines

Uterotonic effect:

- ***methylergometrine***

I: uterine bleeding in connection with childbirth, abortion or gynecological procedures

Sympatholytics – α_1

Therapeutic use: effect on α_1 -rec in smooth muscle of blood vessels and urinary tract → vasodilation of blood vessels, prostate smooth muscle and urinary tract sphincters

- ***doxazosin, terazosin***

I: treatment of hypertension

SE: dizziness, orthostatic hypotension, nasal congestion (full nose)

- ***tamsulosin*** (selective effect on the α_{1A} -rec subtype in prostate and ureter smooth muscle)

I: treatment of benign prostatic hyperplasia

SE: dizziness, ejaculation disorders

Sympatholytics – α_2

Therapeutic use: vasodilation in the pelvic area → effect as an aphrodisiac

- *yohimbin*

I: treatment of erectile dysfunction

SE: tachyarrhythmias and hypertension

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