Zaporizhzhia State Medical University
Pharmacology Department

Lecture №3

Adrenergic Drugs

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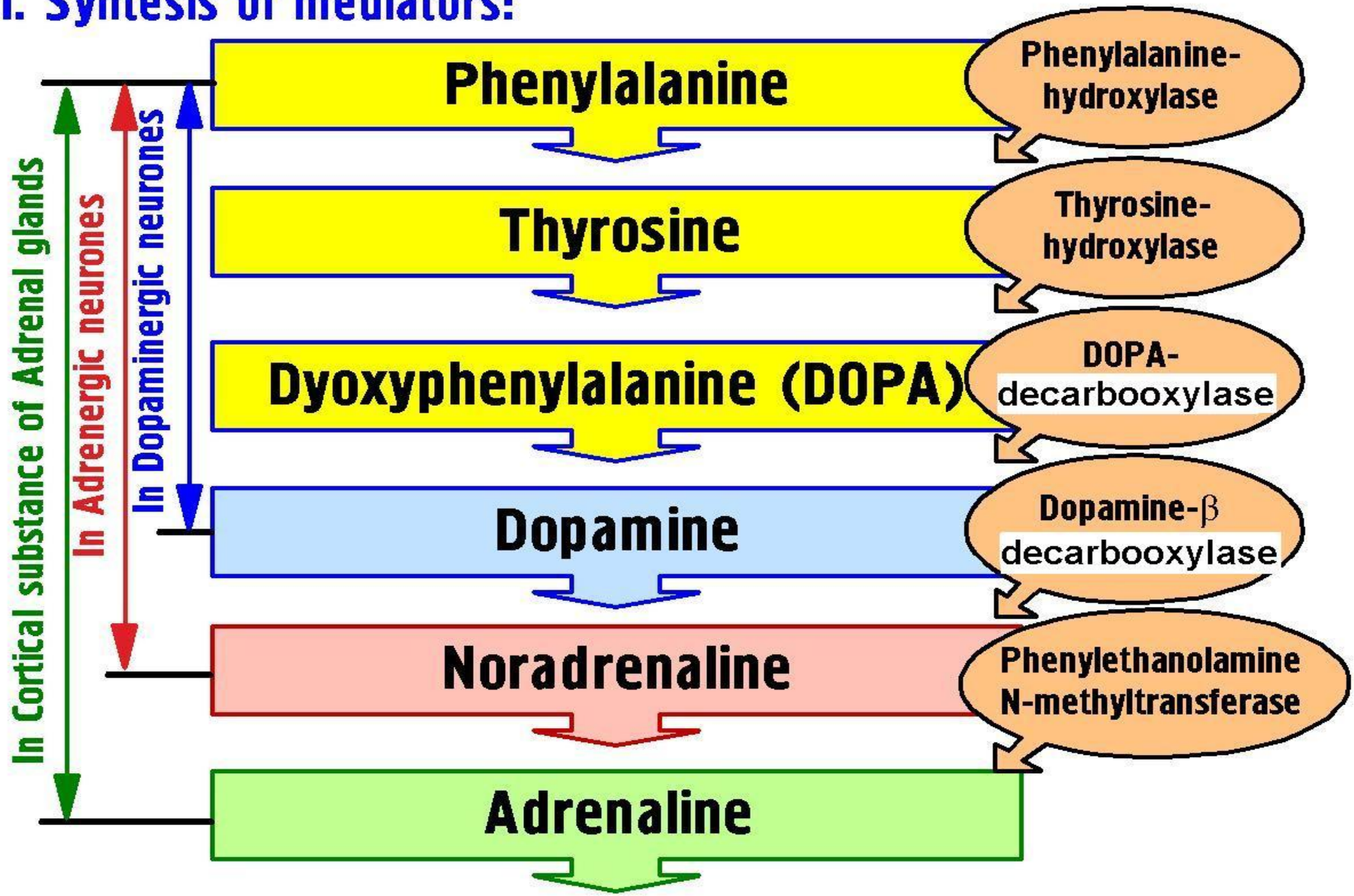
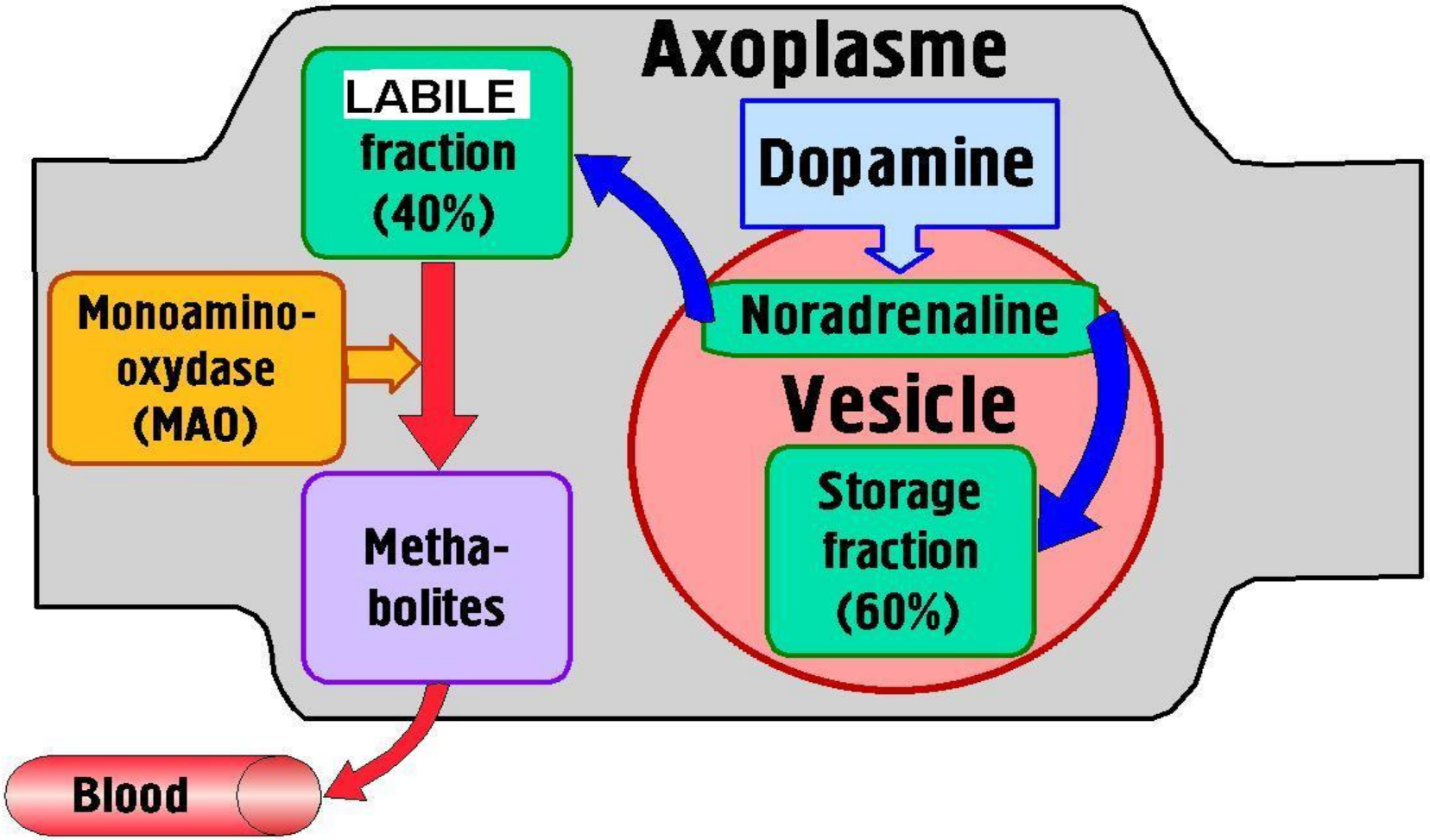
Function of Adrenergic synapse

1. Syntesis of mediators:



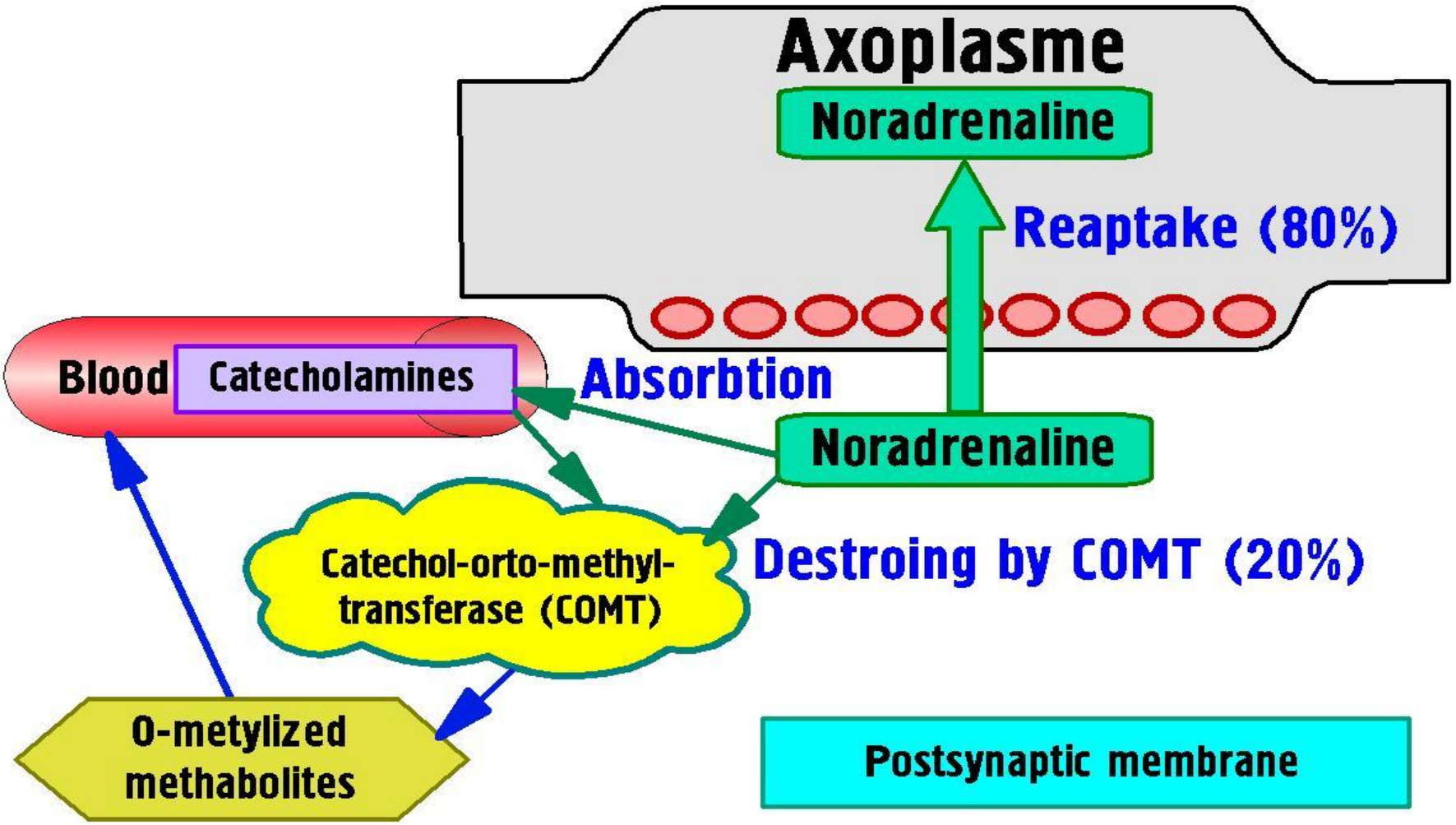
Function of Adrenergic synapse

2. The fate of noradrenaline in varicose thickenings of nerve endings:



Function of Adrenergic synapse

4. The fate of noradrenaline in synaptic slit:



MAO-A - metabolizes Noradrenaline and Serotonin,
MAO-B - Dopamine, Phenylethylamine and Tyramine

Tyramine is a product of tyrosine metabolism and is found in fermented foods:

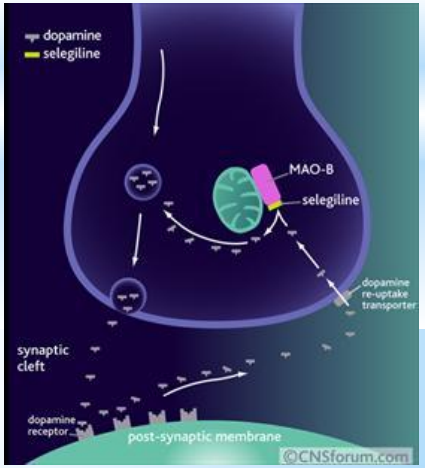
- Cheese - 130 mg/100 g
- Beans - also contain *Dopamine*
- Chicken Liver
- Chocolate - also contains *Phenylethylamine*
- Fermented Sausage, Beer,
- Smoked or Pickled Fish

MAO inhibitors: Nialamid, Transamine and
MAO-A inhibitors: Moklobemid, Pirazidol - □□BP

α_1 Receptors: on the Postsynaptic Membrane of the Effector organs – on smooth muscle and glands and are **excitatory**

α_2 Receptors: on the Pre- and Postsynaptic Membrane of the Effector organs.

The stimulation of the **Presynaptic α_2-Receptors** => **Feedback Inhibition** of **noradrenaline** release from the stimulated Adrenergic neuron – **Negative Feedback**



β_1-receptors: HEART and are **Excitatory**

β_2-receptors: on *Smooth Muscle* of –

Bronchi

Vasculature of Skeletal Muscle

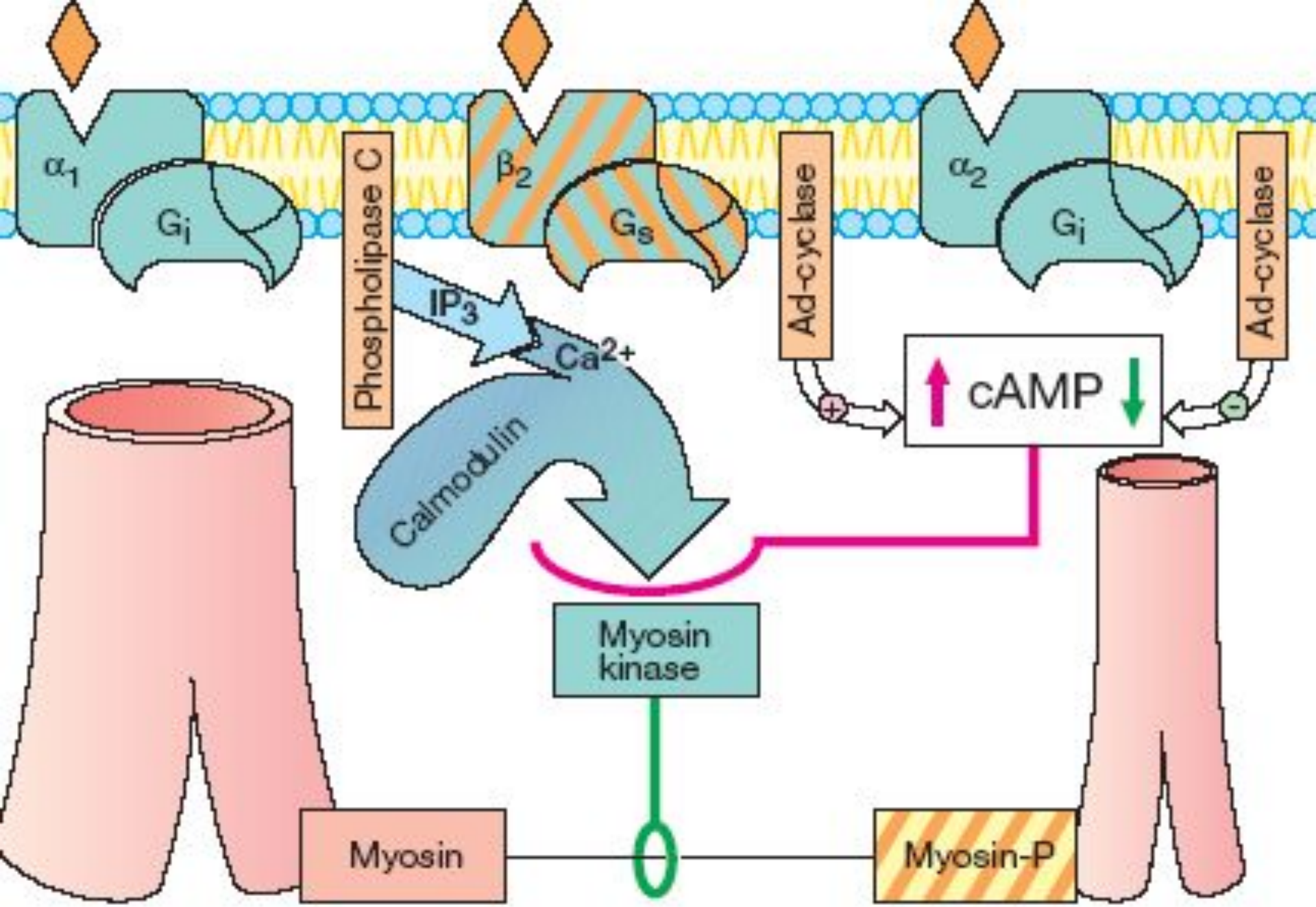
Miometrium

Glands

and are **Inhibitory**

β_3-receptors: Adipose (Fat) cell =>

stimulation of lipolysis



. Vasomotor effects of catecholamines

Localisation of adrenoceptors and effects of their exitation

2. Effects upon the eye:

➡ α_1-adrenoceptors:

- in the smooth muscle - dilatator of pupil.

► Contraction of radial muscle of the iris, dilation of pupil (mydriasis) and photophobia.

► Tightening of Zinn's ligament, decrease of curvature of lens: eye sets for distant point of vision (paralysis of accomodation).

► Narrowing of Schlemms' channel and Fontana's spaces which cause decreasing of the aqueous humor outflow from the anterior chamber of the eye. It contribute to increasing of intraocular pressure.

- in the blood vessels of eye fundus.

► Decreasing of the aqueous humor production. It contribute to decreasing of intraocular pressure.

Result effect - decreasing of intraocular pressure.

Localisation of adrenoceptors and effects of their exitation

3. Effects upon another smooth muscles:

➡ α_1-adrenoceptors:

- in the sphincters of gastrointestinal tract.

► Contraction of sphincters, decreasing of peristaltics.

➡ β_2-adrenoceptors:

- in the smooth muscles of bronchi.

► Dilatation of bronchi (broncholitic effect).

- in the smooth muscles of uterus.

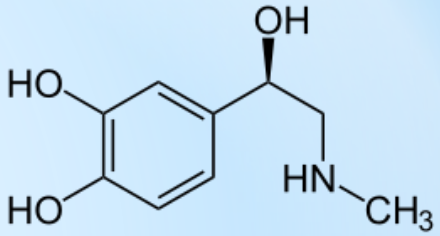
► Decreasing of rhytmic contractions of uterus on labors (tocolitic effect).

- in the skeletal muscles.

► Increasing of contractive activity.

I. Adrenomimetics of Direct Action

1). α-, β- Adrenomimetics:

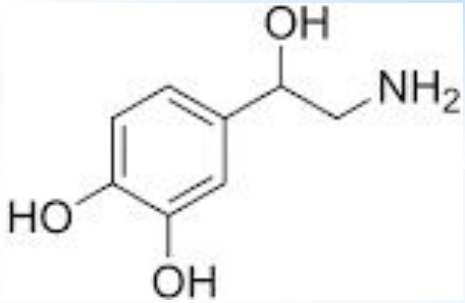


· Adrenaline hydrochloride - **α_1, α_2, β_1, β_2 , β_3**

amp. 0.1%-1ml; vial 0.1%-10 ml

· Noradrenaline hydrotartrate - **α_1, α_2, β_1**

amp. 0.2% -1 ml (IV infusion)



THE MAIN EFFECTS of *ADREANALINE* :

- **Cardiac Stimulation**
- Relaxation of **Bronchial Muscle**
- **Dilation of Skeletal Muscle Vasculature**
- Significant **Hyperglycemia**:
  - ↑**Glycogenolysis** in the Liver (**β_2 effect**)
  - ↓ **Release of Insulin** (α_2 effect).

Adrenaline is metabolized by 2 **enzymatic pathways**:

COMT and **MAO**

Clinical uses:

- Bronchospasm
- Anaphylactic shock: is the drug of choice
- Cardiac arrest and acute AP
- Hypoglycemic coma (overdose with ***Insulin***)
- Glaucoma

Noradrenaline hydrotartrate: α_1, α_2, β_1

the strongest **Peripheral Vasoconstrictor**

↑↑ **Total Peripheral Resistance** => ↓ **HR**

↑ **Systolic and Diastolic AP**

- ↓Blood Flow to Vital Organs, Skin, and Skeletal Muscle
- Constriction of Renal Blood Vessels
- ↑Heart Contraction

Clinical Uses: Acute Hypotensive States,

GI Bleeding.

Adrenomimetics

Indirect α-β-adrenomimetics (sympatomimetics):

- **EPHEDRINE, DEPHEDRINUM *[PSEUDOEPHEDRINE]*, PHENYLPROPANOLAMINE**

- **Mechanism of action: stimulation of noradrenaline release from the synaptic nerve endings and slight direct exitation of adrenoceptors.**

- **Effects of ephedrine similar to adrenaline, but it's activity less by 50-100 times and lasts longer.**

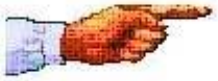
Ephedra distachya

As ADRENALINE, EPHEDRINE is used for Arterial Hypotension, Bronchial Asthma, Bronchospasm

→ **Effects of ephedrine which are different to adrenaline:**

- **Effectiveness on peroral taking.**
- **Significant stimulation of CNS - may cause psychomotor excitement, insomnia, drug dependence.**

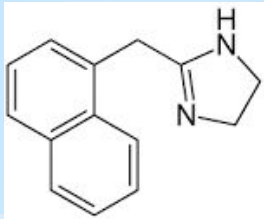
The ephedrine is used for treatment of narcolepsy (pathological sleepeness).



When ephedrine introduction repeated after small interval (10-30 min), weakeing of effect (tachyphylaxis) appears. it's associated with decrease of noradrenaline amount in vesicles.

2). α-**Adrenomimetics**:

Mesatone (*Phenylephrine*) (**α**$_1$)– *amp. 1%-1 ml*



Naphthyzine (*Naphtazoline*) (**α**$_2$)

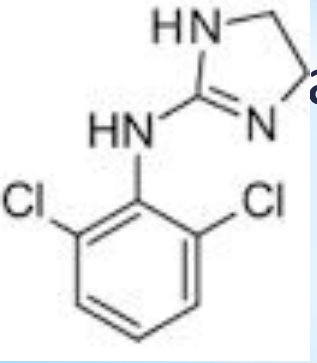
Vial 0.05% and 0.1% - 10 ml

Halazoline (*Xylometazoline*) (**α**$_2$)

Vial 0.05% and 0.1%-10 ml

Clofeline (*Clonidine*) (**α**$_2$) –

Tab. 0.000075 g and 0.00015 g,



amp. 0.01% - 1 ml

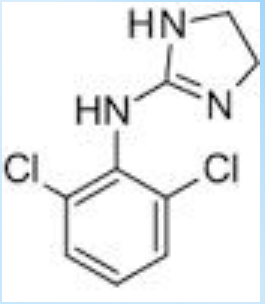
➡ α_1-adrenomimetics: **MESATON** *[PHENYLEPHRINE]*,

- **They are narrowing blood vessels contaning α-adrenoceptors, increase blood pressure and cause reflectory bradicardia.**

They are used for treatment of the acute arterial hypotension intravenously, for rhinitis (intranasally) for glaucoma.

➡ α_2-adrenomimetics: **NAPHTHYZIN** *[NAPHAZOLINE]*, **HALAZOLIN** *[XYLOMETAZOLINE]*

They are used for treatment of the rhinitis (intranasally only) because they are toxic agents.



Clopheline is an α_2-agonist used

in Essential Hypertension to lower BP.

It acts mainly on Central α_2-Receptors =>

Inhibition of **Sympathetic Vasomotor centers** -

Negative Feedback.

↓Peripheral Vascular Resistance =>

=> ↓Cerebral Sympathetic Outflow.

Clopheline may stimulate

Peripheral Postsynaptic α_2-Receptors,

producing **Transient Vasoconstriction**.

Beta - Adrenomimetics

Isadrin (Isoprenaline) (β_1, β_2)
Tab. 5 mg, vial 1%-25.0 ml
Dopamine (β_1)- amp 4%-5 ml; 0.5% - 5 ml
Dobutamine (β_1)- amp 5%-5 ml; 1.25%-20 ml

Salbutamol (β_2)- Tab 2 mg, aeroz
Terbutaline (β_2) - Tab 2.5 mg, aeroz.

Salmeterol (β_2)- aeroz
Fenoterol (Berotec, Partusisten) (β_2)
Formoterol (β_2) (turbuhaler 4.5 and 9 mkg/dose)

Dopamine activates **β_1-Receptors** and

is the metabolic precursor of Norarenaline

D-receptors are prominent in the periphery

(*splanchnic* and *renal vasculature*),

where they mediate Vasodilation => *useful* in SHOCK and Acute Heart Failure.

↑Blood Flow to the Kidney =>

↑ the Glomerular Filtration Rate =>

Na^+ Diuresis

Cardiovascular action:

Stimulation of β_1-Receptors =>

inotropic and chronotropic effects

Renal and viscera :

D_1-receptors => Dilation of Renal Arterioles =>

↑ Blood Flow to the Kidneys and other Viscera.

Dopamine is far Superior to *Noradrenline*, which

↓the Blood Supply to the **Kidney** and

may cause **Kidney Shutdown**.

Dobutamine (amp. 5%-5 ml)

selective β_1 AM -

the most commonly used

Inotropic Agent after Cardiac Glycosides.

↑cAMP => the Activation of Protein Kinase.

Slow Ca^{2+} channels are one important site of Phosphorylation by Protein Kinase.

When phosphorylated, the Entry of Ca^{2+}

into the Myocardial Cells ↑=>

=> CONTRACTION ↑

Beta$_2$ agonists Salbutamol, Terbutaline, Fenoterol, Salmeterol, Formoterol:

- **Relax** smooth muscle of the **Bronchial tree**, **Vasculature**, **Uterus** and **Intestines**
- Hepatic and Muscle **glycogenolysis** =>

  => HYPERGLYCEMIA

Beta$_2$ agonists are used as:

- Bronchodilators
- Tocolytics – to Relax the Uterus and delay delivery in *premature labor*

All β_2-AMs have some degree of β_1-activity => Some degree of Cardiostimulation may occur

I. α- Adrenoblockers:

I. Non-Selective Adrenoblockers:

PHENTOLAMINE (α_1, α_2) – Tab 25 mg

TROPAPHENE (α_1, α_2) – Amp 20 mg

II. Selective Adrenoblockers:

PRAZOSINE (α_1) – Tab 1, 3, 5 mg

DOXAZOSINE (α_1) – Tab 2 and 4 mg

YOHIMBINE (α_2) –Tab 5 mg

Phentolamine – α_1-, α_2- AB

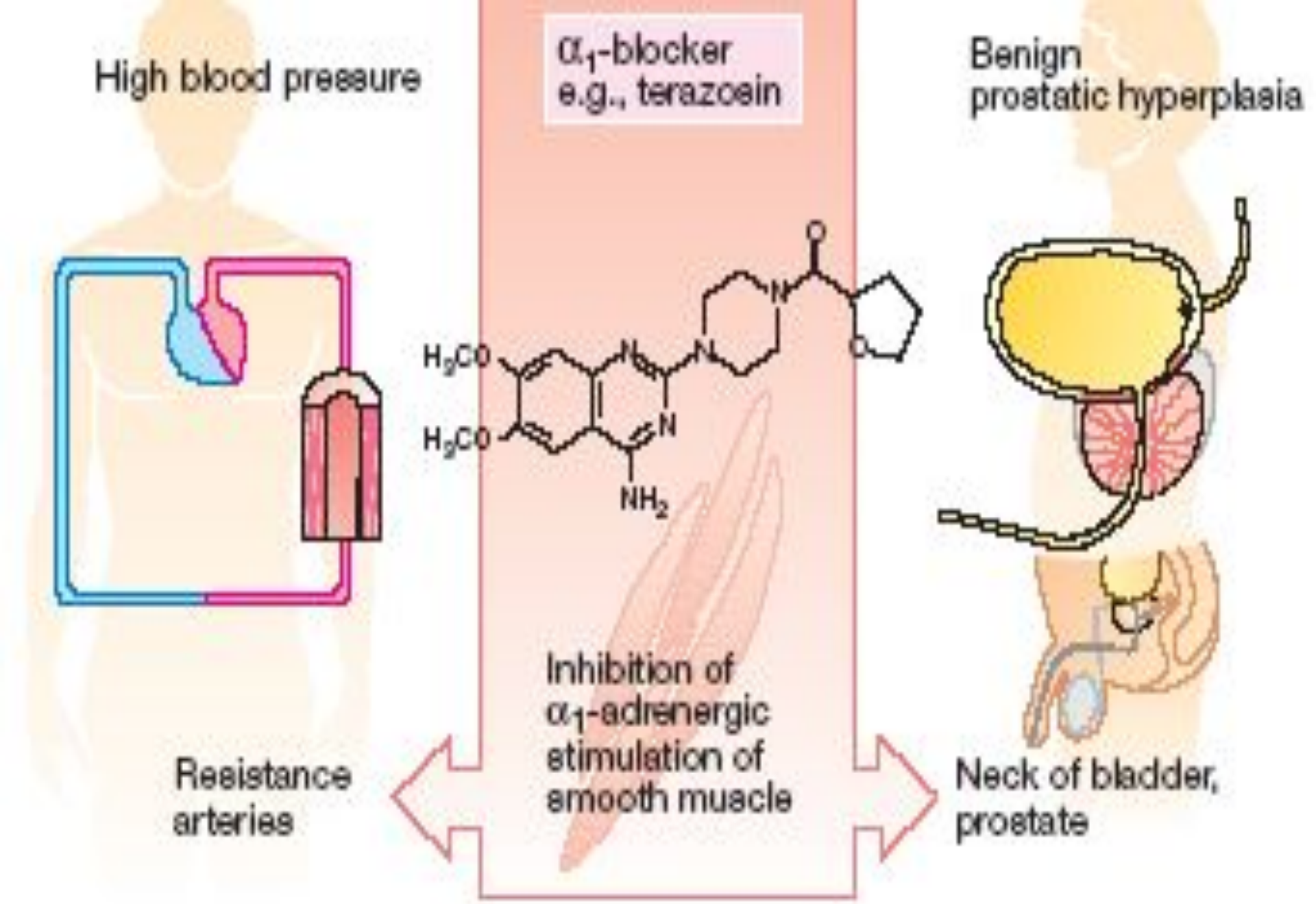
The action lasts for 4 hours.

α-Receptors Blockade =>

Prevention Peripheral Blood Vessels Vasoconstriction by CATECHOLAMINES.

- **Peripheral Resistance** => **Reflex Tachycardia**
- **Postural Hypotension**

Phentolamine had been used in the diagnosis of pheochromocytoma and in other situations associated with excess release of catecholamines.



. Indications for α_1-sympatholytics

PRAZOSIN

TERAZOSINE

DOXAZOSINE (*Cardura*)

- Relaxation of Arterial and Venous Smooth Muscle
- ↓ Peripheral Vascular Resistance
- ↓ AP
- ↓ Tone in the smooth muscle of the Bladder Neck and Prostate
  - Improve Urine Flow

Clinical use: Hypertension,

Benign Prostatic Hypertrophy

β-ADRENOBLOCKERS

1) NON-SELECTIVE:

Propranolol (Anaprilin) (β_1, β_2)

Nadolol (Corgard) (β_1, β_2)

Timolol (β_1, β_2)

2) SELECTIVE:

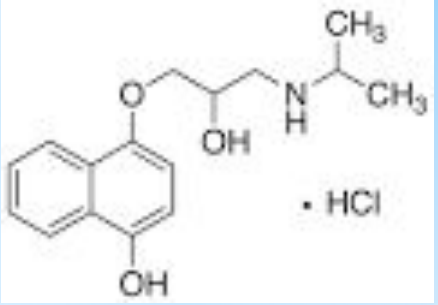
Atenolol (β_1)

Metoprolol (β_1)

3).β_1-, α_1- Blockers:

Labetalol

Carvediol



Propranolol (Anaprilin) – β_1- , β_2- AB

Tab. 10 and 40 mg;

amp. 0.25%-1 ml

Cardiovascular Effects:

- Negative Inotropic - ↓ Cardiac Output
- Negative Chronotropic effects - ↓ HR
- Depresses Sino-Auricular and AV activity

  => ↓ Cardiac Work and O_2 consumption

CLINICAL uses of Propranolol (Anapriline):

- Hypertension
- Angina Pectoris, Myocardial Infarction,
- Arrhythmias
- Glaucoma, Migraine ,
- Hyperthyroidism

Adverse effects:

- Bronchoconstriction
- Peripheral Vasoconstriction
- Arrhythmias, Sexual impairment
- Disturbances in Metabolism:
- ↓Glycogenolysis and ↓Glucagon Secretion

Overdose with Propranolol: ▫AP, ▫HR, heart failure, bronchospasm.

Treatment: Gastric lavage, *Activated charcoal*,

Symptomatic and Supportive care:

Treat Bradycardia with *ATROPINE*, *ISADRINE*

Treat Cardiac Failure with

Cardiac Glycosides: *Strophanthine*

and Diuretics: *Furosemide*

Treat Hypotension with vasopressors:

ADRENALINE is preferred.

Treat Bronchospasm with *ISADRINE* ,

EUPHYLLINE (AMINOPHYLLINE)

SYMPATHOLYTICS:

Reserpine –Tab. 0.1 mg and 0.25 mg
Octadin – Tab. 0.025 g
Ornid – amp, 5% - 1 ml

Reserpine - a Plant Alkaloid from the roots of an Indian plant *Rauwolfia Serpentina*.
It blocks Mg^{2+}/ATP–dependent transport of biogenic amines =>☐the ability of Aminergic Vesicles o take up and store biogenic amines :

Noradrenaline
Dopamine
Serotonine

from the cytoplasm into storage vesicles in the Adrenergic Nerves of ALL BODY TISSUES.

Thank You for Attention!