

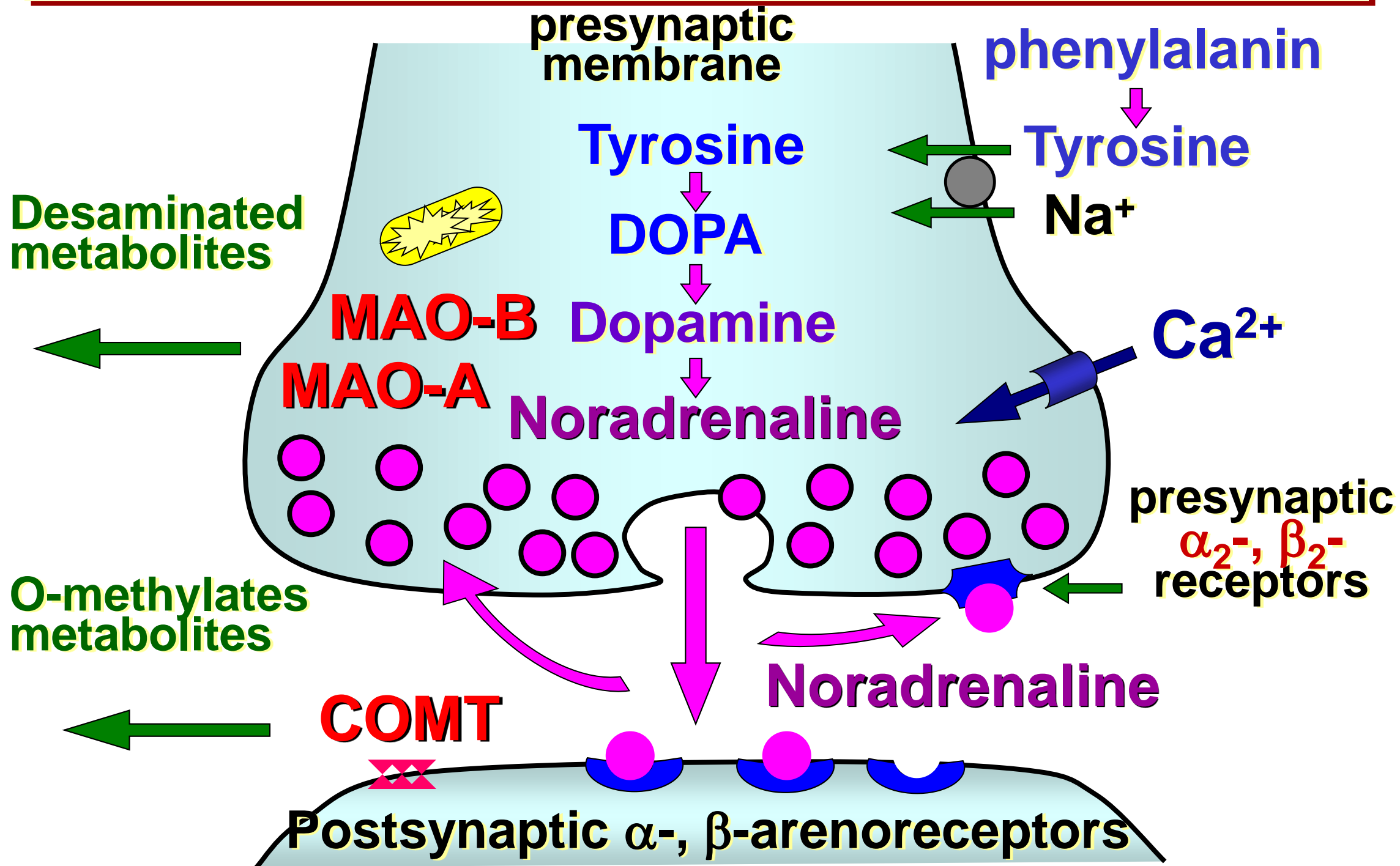
**Odesa National Medical University**  
**Department of General and Clinical**  
**Pharmacology and Pharmacognosy**

**AGENTS INFLUENCING**

**ON ADRENERGIC RECEPTORS**

**(ADRENOMIMETICS, ADRENOBLOCKERS)**

# ADRENERGIC JUNCTION



# SITES OF ACTION OF ADRENOTROPIC AGENTS

## Adrenomimetics (agonists)

## Antiadrenergic agents - antagonists

**Mechanism of action:**

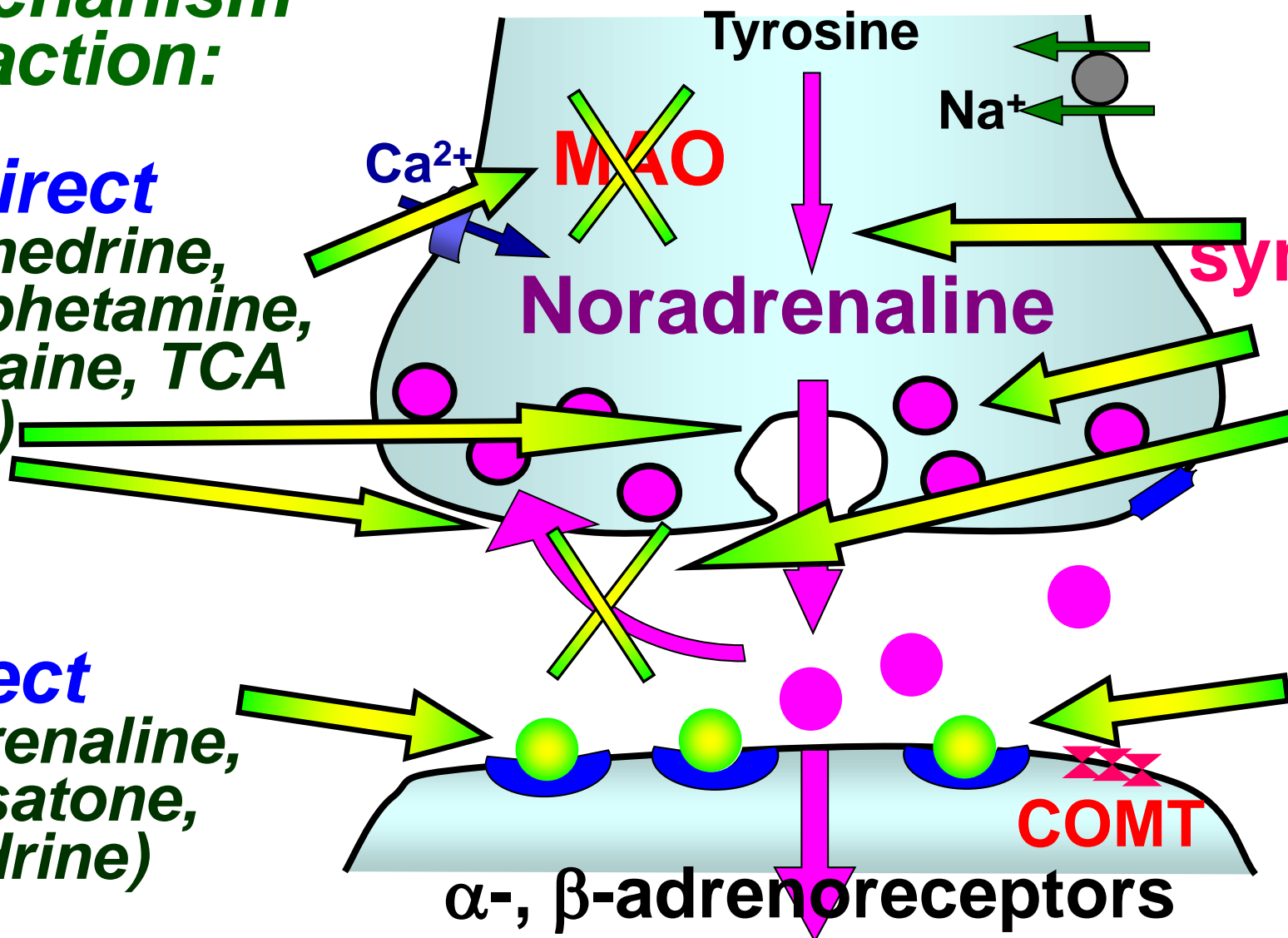
**indirect**  
(ephedrine, amphetamine, cocaine, TCA etc.)

**direct**  
(adrenaline, mesatone, isadrine)

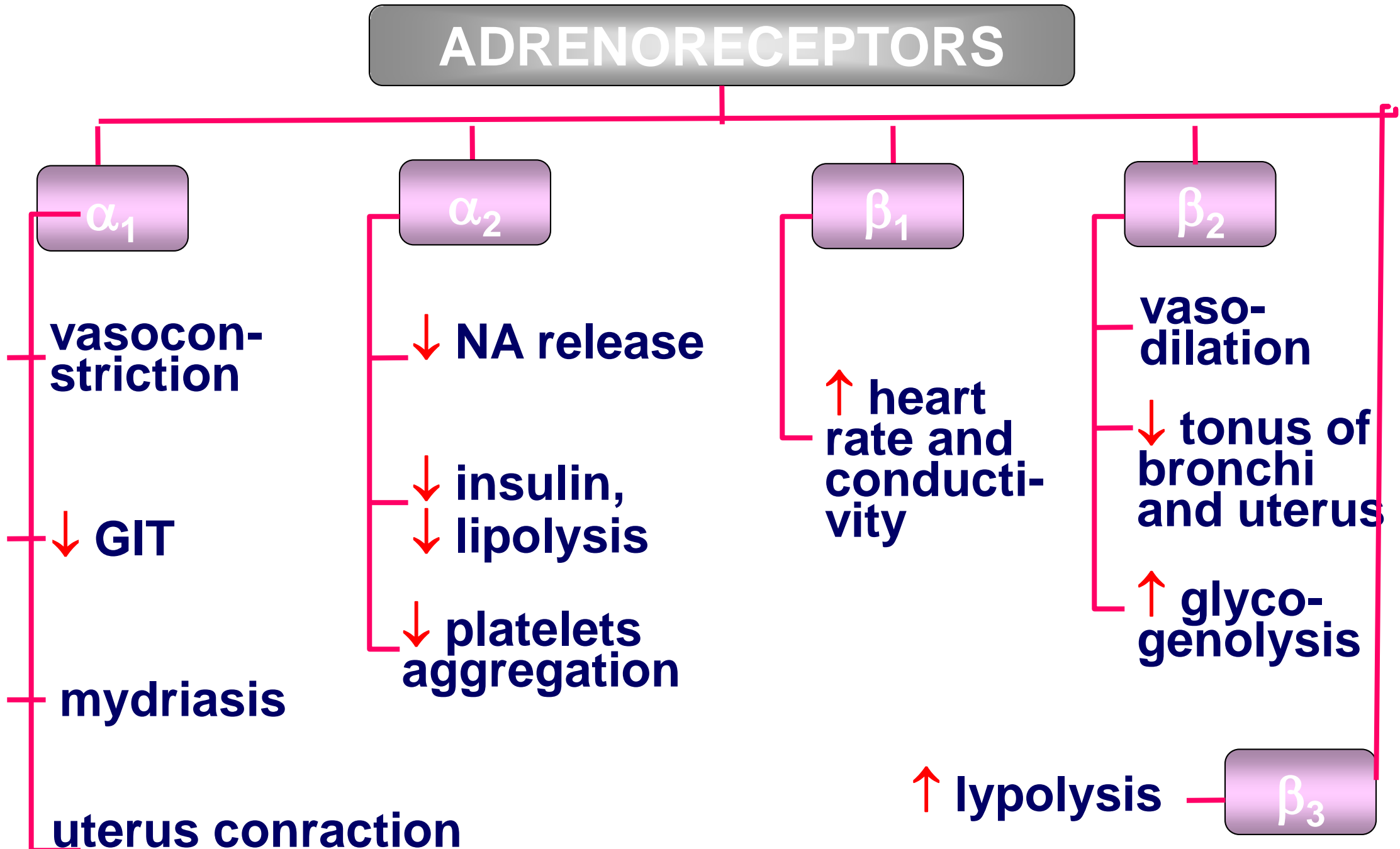
**Mechanism of action:**

**indirect – sympatholytics**  
(reserpine)

**direct**  
(labetalol, prazosine, propranolol, etc.)



# BASIC EFFECTS OF ADRENORECEPTORS





# CLASSIFICATION OF ADRENOMIMETICS / SYMPATHOMIMETICS

⇒ **α-, β- adrenomimetics:**

✓ **direct action:** adrenaline

✓ **indirect action :** ephedrine, dopamine

⇒ **α-adrenomimetics :** noradrenaline, mesaton (phenylephrine), naphthizine (naphazolin) and **central α<sub>2</sub>- (clonidine)**

⇒ **β-adrenomimetics :**

✓ **non-selective (β<sub>1</sub>+ β<sub>2</sub>):** isadrine (isoproterenol), orciprenalin (metoproterenol)

✓ **selective (β<sub>1</sub>):** dobutamine

✓ **selective (β<sub>2</sub>):** **short-acting (3-8 hrs)** – salbutamol, fenoterol; **long-acting (10-12 hrs)** – clinbuterol, formoterol

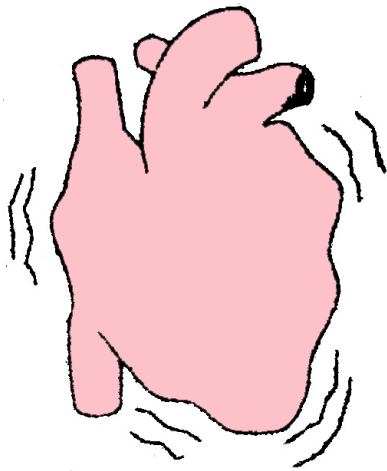
# PHARMACODYNAMICS OF ADRENOMIMETICS

Index	adrenaline ( $\alpha$ , $\beta$ )	mesaton ( $\alpha$ )	isadrine ( $\beta$ )
<b>Blood vessels tonus:</b> <ul style="list-style-type: none"> <li>• skin (<math>\alpha</math>)</li> <li>• skeletal muscles (<math>\beta_2</math>, <math>\alpha</math>)</li> <li>• kidneys (<math>D_1</math>, <math>\alpha</math>)</li> <li>• internal organs (<math>\alpha</math>)</li> <li>• systemic peripheral resistance</li> </ul>	<p style="text-align: center;">↑↑↑</p> <p style="text-align: center;">↓ or ↑</p> <p style="text-align: center;">↑</p> <p style="text-align: center;">↓ or ↑</p> <p style="text-align: center;">↓ or ↑</p>	<p style="text-align: center;">↑↑↑</p> <p style="text-align: center;">↑</p> <p style="text-align: center;">↑</p> <p style="text-align: center;">↑↑↑</p> <p style="text-align: center;">↑↑↑↑</p>	<p style="text-align: center;">0</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">↓</p> <p style="text-align: center;">↓↓↓</p>
<b>Blood pressure:</b> <ul style="list-style-type: none"> <li>• systolic</li> <li>• diastolic</li> <li>• pulse</li> </ul>	<p style="text-align: center;">↑↑↑</p> <p style="text-align: center;">↓ or ↑</p> <p style="text-align: center;">↑↑↑</p>	<p style="text-align: center;">↑↑↑</p> <p style="text-align: center;">↑↑↑</p> <p style="text-align: center;">0</p>	<p style="text-align: center;">0 or ↓</p> <p style="text-align: center;">↓↓↓</p> <p style="text-align: center;">↑↑↑</p>

# ADRENOMIMETICS PHARMACODYNAMICS

## heart

«+» **chrono-, inotropic,**  
 ↑ **O<sub>2</sub> demand of myocardium**

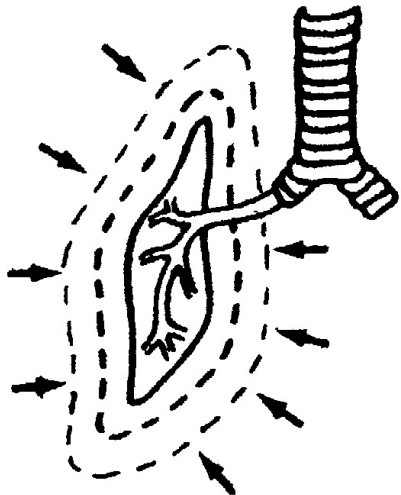


Index	Adrena- line (α, β)	Mesa- ton (α)	Isadrine (β)
• <b>contractility</b>	↑↑↑	0 or ↑	↑↑↑
• <b>heart rate</b>	↓ or ↑	↓↓	↑↑↑
• <b>stroke volume</b>	↑	0, ↓, ↑	↑
• <b>cardiac output</b>	↑	↓	↑↑

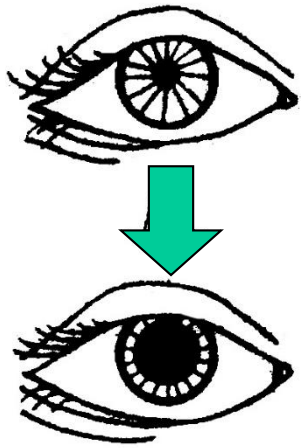
## breathing

(β<sub>2</sub>, vessels of airways – α<sub>1</sub>)

**bronchodilation, decongestive**



# EFFECTS OF ADRENOMIMETICS



**eye**

**mydriasis,**

**$\alpha$ -agonists –  $\uparrow$  fluid outflow,  $\downarrow$  intraocular pressure,**

**$\beta$ -agonists –  $\uparrow$  production**

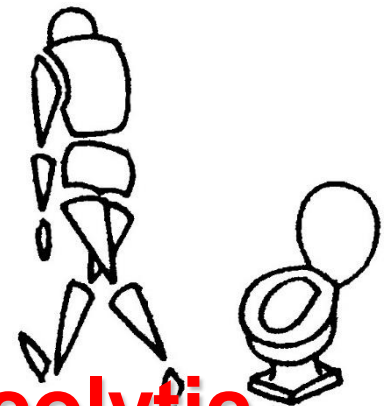
**GIT**

**motorics – decreasing,**  
**sphincters – contraction**

**urogenital system**

**uterus ( $\alpha$ - и  $\beta_2$ ) – relaxation (tocolytic action),**

**urinary bladder ( $\beta_2$ ) - relaxation,**  
**sphincter of urethra and prostate ( $\alpha$ ) – contraction**



**exocrine glands** **apocrine sweat glands ( $\alpha$ ) –  $\uparrow$  secretion**

# EFFECTS OF ADRENOMIMETICS

## *metabolism*

↑ glycogenolysis, ↑ glucose in blood,  
 $\beta_3$  – adipose tissue  $\Rightarrow$   
↑ lipolysis

## **CNS**

Poorly crossing BBB (*catecholamines etc*)  
– nervousness (large doses),  
Well crossing BBB (*indirect acting –  
ephedrine, amphetamine, cocaine etc*) –  
psychostimulation, insomnia etc.



# PHARMACOKINETICS OF ADRENOMIMETICS

**Absorption in GIT:** catecholamines (adrenaline, noradrenaline, dopamine, isadrine) are poorly absorbed unlike phenylalkylamines (ephedrine, amphetamine, tyramine etc.)

**Administration:** adrenaline – S.C., I.M., I.V.; noradrenaline, dopamine – I.V. exclusively (S.C.– poor absorption due to potent vasoconstriction upto ischemic necrosis); the rest agents could be given orally, S.C., I.M., I.V., inhalation, transdermal

**Distribution:** catecholamines are poorly cross BBB; easily can cross BBB indirect adrenomimetics (ephedrine, amphetamine, MAO inhibitors etc.)

**Biotransformation:** catecholamines are quickly metabolized by MAO and COMT + rapid neuronal uptake  $\Rightarrow$  short-lasting effect (5-30 min); the synthetics are metabolized more slowly  $\Rightarrow$  longer effect than in catecholamines

**Excretion:** mainly by kidneys



# ARENOMIMETICS

## *Adrenaline (epinephrine) – $\alpha=\beta$*

- **cardiostimulation** (+ **chrono-**, **inotropic** effect, sharp  $\uparrow$  oxygen demand of myocardium). *At I.V. administration bradycardia can develop!*
- **vasoconstriction**, but dilate the vessels that contain  $\beta$ -receptors (skeletal muscles, heart, brain, liver, lungs)
- $\uparrow$  SAP,  $\downarrow$  or  $\uparrow$  DAP and systemic peripheral resistance
- at adrenoblockers administration **adrenaline** «reversal»  $\downarrow$  BP
- **bronchodilation**
- $\downarrow$  **intraocular pressure, mydriasis**

# ARENOMIMETICS

## **Noradrenaline** – $\alpha_1 = \alpha_2 > \beta_1 > \beta_2$

- **vasoconstrictor** ( $\uparrow$  SAP,  $\uparrow$  DAP,  $\uparrow$  systemic peripheral resistance)
- **+ inotropic effect**
- **only I.V. administration !**

## **Mesaton** – $\alpha$

- **vasoconstrictor** ( $\uparrow$  SAP,  $\uparrow$  DAP)
- **mydriasis**
- **decongestant**
- ***is not inactivated by COMT  $\Rightarrow$  longer action !***

## **Isadrine** – $\beta_1 = \beta_2$

- **vasodilator** ( $\uparrow$  cardiac output, insignificantly  $\uparrow$  SAP +  $\downarrow$  DAP, peripheral resistance)
- **+ chrono-, ino-, dromotropic effects**
- **bronchodilator,  $\downarrow$  GIT tonus,  $\uparrow$  CNS**



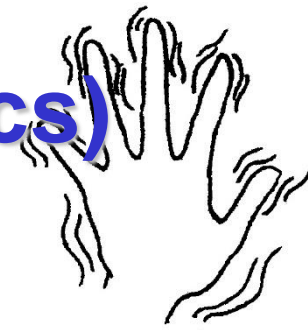
# INDICATIONS FOR ADRENOMIMETICS

- **cardiac arrest** – *adrenaline*
- **acute hypotension (shock, collapse)** – *noradrenaline, dopamine, mesaton*
- **cardiogenic shock** – *isadrine, dobutamine*
- **anaphylactic shock** – *adrenaline*
- **hypoglycemia** – *adrenaline*
- **decreasing of regional blood flow (local anesthesia)** – *adrenaline, mesaton*
- **asthma -  $\beta$ -salbutamol)**
- **risk of miscarriage** – *fenoterol, hexoprenaline*
- **rhinitis** – *naphthizine, halazoline*
- **ophthalmology (glaucoma, diagnost)**  
*mesaton, adrenaline u òp.*



# ADVERSE EFFECTS OF ADRENOMIMETICS

- ✓ **↑ BP (stroke, pulmonary edema)**
- ✓ **arrhythmia, myocardial infarction**
- ✓ **insomnia, tremor (ephedrine etc)**
- ✓ **development of necrosis at S.C. administration (noradrenaline)**
- ✓ **dryness in mouth ( $\beta$ -adrenomimetics)**
- ✓ **dryness of nasal mucosa ( $\alpha$ -adrenomimetics)**
- ✓ **conjunctiva irritation, mydriasis**
- ✓ **tachyphylaxia (ephedrine etc)**
- ✓ **tolerance**
- ✓ **dependence (ephedrine, amphetamine)**



**Odesa National Medical University**

**Department of Pharmacology and Pharmacognosy**

**ADRENERGIC**

**ANTAGONISTS**

# ADRENOBLOCKERS

Sympatholytics	$\alpha_1+\alpha_2$ -adrenolytics	$\alpha_1$ -adrenolytics	$\beta_1+\beta_2$ – adrenolytics	$\beta_1$ -adrenolytics
Reserpine, octadine	Phentolamine, dihydroergotamine	Prazosin, terazosin	Propranolol (anaprilin), pindolol	Atenolol, metoprolol
Decrease peripheral vascular resistance, lower BP	Decrease peripheral vascular resistance, lower BP, facilitation of urination, reflex tachycardia, nasal congestion		Diminish cardiac output, rate, and oxygen consumption; inhibit cardiac excitability and conductivity	

# $\alpha$ -ADRENERGIC ANTAGONISTS

Dihydroergotamine, phentolamine, prazosin, doxazosin etc.

## PHARMACODYNAMICS

*blood*

*vessels* – hypotension (orthostatic collapse !), improvement of the peripheral blood flow

*heart* – reflex tachycardia

*GIT* – motility –  $\uparrow$ , sphincters –  $\downarrow$ ,  
secretion –  $\uparrow$

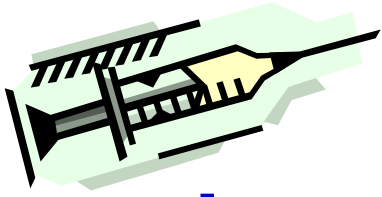
*eye* – miosis

*exocrine glands* –  $\downarrow$  sweating, nasal congestion

*urinary tract* – relaxation of the urinary bladder sphincter



# **$\alpha$ -ADRENERGIC ANTAGONISTS**



## **INDICATIONS**

- **hypertensive emergency** – aminasine
- **arterial hypertension** –  $\alpha_1$ -antagonists (prazosine etc.)
- **disturbances of the cerebral blood flow** – nicergolin
- **disturbances of the peripheral blood flow** (endartheritis, Raynaud's disease)
- **pheochromocytoma** – phentolamine
- **benign prostate hypertrophy** (prostate gland adenoma) – doxazosine, terazosine
- **migraine** – dihydroergotamine etc.

# ADRENOBLOCKERS

Sympatholytics	$\alpha 1 + \alpha 2$ -adrenolytics	$\alpha 1$ -adrenolytics	$\beta 1 + \beta 2$ – adrenolytics	$\beta 1$ -adrenolytics
Hypertension	Hypertension, pheochromocytoma, spasm of blood vessels, benign prostate hyperplasia		Hypertension, angina pectoris, arrhythmia, hyperthyroidism, glaucoma, migraine	
Diarrhea, ulcer of stomach, collapse bradycardia	Orthostatic hypotension, redness of skin, tachycardia		Bronchoconstriction, atrioventricular block, spasm of vessels, hypoglycemia	



# BETA-ADRENOBLOCKERS

## classification:

- **non-selective ( $\beta_1 + \beta_2$ ):** propranolol (anaprilin), nadolol, timolol, oxprenolol\*, pindolol\*
- **selective ( $\beta_1$ ):** atenolol, metoprolol, bisoprolol, nebivolol, acebutalol\*

\* – with intrinsic sympathomimetic activity

## pharmacodynamics

**blood vessels:** vasoconstriction followed by vasodilation; ↓ BP in hypertensive individuals

**heart:**

- ⊕ «–» chronon-, ino-, dromotropic effects
- ⊕ ↓ myocardial O<sub>2</sub> consumption



# $\beta$ -ADRENOBLOCKERS

block  $\beta$ -receptors of the juxtaglomerular apparatus

↓ sympathetic activity

block  $\beta$ -receptors of the heart

↓ renin secretion

↓ heart rate & contractility

↓ automocity, conductivity and excitability of the myocardium

↓ tonus of the peripheral vessels

↓ cardiac output

↓  $O_2$  consumption of the myocardium

**Hypotensive effect**

**Antianginal effect**

**Anti-arrhythmic effect**

# $\beta$ -ADRENOBLOCKERS

## pharmacodynamics

**respiration:** bronchospasm (especially non-selective)

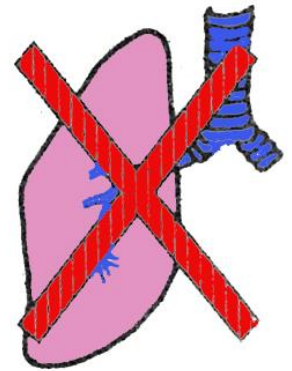
**CNS:** lipid-soluble (propranolol, metoprolol etc.) – anxiolytic effect

**eye:** ↓ intraocular pressure

**metabolism:** ↓ plasma glucose level, cholesterol, ↓ lipolysis, ↓ renin production

✓ propranolol, metoprolol, bisoprolol etc. cause membrane-stabilizing action (block sodium channels)

✓ nebivolol increase NO synthesis ⇒ cause vasodilating effect



# PROPERTIES OF BETA-BLOCKERS

Agents	ISA*	MSA**	Lipid solubility	Bioavail ability	Elimination Half-Life
<i>I. Nonselective <math>\beta</math>- (<math>\beta_1 + \beta_2</math>) adrenergic agonists</i>					
Propranolol	No	Yes	High	$\approx 30$	3-6 hours
Nadolol	No	No	Low	$\approx 33$	14-24 hr
Timolol	No	No	Moderate	$\approx 50$	4-5 hours
Pindolol	Yes	Yes	Moderate	$\approx 90$	3-4 hours
Labetalol	No	Yes	Moderate	$\approx 30$	5 hours
Sotalol	No	No	Low	$\approx 90$	12 hours

Footnote: \* - **Intrinsic sympathomimetic activity** (partial agonists)

\*\* - **Membrane-stabilizing activity** (local anesthetic action)

# PROPERTIES OF BETA-BLOCKERS

Agents	ISA*	MSA**	Lipid solubility	Bioavail ability	Elimination Half-Life
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## *II. Selective $\beta_1$ adrenergic agonists*

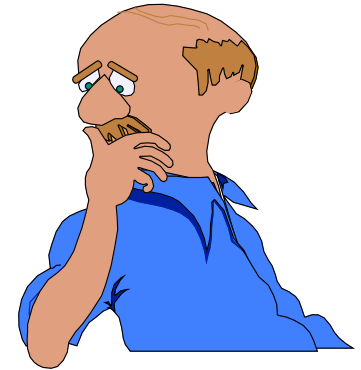
Metoprolol	No	Yes	Moderate	$\approx 50$	3-4 hours
Acebutolol	Yes	Yes	Low	$\approx 50$	3-4 hours
Atenolol	No	No	Low	$\approx 40$	6-9 hours
Esmolol	No	No	Low	...	10 minutes
Sotalol	No	No	Low	$\approx 90$	12 hours

Footnote: \* - **Intrinsic sympathomimetic activity** (partial agonists)  
\*\* - **Membrane-stabilizing activity** (local anesthetic action)

# $\beta$ -ADRENOBLOCKERS

## indications

- Arterial hypertension
- Ischemic heart disease
- Tachyarrhythmia
- Glaucoma – timolol
- Hyperthyroidism – propranolol
- Migraine, alcohol withdrawal – propranolol



# $\beta$ -ADRENOBLOCKERS

## Adverse effects

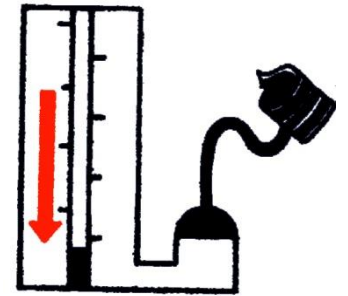
- **cardiovascular: cardiac arrhythmia (AV-block, bradycardia etc.), chronic heart failure**
- **bronchospasm**
- **spasm of the peripheral vessels («claudication»)**
- **hypoglycemia**
- **aetherogenic effect**
- **tolerance (desensitization of the receptors)**
- **rebound syndrome with myocardial ischemia**
- **contraction of pregnant uterus**
- **drowsiness**



# SYMPATHOLYTICS (ADRENERGIC NEURON-BLOCKING AGENTS)

(↓ synthesis, storage and release of the catecholamines into synaptic cleft)

**reserpine** (alkaloid of an Indian plant *Rauwolfia*), **guanethidine**



## PHARMACODYNAMICS

**blood vessels:** **slow onset of maximal effect** (in reserpine after 5-14 days !),

**heart:** ↓ heart rate and cardiac output

**CNS:** sedative and neuroleptic action (reserpine)

**GIT:** motility and secretion – ↑

# SYPMATHOLYTICS

## *Adverse effects*

- **CNS (reserpine): drowsiness, mental depression, extrapyramidal disturbances**
- **vagal effects:**
  - ✓ **bradycardia**
  - ✓ **bronchospasm**
  - ✓ **sweating**
  - ✓ **diarrhea, gastric peptic ulcer**
- **allergic reactions**

