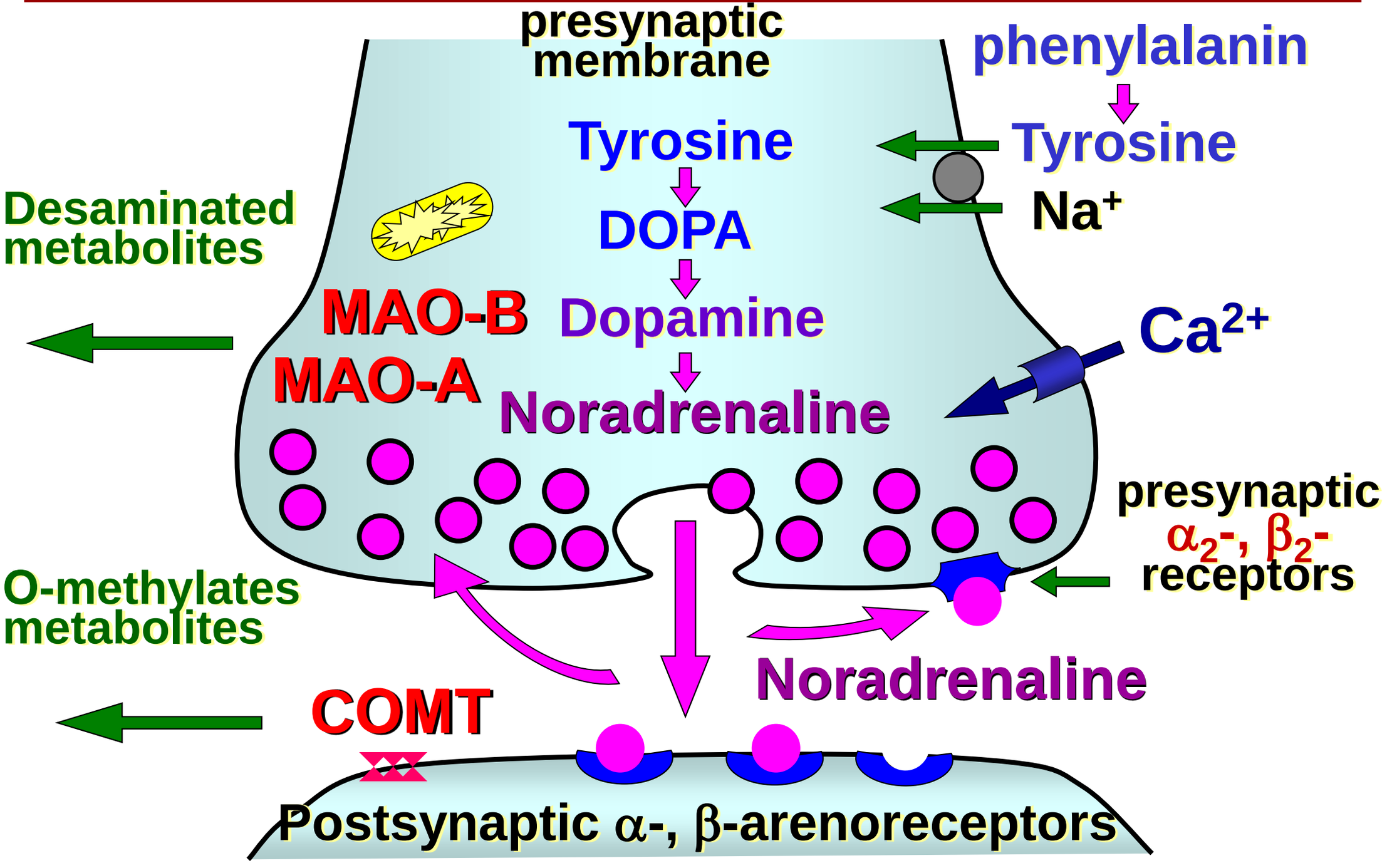
Odesa National Medical University
Department of Pharmacology and Pharmacognosy

AGENTS INFLUENCING ON ADRENERGIC RECEPTORS (ADRENOMIMETICS, ADRENOBLOCKERS)

ADRENERGIC JUNCTION



SITES OF ACTION OF ADRENOTROPIC AGENTS

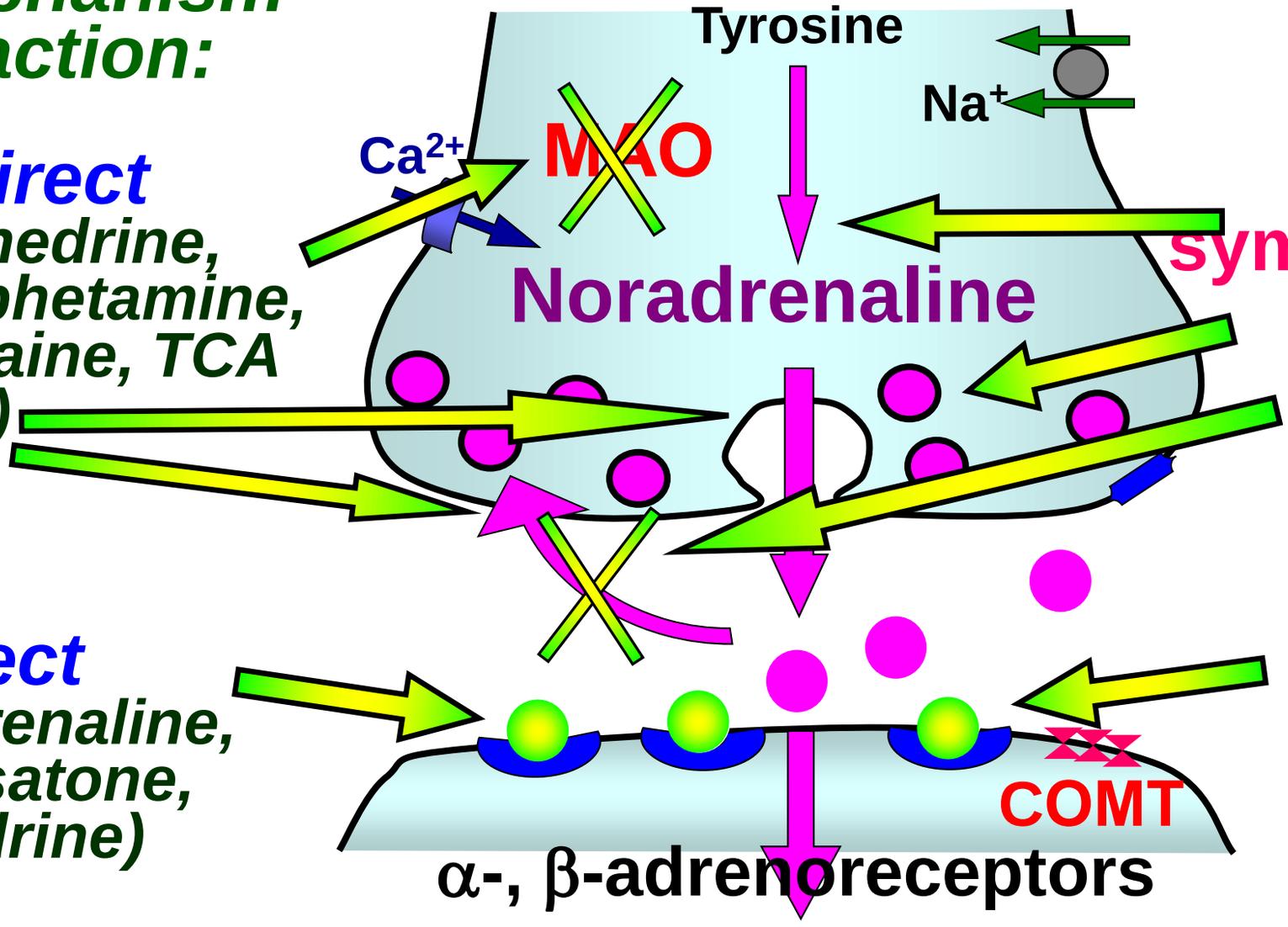
Adrenomimetics (agonists)

Antiadrenergic agents - antagonists

Mechanism of action:

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

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

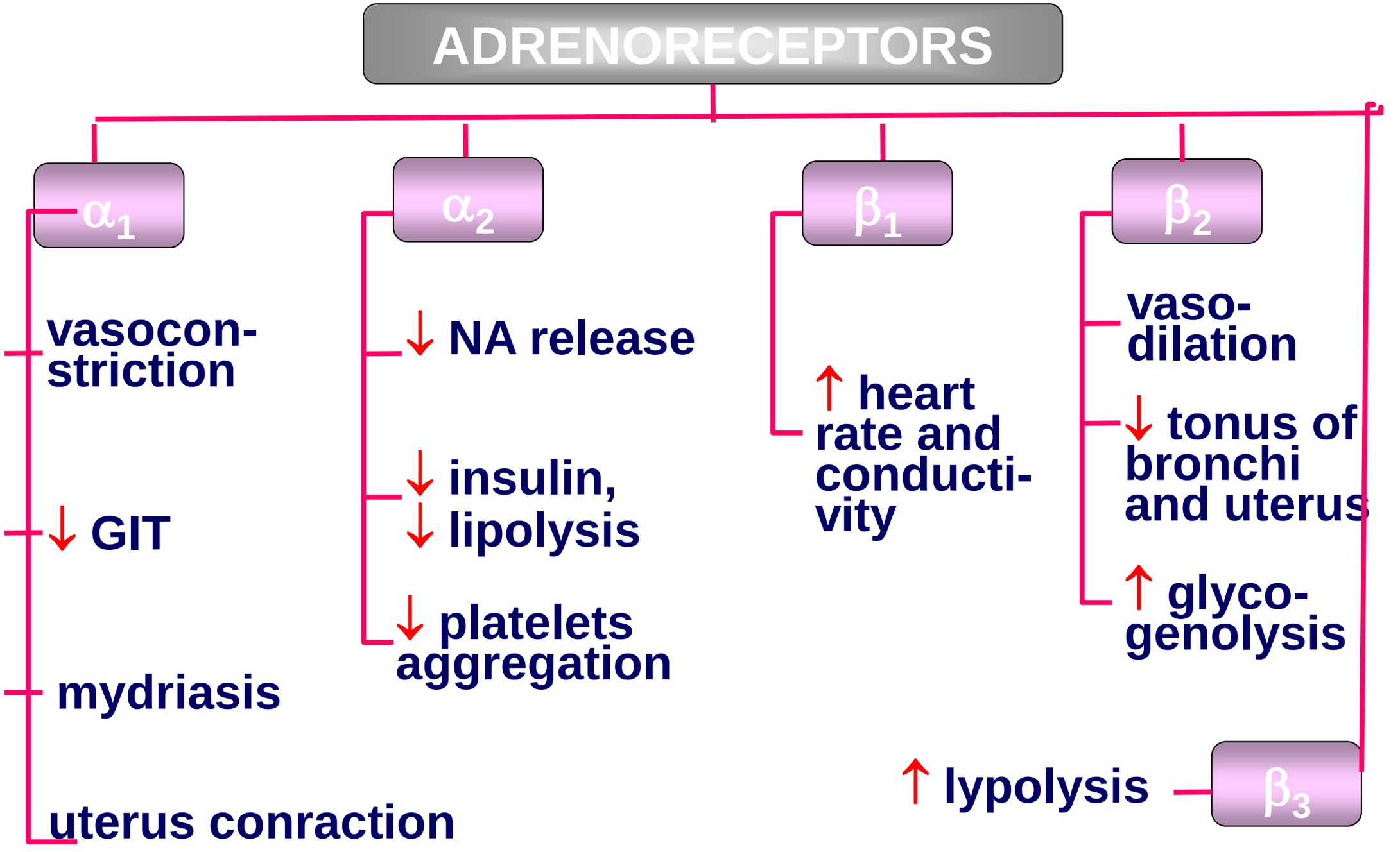


Mechanism of action:

indirect – sympatholytics ***(reserpine)***

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

BASIC EFFECTS OF ADRENORECEPTORS



CLASSIFICTION OF ADRENOMIMETICS / SYMPATHOMIMETICS

⇒ **α-, β- adrenomimetics:**

- ✓ ***direct action:*** **adrenaline**
- ✓ ***indirect action :*** **ephedrine, dopamine**

⇒ **α-adrenomimetics : noradrenaline, mesaton (phenylephrine), naphthizine (naphazolin) and central α_2- (clonidine)**

⇒ **β-adrenomimetics :**

- ✓ ***non-selective (β_1+ β_2):*** **isadrine (isoproterenol), orciprenalin (metoproterenol)**
- ✓ ***selective (β_1):*** **dobutamine**
- ✓ ***selective (β_2):*** ***short-acting (3-8 hrs)*** **– salbutamol, fenoterol;** ***long-acting (10-12 hrs)*** **– clinbuterol, formoterol**

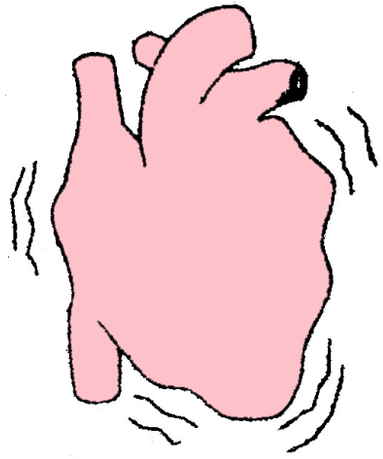
PHARMACODYNAMICS OF ADRENOMIMETICS

Index	adrenaline (α, β)	mesaton (α)	isadrine (β)
Blood vessels tonus:			
• skin (α)	↑↑	↑↑	0
• skeletal muscles (β_2, α)	↓ or ↑	↑	↓
• kidneys (D_1, α)	↑	↑	↓
• internal organs (α)	↓ or ↑	↑↑	↓
• systemic peripheral resistance	↓ or ↑	↑↑↑	↓↓
Blood pressure:			
• systolic	↑↑	↑↑	0 or ↓
• diastolic	↓ or ↑	↑↑	↓↓
• pulse	↑↑	0	↑↑

ADRENOMIMETICS PHARMACODYNAMICS

heart

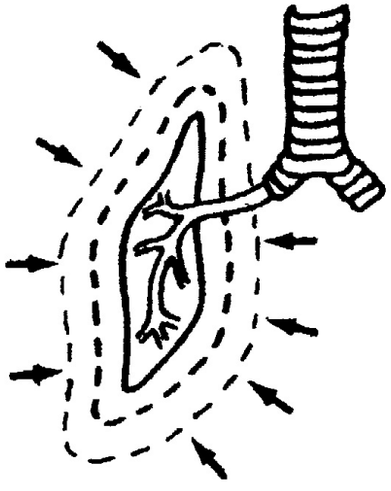
«+» chrono-, inotropic,
↑ O_2 demand of mycardium



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

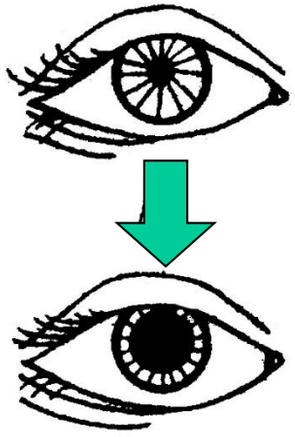
breathing

($β_2$, vessels of airways – $α_1$)



bronchodilation, decongestive

EFFECTS OF ADRENOMIMETICS



eye **mydriasis,**
α-agonists – ↑ fluid outflow, ↓ intraoccular pressure,
β-агонисты – ↑ продукции

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

urogenital system

uterus (α- и β_2) – relaxation (tocolytic action),
urinary bladder (β_2) - relaxation,
sphincter of urethra and prostate (α) – contraction

exocrinic glands **apocrinic sweat glands (α) – ↑ secretion**

EFFECTS OF ADRENOMIMETICS

metabolism

↑ **glycogenolysis, ↑ glucose in blood,**
β_3 – adipose tissue ⇒ ↑ 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 absorbtion 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 ⇒ short-lasting effect (5-30 min); the synthetics are metabolized more slowly ⇒ longer effect than in catecholamines**

Excretion: **mainly by kidneys**

ARENOMIMETICS

Adrenaline (epinephrine) – α=β

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

ARENOMIMETICS

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

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

Mesaton – α

- **vasoconstrictor (↑ SAP, ↑ DAP)**
- **mydriasis**
- **decongestant**
- ***is not inactivated by COMT ⇒ longer action !***

Isadrine – $\beta_1 = \beta_2$

- **vasodilator (↑ cardiac output, insignificantly ↑ SAP + ↓ DAP, peripheral resistance)**
- **+ chrono-, ino-, dromotropic effects**
- **bronchodilator, ↓ GIT tonus, ↑ 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 - *β-salbutamol)***
- **risk of miscarriage – *fenoterol, hexoprenaline***
- **rhinitis – *naphthizine, halazoline***
- **ophthalmology (glaucoma, diagnost *mesaton, adrenaline u ∂p.***

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 (β-adrenomimetics)
- ✓ dryness of nasal mucosa (α-adrenomimetics)
- ✓ conjunctiva irritation, mydriasis
- ✓ tachyphylaxia (ephedrine etc)
- ✓ tolerance
- ✓ dependence (ephedrine, amphetamine)

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ADRENERGIC ANTAGONISTS

ADRENOBLOCKERS

Sympatho-lytics	α1+α2-adrenolytics	α1-adre-nolytics	β1+β2 – adrenolytics	β1-adre-nolytics
Reserpine, octadine	Phentolamine, dihydroergot-amine	Prazosin, terazosin	Propranolol (anaprilin), pindolol	Atenolol, metopro-lol
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	

α-ADRENERGIC ANTAGONISTS

Dihydroergotamine, phentolamine, prazosin, doxazosin etc.

PHARMACODYNAMICS

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

heart – reflex tachycardia

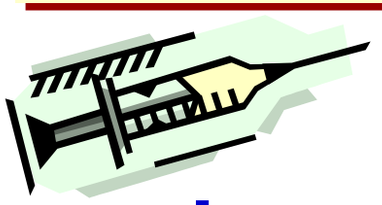
GIT – motility – ↑, sphincters – ↓, secretion – ↑

eye – miosis

exocrinic glands – ↓ sweating, nasal congestion

urinary tract – relaxation of the urinary bladder sphincter

α-ADRENERGIC ANTAGONISTS



INDICATIONS

- **hypertensive emergency – aminasine**
- **arterial hypertension – α_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

Sympatho-lytics	α1+α2-adrenolytics	α1-adre-nolytics	β1+β2 – adrenolytics	β1-adre-nolytics
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*** ***(β_1+ β_2):*** **propranolol (anaprilin), nadolol, timolol, oxprenolol*, pindolol***
- ***selective*** ***(β_1):*** **atenolol, metoprolol, bisoprolol, nebivolol, acebutalol***

* – *with intrinsic sympathomimetic activity*

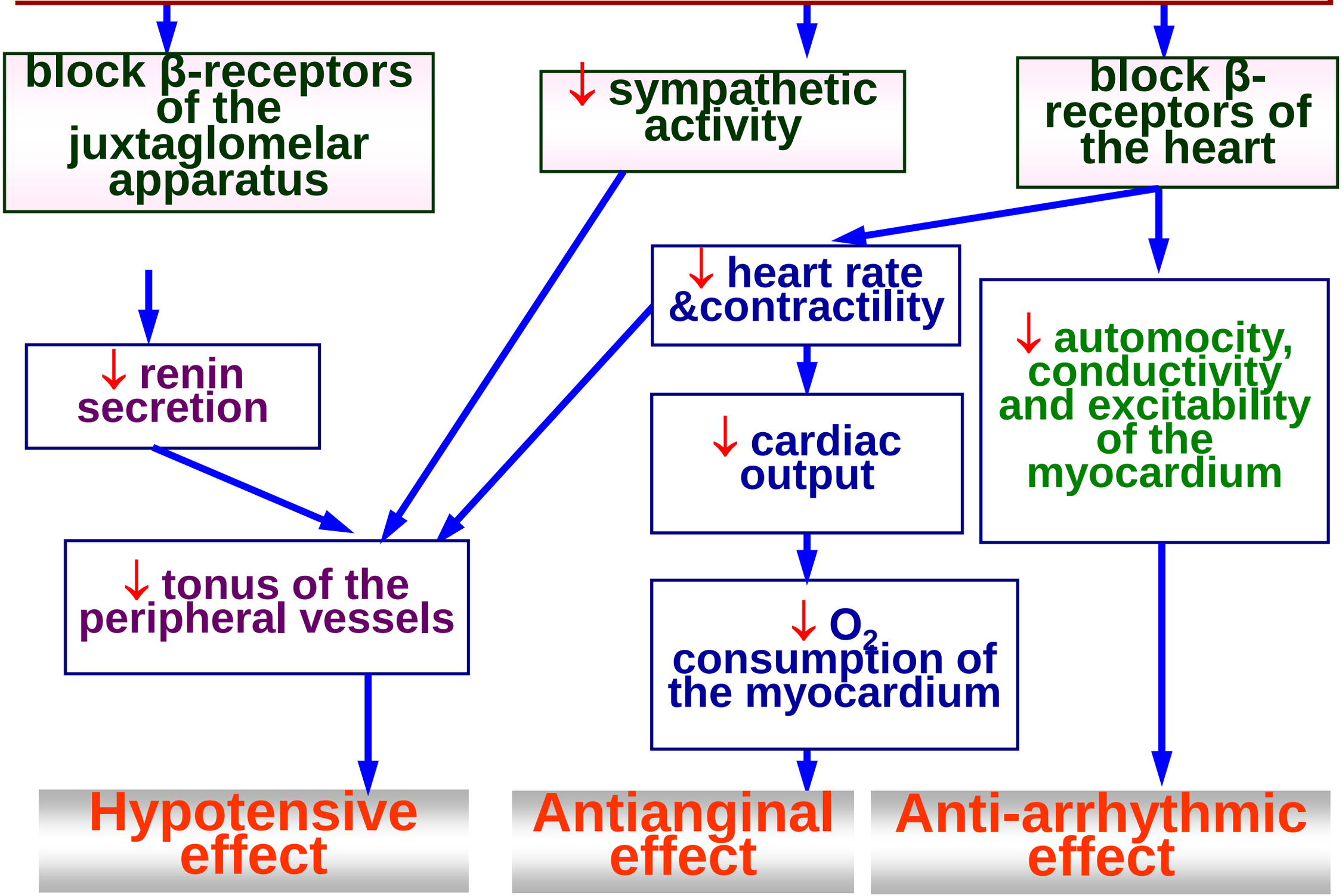
pharmacodynamics

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

heart:

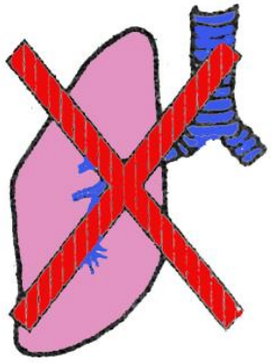
- **«–» chronon-, ino-, dromotropic effects**
- **↓ myocardial O_2 consumption**

β-ADRENOBLOCKERS



β-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 ⇒ causse vasodilating effect**

PROPERTIES OF BETA-BLOCKERS

Agents	**ISA***	**MSA****	**Lipid solubility**	**Bioavail ability**	**Elimination Half-Life**
I. Nonselective β- (β_1+β_2) adrenergic agonists					
Propranolol	No	Yes	High	≈ 30	3-6 hours
Nadolol	No	No	Low	≈ 33	14-24 hr
Timolol	No	No	Moderate	≈ 50	4-5 hours
Pindolol	Yes	Yes	Moderate	≈ 90	3-4 hours
Labetalol	No	Yes	Moderate	≈ 30	5 hours
Sotalol	No	No	Low	≈ 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**
II. Selective β_1 adrenergic agonists					
Metoprolol	No	Yes	Moderate	≈ 50	3-4 hours
Acebutolol	Yes	Yes	Low	≈ 50	3-4 hours
Atenolol	No	No	Low	≈ 40	6-9 hours
Esmolol	No	No	Low	. . .	10 minutes
Sotalol	No	No	Low	≈ 90	12 hours

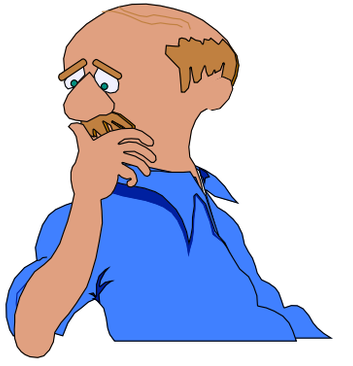
Footnote: * - **Intrinsic sympathomimetic activity** (partial agonists)

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

β-ADRENOBLOCKERS

indications

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



β-ADRENOBLOCKERS

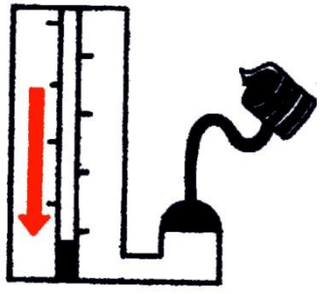
Adverse effects

- **cardiovascular: cardiac arrythmia (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 !),

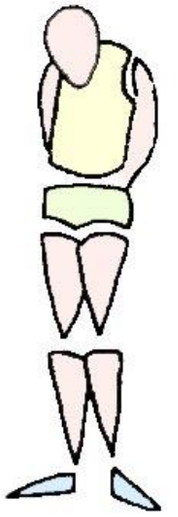
heart: ↓ heart rate and cardiac output

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**