Adrenergic agents

Pharmacology department
SSMA

Adrenergic Synapses

- the main mediator of sympathetic nervous system is Noradrenaline (Norepinephrine), so sympathetic innervation is called as noradrenergic one.

  Adrenergic agents take their action on adrenergic synapses

Where are they located?

Perypheral adrenergic synapses located In postganglionic part of adrenergic nerve fiber

Adrenergic synapses

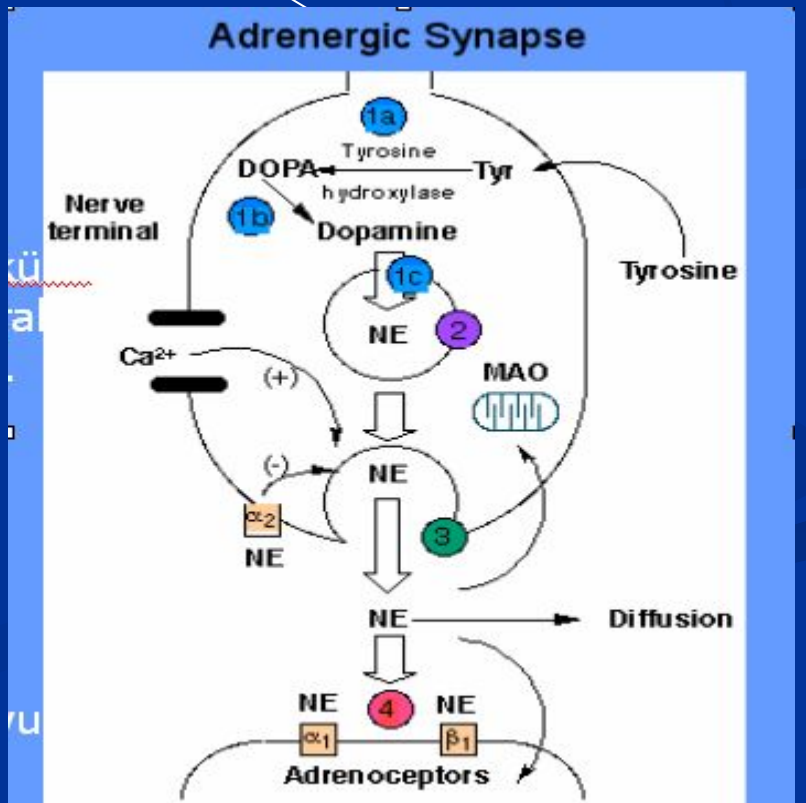
- Adrenergic neurones are located in the CNS (locus coeruleus of midbrain, pons Varolii, medulla and sympathetic ganglia).

Sympathetic synapses

Centers of pre-gangli-onic fibers

N-ChR

AR

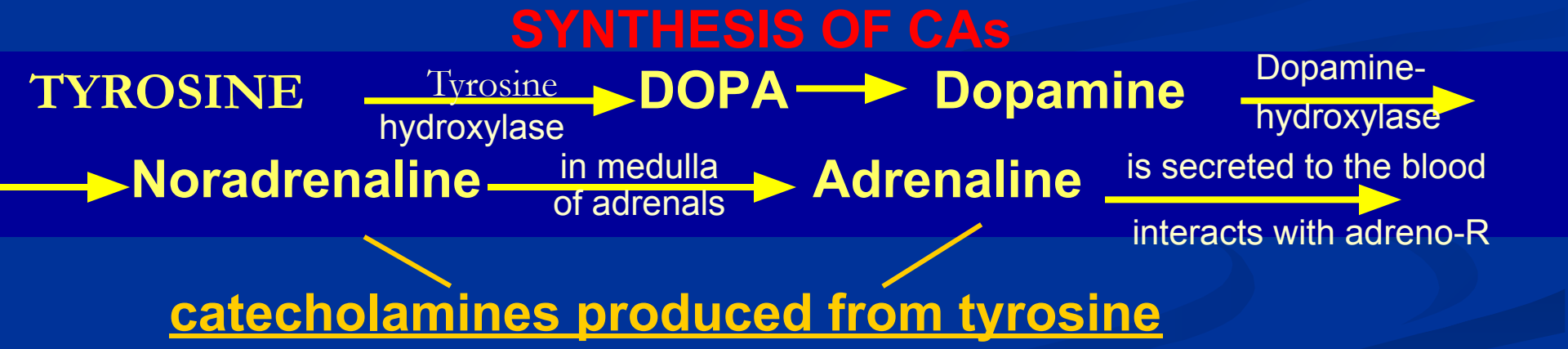


Adrenergic agents

Noradrenaline is the main mediator at postganglionic sympathetic site (except sweet glands, hair follicles and some vasodiating fibers) and in certain areas of brain.

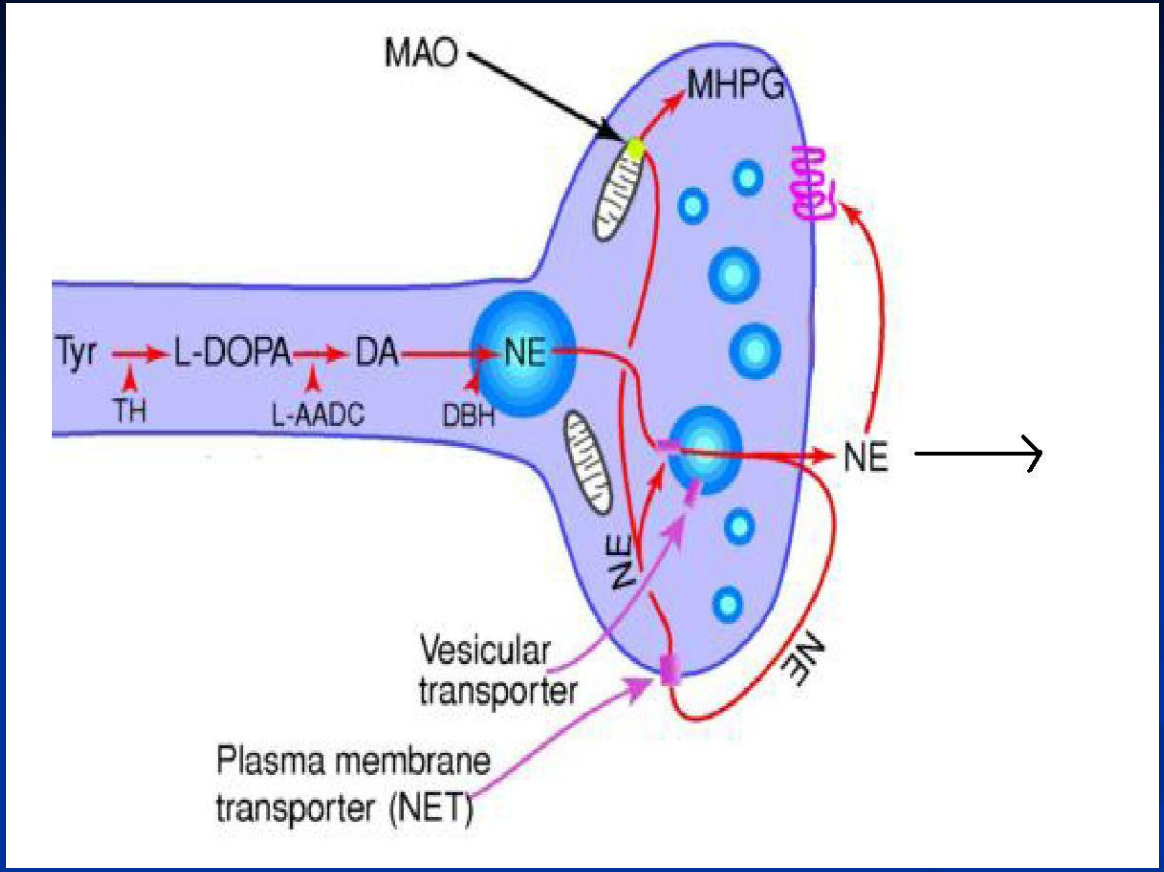
Adrenaline has a transmitter role in brain.

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



Uptake of CAs

- After dissociation of complex "noradrenalin-adrenoceptor", the mediator is inactivated by a few mechanisms.
- Neuronal uptake which occurs in two steps
- Axonal uptake (uptake-1) – active Na^+ coupled transport by amine pump across presynaptic membrane
- Vesicular uptake with another amine pump by exchanging with H^+ ions.



NET – norepinephrine transporter

Uptake of CAs

- Extraneuronal uptake (uptake-2) with neuroglia, fibroblasts, cardiomyocytes, endothelial cells and myocytes of blood vessel wall
- About 80% noradrenaline undergoes neuronal reuptake
- 10% undergoes extraneuronal reuptake
- 10% undergoes enzymatic desintegration

Metabolism of CAs

1. ***MAO (monoamine oxydase)*** ***inactivates CAs in synapse.***

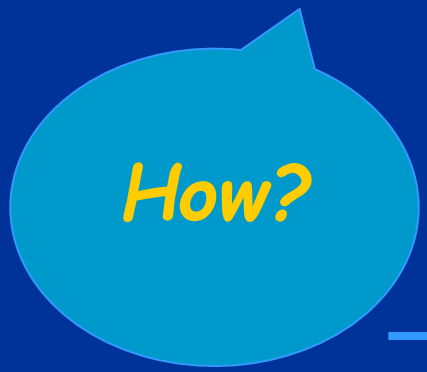
   Part of NA leaking out from vesicle to cytoplasm as well that taken up by axonal transport is first attacked by MAO.

- **There are two types MAO: MAO-A (deaminates NA and Adr) and MAO-B (provides DA catabolism)**

2. ***COMT (catechol-o-methyl-transferase)*** attacks CAs in the liver and other tissues

Adrenergic agents

change activity of sympathetic nervous system



There are 2 big groups:

- ***adrenergic agonists (sympathomimetics)***
- ***adrenergic antagonists (sympatholytics)***

Adrenergic receptors

- R. Ahlquist (1948) classified them into two types α- and β.
- Molecular cloning in the mid 1970s has further identified 3 subtypes of α_1 (α_{1A}- α_{1B}- α_{1D}) and 3 subtypes of α_2 (α_{2A}- α_{2B}- α_{2C})

α_1- adrenoceptors are located on postsynaptic membrane (postjunctional):

α_{1A} receptors in

- Vas deference, seminal vesicle, prostate, prostatic urethra
- radial muscle of iris

Adrenergic receptors

$\alpha_{1B/1D}$ – in blood vessels of skin, mucosa and internal organs.

α_1 - receptors are located also in smooth muscles and sphincters of GIT, and spleen capsule

Stimulation of α_1-adrenoreceptors leads to:

- Vasoconstriction
- Decrease in tone of smooth muscles of GIT and increase in tone of sphincters
- Mydriasis
- Ejaculation

α – adrenoceptors:

- α_2-adrenoreceptors can be located both on postsynaptic and on presynaptic membrane of adrenergic synapses

These can be inhibitory or stimulatory.

- Stimulation of presynaptic (prejunctional) α_2-receptors inhibits release of noradrenaline from vesicles to synaptic cleft <u>according to negative feed back mechanism</u>.
- Stimulation of postsynaptic (postjunctional) central α_2-receptors located in the brainstem inhibits activity of vasomotor center and decreases sympathetic outflow that leads to fall in BP and bradycardia.

α – adrenoceptors:

out-synaptic (non-innervated, extrajunctional) α_2-receptors

- they are located in blood vessels, on platelets, in GIT, pancreas. They are stimulated by adrenaline circulating in the blood
- their activation causes vasoconstriction in skin and mucosa, platelet aggregation, inhibition of GIT motility and insulin secretion.

β-adrenoceptors:

- ***β_1-adrenoreceptors*** are located
  - on *postsynaptic membrane of myocardium cells*
  - *in juxtaglomerular apparatus*

stimulation of β_1-receptors increases all cardiac functions:

- automatism
- A-V conduction
- excitability,
- heart rate
- Contractility
- Myocardium oxygen demand is increased
- Tachycardia occurs at excess amount of CAs in the blood
- Renin secretion is increased in kidney

β-adrenoreceptors:

- ***β_2-adrenoceptors*** can be located presynaptically, postsynaptically and extrasynaptically:
- Extrasynaptic β_2-adrenoceptors are located in
  - Smooth muscles & glands of bronchi & trachea,
  - Platelets
  - Pancreas
  - Liver
- Postsynaptic β_2-adrenoceptors are located in
  - uterus, urinary bladder, gall bladder, GIT
  - in skeletal muscle blood vessels also,
  - in coronary, pulmonary, cerebral & hepatic blood vessels

Presynaptic β_2-adrenoceptors function according to positive feed back and stimulate NA release at insufficient activation of adrenoceptors

β-adrenoceptors:

- *stimulation of β_2-receptors causes*
- Bronchodilation and decrease in bronchial secretion,
- Inhibition of platelet aggregation
- Increase in insulin secretion
- Glycogenolysis and increase in glucose level in blood
- Vasodilation in skeletal muscles, in coronary, pulmonary, cerebral and hepatic vessels
- Decrease in tone of myometrium, urinary bladder detrusor, GIT & biliary tract.

β-adrenoceptors:

- ***β_3-adrenoreceptors have been found on*** *membranes of adipocytes*
- high concentration of catecholamines excite them what stimulates lipolysis and thermogenesis in adipose tissue
- agonists of β_3-receptors are perspective for obesity treatment, and also for complex treatment of diabetes mellitus
- Adrenoceptors participate in regulation of carbohydrate and lipid metabolism
- Their excitation by catecholamines stimulate metabolism and increase oxygen demand

TRANSDUCER MECHANISMS OF ADRENOCEPTORS

- Adrenergic receptors are membrane bound G-protein coupled receptors which function primarily by increasing or decreasing the intracellular production of second messengers cAMP or IP_3/DAG.
- In some cases the activated G-protein itself operates K^+ or Ca^{2+} channels or increases prostaglandin production

TRANSDUCER MECHANISMS OF ADRENOCEPTORS

- α_1-receptors via G-protein are coupled to phospholipase C. Activation of membrane phospholipases leads to increase in Ca^{2+} influx cross membrane and liberation of deposited Ca^{2+} from intracellular depots.
- α_2-receptors (presynaptic) via G-protein inhibit adenylyl cyclase and decreases cAMP formation. They increase permeability of membranes for K^+. That leads to hyperpolarization and block of Ca^{2+} channels.

TRANSDUCER MECHANISMS OF ADRENOCEPTORS

- β_1 receptors via G_s-proteins stimulate phosphorilation of calcium channels that leads to their opening. Ca^{2+} incomes to sarcoplasm and is mobilized from sarcoplasmic reticulum.
- β_2 receptors activate adenylyl cyclase and increase cyclic AMP content. Cyclic AMP binds free Ca^{2+} that leads to hyperpolarization of membrane
- β_2 receptors increase cAMP dependent lipolysis.

CLASSIFICATION OF ADRENERGIC AGONISTS

increase transmission of nerve impulse in adrenergic synapses

Adrenergic agonists of direct action:

α-,β- adrenergic agonists (non-selective) – stimulate all types of adrenoceptors:

Noradrenaline hydrotartrate (Norepinephrine)

Adrenaline hydrochloride (Epinephrine)

- *α-adrenergic agonists:*

α_1-AG:

- ✔ Phenylephrine
- ✔ Etilefrine
- ✔ Midodrine

α_1 -,α_2-AG (non-selective):

- Naphazoline
- Xylometazoline
- Oxymethazoline
- Tetrizoline

α-adrenergic agonists:

α_2- agonists:

- *Clonidine*
- *α-Methyldopa*
- *Apraclonidine*
- *Brimonidine*

CLASSIFICATION OF ADRENERGIC AGONISTS

- *β-adrenergic agonists:*

β_1 -β_2 –adrenergic agonists:

- Isoprenaline
- Orciprenaline

β_1-adrenergic agonists (cardioseletive):

- Dobutamine

β_2-adrenergic agonists:

- Salbutamol , Salmeterol
- Fenoterol
- Terbutaline, Clenbuterol
- Hexoprenaline, Formoterol, Bambuterol

CLASSIFICATION OF ADRENERGIC AGONISTS

Adrenergic agonists of indirect action (indirect sympathomimetics):

- ✔ Ephedrine hydrochloride
- ✔ Phenylpropanolamine

Combined preparations:

- ✔ Aerosol «Berodual» (fenoterol + ipratropium bromide)
- ✔ Aerosol «Ditec» (fenoterol + cromolyn sodium)
- ✔ Intal plus (salbutamol + cromolyn sodium)
- ✔ Coldrex (paracetamol, phenylephrine, ascorbinic acid)

Classification of direct adrenergic agonists according to origin

- Cathecholamines
  - Endogenous
    - Dopamine
    - Adrenaline
    - Dopamine
  - Exogenous
    - Dobutamine
    - Isoprenaline
- Non-cathecholamines

α-,β-adrenergic agonists

The main representatives:

Adrenaline & Noradrenaline

PHARMACOLOGICAL EFFECTS:

Influence on vascular tone

- ✔ Noradrenaline mostly activates α_1-receptors of vessels (pressor action)
- ✔ That leads to vasoconstriction
- ✔ Increase in t.p.r., ABP, preload of the heart and myocardium oxygen demand
- ✔ the main effect of Noradrenaline is **marked, but short-term: increase in ABP with redistribution of the blood to vitally important organs** (the brain, the heart, lungs)

PHARMACOLOGICAL EFFECTS OF α-,β-ADRENERGIC AGONISTS

Influence on vascular tone

- Adrenaline takes marked stimulant action on α_1- и β_2-receptors of vessels
- That leads to constriction of skin vessels and vessels of internal organs (via α_1-receptors) and dilation of cerebral, coronary vessels & vessels of skeletal muscles (via β_2-receptors)
- ABP is increased
- but pressor action of adrenaline is usually changed by moderate hypotension (due to stimulation of β_2-receptors of blood vessels of skeletal muscles and their dilation)

PHARMACOLOGICAL EFFECTS OF α-,β-ADRENERGIC AGONISTS

Influence on the heart

- Noradrenaline stimulates β_1-receptors and increases myocardium contractility
- At that, heart rate decreases what can be explained by reflex mechanism
- Due to Noradrenaline action, ABP and stroke volume are increased what reflexly stimulates baroreceptors in aorta and large vessels, reflex is closed in vagus center
- Reflex vagus bradycardia negates stimulant influence of Noradrenaline on β_1-receptors of the heart
- Finally cardiac output is not significantly changed

PHARMACOLOGICAL EFFECTS OF α-,β-ADRENERGIC AGONISTS

An influence on the heart

- Adrenaline takes more marked action on the heart (mostly stimulates β_1-receptors)
- It increases heart rate and strength of heart beats
- Increases activity of sinoatrial node and rate of impulse conduction along A-V node
- Refractory period ↓, cardiac output ↑
- ABP and ↑heart rate stimulate vagus by reflex

  → reflex cardiac arrhythmia can occur

PHARMACOLOGICAL EFFECTS OF α-,β-ADRENERGIC AGONISTS

Influence on eye

- dilate pupil due to contraction of radial muscle (*dilatator pupillae*) of iris
- decrease in intraocular tension (due to stimulation of α_{1A}-receptors and constriction of ciliary vessels they reduce aqueous humor production; stimulation of α_2-receptors located on ciliary epithelium leads to reduction of aqueous humor secretion too),
- but stimulating β_2-receptors, they increase production of aqueous humor

Action on bronchial muscles

Adrenaline stimulates

β_2-receptors, dilates bronchi, relieves bronchospasm

- The action of Noradrenaline is very weak and has no practical value

PHARMACOLOGICAL EFFECTS OF α-,β-ADRENERGIC AGONISTS

Influence on GIT

- ✔ a tone and motility of g.i.t. are decreased because of stimulation of all adrenergic receptors
- ✔ sphincters of g.i.t., of urinary bladder, urethers and spleen capsule are contracted due to stimulation of α_1-receptors.
- ✔ These effects are brief and of no clinical import

Influence on metabolism

- Adrenaline stimulates glycogenolysis (due to stimulation of β_2-receptors of muscle cells & the liver), α_2-receptors inhibit insulin secretion – hyperglycemia occurs
- and lipolysis (content of free fatty acids is increased in the blood due to stimulation of β_3-receptors)

Indications for administration of α-,β-adrenomimetics

They are used only parenterally as they are destroyed in the stomach

Adrenaline is used as a medicine for emergency

- ✔ in anaphylactic shock (a drug of choice)
- ✔ in acute heart failure and circulatory collapse
- ✔ for relief of bronchospasm in bronchial asthma attack (was used in past)
- ✔ in hypoglycemic coma
- ✔ it acts shortly: at intravenous introduction – 5 minutes, at s.c., i.m. introduction – 30 minutes to 2 hrs.

Indications for administration of α-,β-adrenomimetics

- Adrenaline can be used for elimination of A-V block and in cardiac arrest
- tolerance (resistance) rapidly occurs at repeated introductions; effect decreases due to desensitization phenomenon (loss of receptor sensitivity).
- 0.1% solution of Adrenaline is added to local anesthetic solutions as vasoconstrictive agent for narrowing vessels, it delays absorption of anesthetics, prolongs local anesthesia, prevents resorptive toxic action of anesthetic agents

Adverse effects

At administration of Noradrenaline:

- ✔ headache
- ✔ respiratory disorders
- ✔ cardiac arrhythmia
- ✔ necrosis of tissues at the site of injection (due to arteriole spasm)

Adrenaline can cause:

- ✔ myocardium hypoxia, arrhythmia
- ✔ Adrenaline arrhythmogenic action is especially dangerous when it is injected at use of narcosis agent Halothane

α_1-adrenergic agonists

α_1-adrenergic agonists:

Phenylephrine, Midodrine stimulate α_1-adrenoreceptors of blood vessels mainly

- these cause longer vasoconstrictive action (up to 1 h), in comparison with adrenaline, as they are slower destroyed with enzymes
- these increase ABP
- these do not act on the heart markedly, but they can cause reflex bradycardia
- these partly pass across blood-brain barrier and slightly stimulate the CNS

α_2-adrenergic agonists

- Clonidine and α-Methyldopa, Guanfacin, Guanabenz can be used for hypertension
- Apraclonidine and Brimonidine are used topically for glaucoma.

α_1, α_2- ADRENERGIC AGONISTS

α_1-,α_2-adrenergic agonists:

Naphazoline, Xylometazoline,etc. *stimulate simultaneously synaptic α_1-receptors and extrasynaptic α_2- receptors*

- these have marked vasoconstrictive effect at intranasal application, cause rapid (5-10 min) and long-term (5-12 h) vasoconstriction in mucosa of nasal cavity and upper airways

  that decreases their swelling and secretion of mucous (*decongestant action)*
- At rhinitis, the action of the drugs is symptomatic
- Long-term use of these drugs results in atrophy of mucosa

ADMINISTRATION OF α- ADRENERGIC AGONISTS

- *α_1-adrenergic agonists* are used as vasoconstrictants at hypotension
- Phenylephrine is also used in rhinitis, for treatment of open-angle glaucoma and for prolongation of local anesthetic action
- *α_1-,α_2-adrenergic agonists* are used locally in the form of nasal drops
- in rhinitis, sinusitis, eustachitis to decrease swelling and secretion of mucosa of nasal cavity, paranasal sinuses
- they facilitate nasal breathing

β_1–, β_2-adrenergic agonists

Representatives: Isoprenaline (Isadrinum),
Orciprenaline salfate (Alupent)

- have stimulant action on the heart due to stimulation of β_1-receptors
- increase automatism, myocardium excitability
- facilitate A-V conduction
- increase strength and frequency of heart beats
- stimulate β_2-receptors of smooth muscles of bronchi, vessels and other smooth muscle organs
- as a result, these dilate bronchi
- decrease tone of g.i.t.
- Orciprenaline acts on β_2-receptors of bronchi more evidently, so it causes tachycardia more seldom, as compared with Isoprenaline.

Indications for administration of β_1–, β_2-adrenomimetics

- For prophylaxis and relief of bronchial asthma attacks
- Isoprenaline is sometimes used in marked bradycardia and
- in disorders of atrioventricular conduction

β_1 –adrenergic agonists

A representative is **Dobutamine**

- It takes vigorous inotropic action (increases contractility of myocardium due to stimulation of β_1)
- That leads to increase in cardiac output.
- At that, heart rate and ABP are not practically changed. Against a background of acute hypoxemic hypoxia, Dobutamine decreases a pressure in pulmonary capillaries

  In such condition, Dobutamine is able to prevent development of pulmonary edema
- Dobutamine is rapidly inactivated with MAO, its half-life is 2-3 min.
- it is used as cardiotonic agent in acute cardiac insuficiency, accompanied by respiratory failure, in patients with cardiogenic or septic shock

β_2 –adrenergic agonists

Representatives: Salbutamol, Fenoterol, Terbutaline, Salmeterol, Pirbuterol, Bambuterol

- they are selective stimulants of β_2-adrenoreceptors
- ✔ take more marked action on smooth muscles of bronchi, dilate them
- ✔ produce less adverse effects, than non-selective adrenergic agonists
- ✔ stimulate also β_2-adrenergic receptors of uterus and cause relaxation of myometrium

Use of β2 –adrenergic agonists

- they are widely used as bronchodilatory agents for relief of bronchial obstruction
- the drugs are administered by inhalation, orally, parenterally
- They are used at threatened abortion (for prevention of preterm delivery) –

Fenoterol is used in the form of solution for inj. under the name «Partusisten». Salbupart, Ritodrine & Isoxsupride are also tocolytics (uterine relaxants)

Adverse effects of β-adrenomimetics

- anxiety
- palpitation
- tremor of fingers
- giddiness, headache
- hyperhidrosis

in such cases a dose of a drug is decreased

- in frequent use of β_2-adrenergic agonists, development of tolerance and weakening of the effect are possible

ADRENERGIC AGONISTS OF INDIRECT ACTION (INDIRECT SYMPATHOMIMETICS)

Representatives: Ephedrine hydrochloride and Phenylpropanolamine (Trimex)

- Ephedrine is an alkaloid of plant ephedra;
- it replaces noradrenaline from vesicles, inhibits MAO, inhibits NA reuptake, increases NA concentration in synaptic cleft;
- NA takes stimulant action on α- и β-adrenoceptors
- thus Ephedrine indirectly, by the way of endogenous noradrenaline, takes nonselective activating action on α- и β-adrenoreceptors

Ephedra disthachya

INDIRECT SYMPATHOMIMETICS

- Ephedrine also has direct stimulant action on β-adrenoreceptors mainly
- it narrows vessels and increases ABP (due to stimulation of α_1-receptors)
- it increases strength and frequency of heart beats (due to stimulation of β_1-receptors of myocardium)
- the alkaloid relaxes bronchial muscles (due to stimulation of β_2-receptors)
- but bronchodilatory action is weaker as compared with β_2-adrenergic agonists

INDIRECT SYMPATHOMIMETICS

- Ephedrine dilates pupil (due to stimulation of α_1-receptors of radial muscle)
- it does not change intraocular tension and accomodation
- it increases tone of skeletal muscles, glucose level in the blood
- it sensitizes adrenoreceptors to catecholamines
- Ephedrine passes across blood-brain barrier, takes stimulant action on the CNS

Features of Ephedrine action in comparison with Adrenaline:

- gradual development of pharmacological effects
- less marked, but more long-term action
- it is partly explained by indirect action of the drug on adrenoreceptors and
- gradual development of sympathomimetic action

Administration of sympathomimetics

- in hypotension, collapse to increase ABP
- Pseudoephedrine is administered orally as decongestant in rhinitis (narrows blood vessels of nasal mucous membrane)
- in ophthalmological practice for dilation of pupil
- Ephedrine is used at the CNS inhibition (narcolepsy, overdosage of hypnotics, tranquilizers)
- Nocturnal enuresis (decreases depth of sleep and increases tone of urinary bladder sphincter).

Adverse effects of sympathomimetics

- excitement
- sleeplessness
- tremor
- loss of appetite
- increase in ABP
- palpitation

Combined preparations:

- *Combined preparations are frequently used*
- (they contain preparations with c synergetic action):
- BERODUAL (fenoterol + ipratropium bromide)
- DITEC (fenoterol + cromoglycic acid)

DOPAMINOMIMETICS

- Dopamine is the main neuromediator for dopamine receptors, which differ from α- and β-adrenoreceptors
- different subtypes of dopamine receptors are identified: D_1-, D_2-, D_3-, D_4-, D_5- receptors
- it acts mainly on the CNS
- but sometimes Dopamine is used for regulation of peripheral nervous system function
- Due to activation of D_2-receptors, Dopamine causes narrowing of arterioles of the skin, subcutaneous fat, skeletal muscles. Pressor effect occurs.

Pharmacological characteristics of Dopamine

- At dose 0.5-2.0 mcg dopamine stimulates D1-receptors in blood vessels
- Causes dilation of renal blood vessels, decreases total peripheral resistance of vessels
- as a result, diuresis, natriuresis and creatinine clearance are increased very rapidly
- At dose 2-3 mcg causes stimulation of β_1-adrenoceptors
- that leads to increase in strength of heart beats, cardiac output and elimination of cardiac insufficiency
- More higher doses of dopamine can stimulate also
- α_1-adrenoreceptors of vessels, that leads to increase in vascular tone, ABP and decrease in renal blood flow.

Indications for administration

- dopaminomimetics are used in cardiogenic or septic shock to improve the heart work and to increase ABP
- for improvement of renal blood supply. Sodium nitroprusside is recommended simultaneously
- Dopamine is introduced intravenously to blood stream or drop-by-drop.
- duration of intravenous infusions of Dopamine must not be more than 2-3 days, as tolerance develops during the time and an effect is decreased

Adverse effects of dopaminomimetics

- tachycardia, arrhythmia
- bronchospasm
- pulmonary hypertension
- oliguria
- inhibition of reflex from chemoreceptors of carotid bodies on CO_2.
- high Dopamine doses can worsen blood supply of extremities (gangrene is possible)
- Necrosis of subcutaneous tissue