sympatholytics

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- Centrally acting sympathoplegic drugs: These agents reduce sympathetic outflow from vasomotor centers in the brain stem.
- Adrenergic neuron blocking agents: These drugs prevent normal physiologic synthesis, storage or release of norepinephrine (NE) from postganglionic sympathetic neurons.
- Adrenergic receptor blocking agents: α- and β-blockers.

Centrally acting sympathoplegic drugs

(1) α-Methyldopa

Mechanism of action:

•Stimulation of ***central*** α_2-adrenoceptors with subsequent inhibition of sympathetic outflow.

•Stimulation of **presynaptic α_2** on the cholinergic nerve terminals inhibits the release of ACh so decreases the GIT secretion & motility

Pharmacological action:

•**CNS:** Marked sedation, which may progress to psychogenic depression.

•Deficiency of dopamine may progress to extrapyramidal symptoms.

•**CVS:** drop in the blood pressure and the heart rate.

Therapeutic uses:

1.Methyldopa is the drug of **first choice** for treatment of hypertension associated with pregnancy.

Adverse effects:

•***Type-A:*** Hypotension, bradycardia, depression, extrapyramidal symptoms, dry mouth, nasal stuffiness, salt and water retention.

•***Type B:*** Interaction of the drug with the patient's immune system with the formation of auto-antibodies which may cause hemolytic anemia, aplastic anemia leucopenia, thrombocytopenic purpura, hepatitis… etc.

(2) Clonidine

- **Site and mechanism of action:**
- Central α_2-adrenoceptor stimulation causes a decrease in sympathetic outflow.
- Peripheral α_2 receptors stimulation causes a reduction in release of NE from the adrenergic neurons.
- Summation of both effects results in fall in blood pressure and heart rate.
- **Therapeutic uses:**

1. Treatment of hypertension, especially if rapid effect is needed (hypertensive urgency).
2. Prophylaxis of migraine headache and postmenopausal flushing.
3. In alleviating opiate and alcohol withdrawal symptoms.

Adverse effects:

- Sedation, dry mouth and constipation occur frequently.
- Sudden withdrawal of clonidine is associated with rebound hypertensive overshoot due to sympathetic over activity, thus, the drug should be stopped gradually.
- Rebound hypertension is treated with either reuse clonidine or α plus β blockers.

Adrenergic neuron blocking agents

(1) Alpha-methyltyrosine (metyrosine)

Mechanism of action:

•Metyrosine is a competitive inhibitor of tyrosine hydroxylase

Therapeutic uses:

•It is the only drug which could inhibit biosynthesis of catechalamines in patients with ***pheochromocytoma***.

Adverse effects:

•Sedation, extrapyramidal symptoms, psychogenic depression,

•Crystalluria (due deposition of the drug crystals in the kidney), this could be avoided by increasing water intake.

(2) Reserpine

mechanism of action:

•Reserpine irreversibly inhibits vesicular reuptake of monoamines (reuptake III).

Therapeutic uses: Treatment of mild to moderate degree hypertension.

Adverse effects and contraindications:

1.Sedation and extrapyramidal and psychogenic depression that can lead to suicide.

2.Nasal stuffiness.

3.Exacerbation of peptic ulcer disease.

Alpha-adrenoceptor Antagonists classification

Nonselective (block α1 & α2)	Selective α1 blockers	Selective α2 blockers	α- & β-blockers
Ergot alkaloids Phenoxybenzamine Phentolamine Tolazoline	Prazosin Terazosin Doxazosin Tamsulosin	Yohimbine	Labetalol Carvedilol

I] Non-selective α blockers

(1) Ergot alkaloids

Ergot is a fungus "Claviceps purpurea" that grows parasitically on rye grains

Pharmacological properties:

1. Direct vasoconstrictor effect.
2. α adrenergic blocking effect.
3. Uterine stimulant (oxytocic) effect.
4. Dopaminergic stimulant effect (nausea & vomiting, inhibition of prolactin & growth hormone secretion and anti-parkinsonian effect).

Compounds isolated from the ergot extract:

1.Ergotamine: ***vasoconstrictor*** with moderate α-blocking effect and uterine stimulant effect.

2.Ergometrine: ***potent uterine stimulant effect*** together with moderate vasoconstrictor and α-blocking effect.

3.Ergotoxine: ***marked α-blocking effect*** with moderate vasoconstrictor & uterine stimulant effect

Therapeutic uses:

- Migraine headache: Ergotamine orally, alone or in combination with caffeine (cafergot), can be used for ***acute attacks*** of migraine headache.
- Senile dementia: ergotoxine [increases cerebral blood flow].
- Postpartum hemorrhage: ergometrine.
- To suppress prolactin & growth hormone secretion: **Bromocriptine** is used.
- Parkinsonism: **Bromocriptine** is used.

Contraindications:

- During pregnancy (Except for bromocriptine).
- Ergotamine and ergometrine are contraindicated in hypertension, coronary heart disease and peripheral vascular diseases.

(2) Phenoxybenzamine

Phenoxybenzamine blocks α_1 and α_2 adrenergic receptors ***irreversibly***.

Therapeutic uses: Treatment of ***pheochromocytoma*** either for:

- Preoperative preparation of the patient for surgery.
- Life-long management of the disease in patients with inoperable cases.

Adverse effects:

1. Postural hypotension with reflex tachycardia and other arrhythmias.
2. Nasal stuffiness.
3. Inhibition of ejaculation because of impaired smooth muscle contraction in the vas deferens and ejaculatory ducts.

(3) Phentolamine & Tolazoline

- Competitive α-blockers.
- Block 5-HT receptors and causes release of histamine from mast cells.
- Stimulate GIT and enhance gastric acid secretion.

Therapeutic uses:

Phentolamine:

1. Short-term control of hypertensive crises due to:
2. To inhibit tissue necrosis caused by extravasation of α-agonist drugs.

Tolazoline:

1. Treatment of pulmonary hypertension of the newborn.
2. To visualize distal peripheral vessels during arteriography.

Alpha-1 Selective Blockers

- Prazocin
- Doxazocin
- Terazocin
- Tamsulosin

Mechanism of action:

1. Highly selective for α_1 receptors. This may explain the relative absence of tachycardia compared with that of Phentolamine and Phenoxybenzamine.
2. It also inhibits phosphodiestrase enzymes responsible for degradation of cAMP, and cGMP, both produce vasodilatation.
   - cAMP could produce tachycardia, which could be counteracted by cGMP produce bradycardia, the net effect is vasodilatation with little tachycardia**.

Therapeutic uses of prazocin:

1) Hypertension especially if associated with benign prostatic hyperplasia (BPH).
2) Effective in the management of hypertension urgency.

- Terazosin and Doxazosin are effective in treatment of hypertension with benign prostatic hyperplasia (BPH).

Adverse Effects:

1) **First-dose phenomenon** [marked postural "orthostatic" hypotension and syncope].
   - **This can be minimized by:**
   i. limiting the initial dose to 1 mg at bedtime.
   ii. increasing the dosage slowly.
   iii. introducing additional antihypertensive drugs cautiously.
2) **Non-specific adverse effects** such as headache, dizziness, drowsiness, and nausea.

Tamsulosin

- It is used in BPH if not associated with hypertension.
- The drug has higher affinity for α_{1A}** receptors (in the prostatic capsule & prostatic urethra) than for the vascular α_{1B} subtype.

→→→ Thus it produces relaxation of prostate and prostatic urethra without significant effect on blood pressure.

Beta Adrenoceptor Antagonists

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Drugs which could block the β-adrenergic receptor are called β-adrenergic receptor antagonists (β-blockers).

Classification of β-blockers:

- **First generation: (Non-selective β blockers)**
  - **Propranolol, timolol, sotalol, pindolol, nadolol.**
- **Second generation: (β_1-selective blockers)**
  - **Acebutolol, metoprolol, esmolol, bisoprolol, atenolol.**
- **Third generation:**
  - **β blockers with additional mechanisms of vasodilatation e.g. carvedilol.**

- Some β blockers are partial agonists; have intrinsic sympathetic activity "ISA"; e.g. Oxyprenolol, pindolol and acebutolol.
  - ISA prevent profound bradycardia or negative inotropy in a resting heart.
- Some β blockers have membrane-stabilizing properties (e.g. propranolol), or increase the effective refractory period of the heart (e.g. sotalol).
  - These actions contribute to their anti-arrhythmic effects.

Pharmacokinetics of β-blockers:

- **Absorption:**
  - β-blockers are well-absorbed after oral administration, except esmolol is not absorbed orally.
- **Bioavailability:**
  - ❖ Low bioavailability: propranolol and metoprolol (undergoes extensive hepatic 1st pass metabolism).
  - ❖ Moderate bioavailability for most β-blockers.
  - ❖ High bioavailability: betaxolol, penbutolol, pindolol, and sotalol.

- **Distribution and elimination:**
  - **Propranolol is lipophilic and readily crosses the blood-brain barrier.**
  - **Most β-blockers have half-lives in the range of 3-10 hours.**
  - **Nadolol and atenolol are water soluble excreted unchanged in the urine. They have long half-lives (Nadolol has the longest half-life about 24 hours). They are contraindicated in renal failure.**

- Propranolol and metoprolol are extensively metabolized by the liver CYP_{450} 2D6.
- Their elimination half-life is prolonged in:
  i. liver diseases
  ii. diminished hepatic blood flow
  iii. hepatic enzyme inhibition
- Esmolol is rapidly hydrolyzed by red cell esterases and has a half-life of approximately 10 minutes.

Pharmacological actions of β-blockers

I. Cardiovascular system:

Heart:

β-blockers decrease all cardiac properties:

- They decrease the automaticity.
- They slow conduction in the atria and in the AV node.
- They decrease heart rate.
- They decrease myocardial contractility.

Coronary blood flow:

- β-blockers decrease myocardial oxygen consumption by reduction of the heart rate and myocardial contractility.
- This effect improves the balance between cardiac oxygen supply and demand.

Blood Vessels:

- Beta blockers reduce cardiac output → reflex sympathetic stimulation → initial rise in peripheral resistance from α-receptor-mediated vasoconstriction [with no β_2-mediated vasodilatation due to their block].
- However, with long-term use of β-blockers, total peripheral resistance returns to initial values.
- β-blockers have antihypertensive action but, do not cause a reduction in blood pressure in patients with normal blood pressure.

The mechanisms of antihypertensive action:

1) Reduction of the cardiac output.
2) Inhibition of renin release.
3) Inhibition of NE release from the sympathetic neurons due to block of presynaptic β-receptors on adrenergic neurons.
4) Re-setting of the baroreceptors.
5) Reduction of the sympathetic outflow centrally.
6) Increase vasodilator prostaglandins.

7) Additional vasodilator mechanisms:

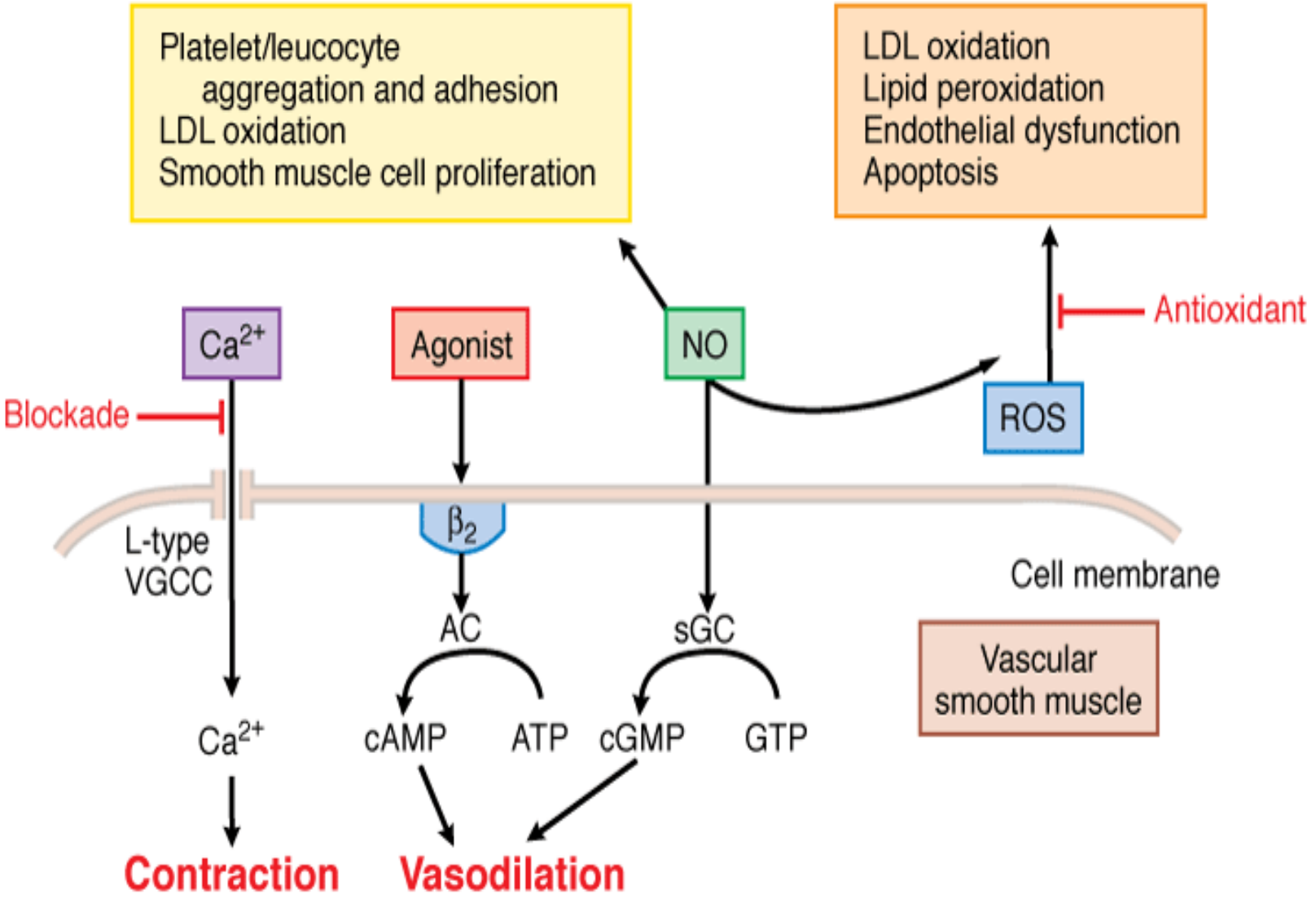
i. α_1-receptor antagonism: Labetalol & carvedilol.

ii. β_2-receptor agonism: Celiprolol.

iii. Calcium channel block: Carvedilol & betaxolol.

iv. Nitric oxide production: Nebivolol & carteolol.

Mechanisms of vasodilator β-blockers



II. Pulmonary system:

- **Non-selective β-blockers block β_2-receptors in bronchial smooth muscles. This usually has little effect on pulmonary function in normal individuals.**
- **Also, β_1-selective antagonists or antagonists with intrinsic sympathomimetic activity should be used only with great caution in patients with asthma.**

III. Metabolic effects:

- Non-selective β-blockers may delay recovery from hypoglycemia in insulin-dependent diabetic patients and mask the tachycardia [warning sign] that is typically seen with hypoglycemia.
- Increase triglycerides and decrease HDL. β_1-selective blockers and those with "ISA" may cause less effects on lipid metabolism.
- Beta blockers inhibit K^+ influx into skeletal muscles that occurs with sympathetic activation.

IV. Other Effects:

- β-blockers prevent catecholamines-induced tremors.

Therapeutic uses of β blockers:

I. Cardiovascular diseases:

1) **Hypertension:**
   - **Alone in mild degree hypertension.**
   - **In combination with other drugs to control moderate and severe degree hypertension.**
2) **Angina pectoris: Prophylaxis of angina due to coronary atherosclerosis. However, these drugs are may worsen vasospastic angina.**
3) **Acute myocardial infarction and in the prevention of recurrence.**

4) Supraventricular arrhythmias.

5) Heart Failure:

- Small doses of metoprolol, bisoprolol, and carvedilol reduce mortality in selected patients with chronic heart failure.
- This may be due to their beneficial effects on myocardial remodeling and in decreasing the risk of sudden death.

6) Hypertrophic obstructive cardiomyopathy:

- β-blockers slow ventricular ejection and decrease outflow resistance.

7) Medical management of acute dissecting aortic aneurysm:

- β blockers decrease the rate of development of systolic pressure.

II. Non-cardiovascular diseases:

1) **Prophylaxis of migraine:** (not useful for treatment of acute attacks of migraine).

2) **Essential tremors:** (as sympathetic activity may enhance skeletal muscle tremors).

3) **Glaucoma**: Topically administered β-blockers decrease "IOP" by decreasing the rate of production of aqueous humor by the ciliary body.

4) **Esophageal varices:** Prevent bleeding from esophageal varices in patients with portal hypertension.

5) **Hyperthyroidism:** β-blockers prevent the excessive catecholamine activity especially on the heart. Propranolol can inhibit de-iodinase enzyme that convert T4 to T3 and has been used extensively in patients with thyroid storm.

Adverse effects:

I. Cardiovascular system:

1) β-blockers exacerbate heart failure in patients with compensated heart failure.
2) Bradycardia may progress to life-threatening partial or complete heart block.
3) Symptoms of peripheral vascular disease may worsen.
4) Abrupt discontinuation of β-blockers after long-term treatment can exacerbate angina and may increase the risk of sudden death. This may due to upregulation of β-receptors. Such enhanced sensitivity can be attenuated by tapering the dose of β-blockers for several weeks before discontinuation.

II. Central nervous system:

1) Fatigue.
2) Sleep disturbances (including insomnia and nightmares).
3) Depression

These may occur especially with lipophilic β-blockers.

III. Pulmonary function:

- In patients with bronchial asthma or chronic obstructive lung disease (COPD), a life-threatening bronchospasm may occur.
- Drugs with selectivity for β_1-receptors or those with "ISA" at β_2-receptors may be somewhat less likely to induce bronchospasm. However, the selectivity of current β-blockers is lost with increasing the dose.
- Consequently, these drugs should be avoided in patients with asthma.

VI. Metabolism:

- β-blockers may blunt recognition and delay recovery from insulin-induced hypoglycemia.
- β-blockers cause an increase of plasma triglycerides and decrease of HDL-cholesterol.

Drug interactions

Pharmacokinetic interactions:

1. Aluminum salts, cholestyramine, and colestipol may decrease the absorption of β-blockers.
2. Drugs such as phenytoin, rifampicin, and phenobarbital (enzyme inducers) decrease plasma concentrations of β-blockers that are metabolized extensively (e.g. propranolol).
3. Cimetidine and hydralazine (enzyme inhibitors) may have the reverse effect.
4. β-blockers can impair the clearance of lidocaine. Its clearance by the liver is flow-dependant and beta blockers decrease the portal blood flow.

Pharmacodynamic interactions:

1. Ca^{2+}-channel blockers (e.g. verapamil) and β-blockers have additive effects on the cardiac conducting system and myocardium and may progress to heart failure and heart block.
2. Additive effects on blood pressure between β-blockers and other antihypertensive agents.
3. The antihypertensive effects of β-blockers could be opposed by indomethacin and other non-steroidal anti-inflammatory drugs (NSAIDs) due to reduction of prostaglandin production.

Overdose

- Hypotension, bradycardia and seizures may occur.
- Bradycardia should be treated with atropine, but a cardiac pacemaker is often required.
- Glucagon has positive chronotropic and inotropic effects on the heart that are independent of interactions with β-receptors, so useful in some patients.


Thank
you!!