Drugs acting on PNS

DRUGS AFFECTING THE SYMPATHETIC NERVOUS SYSTEM

adrenomimetics, dopaminomimetics

(Drugs Affecting Adrenergic Synapses, Adrenergic Substances)
• The cell bodies of the sympathetic preganglionic neurons lie in the lateral horn of the grey matter of the thoracic and lumbar segments of the spinal cord.

• Fibres leave the spinal cord in the spinal nerves as the thoracolumbar sympathetic outflow.

• The preganglionic fibres are short.

• They synapse in the paravertebral chains of sympathetic ganglia, lying on either side of the spinal column.

• These ganglia contain the cell bodies of the postganglionic sympathetic neurons, the axons of which rejoin the spinal nerve.
• The postganglionic fibres are long

• The catecholamine-secreting cells of the adrenal medulla are innervated by preganglionic fibres, and are, in effect, modified postganglionic sympathetic neurons (the only exception to the two-neuron arrangement in ANS).
• Neurons that release Noradrenaline (NA) substance are called adrenergic or noradrenergic neurons.

• Not all sympathetic postganglionic neurons are noradrenergic. The sympathetic postganglionic neurons that innervate the sweat glands and some of the blood vessels in skeletal muscle are cholinergic (they release acetylcholine rather than norepinephrine, even though anatomically they are sympathetic neurons).
STEPS IN ADRENERGIC TRANSMISSION

1. Synthesis of the transmitter
2. Storage of the transmitter
3. Release of the transmitter by a nerve action potential
4. Interaction of the released transmitter with receptors
5. Rapid removal of the transmitter from the vicinity of the receptors
6. Recovery of the effector cell
Synthesis of the transmitter

Phenylalanine → Tyrosine → DOPA → Dopamine → Noradrenaline → Adrenaline
Removal of the transmitter
Adrenoreceptors – the receptors with which norepinephrine, epinephrine, or other adrenomimetic drugs combine.
Locations of the AR in ANS

- Cardiac muscle,
- Smooth muscles,
- Gland cells,
- Nerve terminals
Two subtypes of adrenoceptors (α and β)

- α - excitatory in most tissues
  (except - intestinal smooth muscle)
- β - inhibitory in most tissues
  (except - heart)
Types of adrenoceptors

- $\alpha_1 (\alpha_{1A}, \alpha_{1B}, \alpha_{1D})$, $\alpha_2 (\alpha_{2A}, \alpha_{2B}, \alpha_{2C})$
- $\beta_1$, $\beta_2$, $\beta_3$
Types of adrenoceptors

- The $\alpha_1$-adrenoceptors are located at postjunctional (postsynaptic) sites on tissues innervated by adrenergic neurons.

- $\alpha_2$-Adrenoceptors having a presynaptic location are involved in the feedback inhibition of norepinephrine release from nerve terminals.

- $\alpha_2$-Receptors also can occur postjunctionally and, more often, extrajunctionally.
Types of adrenoceptors

- The $\beta_1$-adrenoceptors are found chiefly in the heart and adipose tissue, while $\beta_2$-adrenoceptors are located in a number of sites, including bronchial smooth muscle and skeletal muscle blood vessels, uterus, and are associated with smooth muscle relaxation.

- Presynaptic $\beta_2$-adrenoceptors are involved in the feedback activation of norepinephrine release from nerve terminals.
Mechanisms of action of adrenomimetic drugs

- $\alpha_1$ via coupling protein $G_q$
- $\alpha_2$ via coupling protein $G_i$
- $\beta_1, \beta_2, \beta_3$ via coupling protein $G_s$
**Cell Membrane**

- **Ca$^{2+}$**
- **$\alpha_1$-Agonist**
- **Gq**

**Phosphatidylinositol 4, 5-diphosphate**

**Phospholipase C**

**IP$_3$**

**DAG**

**SR**

**Ca$^{2+}$**

**Ca$^{2+}$-dependent protein kinase**

**Protein kinase C**
Cell Membrane

\[ \alpha_2 - \text{Agonist} \]

\[ \alpha_2 \]

\[ \text{AC} \]

\[ \text{G}_i \]

\[ \text{ATP} \]

\[ \text{cAMP} \]

\[ \text{Enzyme-PO}_4 \]

No biological effect

\[ \text{AC} = \text{Adenylyl cyclase} \]
**Cell Membrane**

- **β -Agonist**
- **β -receptor**

**Enzyme**

**G\_s**

**AC**

**ATP**

**cAMP**

**Enzyme-PO\_4**

**Biological effect**

**AC = Adenylyl cyclase**
Heart rate
Conduction
Contraction

Heart

Ca^{2+}

Vagus

ATP

kinase

cAMP

Gs

AC

Gi

β_{1}-Agonist

β_{1}-receptor

M

Ca^{2+}
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Generally

- $\alpha_1$ – Contraction of smooth muscle
- $\beta_2$ – Relaxation of smooth muscle
- $\beta_1$ – Stimulation in heart
- $\alpha_2$ – Inhibition, for GI tract – Relaxation
• Noradrenaline – adrenergic transmitter
• Adrenaline – adrenal medullary hormone

Drugs are called:
  – Norepinephrine (NE)
  – Epinephrine (Epi)
• The adrenomimetic drugs mimic the effects of adrenergic sympathetic nerve stimulation (the actions of epinephrine (Epi) and/or norepinephrine) on sympathetic effectors.

• Drugs that antagonize the actions of norepinephrine are known as adrenoceptor antagonists (adrenoblockers, sympatholytics).
ADRENERGIC DRUGS

CL According to the site of action:

• Drugs with direct action (on the receptors of the postsynaptic membrane):
  – Adrenomimetics:
    • Norepinephrine,
    • Phenylephrine,
    • Dobutamine
  – Adrenoblockers
    • Phentolamine
    • Propranolol

• Drugs with indirect action (presynaptic action, acting on release and/or storage of noradrenaline):
  – Indirect sympathomimmetic or adrenomimetic drugs:
    • Ephedrine
    • Pseudoephedrine
    • Tyramine
  – Sympatholytics
    • Reserpine
    • Guanethidine sulphate
• Adrenomimetic drugs
• Adrenergic agonists
• Adrenoceptor agonists
• Sympathomimetic drugs
Classification of adrenomimetics
According to the chemical structure

A. Catecholamines

1. Natural
   • Of animal origin
     ➢ Epinephrine
     ➢ Norepinephrine
   • Of vegetal origin
     ➢ Ephedrine

2. Synthetic
   • Phenylephrine
   • Ethylephrine

B. Non-catecholamines

– Naphazoline
– Xylomethazoline
– Oxymethazoline
Chemical structure of parent compound of Catechololamines
Catecholamines

– cannot be given orally
– short half-life, short duration
– high polarity
– Do not cross blood-brain barrier (BBB)
– rapid destruction by MAO and COMT (locate at gut wall, liver)
Classification of adrenomimetics

A. Alpha-, beta-adrenomimetics

I. Direct acting
   • Epinephrine (adrenaline hydrochloride)
   • Norepinephrine (Nordrenaline hydrotartrate)
   • Dopamine (middle dose (β) and large - (α)

II. Indirect acting (sympathomimetics)
   • Ephedrine hydrochloride
   • Pseudoephedrine
B. Alfa – adrenomimetics

I. With peripheral action

➢ $\alpha_1$
  - Phenylephrine (Mezaton)
  - Ethylephrine (Fetanol, Efortil)
  - Methoxamine
  - Metharaminol

➢ $\alpha_2$
  - Naphazoline
  - Xylometazoline hydrochloride

II. With central action

➢ $\alpha_2$
  - Clonidine hydrochloride
  - Dexmedetomidine
  - Alfa - methyldopa
C. Beta-adrenomimetics

1. **β1, β2**
   - Isoprenaline
   - Orciprenaline sulphate

2. **β1**
   - Dobutamine hydrochloride
   - Dopamine (middle dose)

3. **β2**
   - Terbutaline sulphate
   - Salbutamol (Ventolin)
   - Fenoterol
   - Hexoprenaline
   - Ritodrine
   - Salmeterol
   - Formoterol

4. **β3**
   - Mirabergon
Epinephrine

It stimulates:

- $\alpha_1$, $\alpha_2$ (vasoconstriction, pressor effects),
- $\beta_1$ (increased myocardial contractility and conduction),
- $\beta_2$-adrenergic (bronchodilatation and vasodilation) receptors.
Epinephrine Effects CVS

CVS

- ↑ HR, contractility, conduction,
- ↑ H excitability of VM
- ↑ Myocardial oxygen consumption
- ↑ tonus of arterioles, metarterioles, precapillary sphincters:
  - ↓ microcirculation
  - leads hypoxia, acidosis, necrosis.
Epinephrine Effects

- BP:
  - I Phase ↑TPR and BP
  - II Phase ↓TPR and BP
Eye

• Radial muscle, iris (pupillary dilator)
  – contraction \((\alpha_1)\) \(\Rightarrow\) mydriasis
  – topical phenylephrine and similar alpha agonists
  – accommodation is not significantly affected
  – outflow of aqueous humor may be facilitated
    \(\Rightarrow\) reduce intraocular pressure (IOP)

• Ciliary muscle: relaxation for far vision \((\beta_2)\)
Respiratory System

Relaxation of tracheal and bronchial muscle ($\beta_2$)
Gastrointestinal tract

• alpha and beta receptors locate on smooth muscle and on neurons of enteric nervous system

• Stomach and intestine
  – Motility and tone: \((\alpha_2 , \beta_2)\)
  – Sphincters: contraction \((\alpha_1)\)
  – Secretion (intestine): inhibition \((\alpha_2)\): inhibit salt and water secretion
Genitourinary tract

• Urinary bladder
  – Detrusor or bladder wall: relax ($\beta_2$)
  – Trigone, sphincter, prostate gland: constrict ($\alpha_1$)

• Uterus
  – non-pregnant: relax ($\beta_2$)
  – pregnant: contract ($\alpha_1$), relax ($\beta_2$)
Metabolic and hormonal effects

• Kidney
  – renin release (\(\beta_1\))

• Pancreatic \(\beta\) cells
  – inhibit insulin release (\(\alpha_2\))
  – stimulate insulin release (\(\beta_2\))

• Glycogenolysis in liver and skeletal muscle (\(\beta_2\)) - ↑lactic acid (metabolic acidosis)
Metabolic and hormonal effects

- Glucose out of liver associated with initially hyperkalemia, then transport into skeletal muscle resulting in a later hypokalemia.

- Lipolysis ($\beta_3$) : break down of triglycerides (TGs) into free fatty acids (FFAs) $\Rightarrow$ increase lactate from lipid metabolism
Epinephrine Indications:

- Allergic reaction
- Bronchospasm and Status astmaticus
- Hypotension
- Cardiorespiratory arrest
- Severe anaphylactic shock
- Hypoglycemic coma
- Epinephrine is added to solutions of local anesthetic to:
  - retard its absorption from the injection site:
    - Increase duration of the anesthesia
    - Decrease toxicity of local an.
    - Reduce expense of procedure
  - decrease bleeding
- Open-angle glaucoma
Adverse Reactions

- Restlessness,
- Anxiety
- Tremor
- Cardiac arrhythmias
- Palpitations
- Hypertension
- Weakness
- Dizziness
- Headache
- Cerebral hemorrhage
- Breathing difficulty, chest pain,
- Angina can be precipitated when coronary insufficiency is present,
- Elevation of blood glucose
- Local necrosis from repeated injections
- Tolerance
Contraindications

- Intra-arterial administration
- Do not use with local anesthetics in fingers or toes
- Do not use during general anesthesia with halogenated hydrocarbons.
- $\alpha$-adrenergic blocker-induced hypotension;
- Cerebral arteriosclerosis;
- Organic heart disease;
- Cardiac dysrhythmias
- Narrow-angle glaucoma;
- Cardiogenic shock?
- Labor.
Cautions

• Cardiovascular disease
• Hypertension
• Diabetes
• Hyperthyroidism
• Psychoneurotic patients
Norepinephrine

- $\alpha_1$, $\alpha_2$ (vasoconstriction, pressor effects),
- $\beta_1$ (increased myocardial contractility and conduction),
- It has little action on $\beta_2$-receptors
Indications

• Restoration of blood pressure in controlling certain acute hypotensive states (pheochromocytomectomy, sympathectomy, poliomyelitis, spinal anesthesia, MI, septicemia, blood transfusion, and drug reactions)

• Adjunct in the treatment of cardiac arrest and profound hypotension
Adverse Reactions

- hypertension
- headache
- reflex bradycardia
- increased peripheral vascular resistance
- decreased cardiac output
- volume depletion
- Arrhythmias can occur in extreme hypoxia or hypercarbia.
Contraindications

- Hypotension secondary to uncorrected blood volume deficit (hypovolemia);
- severe visceral or peripheral vasoconstriction;
- mesenteric or peripheral vascular thrombosis, unless drug is life-saving;
- halogenated hydrocarbon anesthesia.
α₁-Adrenergic receptor agonists

• Phenylephrine

– Mechanism of action
  • Directly stimulate α₁-receptors
  • Phenylephrine when injected intravenously produces effects similar to NE

– Indications
  • Blood pressure elevation
  • Nasal decongestant
  • Mydriasis induction
Clonidine

• Stimulates postsynaptic $\alpha_2$-adrenergic receptors in the CNS by activating inhibitory neurons to decrease sympathetic outflow.
  – These actions reduce peripheral vascular resistance, renal vascular resistance, heart rate, and blood pressure.

• Sedative action

• Analgesic effect
Indications

- Hypertension
- Open-angle glaucoma
- Opiate, alcohol and tabacco withdrawal
- Diagnosis of pheochromocytoma
- As an analgesic
- ADHD
• dry mouth
• drowsiness
• dizziness
• constipation
• weakness
• sedation
• nausea or vomiting
• nervousness and agitation
• orthostatic hypotension
• sexual dysfunctions

• Rash, weight gain, anorexia, transient abnormalities in liver function tests, insomnia or vivid dreams, palpitations, tachycardia or bradycardia, or urinary retention.
• Hepatitis, thrombocytopenia, parotitis, elevations of blood glucose or CPK, or cardiac conduction disturbances.
• Allergic contact dermatitis
• Abrupt withdrawal of oral therapy can result in a withdrawal reaction characterized by rapid reversal of the antihypertensive effect
Dopamine

- Precursor of epinephrine
- Low dose (0.5-2 mcg/kg/min): activate Dopamine receptors
  - Dilates renal and mesenteric vessels
  - Venoconstricts
  - Arterial resistance may vary
- Intermediate dose (2-10 mcg/kg/min): activate Beta1 receptors
- High dose (>10 mcg/kg/min): activate Alpha receptor
  - Alpha effects dominate
  - Arterial and venous constriction including renal and mesenteric vessels
- Very useful in treatment of renal failure associated with shock (low to moderate dose)
DOPAMINE

Indications
• Cardiogenic shock
• Hemodynamically significant hypotension
• Congestive heart failure – with other agents

Dosage
• Intravenous only
• Initial infusion rate: 2µg/kg/min
• Increase infusion rate according to BP, urine flow response, and clinical response
• Adjust infusion rate as needed
DOPAMINE

Precautions
- Excessive vasoconstriction
- Fall in BP
- Arrhythmias
- Nausea and vomiting
- Extravasation
- Monoamine oxidase inhibitors
- Pheochromocytoma
EPHEDRINE

- Hypotensive states, bronchospasm, nasal congestion, orthostatic hypotension
- Hay fever, sinusitis and allergic rhinitis
- Causes tissue necrosis in IV lines
ISOPRENAline

Mechanisms of Action
• Pure beta-adrenergic stimulator (beta-1 and beta-2)
  – Potent inotropic effect
  – Potent chronotropic effect
• Increases cardiac output
• Increases myocardial oxygen consumption
• Vasodilation – diastolic and mean BP may fall but systolic pressure maintained or increased due to increased cardiac output
• Bronchodilation
ISOPRENAINE

Indications
• Hemodynamically significant atropine-refractory bradycardia
• Pacemaker better – as soon as possible
• Contraindicated during cardiac arrest
• Bronchospasms in asthma, bronchitis, COPD

Dosage
• 2-10 µg/min
• Titrate to increase heart rate to 60/min
Precautions

- Excessive tachycardia
- Arrhythmias
- Increased myocardial oxygen consumption
- Exacerbate digitalis intoxication
- Hypokalemia
DOBUTAMINE

Mechanisms of Action

• Direct beta-adrenergic stimulator
• Potent inotropic effect but less chronotropic
• Renal and mesenteric flow follows cardiac output
• Myocardial work is balanced by increases in coronary flow at clinical doses

Indications

• Congestive heart failure
• Cardiogenic shock
• Hemodynamically significant hypotension
DOBUTAMINE

Dosage

- Initial infusion rate: 0.5µg/kg/min IV
- Usual infusion rate: 2.5-20.0 µg/kg/min IV
- Titrated to not increase heart rate > 10%

Precautions

- Tachycardia
- Arrhythmias
- Caution in coronary artery disease
Salbutamol

- Treat bronchospasms in asthma, bronchitis, COPD
- Adverse reactions: palpitations, tachycardia
- Drug interactions
  - MAO inhibitors → hypertensive crisis
  - Tricyclic antidepressants
  - B blockers
  - Contraindications severe heart disease, HPN, hyperthyroidism, DM
TERBUTALINE

– B2
– To correct bronchospasm
– Abort preterm labor