Pharmacology of Drugs Acting on ANS

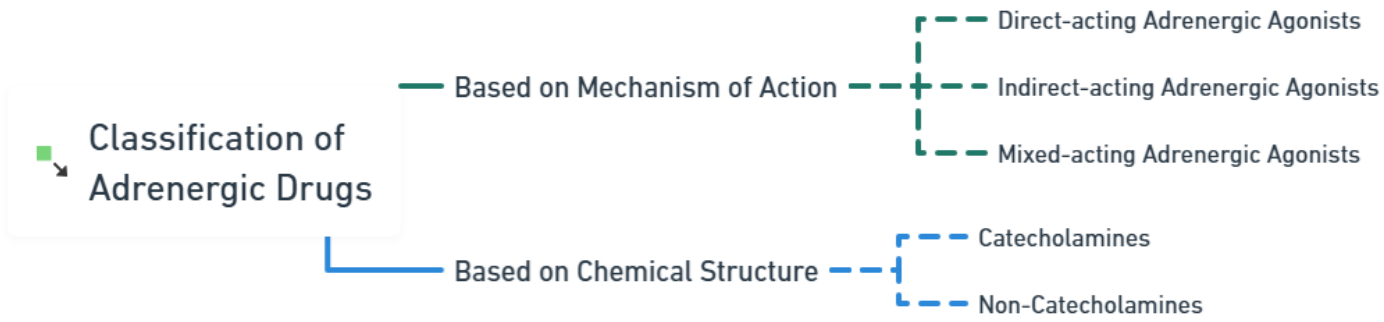
Adrenergic Drugs (Sympathomimetics)

Introduction

- Adrenergic drugs (also called *sympathomimetics*) are agents that mimic the effects of the sympathetic nervous system by acting on adrenergic receptors.
- These receptors are the sites where catecholamines like norepinephrine, epinephrine, and dopamine exert their physiological effects.
- The sympathetic nervous system is responsible for the body's "fight or flight" response and modulates various functions such as heart rate, bronchial dilation, pupil dilation, vasoconstriction or vasodilation, and metabolic changes.
- Adrenergic drugs can be either:
    - **Direct-acting (bind directly to adrenergic receptors)**
    - **Indirect-acting (increase endogenous catecholamines)**
    - **Mixed-acting (combination of both actions)**
- These drugs are used in various clinical settings including cardiac arrest, asthma, hypotension, and anaphylaxis.

Classification

Adrenergic drugs can be classified in several ways. The two main methods are:



A. Based on Mechanism of Action:

i. Direct-acting Adrenergic Agonists

- Bind directly to adrenergic receptors and activate them.
- **Non-selective**
    - Epinephrine (acts on α1, α2, β1, β2)
    - Norepinephrine (α1, α2, β1)
    - Dopamine (dose-dependent: D1/D2 → β1 → α1)
- **Selective**
    - α1: Phenylephrine

- α2: Clonidine, Methyldopa
- β1: Dobutamine
- β2: Salbutamol, Terbutaline

ii. Indirect-acting Adrenergic Agonists

- Do not bind to the receptors directly but increase availability of endogenous catecholamines.
- Amphetamine (releases stored norepinephrine)
- Tyramine (displaces norepinephrine from vesicles)
- Cocaine (inhibits reuptake of norepinephrine)

iii. Mixed-acting Adrenergic Agonists

- Act both directly and indirectly.
- Ephedrine
- Pseudoephedrine

B. Based on Chemical Structure:

i. Catecholamines

- Have hydroxyl groups at 3 and 4 positions on the benzene ring
- Rapid onset, short duration, do not cross BBB
- e.g., Epinephrine, Norepinephrine, Dopamine, Isoproterenol

ii. Non-Catecholamines

- Lack catechol structure, longer duration, can be given orally, may cross BBB
- e.g., Phenylephrine, Albuterol (Salbutamol), Clonidine

Mechanism of Action

- Adrenergic drugs act by **stimulating adrenergic receptors**, which are G-protein coupled receptors (GPCRs).

These are divided into two major types:

1. Alpha Receptors (α)

- **α1**: Mainly postsynaptic. Activation causes:
  - Vasoconstriction → ↑ BP
  - Pupil dilation (mydriasis)
  - Bladder sphincter contraction
- **α2**: Mainly presynaptic. Activation inhibits norepinephrine release (negative feedback).

2. Beta Receptors (β)

- **β1**: Found in heart and kidneys. Activation causes:
  - ↑ Heart rate (positive chronotropic)
  - ↑ Contractility (positive inotropic)
  - ↑ Renin release → ↑ BP
- **β2**: Found in lungs, skeletal muscle vessels, uterus. Activation causes:
  - Bronchodilation
  - Vasodilation in skeletal muscle
  - Uterine relaxation
- **β3**: Involved in lipolysis and bladder relaxation

- Each drug's clinical effect depends on **which receptor subtype** it activates and **in which tissue**.

Pharmacokinetics

This varies widely between catecholamines and non-catecholamines.

1. Catecholamines:

- Poor oral bioavailability: Due to rapid degradation by COMT (catechol-O-methyltransferase) and MAO (monoamine oxidase) in liver and gut.
- Administered parenterally
- Short half-life
- Do not cross blood-brain barrier (BBB) due to polarity

2. Non-catecholamines:

- Resistant to COMT and/or MAO
- Can be administered orally
- Longer duration of action
- Some may cross the BBB → CNS effects

3. Example:

- Epinephrine: IV, IM, SC, inhalation; onset within minutes; short half-life
- Salbutamol: Inhaled or oral; duration of action 4–6 hours

Pharmacodynamics

- The pharmacodynamic response depends on:
  - Receptor selectivity
  - Dose
  - Route of administration

- For example:
    - **Epinephrine**: At low doses → β effects (vasodilation, bronchodilation); high doses → α effects (vasoconstriction)
    - **Dopamine**: Low dose → D1 receptors (renal vasodilation); medium → β1 (increased cardiac output); high → α1 (vasoconstriction)

Adverse Effects

- Common adverse effects of adrenergic agonists include:
- **Cardiovascular**:
    - Hypertension
    - Tachycardia
    - Arrhythmias
    - Palpitations
- **CNS** (especially with drugs crossing BBB):
    - Anxiety
    - Tremors
    - Restlessness
    - Insomnia
- **Metabolic**:
    - Hyperglycemia (via glycogenolysis)
    - Hypokalemia (via β2 stimulation)
- **Local**:
    - Necrosis at injection site (extravasation of norepinephrine)

Contraindications

- Adrenergic drugs should be avoided or used cautiously in:
    - Hypertension
    - Hyperthyroidism (enhanced sensitivity to catecholamines)
    - Cardiac arrhythmias
    - Ischemic heart disease
    - Closed-angle glaucoma (α1 agonists can worsen condition)
    - Pregnancy (β2 agonists may affect uterine tone)
    - Monoamine oxidase inhibitor (MAOI) use: Risk of hypertensive crisis

Therapeutic Uses

A. Cardiovascular

- **Hypotension, Shock** – Norepinephrine, Dopamine
- **Cardiac arrest** – Epinephrine
- **Heart failure (short-term)** – Dobutamine

B. Respiratory

- **Asthma, COPD** – Salbutamol, Formoterol (β2 agonists)
- **Anaphylaxis** – Epinephrine

C. Nasal Congestion

- **Phenylephrine, Pseudoephedrine**

D. Eye

- **Mydriasis for eye exams** – Phenylephrine

E. Premature labor

- **Tocolysis (delay of labor)** – Ritodrine, Terbutaline (β2 agonists)

Drug Interactions

- **MAO inhibitors**: Can precipitate hypertensive crisis by inhibiting catecholamine breakdown
- **Tricyclic antidepressants (TCAs)**: Block reuptake of norepinephrine → potentiated effects
- **Beta blockers**: May antagonize β agonist effects
- **Anesthetics (e.g., halothane)**: Increased risk of arrhythmias with catecholamines

Dose and Route of Administration

- Each drug differs. A few examples:

1. **Epinephrine:**
   - Anaphylaxis: 0.3–0.5 mg IM (1:1000 solution)
   - Cardiac arrest: 1 mg IV (1:10,000 solution) every 3–5 minutes
2. **Salbutamol:**
   - Inhaled: 100–200 mcg per dose (MDI), up to 4x/day
   - Oral: 2–4 mg three times daily
3. **Phenylephrine:**
   - Nasal spray: 0.25%–1%
   - IV (hypotension): 100–180 mcg/min initially

- Dosages must be tailored based on age, condition, and desired effect.

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