Signal Transduction

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Mechanisms of Drug Action
Why do some drugs produce effects that persist for long after the drug is no longer present?

Why do response to other drugs diminish rapidly with repeated administration?

Do these mechanisms provide targets for developing new drugs?
Effects of Drugs

Normal physiological processes

- Receptor
- Enzyme
- Ion channel
- Carrier molecule
Types of target for drug action
Receptors: Recognition and signal transduction

Who? Proteins, Glycoproteins

Where? Cell surface, cytoplasm or nucleus

How? Structure-activity
Mechanisms of signal transduction

Structure-Activity determines type and duration of effect

- Specific binding
  Duration, dose-effect
- Type of binding
  Reversibility
- Selectivity
  Therapeutic/toxic effect, side-effects
Mechanisms of signal transduction

Intracellular receptor
Intracellular receptors for lipid-soluble agents

1. Lipid-Soluble chemical (corticosteroids, sex steroids, vitamine D, etc.) crosses the plasma membrane
2. Acts on an intracellular receptor
3. Cytoplasmic receptor **translocates** into the nucleus
4. DNA-binding
5. Regulate transcription of specific **genes**
Mechanisms of signal transduction

Receptor tyrosine kinase
Receptor tyrosine kinase
Mechanisms of signal transduction

G-protein signaling
Mechanisms of signal transduction

G-protein signaling
G-protein signaling
Mechanisms of signal transduction

G-protein signaling: **Gq**
second messenger: **PLC**

**Effectors**

Inositol trisphosphate (InsP₃)

- Release of Ca²⁺ ions from intracellular stores

Diacylglycerol (DAG)

- Activation of protein kinase C

Biological response = MUSCLE CONTRACTION
Mechanisms of signal transduction

G-protein signaling: $\text{Gs}$
second messenger: Adenylyl Cyclase

Biological response = MUSCLE RELAXATION
Protective mechanisms

Target cell *desensitization* and *hyper*sensitization

- Protective mechanisms to prevent over or understimulation of target cells

- Different levels:
  - **Receptor**
  - **Effectors**

- Homeostatic control of Receptor – internalization, recycling or *de novo* synthesis
Protective mechanisms

Target cell desensitization and hypersensitization

• Homologous desensitization
  Albuterol and down-regulation of β-adr. R

• Heterologous desensitization
  G-proteins

• Hyperreactivity or supersensitivity
  long-term exposure to antagonists and abrupt cessation of administration of the drug (up-regulation through synthesis of new receptors)
Mechanisms of Drug Action

1. Binding to receptors: Agonists, antagonists, partial agonists

2. Interaction with enzymes: Activation, inhibition

3. Interaction with DNA / RNA formation and function: Antimetabolites, inhibition of synthesis

4. Inhibition of protein synthesis

5. Interaction with cell membranes

6. Nonspecific action
2. Interaction with enzymes

Activation

- $\uparrow$ synthesis

- **Allosteric binding** $\Leftrightarrow \uparrow$ affinity for substrate

- **Cofactors** – complex formation and stereochemical interaction
2. Interaction with enzymes

Inhibition

- Reversible – noncovalent binding
- Competitive

- Irreversible – covalent binding / allosteric binding
- Noncompetitive
3. Interaction with DNA/RNA formation and function

Inhibition of DNA or RNA biosynthesis (1)

**Antimetabolites** – folic a., purine or pyrimidine analogues

*Methotrexate, cytarabine, 5-fluorouracil*

**Intercalating agents**

*Anthracline, dactinomycin*

**Alkylating agents** - G crosslinking

*Nitrogen mustards, nitrosurea*
3. Interaction with DNA/RNA formation and function

Inhibition of DNA or RNA biosynthesis (2)

Free radicals producing compounds

*Bleomycin*

Topoisomerase inhibitors

*Mitoxantrone, irinotecan*
3. Interaction with DNA/RNA formation and function

Inhibition of DNA or RNA biosynthesis (3)

Microtubule assembly

Vinca alkaloids, paclitaxel
4. Inhibition of protein synthesis

**Tetracyclines**
↓tRNA binding to ribosome

**Chloramphenicol, erythromycin**
↓Peptidyl transferase

**Aminoglycosides**
Bind to ribosome  ➔ incorrect protein

**Quinupristin + dalfopristin**
Exit channel of rRNA  ➔ no protein release
5. Interaction with cell membranes

- Na/K pump - *Digitalis glycosides*
- Na channels – *local anesthetics*
- H/K pump - *omeprazole*
- CD33, CD52 – *gemtuzumab, alemtuzumab*
- Cell permeability – *polyene antifungal drugs, polymixin B, colistin*
6. Non-specific action

- Monomolecular layer over entire area of certain cells

- Colligative effect – depends on number of molecules, non specific interactions

- Large doses

Volatile general anesthetics (*nitrous oxide*)
Depressants (*ethanol, chloral hydrate*)
Antiseptic drugs (*chlorhexidine, iod, ethanol*)
6. Nonspecific action

- **Cathartics** – osmolarity of intestinal fluids
  *MgS or sorbitol*

- **Antacids** – neutralizing gastric acid
  Aluminium hydroxide, calcium carbonate, magnesium hydroxide