Mechanisms of Drug Action

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Mechanisms of Drug Action

Direct Effect: antacid (base) neutralizes excess acid in stomach

Indirect Effect: drug interacts with cell receptor and initiates a sequence of cellular events.

Procaine’s Mechanism of Action

Drug Action (mechanism)
Drug Effect (therapeutic effect)

Procaine ⇒ Action Site ⇒ Mechanism ⇒ Effect

Local Anesthetic
Sodium Channels
Nerve Cells

Nerve Cell Conductance

Drug Action Sites

Drugs influence normal cellular processes.

Drugs do not produce new cell functions.

Extracellular Sites of Drug Action

Stomach: neutralize acid with base (antacids)
Blood: bind metals (chelation) like lead with EDTA
GI Tract: bind drugs (adsorption) with Cholestyramine.
GI Tract: increase water by osmotic effects (laxatives)
Kidney: increase water elimination (diuretics)

Cellular Sites of Drug Action

Antibiotics inhibit bacterial but not host functions.
Penicillin inhibits cell wall formation.
Tetracycline inhibits protein synthesis.
Erythromycin inhibits protein synthesis.
Cellular Sites of Drug Action

Hormones, Steroids, Vitamins and Neurotransmitters alter cell functions by interacting with cellular receptors.

Four specific examples of receptor-mediated transmembrane signaling processes.

Signal Transduction I

Lipid-soluble drug cross membrane and interacts with receptor. Receptor may be enzyme(activated) or gene regulator. Gene regulator enters nucleus and increases protein synthesis. Results in increased enzyme activity.

Signal Transduction II

Drugs bind to sodium and calcium channels allowing the influx of sodium and calcium. Increase in cellular sodium and calcium alters cell functions.

Signal Transduction III

Drug binds to extracellular domain of transmembrane protein and activates intracellular proteins such as Tyrosine Kinase (TK). Activated TK alters enzyme activity as a result of protein phosphorylation.

Signal Transduction IV

Drugs bind to receptor linked to effector enzymes (AC, GC, PLC) by a G protein. Activated effector enzyme generates second messengers (cAMP, cGMP, IP3 and DG) that alter cell functions.
**Calcium/Phosphoinositide pathway**

- **Agonist**: R → G → PLC → PK-C → DAG
- **ER**: CaM
- **PK-C**: CaM-E^*
- **S-P**: S-P
- **Pi**: Pi
- **Response**: Ca^2+

**Examples of Cell Receptors**

- **Cellular Enzymes (altered activity)**
- **Transmembrane Signaling Processes**
- **Cellular Macromolecules (DNA, RNA, etc.)**

**Drug Receptor Complex**

- **D + R → DR**
- **Possible H-bond site**
- **Possible electron donor group**
- **Anionic group**
- **Cavity**
- **Flat region**
- **Possible**
- **Cavity**
- **Possible**
- **N**
- **C**
- **CH**
- **CH**
- **CH**
- **CH**
- **CH**
- **OH**
- **O**
- **VDW**
- **ACETYLCHOLINE**

**Drug-Dependent Dose Response**

**RECEPTOR THEORY**

<table>
<thead>
<tr>
<th>Mass Action Law</th>
<th>Affinity</th>
<th>Efficacy</th>
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<tbody>
<tr>
<td>R + D → DR</td>
<td>k1</td>
<td>e2</td>
</tr>
<tr>
<td>Effect</td>
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<td>e3</td>
</tr>
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<td>75%</td>
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**Terminology of Antagonists**

- **Competitive**: competes with agonist for receptor, Ic effect is reduced by increasing dose of agonist.
- **Non-Competitive**: reduces number of active receptors, Inc effect is not reduced by increasing dose of agonist.
- **Reversible Antagonist**: I and R have weak chemical bonds.
- **Irreversible Antagonist**: I and R have strong chemical bonds.

**Michaelis-Menten Dose Response Curves**

- **Competitive Inhibitor**
- **Non-competitive Inhibitor**
Summary of Antagonist Effects

Competitive: same Emax (efficacy)
higher KD (lower affinity and potency)

Non-Competitive: same KD (affinity and potency)
lower Emax (efficacy)

Occupancy Theory of Drug Action

2. Reversible drug-receptor interaction
3. Response is proportional to number of receptors occupied.
4. Maximum response when all receptors are occupied.
5. Agonist (high K1, K2 and K3)
5. Antagonist (high K1, little or no K2 and K3).

Modifications of Occupancy Theory

Drug concentration that produces 50% of maximal response (EC50) is not equal to KD (saturation of 50% of receptors).
EC50 is not equal to KD when tissues have spare receptors.
Heart tissue has spare receptors (90%) which means that only 10 of 100 receptors have to be occupied to obtain maximal response.
Under these conditions EC50 is equal to 5 (50% of 10 receptors) and KD is equal to 50 (50% of 100 receptors).