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**	**Blocks Nerve Cell Conductance**	**Reduced Pain**

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.

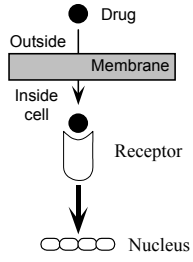
Erythromycin inhibits protein synthesis.

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



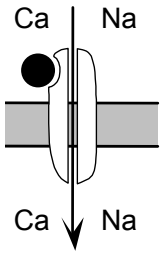
Lipid-soluble drug cross membrane and interacts with receptor.

Receptor may be enzyme(activated) or gene regulator.

Gene regulator enters nucleus and increases protein synthesis

Results in increased enzyme activity.

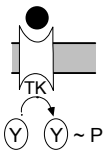
Signal Transduction II



Drugs bind to sodium and calcium channels allowing the influx of sodium and calcium.

Increase in cellular sodium and calcium alters cell functions.

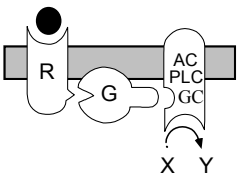
Signal Transduction III



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.

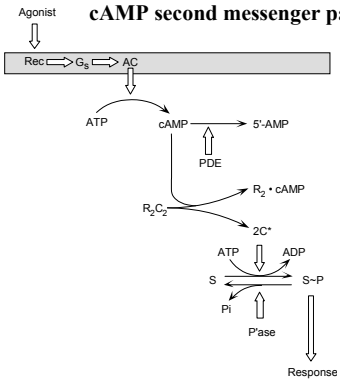
Signal Transduction IV

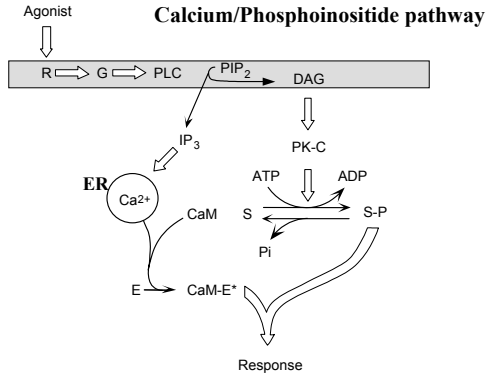


Drugs bind to receptor linked to effector enzymes (AC, GC, PLC) by a G protein.

Activated effector enzyme generates second messengers (cAMP, cGMP, IP3 and DG) that alter cell functions.

cAMP second messenger pathway





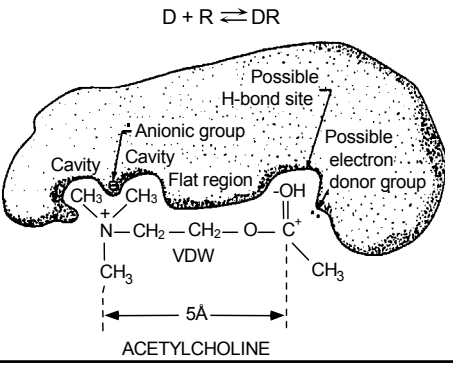
Examples of Cell Receptors

Cellular Enzymes (altered activity)

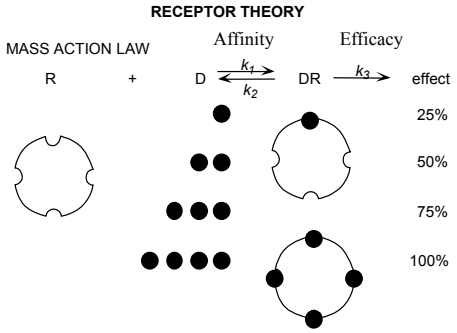
Transmembrane Signaling Processes

Cellular Macromolecules (DNA, RNA, etc.)

Drug Receptor Complex



Drug-Dependent Dose Response



Terminology of Antagonists

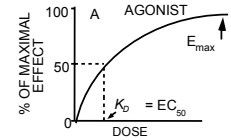
Competitive: competes with agonist for receptor, Ic effect is reduced by increasing dose of agonist.

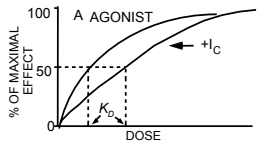
Non-Competitive: reduces number of active receptors, Inc effect is not reduced by increasing dose of agonist.

Reversible Antagonist: I and R have weak chemical bonds.

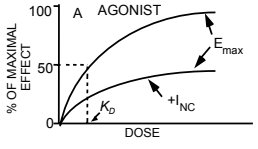
Irreversible Antagonist: I and R have strong chemical bonds.

Michaelis-Menten Dose Response Curves

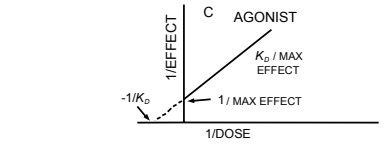




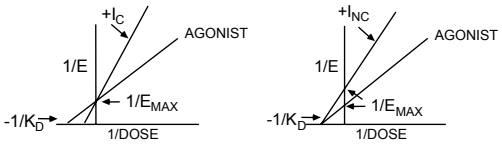
Competitive Inhibitor



Non-competitive Inhibitor

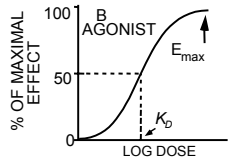


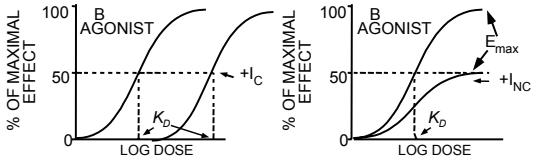
Competitive Inhibitor Non-competitive Inhibitor



Lineweaver-Burke Dose Response Curves

Log Dose Response Curves





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

$$D + R \underset{K2}{\overset{K1}{\leftrightarrow}} DR \xrightarrow{K3} \text{Response}$$

2. **Reversible drug-receptor interaction**
3. Response is proportional to number of receptors occupied.
4. **Maximum response when all receptors are occupied.**
4. **Agonist** (high Kl, K2 and K3)
5. **Antagonist** (high Kl, 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).

Effect of Spare Receptors on Dose Response