Drug Receptor Interactions
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• The ability of a drug to produce an effect results from specific chemical interactions between the drug and specific sites (lipoprotein receptors, enzymes, biomembranes, nucleic acids or small molecules).
• When a drug interacts with a receptor, a number of chemical attractive forces are believed to be responsible for the initial interaction.

• Compounds that are attracted to a receptor macromolecule are said to have affinity for that receptor and may be classified as agonist and antagonist.

• Compounds with affinity also are referred to as ligands.
• Agonists are those compounds that have affinity for the receptor and are capable of producing biological response as a result of its interaction with the receptor. The ability to produce a response is termed “efficacy” or “intrinsic activity”.

• Drugs that are capable of interacting with the receptor but not of activating it to produce a response are classified as antagonists. This class of drugs is said to have affinity, but it lacks intrinsic activity.
Drug Receptor Interactions, Inverse agonist

- Inverse agonist
  “An agent which binds to the same receptor binding-site as an agonist for that receptor but exerts the opposite pharmacological effect”
  - Difference from Antagonist: Antagonist binds to the receptor, **but does not reduce basal activity**
    - Agonist → **positive** efficacy
    - Antagonist → **zero** efficacy
    - Inverse agonist → **negative** efficacy
  - Inverse agonists are effective against certain types of receptors (e.g. certain histamine receptors and GABA receptors) which have constitutive activity

- Example 1: the agonist action of benzodiazepines on the benzodiazepine receptor in the CNS produces sedation, muscle relaxation, and controls convulsions. β-carbolines (inverse agonists) which also bind to the same receptor cause stimulation, anxiety, increased muscle tone and convulsions.

- Example 2: the histamine H₂ receptor has constitutive activity, which can be inhibited by the inverse agonist cimetidine. On the other hand, burimamide acts as a neutral antagonist
• The affinity of a compound for a receptor is dependent on its proper three-dimensional characteristics, such as its size, stereochemical orientation of its functional groups, and its physical and electrochemical properties (e.g. ionic and dipole interactions).

• The binding of the drug to the receptor initially depends on the types of bonds that can be established between the drug and its receptor.
• The overall strengths of these bonds will vary and will determine the degree of affinity between the drug and the receptor.

• Interaction between the drug and the biologic receptor would be expected to take place by utilizing the same bonding forces involved as those when simple molecules interact.
<table>
<thead>
<tr>
<th>Bond Type</th>
<th>Bond strength (kcal/mol)</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covalent</td>
<td>40-140</td>
<td>$\text{H}_3\text{C} - \text{OH}$</td>
</tr>
<tr>
<td>Reinforced ionic</td>
<td>10</td>
<td>$\text{R} - \text{N} - \text{H} \quad \text{O} \quad \text{H}^+ \quad \text{O}^- \quad \text{R}'$</td>
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<tr>
<td>Ionic</td>
<td>5</td>
<td>$\text{R}_4\text{N}^+ \quad \text{O}^- \quad \text{I}$</td>
</tr>
<tr>
<td>Hydrogen</td>
<td>1-7</td>
<td>$\quad \text{OH} \quad \text{O}=\text{O}$</td>
</tr>
<tr>
<td>Ion-dipole</td>
<td>1-7</td>
<td>$\text{R}_4\text{N}^+ \quad \text{O}^- \quad \text{NR}_3$</td>
</tr>
<tr>
<td>Dipole-dipole</td>
<td>1-7</td>
<td>$\delta^- \text{O}=\text{C} \quad \delta^+ \quad \text{NR}_3$</td>
</tr>
<tr>
<td>van der Waals'</td>
<td>0.5-1</td>
<td>$\text{C} \quad \text{C}$</td>
</tr>
<tr>
<td>Hydrophobic</td>
<td>1</td>
<td>$\text{C} \quad \text{C}$</td>
</tr>
</tbody>
</table>
Drugs bind to their target by:

1- **Irreversible bonds**: When relatively long lasting or irreversible effects are desired (e.g. antibacterial, anticancer), drugs that form covalent bonds with the receptor are effective and useful.

2- **Reversible bonds**: In most cases, it is desirable that the drug leave the receptor site when the concentration decreases in the extracellular fluids. Therefore, most useful drugs are held to their receptors by ionic or weaker bonds.
Irreversible Bonds: Covalent Bond

• The strongest bonds involved in drug-receptor interactions is the covalent bond, in which two atoms, one from the ligand and one from the receptor, share a pair of electrons.

• The ligand is irreversibly bound by the receptor (40-140 kcal/mole) and, thus, leads to the receptor’s eventual destruction via endocytosis and chemical destruction.

• Full recovery of the cellular function, therefore, requires the synthesis of new receptors.
Drug-Receptor Bonds

1. Covalent Bond
   - Very strong
   - Not reversible under biologic conditions \( \rightarrow \) unusual in therapeutic drugs

   Example: phenoxybenzamine at \( \alpha \) adrenergic receptors

2. Ionic bond
   - Weak, electrostatic attraction between positive and negative forces
   - Easily made and destroyed

3. Dipole - dipole interaction
   - A stronger form of dispersion forces formed by the instantaneous dipole formed as a result of electrons being biased towards a particular atom in a molecule (an electronegative atom).
   - Example: Hydrogen bonds
4. Hydrophobic interactions

“The tendency of hydrocarbons (or of lipophilic hydrocarbon-like groups in solutes) to form intermolecular aggregates or intramolecular interactions in an aqueous medium”
-usually quite weak
-important in the interactions of highly lipid-soluble drugs with the lipids of cell membranes and perhaps in the interaction of drugs with the internal walls of receptor “pockets”

5. Dispersion (Van der Waal) forces

-Attractive forces that arise between particles as a result of momentary imbalances in the distribution of electrons in the particles.
-These imbalances produce fluctuating dipoles that can induce similar dipoles in nearby particles, generating a net attractive force.
Covalent Bond: Alkylation

Phenoxybenzamine

\[ \text{X is a nucleophile, such as S, N, or O.} \]
Covalent Bond: Acylation

H₂N–Protein → O

O

H

N

COOH

R

TH

TH

R

O

H

N

COOH

TH

TH

H

N

Protein

Dr. Amged SirElkhatim
Reversible Bonds: Ionic Bond

• Ionization at physiologic pH would normally occur with the carboxyl, sulfonamide, and aliphatic amino groups, as well as the quaternary ammonium group at any pH.
Reversible Bonds: Dipole-Dipole or Ion-Dipole

• Differences in electronegativity between carbon and other atoms, such as oxygen and nitrogen, lead to an unsymmetric distribution of electrons (dipoles) that are also capable of forming weak bonds with regions of high or low electron density, such as ions or other dipoles.

• Carbonyl, ester, amide, ether, nitrile, and related groups that contain such dipolar functions are frequently found in equivalent locations in structurally specific drugs.
\[ \delta^+ \quad \delta^- \quad \delta^+ \quad \delta^- \]

dipole  dipole

dipole  ion
Reversible Bonds: H-Bond

- Many drugs possess groups, such as carbonyl, hydroxyl, amino, and imino, with the structural capabilities of acting as acceptors or donors in the formation of hydrogen bonds.

- However, such groups would usually be solvated by water, as would the corresponding groups on a biologic receptor.

- Relatively little net change in free energy would be expected in exchanging a hydrogen bond with a water molecule for one between drug and receptor.
Reversible Bonds: van der Waals’ Forces

• For these forces to operate, a momentary dipolar structure needs to exist to allow such association. Although individually weak, the summation of their forces provides a significant bonding factor in higher molecular-weight compounds.
• The aromatic ring is frequently found in active drugs, and a reasonable explanation for its requirement for many types of biologic activity may be derived from the contributions of this flat surface to van der Waals’ binding to a correspondingly flat receptor area.

flat hydrophobic region
Reversible Bonds: The Hydrophobic Bond

• The hydrophobic bond is a concept used to explain attractive interactions between nonpolar regions of the receptor and the drug. Explanations such as the “isopropyl moiety of the drug fits into a hydrophobic cleft on the receptor composed of the hydrocarbon side chains of the amino acid valine, isoleucine, and leucine” are commonly used to explain why a nonpolar substituent at a particular position on the drug molecule is important for activity.
• Because the nonpolar molecules of a hydrocarbon are not solvated in water owing to their inability to form hydrogen bonds with water molecules, the latter become more ordered around the hydrocarbon molecule, forming an interface, at a molecular level, that is comparable to a gas-liquid boundary.
• By displacing part of water phase, the two alkyl chains (one from the drug and the other from the receptor) occupy the same water cavity, while many of the water molecules (represented by circles) become randomized. Once the hydrocarbon chains are in sufficient proximity, van der Waals’ forces become operative between them.
Reversible Bonds: Charge Transfer Complex

• Drug-receptor interactions often involve CT complex formation. Examples include the reactions of antimalarials with their receptors and some antibiotics that interact with DNA. Charge transfer (CT) complexes are formed between electron-rich donor molecules and electron-deficient acceptors.
Typically, donor molecules are $\pi$-electron-rich heterocycles (furan, pyrrole, thiophene), aromatics with electron-donating substituents, and compounds with free, nonbonding electron pairs.
• Acceptor molecules are $\pi$-electron-deficient systems such as purines and pyrimidines, aromatics with electron-withdrawing substituents.
acetylcholine

dipole-dipole or ion-dipole
van der Waals
ion-ion