20.201 Mechanisms of Drug Action

Lecture #20: Omeprazole Case Study
November 7, 2005
Review of Lecture #19

• Covered the concepts of PBPK’s

• Constructed a PBPK model based on cisplatin

Today

• Brief lecture on receptors and drug-receptor interactions

• Begin omeprazole case study
Drug-receptor interactions

- **Pharmacodynamics** - Quantitative relationship between drug binding to a receptor and the pharmacological effect

- **Definition of a receptor** - Cellular macromolecule that specifically (chemically) recognizes a ligand and carries out a function in response to ligand binding.

  Limitations: Fat cells are not receptors for lipophilic drugs: no specific function follows

- Receptors provide means to "amplify" drug
  ~ Example: 70 µg sufentanil causes respiratory arrest
  ~ 1 billionth the mass of 70 kg adult

- **Types of receptors**
  - Trans membrane ion channels: conduct ions across membrane in response to ligand binding, voltage gradient or second messenger; e.g., H⁺/K⁺-ATP’ase
  - Transmembrane linked to intracellular G protein; e.g., adrenergic receptors
  - Transmembrane with enzymatic cytosolic domain; e.g., receptor tyrosine kinases
  - Intracellular: cytoplasm or nucleus; e.g., DNA, estrogen receptor

- **Drugs not acting through “receptors”**
  - ethanol (?)
  - general anesthetics
  - antacids
  - osmotic diuretics
Types of receptors

• Trans membrane ion channels:
  ~ conduct ions across membrane in response to ligand binding, voltage gradient or second messenger
  ~ e.g., H⁺/K⁺-ATP’ase

• Transmembrane linked to intracellular G protein; e.g., adrenergic receptors

• Transmembrane with enzymatic cytosolic domain; e.g., receptor tyrosine kinases

• Intracellular: cytoplasm or nucleus; e.g., DNA, estrogen receptor

Figure by MIT OCW.
Characteristics of a Receptor

- **Specificity**
  - Receptor interacts with one type of ligand or a structurally related family of ligands
  - Competition between related ligands
  - Example: glucose transporter binds D-glucose specifically

- **Affinity**
  - Energetics of ligand receptor interactions
  - Energetics of binding determine specificity

- **Intrinsic activity**
  - A measure of the ability of a bound drug to activate the receptor
  - Distinguishes agonist from antagonist

- **Saturability**
  - Finite number of binding sites on a receptor, along with specificity of interactions, implies that binding sites can become fully occupied with ligand molecules
  - Additional ligand leads to non-specific binding

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$K_m$</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-Glucose</td>
<td>&gt;3000</td>
</tr>
<tr>
<td>Galactose</td>
<td>30</td>
</tr>
<tr>
<td>Mannose</td>
<td>20</td>
</tr>
<tr>
<td>D-Glucose</td>
<td>1.5</td>
</tr>
</tbody>
</table>
Types of Chemical Bonds in Ligand-Receptor Interactions

- Affinity and Specificity based on chemical bonds
- Covalent binding of omeprazole occurs only after non-covalent, specific interaction with H⁺/K⁺-ATPase
- Ionic bonds initial attraction
- Cation-π interactions, hydrogen bonds improved binding, some specificity
- Van der Waals forces, hydrophobic interactions most specificity

Figure by MIT OCW.
Quantitation of Ligand-Receptor Interactions

Consider interaction of drug (X) with receptor (R) single binding site
Equivalent to multiple non-interacting binding sites on a single receptor molecule

\[ K_a = \frac{1}{K_d} = \frac{[RX]}{[R][X]} \]

- Association constant; not acidity
- [R] = unoccupied receptor
- [X] = free (unbound) drug concentration

\[ \Delta G^\circ = -RT \ln(K_a) \]

- R = gas constant; T = temperature
- -\Delta G = tight binding

Define "saturation fraction" = \( r \)
average number of ligands bound per receptor molecule (Langmuir isotherm)

\[ r = \frac{[X]_{\text{bound}}}{[R]_{\text{total}}} = \frac{[RX]}{[R]_{\text{free}} + [RX]} \]

\[ K_a = \frac{[RX]}{[R]_{\text{free}}[X]_{\text{free}}} \implies r = \frac{K_a [R]_{\text{free}}[X]_{\text{free}}}{[R]_{\text{free}} + (K_a [R]_{\text{free}}[X]_{\text{free}})} = \frac{K_a [X]_{\text{free}}}{1 + [X]_{\text{free}}} \]

For receptor with "n" binding sites:

\[ r = \frac{nK_a [X]_{\text{free}}}{1 + [X]_{\text{free}}} \]
Quantitation of Ligand-Receptor Interactions

- Binding isotherm: increase ligand concentration and measure bound and free (at constant temp)
- Nonlinear regression to fit the data and determine $K_a$

\[
r = \frac{nK_a[X]_{free}}{1 + [X]_{free}}
\]

\[
r = 0.5 = \frac{K_a[X]_{free}}{1 + [X]_{free}}
\]

\[
r = 0.5 \Rightarrow [R]_{free} = [RX] \Rightarrow K_a = \frac{1}{[X]_{free}} \quad \text{and} \quad \frac{1}{K_a} = [X]_{free}^{1/2}
\]

- More useful presentation of binding data
- "Scatchard plot": $r/[X]_{free}$ versus $r$

\[
r = \frac{nK_a[X]_{free}}{1 + [X]_{free}} \Rightarrow \frac{r}{[X]_{free}} = nK_a - K_a r
\]

Slope = $-K_a$

$Y_i = nK_a$

$X_i = n$
**Agonists and Antagonists**

- **Agonist**
  - Ligand that binds to receptor and stabilizes an “active state” of the receptor
  - “Active state” is defined as the functionally activated form (e.g., open ion channel, activated tyrosine kinase)
  - Endogenous ligands are generally agonists: neurotransmitters

- **Antagonist**
  - A ligand that binds to the receptor with affinity/specificity but does not have intrinsic activity
  - Inhibits the action of an agonist but has not activity in the absence of agonist
  - **Receptor antagonist**: binds to the active site or an allosteric site *reversibly* or *irreversibly*
  - **Non-receptor antagonist**: binds to molecule downstream in activation pathway, or acts in a pathway that opposes the agonist pathway
    - *Chemical antagonist*: protamine binds to and inhibits heparin, an anticoagulant
    - *Physiological antagonist*: β-adrenergic receptor agonists block the tachycardia caused by hyperthyroidism (though thyroid hormone acts by a different receptor)
**Agonists**

- Ligand that binds to receptor and stabilizes an “active state” of the receptor
- “Active state” represents conformational change caused by agonist binding
- Binding can occur at the active site or at another region of the receptor (exerts allosteric effects)
- The kinetics of drug binding and receptor activation are distinct

\[
\begin{align*}
D + R & \rightleftharpoons DR \rightleftharpoons DR^* \\
& \text{Potency} \quad \text{Efficacy}
\end{align*}
\]

- **Potency** related to drug binding affinity (i.e., association constant)
- **Efficacy** related to the rate and extent of receptor activation AFTER drug binding
Agonists

\[ \text{D} + \text{R} \rightleftharpoons \text{DR} \rightleftharpoons \text{DR}^* \]

\[ k_{\text{on}}, k_{\alpha}, k_{\text{off}}, k_{\beta} \]

**Potency**  **Efficacy**

- **Potency** related to drug binding affinity (i.e., association constant)
- **Efficacy** related to the rate and extent of receptor activation AFTER drug binding
- **Partial agonist**: sub-maximal response when drug binds to receptor; judged relative to the most efficacious drug in class

![Graph showing dose-response curves for different efficacies](image)

Partial agonist: less efficacious

\[ \frac{E}{E_{\text{max}}} \]

\[ \log \text{dose} \]
Irreversible Antagonists

- **Irreversible Antagonist = Noncompetitive Antagonist**
  - Drug binds to receptor at active or allosteric site with extremely high affinity or by covalent bonds
  - Example: omeprazole
  - Antagonist action terminates when receptor degraded

![Diagram showing irreversible antagonists](image-url)
Gastric anatomy

- Esophagus
- Cardia
- Fundus
- Lower esophageal sphincter
- Body
- Duodenum
- Stomach
- Antrum
- Pylorus

Figure by MIT OCW.
• 2 glandular elements in the stomach  
  ~ Gastric (oxyntic) gland  
  ~ Pyloric (antral) gland

• **Gastric gland** - body and fundus  
  ~ Oxyntic (parietal) cells  
    - HCl  
    - Intrinsic factor (B12 absorption)  
  ~ Peptic (chief) cells - pepsinogen  
  ~ ECL cells (enterochromafin-like): histamine  
  ~ Mucous secreting cells

• **Pyloric gland** - antrum  
  ~ Shallower pit  
  ~ Gastrin (G) cells - gastrin  
  ~ Peptic cells - pepsinogen (minor)  
  ~ ECL cells (enterochromafin-like): histamine  
  ~ Mucous secreting cells
Gastric physiology

Images of Acetylcholine Pathways, Gastrin Pathways, Histamine Pathways removed due to copyright restrictions.

Acid Secretion Pathways

http://hopkins-gi.org/multimedia/database/intro_247_Parietal.swf
Mechanism of action of omeprazole et al.