Introduction to Pharmacologic Principles
Phar 735 and 590, Winter 2006
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Objectives: By the end of this section of lectures, students are expected to be able to:

1. Define a receptor based on the five principle characteristics.
2. Provide examples of non-receptor-mediated drug action.
3. Define the different kinds of drugs (full, partial, mixed and inverse agonist; irreversible, competitive and non-competitive antagonist; etc).
4. Describe and compare the effects of different kinds of agonists (full, partial and inverse) on receptor structure as it relates to activation.
5. Compare and contrast graded versus quantal dose response curves.
6. Graph different quantal dose response curves based on differences in variability in a population.
7. Develop a theoretical graded dose response curve for any kind of drug.
8. Compare and contrast the terms affinity, potency, efficacy, and intrinsic activity.
9. Define and compare chemical, physiological and pharmacological antagonists.
10. Develop a theoretical graded dose response curve for a full dose range of any kind of drug in combination with a single dose of any other kind of drug.
11. Interpret radioligand binding curves to reveal $K_D$ and $B_{max}$ values.
12. Define spare receptor theory and interpret the changes resulting in a theoretical graded dose response curve for a full agonist under spare receptor theory.
13. Interpret competition binding curves to reveal $K_i$ values.
14. Develop a pharmacological profile for a receptor based on EC50 and Ki data.
15. Define and compare the terms potentiation, summation and synergism with respect to drug action. Interpret dose response curves using knowledge of these terms.
Before beginning this section of lectures, we expect students to be able to:

1. Interpret graphs

![Graph showing exam grade vs. study time]

For example, looking at the slightly complex graph above, you should be able to quickly answer the following questions:

- What is the minimum grade that you can receive on the exam with no studying?
- What is the optimal amount of time to study to achieve a perfect score?
- What minimal amount of time should be spent studying to receive a grade of 70%?
- What happens if you stop sleeping and study constantly?

2. Describe the difference between a linear and a log scale.

3. Plot data using semilog graph paper.

4. Define Km and Vmax for enzyme reactions and find these values on a graph of substrate versus reaction velocity.

5. Describe how various kinds of enzymatic inhibitors influence Km and Vmax values.

6. Define a lipid, protein, hormone and neurotransmitter.

7. Draw a theoretical normal distribution for some variable in a population, identify the mean, and describe the significance of the slopes of the distribution.

8. Define the term “Brownian motion” as it relates to molecular scale events.

9. Describe the structure and function of cell components including the plasma membrane, cytosol, and nucleus.

10. Describe a few of the different kinds of responses of drugs (or any molecule) that might be observed at a cellular level, an organ level, an organismal level, and a population level.

Reading assignment: Before lecture on Tuesday, Feb 21st, students are expected to have read Chapters 1 and 2 in Golan, *Principles of Pharmacology*. 

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I. Basic Pharmacologic Concepts

**Ultimately our concern will be to understand qualitatively and quantitatively the relationship between drug concentration, drug binding at the site of action and a biological response.**

A. Definitions

1. **Pharmacology**
   Greek derivation: pharmakon / logia

2. **Drug**
   Any chemical that can effect a biological system.

   **Pharmacology is the study of the actions, or effects, of drugs on living systems.**
   
   *Oscar Schmeideberg*

B. Receptors (or not?)

1. **Historical development**
   Claude Bernard (1813 – 1878)
   Caught between a nerve and a muscle

   J.N Langley (1852 – 1926)
   A ‘Receptive Substance’?

   Paul Ehrlich (1845 – 1915)
   ‘Receptor’ – like a key into a lock

2. **Non-receptor (non-protein?) - mediated drug actions**
   See Blackboard for examples

3. **Classical drug - receptor interaction**

   **First principles**
   * Drugs do not create effects.
   * No drug has a single action.
   * The intensity of a drug’s effect is typically proportional to the concentration of free drug.
   * Agents can not act unless they bind

   *Corpora nun agunt nisi fixata*  
   *Paul Ehrlich*
C. Characteristics of Drug and Receptor Binding

*The response elicited by a drug is intimately related to the tendency of a drug to bind to a particular receptor.*

1. Saturability
Drugs must act through specific sites, usually proteins, to cause effects in the body. Therefore, the number of specific drug action sites, or receptors, in the body is **saturable**.

2. Reversability
Interaction with a binding site does not change a drug (unlike an enzyme substrate), therefore drug receptor interactions are **reversible**.

**Law of MassAction**
Describes the **reversible** reaction between a drug and a receptor in an isolated system

\[
\text{Drug} + \text{Receptor} \rightleftharpoons \frac{k_1}{k_{-1}} \text{Drug Receptor Complex} \rightarrow \text{Response}
\]

The rate at which a drug binds to the receptor \(k_1; k_{on}\) is independent of the rate at which it leaves the receptor \(k_{-1}; k_{off}\).

At **equilibrium**, the number of drugs binding to receptors equals the number leaving receptors. The equilibrium is **dynamic** because the system is **reversible**.

With rare exceptions, drug interactions with binding sites always reach a **dynamic equilibrium** such that a specific proportion of receptors are always bound at a specific drug concentration.

3. High affinity
A constant \(K_D\), (a.k.a the **equilibrium dissociation constant**, or the **affinity** constant) is defined as

\[
\frac{k_{off}}{k_{on}}
\]

Because drugs have specific actions in the body, the drug-receptor interaction must be **high affinity**.

4. Stereoselectivity
Stereoselectivity is a consequence of specific, high affinity interactions.

5. Effect
D. Experimentally obtaining $K_D$ and $B_{\text{max}}$ values

Tagged drug is added to a system containing receptors and the system is allowed to reach dynamic equilibrium. The number of tagged drugs bound is then detected and quantified. Some of this binding is non-specific background and must be subtracted out.

Specific binding = (Total binding) - (Non-specific binding)

From a plot of specific binding (Bound) versus concentration of drug added, we can obtain a $B_{\text{max}}$ value by estimating the amount of binding at infinite drug concentration (extending the flat top of the curve). The $K_D$ value can be estimated by interpolating the concentration of radioligand required to achieve 50% binding (at which half of the receptors are bound).

The $B_{\text{max}}$ value is a measure of the total number of specific binding sites, i.e. receptors, in a system.

$K_D$ is the measure of the affinity of a receptor for a drug. The $K_D$ value is unique for a receptor's interaction with any drug and is dependent only upon how well the drug fits the receptor and the receptors tendency then to continue to bind the drug.

The $K_D$ value is the concentration of drug required for 1/2 of all receptors to be in a bound state. Consequently, the higher the affinity of a receptor for a drug (the more tenaciously it binds), the lower the $K_D$ value. Only a low concentration of a high affinity drug is needed to occupy 1/2 of the receptors.
E. Occupancy vs Response

At the simplest level, we would expect response to be directly proportional to the number of drug-receptor complexes formed. (100% occupancy = 100% response) …….. This is rarely the case ……..

1. Agonists
   a. Agonists bind to receptors and elicit a response.
      Agonists have:
      **Intrinsic activity** – the capacity of a drug molecule to activate transduction as a function of binding to its receptor; *and display*

      **Efficacy** – the capacity of a population of receptors to elicit a maximal response when occupied by an adequate quantity of agonist molecules. (Maximal response = efficacy of 1)

      **Potency** – the dose required to cause a specific effect
   
   b. Agonists can be compared with respect to their efficacy and potency
   
   c. Observation of a synergistic response following drug administration is characteristic of independent mechanisms or sites of action.

2. Types of Agonists
   a. Full agonist
      An agonist that can cause a maximal response
   
   b. Partial agonists
      An agonist that fails to cause a maximal response even when all receptors are bound.
      (*Intrinsic activity and efficacy are less than 1*)
   
   c. Inverse agonists
      An agonist that upon binding to a receptor causes an effect opposite to that observed for a typical agonist.

      *This is most obvious in systems where there is a high level of activity in the absence of drug, high basal activity. Inverse agonists hold receptors in an off position and decrease the basal activity of the system*
E. Analysis

Quantitation of drug-receptor interactions and dose response relationships allows us to make useful comparisons between drugs

Creating Dose Response curves

1. The log dose – response plot
   A means to compare efficacy (Emax) and potency (ED50)

2. Generating Data
   Graded responses – degree of response in a system or individual to varying stimuli
   vs
   Quantal response - All or None – percent of a population observed to reach a threshold
   (most common in clinical studies and estimates biological variation)
F. Combinations of agonists

**Summation:** For a given response, the effect of two agonists in combination is the predicted sum of the effect of each agonist in isolation. The agonists may be acting by the same mechanism.

**Synergism:** For a given response, the effect of two agonists in combination is greater than the predicted sum of the effect of each agonist in isolation. The two agonists must be acting by different mechanisms.

**Potentiation:** For a given response, the effect of one agonist in combination with an ineffective drug is greater than the effect of the agonist by itself. The two drugs must be acting by different mechanisms.

G. Spare receptors – A divergence of intrinsic activity and efficacy

Some full agonists only bind to a fraction of receptors and yet elicit a full response. When this happens, the system is described as having **spare receptors**.

\[
\text{Drug Receptor Complex} \rightarrow \text{Response}
\]

Spare receptors occur in a system because of amplification in the signal transduction pathway between binding and response.

One should only see spare receptors in a system with a full agonist.
3. **Antagonists**

a. Non-pharmacologic antagonists
   
   Chemical antagonist – Chelation
   
   Physiologic antagonist –
   
   Acting at an independent site to cause opposing effects.

   *(Physiologic antagonists are actually agonists)*

b. Pharmacologic antagonists
   
   Bind receptors and do not cause a response, but block agonist-receptor interactions.

   *By definition* antagonists lack efficacy, Efficacy = 0

   Antagonist potency is measured as inhibition of an agonist effect in the system.

   Antagonists may be reversible or irreversible

\[
\text{% response} = \frac{\text{agonist}}{\log_{10} [\text{drug}]} - \frac{\text{agonist} + \text{competitive antagonist}}{\log_{10} [\text{drug}]} - \frac{\text{agonist} + \text{irreversible or non-competitive antagonist}}{\log_{10} [\text{drug}]} - \frac{\text{pure antagonist}}{\log_{10} [\text{drug}]} \]
F. Indirect radioligand binding/Competition binding

One can not always obtain a tagged version of every ligand to determine $K_D$ values by direct binding experiment. However, a singletagged drug used in excess (100X $K_D$) can label receptors in a tissue and the affinity of un-labeled compounds can be estimated by competition binding. Increasing concentrations of non-radiolabeled compound are incubated with a single, high concentration of tagged compound. Increasing with the concentration of the un-labeled compound, the tagged drug is competitively displaced from the binding site. The concentration of un-labeled ligand which displaces half of the tagged is interpolated from the curve and refered to as the $IC_{50}$ value.

![Graph showing competition binding](image)

The $IC_{50}$ value can be used to estimate the affinity of the unlabeled ligand for the receptor. Affinity values obtained by competition binding are often referred to as $K_i$ values.

II. Pharmacologic Profiles

Rank order $K_i$ values are a type of fingerprint for a receptor subtype. Comparisons of $K_i$ values in different tissues provide evidence for the existence of similar or different receptors in those tissues.

Comparison between EC50 values (rank order potency) and $K_i/K_D$ values (rank order affinity) provides information regarding the receptor through which a drug acts to cause an effect.