Goals and Objectives

- Sites of Drug Action / Drug Targets
- Drug Properties
  - Agonists and Antagonists
  - Partial and Inverse agonists
  - Efficacy
  - Potency
- Dose-Response Curves
- Therapeutic Index & Margin of Safety

Receptor Theory: Evaluating my therapeutic?

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Sites of Drug Action

- Physical Actions
  - fecal softener
  - laxatives
  - osmotic diuretics

- Chemical Actions
  - antacids
  - chelators
  - resins

- Enzymatic Actions
  - digestive
  - thrombolytic
  - anti-cancer

- Receptor-mediated Actions
  - membrane and intracellular targets

- Nonreceptor-mediated Actions
  - Disinfectants
  - volatile anesthetics

Most Agents work via Receptors

What is a receptor?
It is a bifunctional molecule
—Recognizes and binds reversibly and with extraordinary specificity
—Initiates a functional consequence
  i.e. the receptor does something with the information that it is occupied

Receptors represent a diverse array of structural and functional entities.
Definitions

Agonist Drug which binds to the same receptor as the endogenous compound and produces the same type of signal as the endogenous hormone/neurotransmitter.

Antagonist Drug which binds to the same receptor as the endogenous compound and inhibits the signal produced by the activating hormone/neurotransmitter.

Partial Agonist Drug which when maximally bound to the receptor causes a sub-maximal response.

Inverse Agonist (Negative Antagonist) Drugs which cause a decrease in basal receptor activity i.e. in the absence of agonist.

Affinity A measure of the strength of interaction between a receptor and its cognate ligand; $K_D$ is defined as the concentration at which half of the receptor is occupied.

Efficacy A measure of the efficiency in which a bound ligand activates its target receptor’s signal transduction/biological response.

Potency An overall measure of the ability of a ligand to activate its target receptor. Related to the $EC_{50}$, the concentration at which a half maximal effect is achieved.

Receptor Theory 101

Enzyme Kinetics:

Substrate (S) + enzyme (E) $\rightarrow$ ES $\rightarrow$ E + Product (P)

Agonist (A) + Receptor (R) $\rightarrow$ AR $\rightarrow$ effects

Agonist is a Drug that elicits a biological effect.

The agonist does not get modified, or changed, by interaction with the receptor.

Clark - ”Simple Occupation Theory”

Law of Mass Action

$D + R \rightleftharpoons DR$

$K_c = \frac{k_1}{k_2} = \frac{[DR]}{[D][R]}$

$D = $ drug

$R = $ receptor

$DR = $ receptor/drug complex

$K_c = $ equilibrium dissociation constant $K_c = k_1/k_2$ units are M

$K_a = $ equilibrium association constant $K_a = k_2/k_1$ units are M$^{-1}$

$K_c = 1/K_a$

The concentration of DR is affected by both [D] and [R]

Therefore receptor density will affect the dose response.

The more receptors are present, the more leftward shifted will be the dose response curve.

Assumptions of A. J. Clark:

Responses to drugs result from formation of reversible complexes with receptors.

One molecule of drug occupies one receptor.

The response to a drug is proportional to the number of receptors occupied.*

A maximum response to a drug occurs when all receptors are occupied (clearly not always true).*

The total amount of drug bound to receptors is negligible relative to the total amount of drug present.
Two of Clark's assumptions do not hold:

A maximum response to a drug occurs when all receptors are occupied (clearly not always true).*

The response to a drug is proportional to the number of receptors occupied.*

**Key Concepts**

Receptor activation can be described with mathematical models.

Receptor activation is not linear with ligand binding.

Usually relatively low receptor occupancy is required to elicit relatively high response. I.e., 25% activation takes place at less than 25% occupancy.

Receptor mediated activity is affected by the inherent properties of the ligand, the number of receptors present and the characteristics of the signal transduction machinery.

**Depletion of agonist receptor interaction**

response = $f_{agonist}[receptor]K_Ae$

where $K_A$ = equilibrium affinity constant and $e$ = efficiency of receptor-effector coupling leading to biological response.

In various diseases a change in response is observed.

Classic endocrine disorders: due to a change in agonist availability

Change in $K_A$ = consequence of receptor mutations, post-translational modifications (especially phosphorylation)

Changes in $e$ = typically due to post-translational modifications mediated by downstream kinases, phosphatases, or changes in expression levels of downstream proteins

Changes in $R$ = mutation; perturbation of expression or turnover by other biological processes.

Numerous biological processes reflect changes in signal transduction with development, disease, aging, etc., it has been necessary to obtain quantitative data on RECEPTOR OCCUPANCY and SIGNALING EFFICIENCY.
Definitions of therapeutic drugs

1. Agonists - “doer” drugs
   - Mimic the actions of endogenous agents
   - Activate receptors
   - Both “full” and partial agonists

2. Antagonists- Blocker drugs
   Classically, have no effect of their own, other than to block the receptors, so agonists can’t bind (null, competitive antagonists)
   ....but there are other antagonist mechanisms that we now understand

What dose response curves look like for these various types of drugs....

Simple Model

Quantifying Drug Effects

1) **Affinity** – describes “tightness” of interaction between a receptor and drug
2) **Efficacy** – describes the “strength” or “extent” of the pharmacological effect
3) **Potency** – in clinical settings, reflects both 1 and 2.
Potency & Efficacy

Driving home the difference between potency and efficacy

- Equal efficacy - curves A & B
- Equal efficacy - curves C & D
- Equal potency – curves A & D curves B & C

Log [Drug] vs. Response
Variability among individuals manifests itself in multiple aspects of dose-response curves.

**Variability**
- Intensity of effect
- Maximal effect
- Variability
- Potency
- Concentration

Fixed dose-varying magnitudes vs. Varying doses required to get a specific response.

[Response] Relationships Define Receptor Specificity

- Decreasing Potency
- EC_{50} Log [Agonist]

Alpha- & Beta-adrenergic receptors: Ahlquist’s landmark hypothesis of a single Mediator with two receptors

Smooth Muscle Contraction

Cardiac Chronotropy & Inotropy

Blood Pressure Effects
Using dibenamine as an irreversible blocking agent, in rabbit aortic strips, Furchgott demonstrated that in rabbit aortic strips, cross-protection occurred among epinephrine (epi), norepinephrine (norepi) and isoproterenol (iso). This was taken as evidence that they all acted on the same receptor. None of the catecholamines (epi, norepi, iso) protected against inactivation of receptors for histamine, acetylcholine or serotonin, and none of the latter protect among themselves or towards catecholamines.

Based on these findings, Furchgott deduced the existence of four receptor subtypes in rabbit aorta, all of which could mediate contraction. Furchgott conceptualized protection experiments as either “self protection” or “cross protection”:


Estimation of Dissociation Constants of Agonists

For the following derivations and approach, the following assumptions are made:

1. Irreversible Blockade
2. Competitive antagonists acting on the same receptor will have the same $K_D$ regardless of the agonist which is displaced.
3. Identical receptors in different tissues or experimental preparations should display the same dissociation constant for the same competitive antagonist.
4. Theory/Calculations

Determinant of antagonist $K_D$ on tissues

Schild Analysis of Antagonist binding.

General Principles

Competitive antagonist acting on the same receptor will have the same $K_D$ regardless of the agonist which is displaced.

Identical receptors in different tissues or experimental preparations should display the same dissociation constant for the same competitive antagonist.

Theory/Calculations

This is for strictly competitive, reversible antagonists. The ability to shift the dose-response curve is influenced by the antagonist affinity ($K_D$) for the receptor and the antagonist concentration ([B]).
Schlid Analysis

\[ pA_2 = -\log K_{D8} \]

Antagonists

- Competitive

Most common pharmacological antagonists are competitive antagonists

Non-competitive Antagonists also exist

- Non-competitive antagonism can be due to pseudo irreversibility of antagonist binding

Non-competitive antagonism also can be due to *allosteric* effects
Allosteric Modifiers can also potentiate, or sensitize, the response.

Note the opportunity for drug effect at very low [agonist/endogenous agent] when a Positive allosteric modifier is present.

**Therapeutic Index** describes relationship desired biological effect and toxicity.

- Dose-dependent
- Therapeutic ratio or index
  - Toxic (Lethal) dose$_{50}$
  - Effective dose$_{50}$
- Margin of safety
  - Toxic (Lethal) dose$_{99}$
  - Effective dose$_{99}$
- Ratios less helpful when non-parallel curves

**Quantal Response Curves**

- Used when not able to do full dose-response curve
- Y axis can be
  - Cumulative response or
  - Frequency distribution

**Therapeutic Index versus Margin of Safety**

$$\text{Therapeutic Index} = \frac{\text{toxic dose}_{50}}{\text{therapeutic dose}_{50}}$$

$$\text{Margin of Safety} = \frac{\text{toxic dose}_{99}}{\text{therapeutic dose}_{99}}$$
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