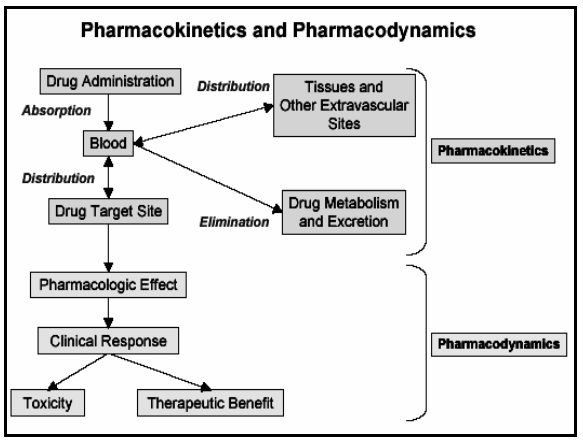


Pharmacodynamics

(how drugs work on the body)

- The action of a drug on the body, including receptor interactions, dose-response phenomena, and mechanisms of therapeutic and toxic action.
- Pharmacodynamics is often summarized as the study of what a drug does to the body, and is abbreviated as "PD",

Pharmacodynamics

(how drugs work on the body)

- **Many drugs inhibit *enzymes***
  - Enzymes control a number of metabolic processes
    A very common mode of action of many drugs
  - **in the patient (ACE inhibitors)**
  - **in microbes (sulfas, penicillins)**
  - **in cancer cells (5-FU, 6-MP)**
- **Some drugs bind to:**
  - **proteins (in patient, or microbes)**
  - **the genome (cyclophosphamide)**
  - **microtubules (vincristine)**

Pharmacodynamics

(how drugs work on the body)

- **Most drugs act (bind) on *receptors***
  - in or on cells
  - form tight bonds with the *ligand*
  - exacting requirements (size, shape, stereospecificity)
  - can be *agonists* (salbutamol), or *antagonists* (propranolol)
- **Receptors have *signal transduction* methods**

Drug Receptor

- **A macromolecular component of the organism that binds the drug and initiates its effect.**
- **Most receptors are proteins that have undergone various post-translational modifications such as covalent attachments of carbohydrate, lipid and phosphate.**

CELL SURFACE RECEPTOR

- **A receptor that is embedded in the cell membrane and functions to receive chemical information from the extracellular compartment and to transmit that information to the intracellular compartment.**

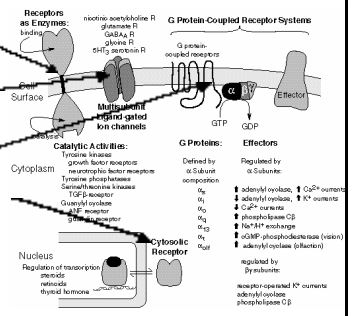
Types of Protein Receptors

1. Regulatory
   – change the activity of cellular enzymes
2. Enzymes
   – may be inhibited or activated
3. Transport –
   e.g. Na^+/K^+ ATP'ase
4. Structural
   – these form cell parts

Major Classes of Receptors

Signal transduction

1. **Enzyme linked** (multiple actions)
2. **Ion channel linked** (speedy)
3. **G protein linked** (amplifier)
4. **nuclear (gene) linked** (long lasting)



Ion-channel-linked receptors

•There are two general classes of ion channels:

- •Voltage gated
- •Ligand gated.

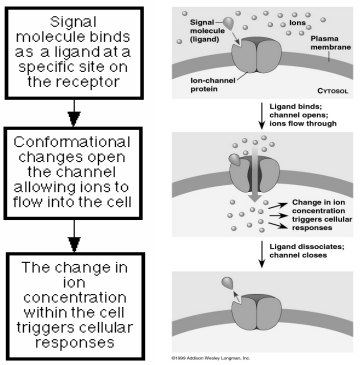
•Voltage-gated ion channels are activated by alterations in membrane voltage.

- •e.g. voltage-gated sodium (Na+) channels open when the membrane is depolarized to a threshold potential and contribute to further membrane depolarization by allowing Na+ influx into the cell.

•Ligand-gated ion channels are activated after binding to specific ligands or drugs.

- •Many neurotransmitters and drugs activate membrane-bound ligand ion -gated channels, including several types of glutamate receptors

Ion-channel-linked receptors



G-protein-linked receptors

•G-protein-linked receptors compose a large class of membrane-bound receptors.

•**The protein structure of these receptors includes a common seven-membered transmembrane domain**.

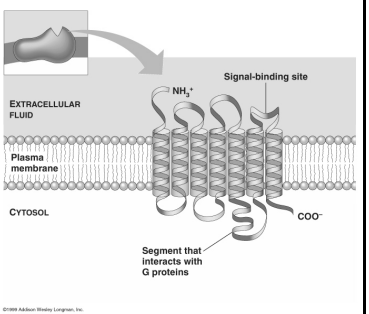
•In general, receptors linked to G proteins greatly amplify the biologic signal because they activate G proteins, which in turn activate ion channels or, more commonly, other enzymes (e.g., adenylate cyclase), leading to stimulation of still other enzymes (e.g., protein kinase A)."

•This amplification system, which generally involves an extended duration of activation of the G protein relative to the binding of drug to the receptor, may explain why maximal pharmacologic effects are often observed when only a small proportion of receptors are activated

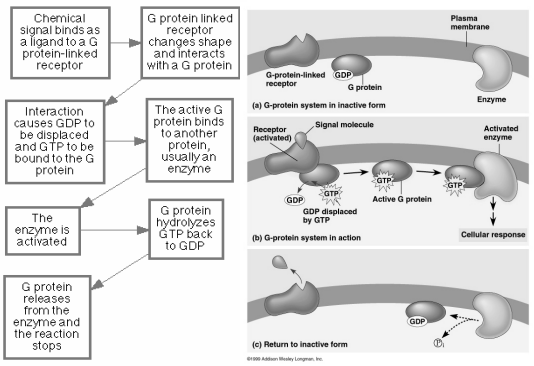
G-protein-linked receptors

•Single polypeptide chain threaded back and forth resulting in 7 transmembrane å helices

•There's a G protein attached to the cytoplasmic side of the membrane (functions as a switch).



G-protein-linked receptors



Enzyme-linked receptors

- Enzyme-linked receptors have only one transmembrane domain per protein subunit, with "an enzymatic catalytic site on the cytoplasmic side of the receptorgy.
- Dimerization of activated receptors provides the confirmational change required for expression of enzymatic activity.
- The catalytic sites are commonly protein kinases that phosphorylate tyrosine,

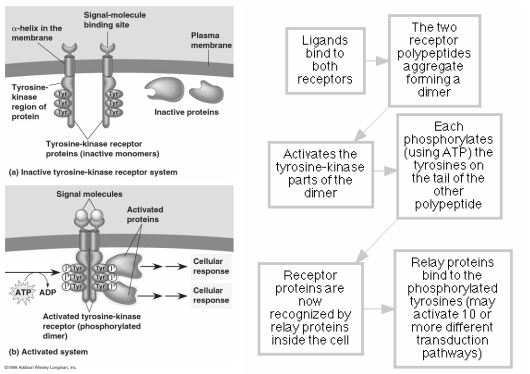
Enzyme-linked receptors

Tyrosine-kinase receptors

Receptors exist as individual polypeptides

- Each has an extracellular signal-binding site
- An intracellular tail with a number of tyrosines and a single å helix spanning the membrane

Enzyme-linked receptors



Intracellular receptors

- Lipophilic substances capable of crossing the plasma membrane may activate intracellular receptors.
  - Sex steroids, mineralocorticoids, glucocorticoids, and thyroid hormones all activate specific intracellular receptors

Mechanisms of transmembrane Signaling

1. A lipid soluble ligand (agonist, drug) crosses the membrane and acts on an intracellular receptor
2. Ligand binds to the extracellular domain of the transmembrane receptor activating enzymatic activity of it's cytoplasmic domain
3. Ligand binds to the extracellular domain of the transmembrane receptor which in turn is bound to and activates tyrosine kinase in the cytoplasm
4. Ligand binds to and directly regulates the opening and closing of a transmembrane ion channel
5. Ligand binds to a transmembrane receptor linked to an effector (enzyme or ion channel) by a G-protein

Theory and assumptions of drug-receptor interaction

- Combination or binding to receptor causes some event which leads to the response.
- Response to a drug is graded or dose-dependent.
- Drug receptor interaction follows simple mass-action relationships, i.e., only one drug molecule occupies each receptor site and binding is reversible.
- For a given drug, the magnitude of response is directly proportional to the fraction of total receptor sites occupied by drug molecules (i.e. the occupancy assumption).
- The number of drug molecules is assumed to be much greater than the number of receptor sites.

Theory and assumptions of drug-receptor interaction

- Combination of drug with a receptor produces a specific response. "lock and key".
- Drug-receptor interactions are analogous to enzyme-substrate interactions. Most of the same principles apply.
- Endogenous ligands (e.g. enkephalin versus morphine).
- Drugs without specific receptors (e.g. gaseous anesthetics).

Drug - Receptor Binding

$$D + R \underset{\text{Affinity}}{\rightleftharpoons} DR \text{ Complex}$$

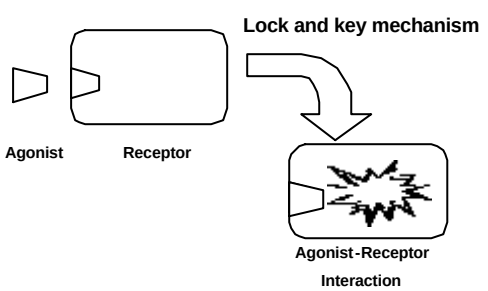
- Affinity – measure of propensity of a drug to bind receptor; the attractiveness of drug and receptor
  - Covalent bonds are stable and essentially irreversible
  - Electrostatic bonds may be strong or weak, but are usually reversible

Drug-Receptor Interaction

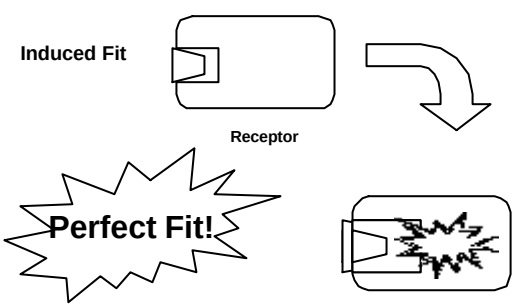
- Drug-receptor interactions can be treated with an equation analogous to the Michaelis Menten equation utilized for enzyme-substrate interactions.

$$D + R \underset{k_2}{\overset{k_1}{\rightleftharpoons}} DR \xrightarrow{k_3} \text{Effect}$$

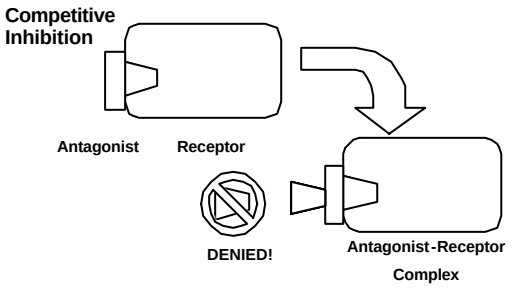
Receptor Interactions



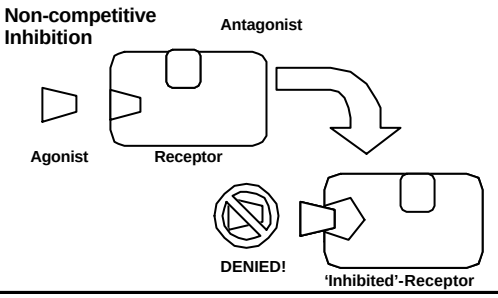
Receptor Interactions



Receptor Interactions



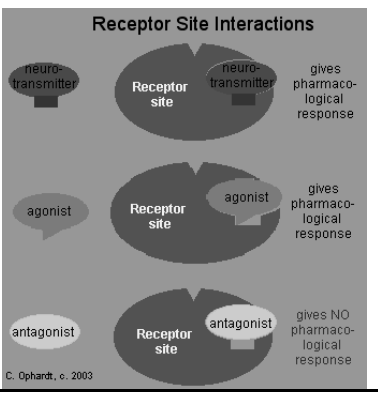
Receptor Interactions



Drug Interaction with Receptor Site

- A **neurotransmitter** has a specific shape to fit into a receptor site and cause a pharmacological response such as a nerve impulse being sent. The neurotransmitter is similar to a substrate in an enzyme interaction.
- After attachment to a receptor site, a drug may either initiate a response or prevent a response from occurring. A drug must be a close "mimic" of the neurotransmitter.
- An **agonist** is a drug which produces a stimulation type response. The agonist is a very close mimic and "fits" with the receptor site and is thus able to initiate a response.
- An **antagonist** drug interacts with the receptor site and blocks or depresses the normal response for that receptor because it only partially fits the receptor site and can not produce an effect. However, it does block the site preventing any other agonist or the normal neurotransmitter from interacting with the receptor site.

Drug Interaction with Receptor Site



Dose Response Curves

$$[D] + [R] \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [DR] \xrightarrow{\alpha} \text{effect}$$

at equilibrium:

$[D] \times [R] \times k_1 = [DR] \times k_{-1}$

so that: $\frac{[DR]}{[D][R]} = \frac{k_1}{k_{-1}}$

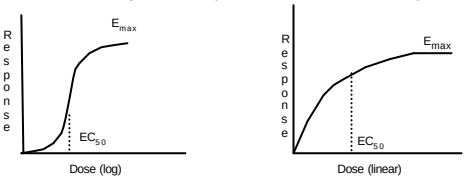
k_1/k_{-1} = affinity const.

k_{-1}/k_1 = dissociation const.(k_d)

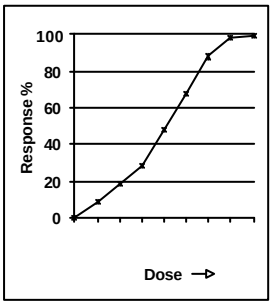
the *lower* the k_d the more *potent* the drug

Dose-Response Curve

- Advantages of expression as log versus response
  - Dose-response relationship expressed as a nearly straight line over a large range of drug doses.
  - Wide range of doses can be plotted on a single graph, allowing easy comparison of different drugs.
  - Use of log dose-response curves to compare different drugs which produce the same response

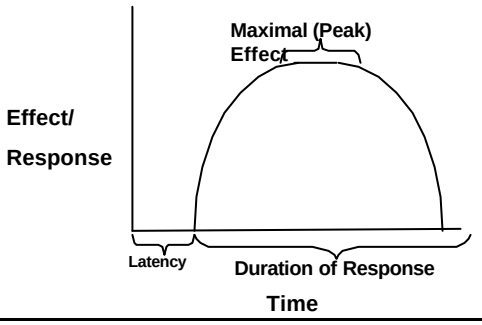


Dose-Response Curves

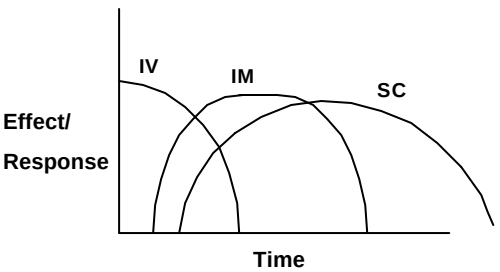


- The dose-response curve relates the amount administered to the response.
- Response may be measured as % responding or as intensity of response

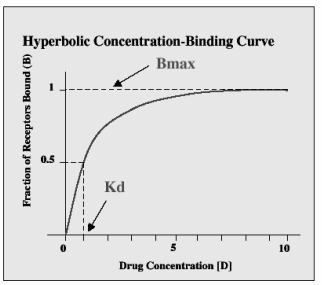
Time Response Relationships



Time Response Relationships



Relationship of Drug Concentration and Receptor Binding



$$B = \frac{B\max \times [D]}{[D] + Kd}$$

B -Fraction of available receptors bound

Bmax -Maximal binding of receptors (=1)

[D] -Concentration of drug

Kd -Equilibrium Dissociation Constant
-Drug concentration at which 1/2 of available receptors are bound
-Measure of affinity of drug/receptor interaction

Drug variability and toxicity assessment

- ED_{50}: Effective dose for 50% of subjects
- LD_{50}: Lethal dose for 50% of subjects
- The therapeutic index

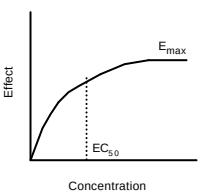
  $TI = LD_{50} / ED_{50}$

  No drug is 100% safe

Drug concentration-effect curve

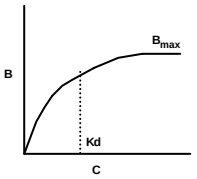
- **E_{max}**– maximal response that can be produced by the drug
- **EC_{50}** – conc. of drug that produces 50% of maximal effect
- Responses to low doses of a drug usually in direct prop. to dose
- As a dose ‘s, it reaches a point at which no in response can be achieved

- At a low concentration, effect is changing rapidly
- At a high concentration, effect is changing slowly



Drug concentration-receptor bound curve

- **B** – drug bound to receptors
- **C** – concentration of free (unbound) drug
- **Kd** – the concentration of free drug at which half-maximal binding is observed (characterizes the binding affinity of receptor for drug)
- **B_{max}** – total concentration of receptor sites (at high concentration of drug)
- If Kd is low, binding affinity is high



Drug Response

Target is to give a dosage regimen that will produce maximal benefit and minimal toxicity

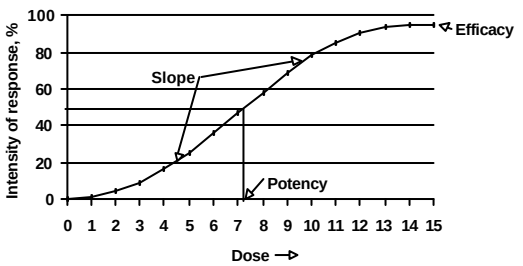
– **Graded Dose Response**
- Measures potency of a drug and efficacy of a drug
- **Potency** – the amt of drug needed to produce a given effect
  – The lower the dose needed to produce a response, the more potent the drug. The smaller the EC_{50}, the > the potency of the drug.
  – Is determined mainly by:
    » Affinity of receptor for the drug
    » Efficiency with which drug-receptor interactions is coupled to response
  – Want a drug to be low in potency if administering in inconveniently large amts

Drug Response

Target is to give a dosage regimen that will produce maximal benefit and minimal toxicity

– **Clinical effectiveness** – depends on maximal efficacy and drugs ability to reach the relevant receptors
  – Depends on route, absorption, distribution, and clearance of drug
- **Efficacy** – the largest response or maximal effect (E_{max}) a drug can produce
  – Is determined mainly by:
    » The nature of the receptor and its associated effector system
    » Drugs mode of interaction with receptors
  – Partial agonist have lower maximal efficacy than full agonists

The dose-response curve: Effectiveness and safety



Agonist Drugs

- Drugs that interact with and activate receptors; they possess both affinity and efficacy
- two types
  – Full – an agonist with maximal efficacy
  – Partial – an agonist with less then maximal efficacy

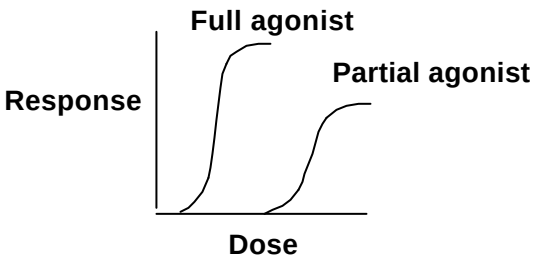
Full Agonists

- Drugs that occupy receptors and bring about a full or maximal response.
- The maximal response is usually defined as that produced by the most powerful agonists, or that produced by a drug associated classically with the response.

Partial Agonists

- Drugs that occupy receptors but bring about less than the maximum response.
- That is, these drugs are less powerful and 100% occupancy produces a lesser response
  - (correspond to substrates with a lower Vmax in enzyme analogy).

Agonist Dose Response Curves



Antagonists

- Drugs that occupy or change the receptor but do not bring about any response. Occupancy by an antagonist interferes with occupancy by a drug capable of causing a response

Types of Antagonisims

Chemical
-interaction of two drugs in solution such that the effect of active drug is lost
e.g. metal chelators plus toxic metals

Physiological
-interaction of two drugs with opposing physiological actions
e.g. histamine: lowers arterial pressure through vasodilation (H1 receptor); epinephrine raises arterial pressure through vasoconstriction (â-adrenergic receptors)

Pharmacological
-blockage of the action of a drug-receptor interaction by another compound
e.g. cimetidine blocks interaction of histamine with H2 receptors resulting in lower gastric acid secretion

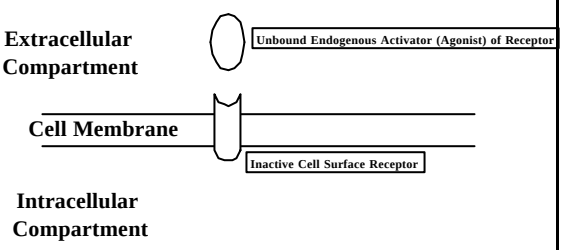
Types of Antagonisims

Pharmacological Antagonists
• Bind to receptors, but do not activate signal transduction mechanisms
• Biological effects derive from preventing agonist (drugs, endogenous) binding and receptor activation

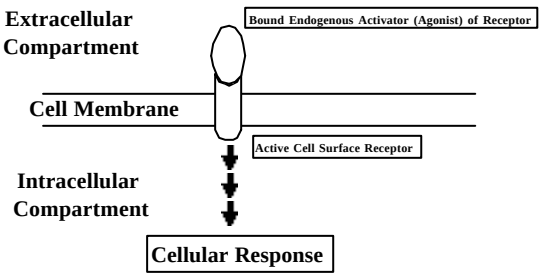
Competitive Antagonists
-bind to same site on receptor as agonists
-inhibition **can** be overcome by increasing agonist concentration (reversible)
-primarily affect agonist potency
-clinically useful

Non-Competitive Antagonists
-bind covalently to same site as agonist (irreversible) or to a site distinct from that of agonist (irreversible or reversible)
-inhibition **cannot** be overcome by increasing agonist concentration
-primarily affect efficacy
-limited clinical use

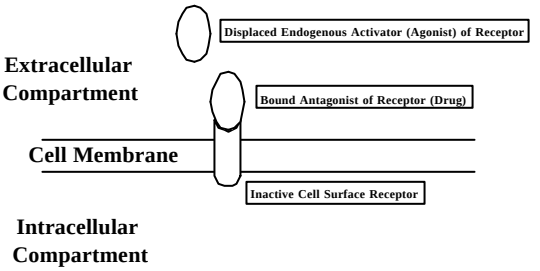
Antagonists at Work



Antagonists at Work



Antagonists at Work



Antagonists at Work

Most antagonists attach to binding site on receptor for endogenous agonist and sterically prevent endogenous agonist from binding.
•If binding is reversible - Competitive antagonists
•If binding is irreversible - Noncompetitive antagonists

•However, antagonists may bind to remote site on receptor and cause allosteric effects that displace endogenous agonist or prevent endogenous agonist from
•activating receptor. (Noncompetitive antagonists)

Synergism

- A certain dose of Drug A alone produces an effect equal to 10 units. A certain dose of Drug B alone produces an effect equal to 10 units. Administration of the same doses of A and B simultaneously produces an effect equal to 50 units

Additivity

- Administration of the dose of A and B simultaneously gives an effect equal to 20 units

Effectiveness, toxicity, lethality

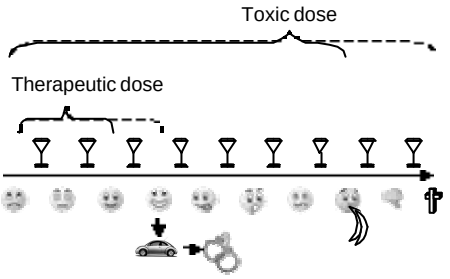
- **ED_{50}** - Median Effective Dose 50; the dose at which 50 percent of the population or sample manifests a given effect; used with quantal dr curves
- **TD_{50}** - Median Toxic Dose 50 - dose at which 50 percent of the population manifests a given toxic effect
- **LD_{50}** - Median Toxic Dose 50 - dose which kills 50 percent of the subjects

The Therapeutic Index

Quantification of drug safety

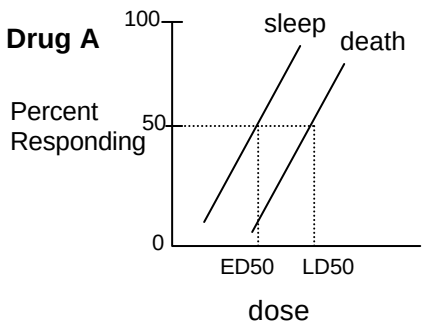
$$\textbf{Therapeutic Index} = \frac{\textbf{TD50 or LD50}}{\textbf{ED50}}$$

The Therapeutic Index

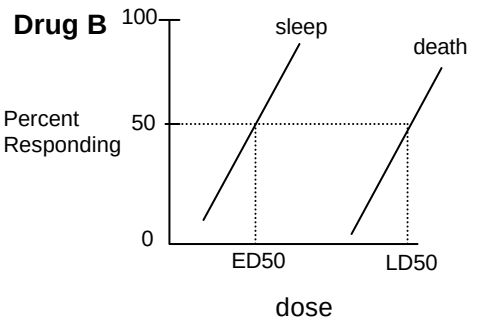


$$\text{Therapeutic index} = \frac{\text{Toxic dose}}{\text{Therapeutic dose}}$$

The Therapeutic Index



The Therapeutic Index

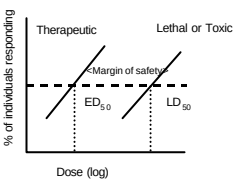


The Therapeutic Index

- The higher the **TI** the better the drug.
- **TI's** vary from: 1.0 (some cancer drugs)
  to: >1000 (penicillin)
- Drugs acting on the same receptor or enzyme system often have the *same* **TI**: (eg 50 mg of hydrochlorothiazide about the same as 2.5 mg of indapamide)

Quantal Dose Response

- Considers variability among patients in severity of disease and responsiveness to drugs
- Measures the effect (response) in a large # of individual patients at various doses
- Measures and compares the potencies of drugs
- Therapeutic index – relates the dose of a drug required to produce a desired effect to that which produces an undesired effect
- A high therapeutic index indicates that the drug produces the desired effect at a dose that is rarely lethal; there is a large margin of safety



Variation in Drug Responsiveness

Individuals may vary considerably in their responsiveness to a drug

- **Idiosyncratic drug response** – unusual, one that is infrequently observed in most patients
  - Caused by:
    - Genetic differences in metabolism
    - Immunologic mechanism (allergy)
- **Hyporeactive** – intensity of effect is decreased
- **Hyperreactive** – intensity of effect is increased
- **Hypersensitivity** – allergic or other immunologic response to drugs resulting from previous sensitizing exposure
- **Tolerance** – responsiveness usually decreases as a consequence of continued drug administration.
  - Need greater doses of a drug to produce original degree of effect as time progresses or need to substitute different drug
- **Tachyphylaxis** – responsiveness diminishes rapidly after administration of a drug (the first few doses), very rapid tolerance

Variation in Drug Responsiveness

Four general mechanisms:

- **Mechanism 1**
  - Patients may differ in the rate of absorption of a drug, in distributing it through body compartments, or in clearing the drug from the blood which may alter the conc of drug that reaches receptor
    - This can be due to age, weight, sex, disease state, liver and kidney function, and genetic differences

Variation in Drug Responsiveness

Four general mechanisms:

- **Mechanism 2**
  - Patients may vary in their concentrations of endogenous receptor ligand
    - Can vary in the response to pharmacologic antagonist
    - Ex: Propranolol (â blocker)
      - » Pt with pheochromocytoma as opposed to healthy runner

Variation in Drug Responsiveness

Four general mechanisms:

- **Mechanism 3**
  - Patients may have differences in the # of receptor sites or differ in the function of their receptors due to the efficiency of coupling receptor to effector
    - Drug Induced down-regulation
    - The "overshoot" phenomena
      - » Antagonists – when discontinued, the elevated # of receptors can produce an exagerated response to physiologic conc of agonist
      - » Agonist – when discontinued, # of receptors that have been dec by down regulation is too low for endogenous agonist to produce effective stimulation
      - » Ex: Clonidine (á agonist) decreases blood pressure. When withdrawn, can produce hypertensive crisis. Pt will have to be weaned slowly

Variation in Drug Responsiveness

Four general mechanisms:

- **Mechanism 4**
  - Patients vary in functional integrity of biochemical processes in the responding cell and physiologic regulation by interacting organ systems
    - Can be caused by age of pt or general health of pt. Most importantly, severity and pathophysiologic mechanism of the disease
- **Drug therapy will be most successful when there is correct diagnosis and if it is accurately directed at the pathophysiologic mechanism responsible for the disease**

Spare receptors – unoccupied receptors

- Maximal response can be achieved by an agonist even if a fraction of receptors (spare receptors) are unoccupied
  - Maximal drug response (the response you want) only requires so many receptors
- Sensitivity of cell to the agonist concentration depends on affinity of receptor for drug, in addition to, *total receptor concentration*
  - With more receptors available, the chance of binding is greater

Spare receptors – unoccupied receptors

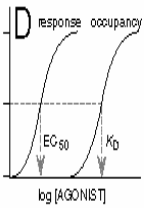
– There are spare receptors if the concentration of drug that produces 50% of the maximum effect (EC_{50}) is less than the concentration of free drug at which 50% of maximum binding is observed (Kd)

– Reasons for having spare receptors:

1. the effect of the drug-receptor interaction may last longer than the interaction itself
2. the number of receptors may exceed the number of effector molecules available

Why are there spare receptors?

- allow maximal response *without* total receptor occupancy – increase sensitivity of the system
- spare receptors can bind (and *internalize*) extra ligand preventing an exaggerated response if too much ligand is present
- The receptor theory assumes that all receptors should be occupied to produce a maximal response. In that case at half maximal effect EC50=kd. Sometimes, full effect is seen at a fractional receptor occupation



Drug-Response Relationship

- Drugs are studied for the following:
  – Plasma levels
- How fast they reach active levels
  – Biologic half-life
- How long it takes to break down half of the drug
  – Minimum effective concentration
- How much of the drug it takes to create a response
  – Therapeutic threshold
- How much of the drug is too much, or toxic

Summary

- Most drugs act through receptors
- There are 4 common signal transduction methods
- The interaction between drug and receptor can be described mathematically and graphically
- Agonists have both *affinity* (k_d) and *intrinsic activity* (α)
- Antagonists have affinity only
- Antagonists can be *competitive* (change k_d) or
- *Non-competitive* (change α) when mixed with agonists
- Agonists *desensitize* receptors.
- Antagonists *sensitize* receptors.