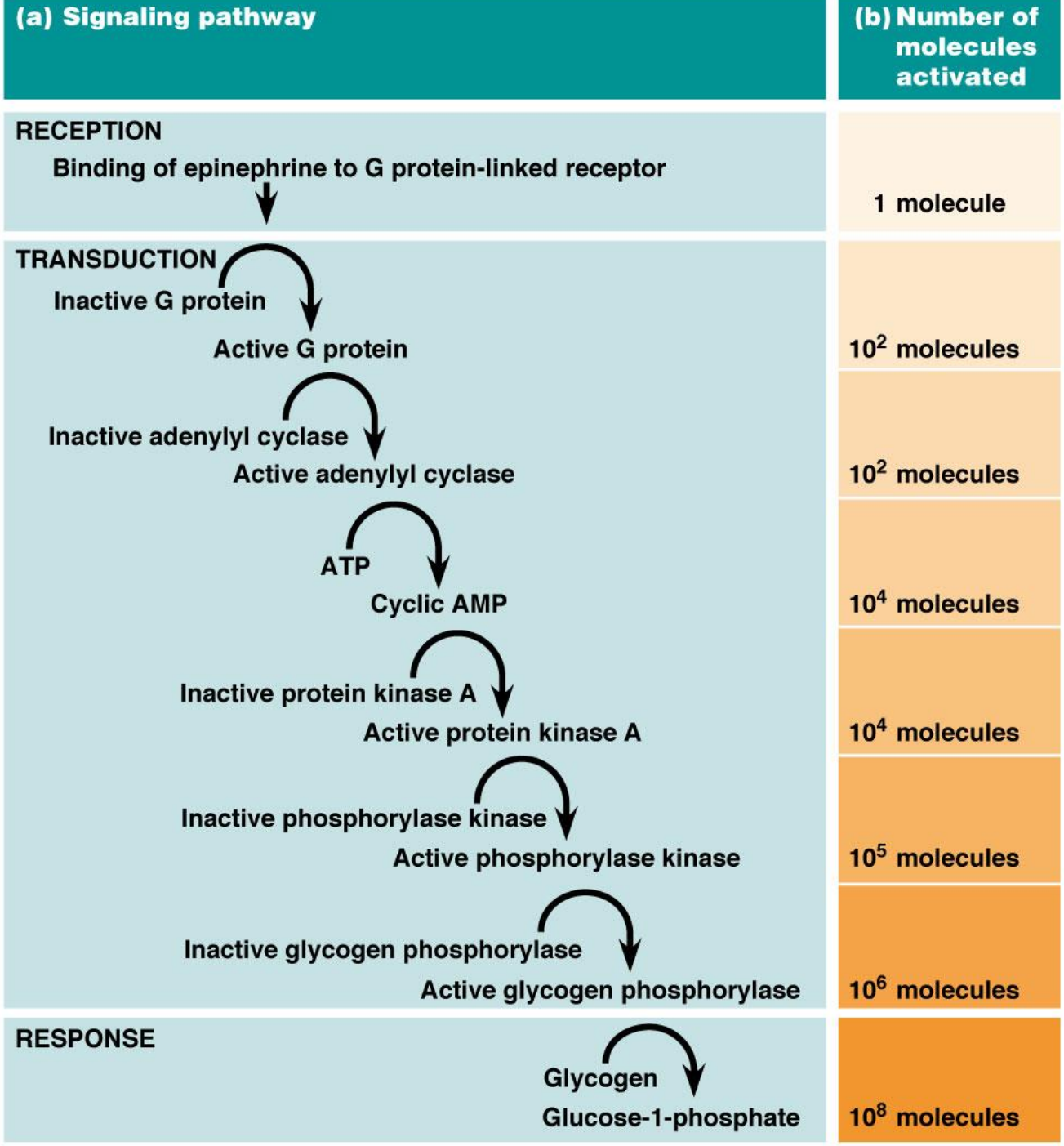
Pharmacodynamics

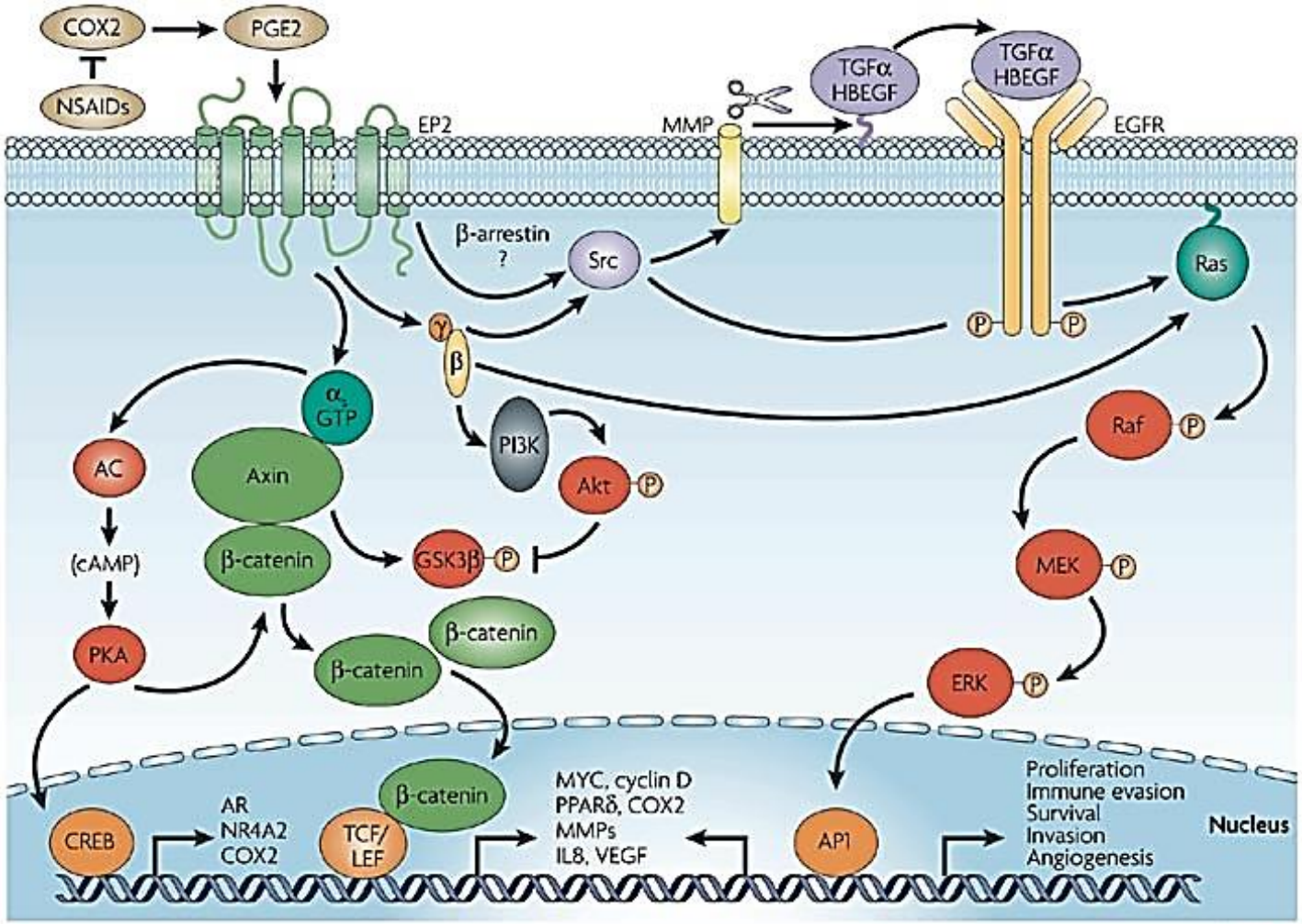
Characteristics of Drug-Receptor Interactions

- Chemical Bond: ionic, hydrogen, hydrophobic, Van der Waals, and covalent.
- Saturable
- Competitive
- Specific and Selective
- Structure-activity relationships
- Transduction mechanisms

Receptors are an Excellent Drug Target

- Activated receptors directly, or indirectly, regulate cellular biochemical processes within and between cells to change cell function.
- Recognition sites are precise molecular regions of receptor macromolecules to which the ligand binds providing:
- Specificity
- Selectivity
- Sensitivity





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Receptor Occupancy Theory

The “Law” of Mass Action

- **Activation of membrane receptors and target cell responses is *proportional to the degree of receptor occupancy.***
- Assumptions:
  - Association is limited by collision, orientation and energy
  - All receptors are equally accessible
  - All receptors are either free or bound, there is no “partial” binding
  - Neither drug or receptor are altered by binding
  - Binding is reversible

Drug-receptor binding

$$D + R \xrightarrow{k} DR$$

$$DR \xrightarrow{k^{-1}} D + R$$

$$\frac{k^{-1}}{k} = K_D$$

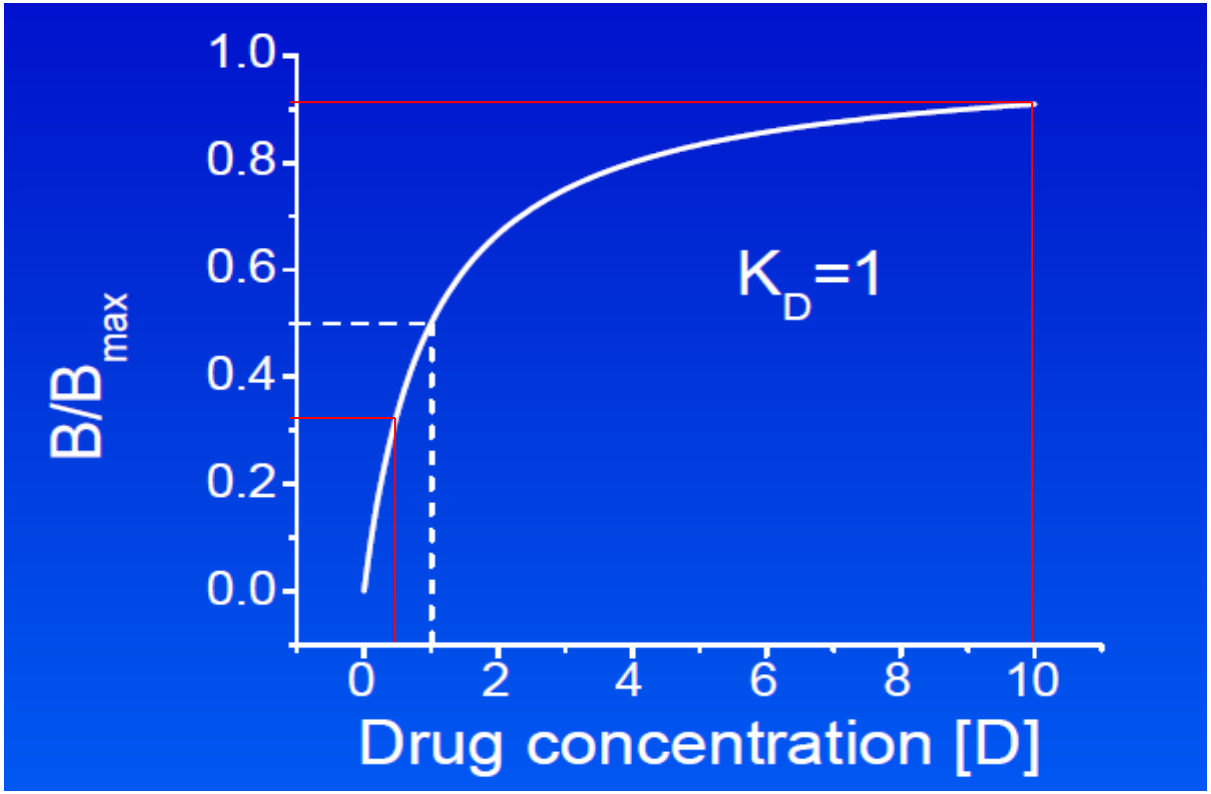
$$\frac{\text{sec}^{-1}}{M^{-1}\,\text{sec}^{-1}} = M$$

» **This ratio is the equilibrium dissociation constant or KD**

» **This <u>dissociation constant</u>, Kd, indicates the strength of binding between R and D in terms of how**

Hill-Langmuir equation

$$B/B_{max} = \frac{[D]}{[D] + K_D}$$



KD: concentration at which binding site is 50% occupied.

Affinity 1/Kd

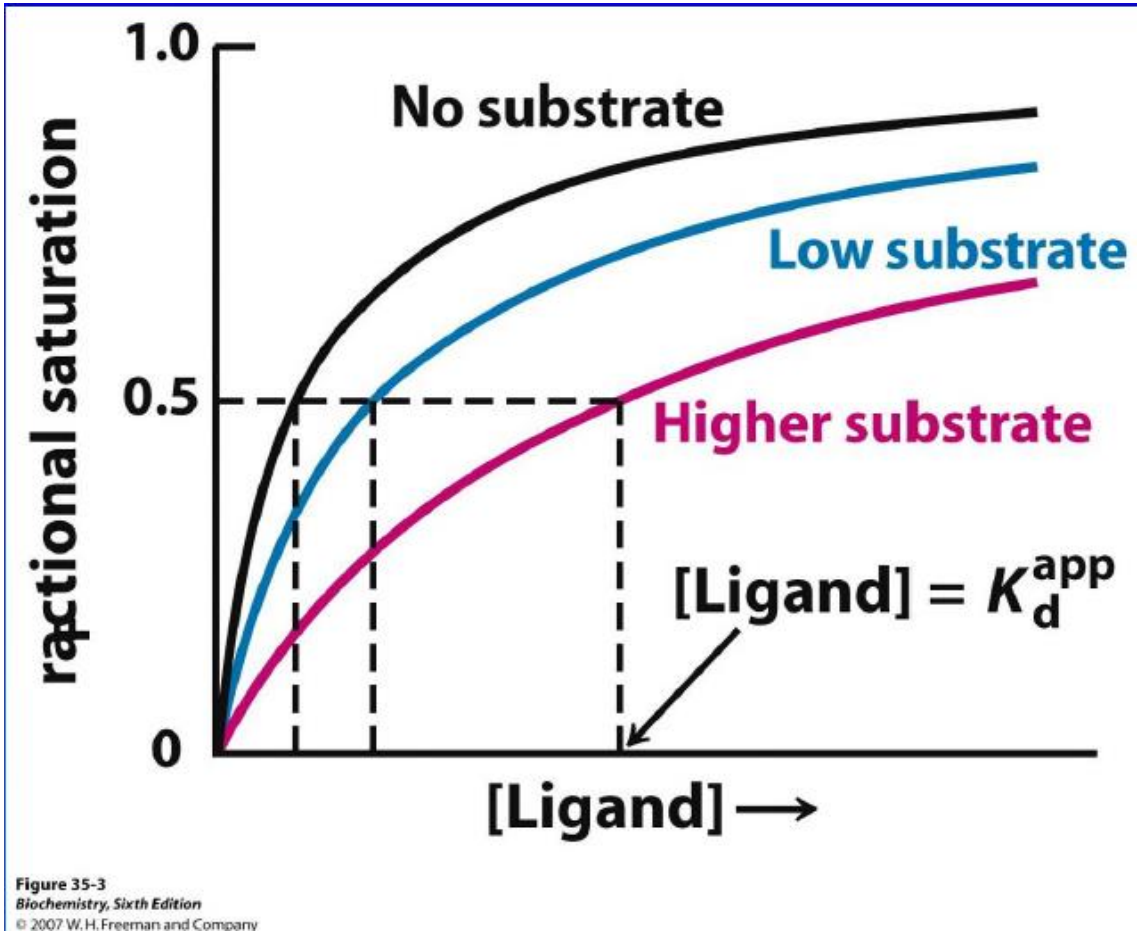


Figure 35-3
Biochemistry, Sixth Edition

Kdapp = Kd(1+[S]/Km)

Apparent K_d. In the presence of an endogenous substrate, it may require more drug to have an effect

Dose response relationships

» Graduate dose-response relations

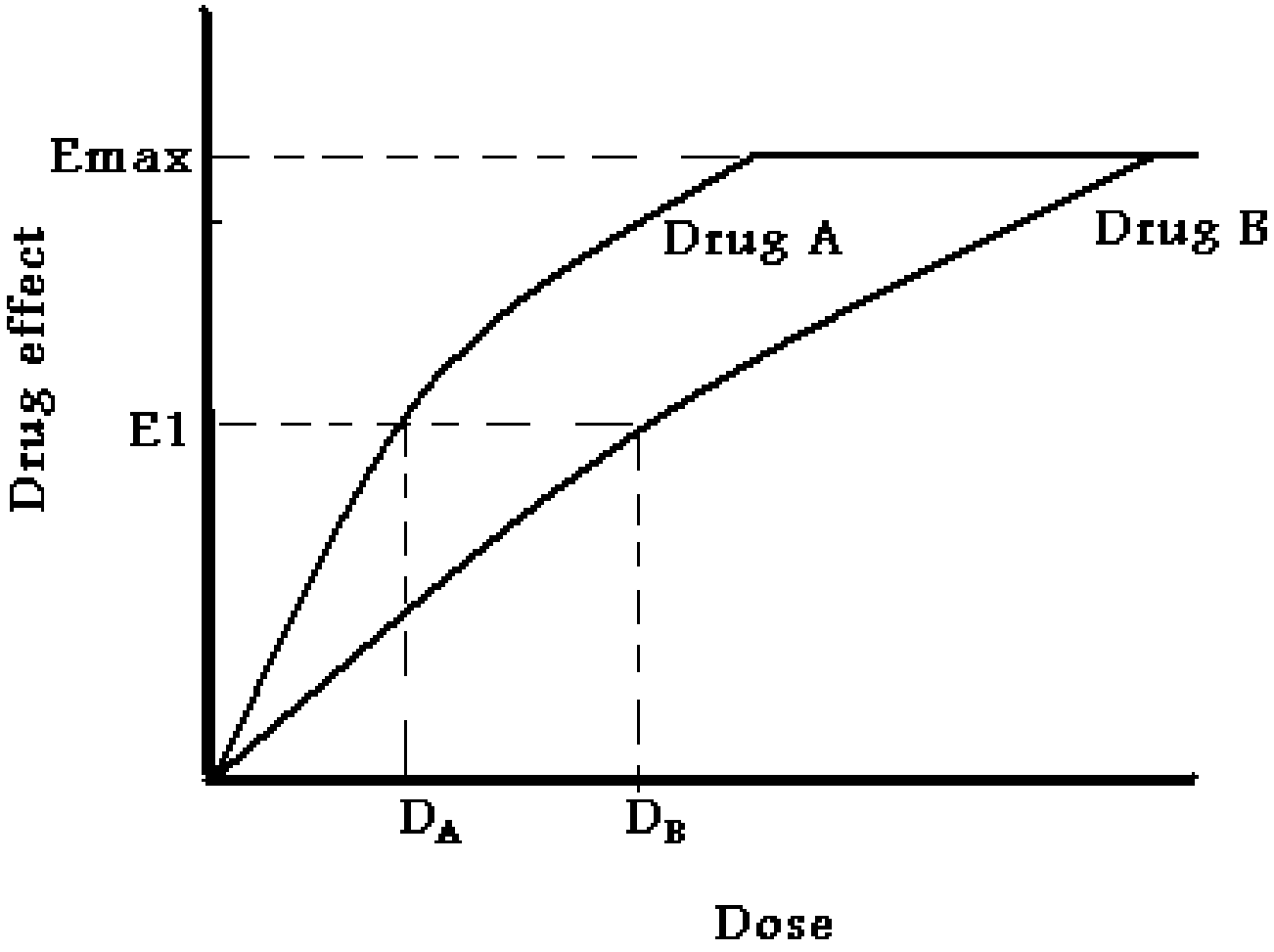
As the dose administrated to single subject or isolated tissue is increased , the pharmacologic effect will also increase.

At a certain dose, the effect will reach a maximum level, which is called the ceiling effect or Emax.

Potency

- Potency refers to the affinity of a drug for its receptor or the concentration of drug required to produce a given effect. Low KD, high potency
- • Potency refers to the amount or concentration of drug required to produce a response.
- • On dose-response curves potency is measured on the X-axis.
- • ED50, EC50, and Kd are measures of potency.

Graduate dose-response curve



efficacy

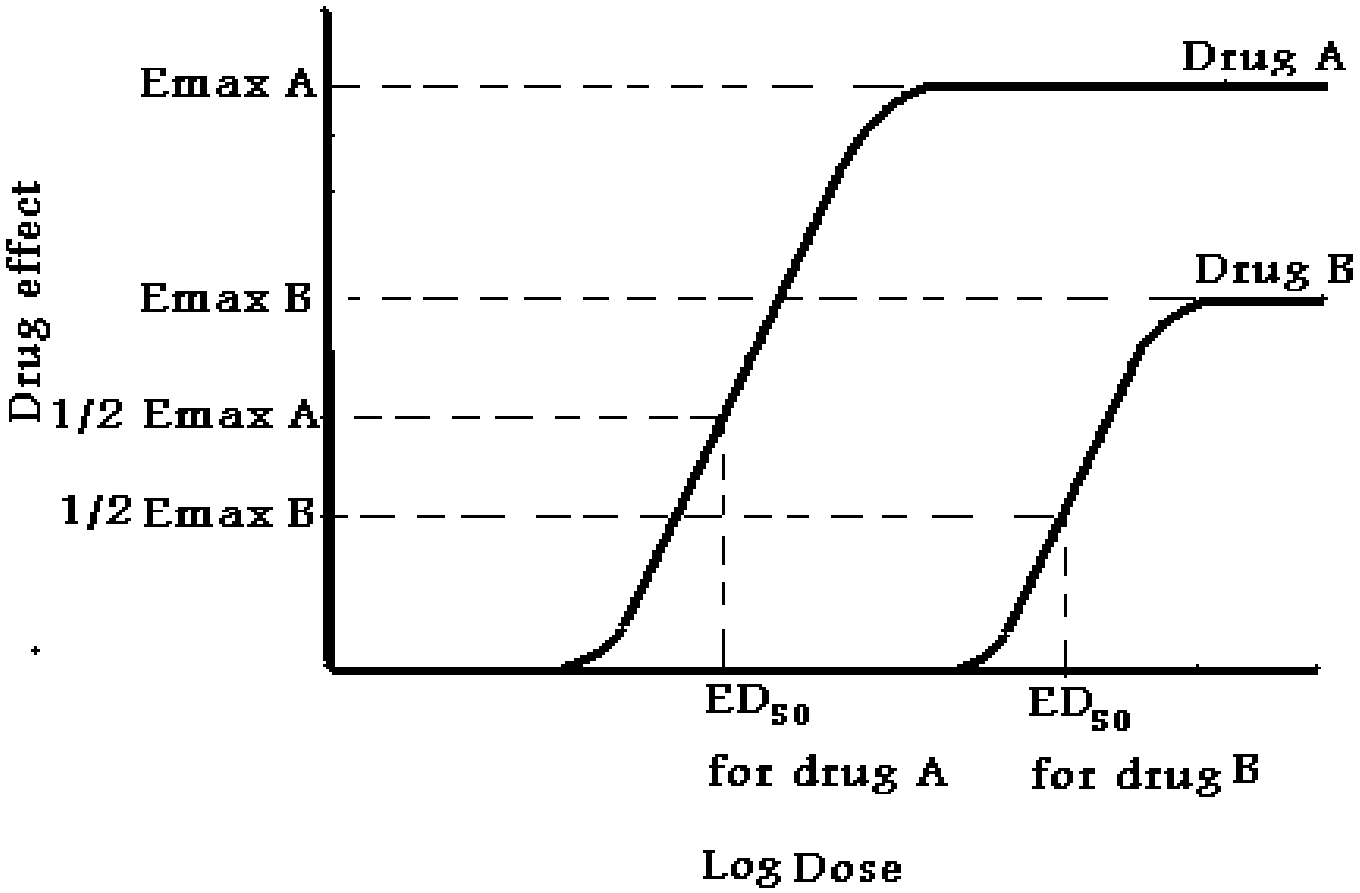
- Efficacy is the maximum effect of a drug, Emax, and does depend on the number of drug-receptor complexes formed, and also on the efficiency of the of coupling of receptor activation to cellular responses.

- Aspirin and morphine produce the same pharmacologic effect (analgesia) but have very different levels of efficacy.

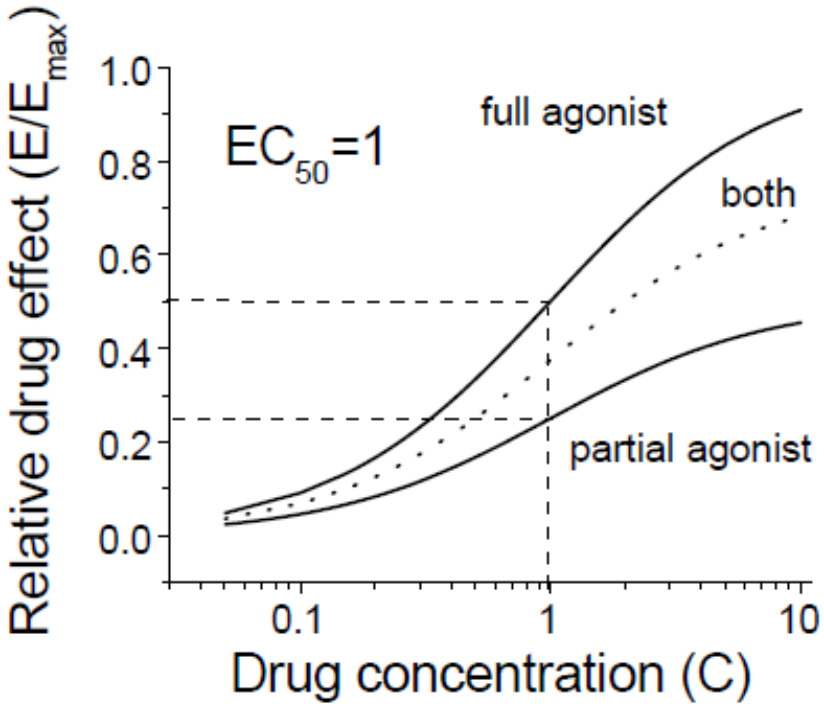
efficacy

- If drug can stimulate a receptor to produce a biological response it is said to have efficacy or intrinsic activity.
- Efficacy refers to the capacity of a drug to produce an effect or the overall magnitude of the maximum response, synonymous with intrinsic activity
- If a drug stimulates a full response, it might to said to be a full agonist and to be very efficacious.

Log dose response curve



- The smaller the EC50, the greater the potency.
- Efficacy is indicated by the height of the log dose response


Relative drug effect (E/E$_{max}$)
1.0
0.8
0.6
0.4
0.2
0.0
EC$_{50}$=1
full agonist
both
partial agonist
0.1
1
10
Drug concentration (C)

Antagonism between drugs

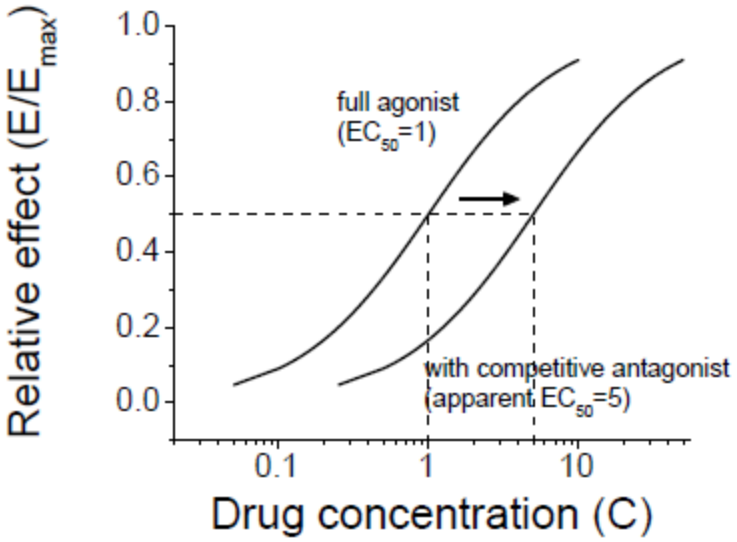
A. Pharmacologic antagonism: occurs when an antagonist prevent an agonist from interacting with its receptors to produce an effect, and it can be either competitive or noncompetitive.

Competitive antagonist compete with agonist in a reversible fashion in the receptors. The log dose-response curve is shifted to the right, indicating that a higher concentration of agonist is necessary to achieve the response.

Noncompetitive antagonist binds irreversibly to the receptors site or to another side that inhibit the response to the agonist. And no matter how much agonist is given, the action of the antagonist can not overcome. The shift in the log response curve in this case is a nonparallel shift.

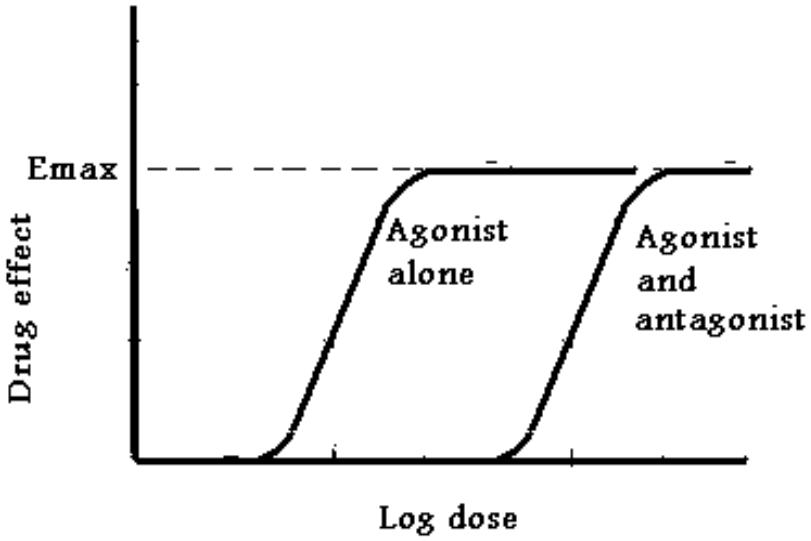
Competitive antagonists

- Bind agonist site
- Do not shift equilibrium towards active or inactive conformation
- “Neutral” antagonists

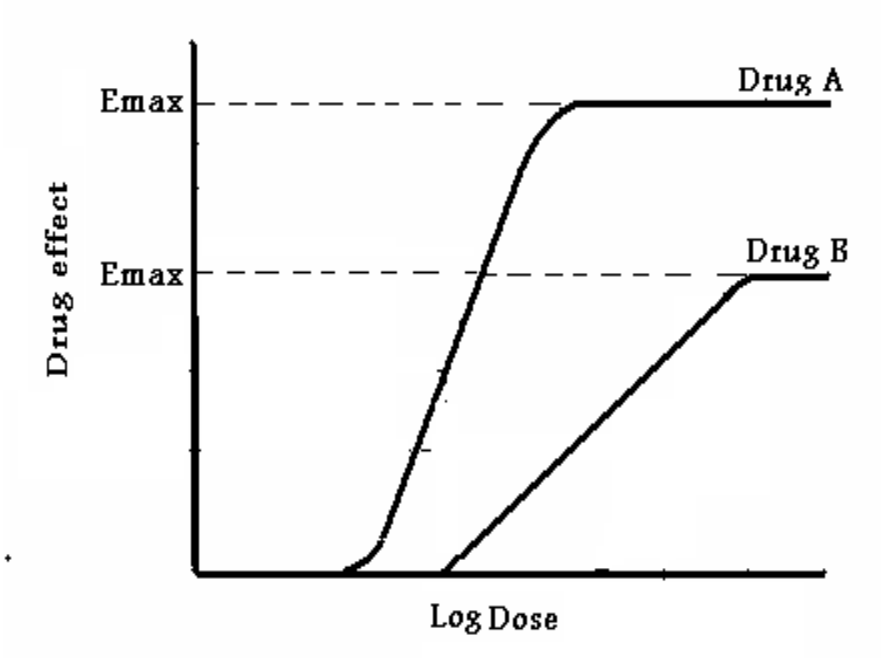


Shift in the log-dose response

Competitive antagonist

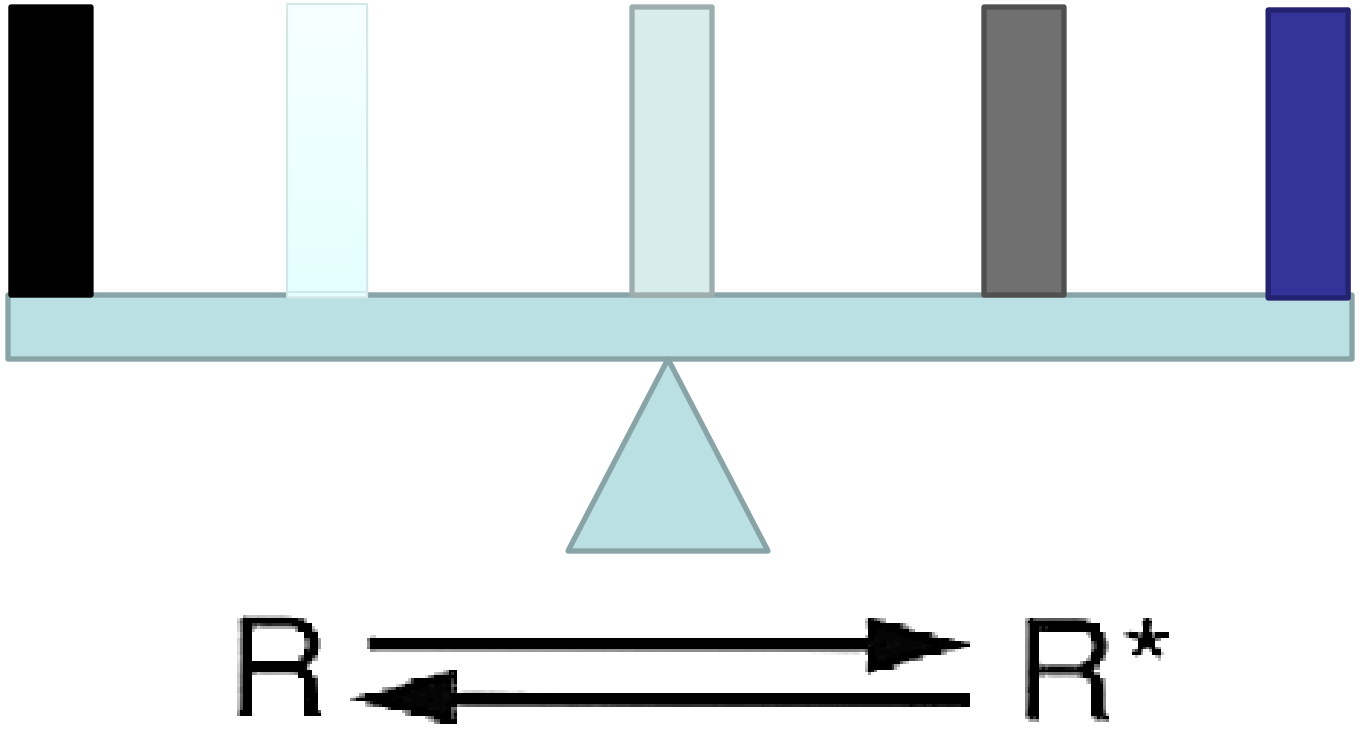


Noncompetitive antagonist



Inverse agonists

- Inverse agonists shift equilibrium towards the inactive conformation
- Effect obvious *if* much constitutive activity



- Full agonist
- Partial agonist
- Antagonist

- Partial inverse agonist
- Full inverse agonist

Antagonism between drugs

B. Physiologic Antagonist: here the drugs act independently on two different receptors, and exemplified by one drug acting on the sympathetic nervous system causing the heart rate to increase and causing vasoconstruction; while another drug acting on the parasympathetic nervous system decrease the heart rate and causes vasodilation.

C. Chemical antagonist (Antagonism by neutralization):

Occurs when two drugs combine with one another to form an inactive compound, and the best example being the drugs containing sulfhydryl (SH) groups, when combine with mercury or arsenic.

Enhancement of drug effects

A. Additive drug effect occurs if two drugs with the same effect , when given together produce an effect that is equal in magnitude to the sum of the effect.

$E_{AB} = E_A + E_B$ $\qquad$ $1 + 1 = 2$

B. Synyrgic drug effect occurs if two drugs with the same effect, when given together, produce an effect that is greater in magnitude than the sum of effects when the drugs are given individually.

$E_{AB} > E_A + E_B$ $\qquad$ $1 + 1 > 2$

C. Potentiation drug effect occurs if a drug lacking an effect of its own increase the effect of a second active drug.

$E_{AB} > E_A + E_B$ $\qquad$ $0 + 1 > 2$

Therapeutic index and margin of safety

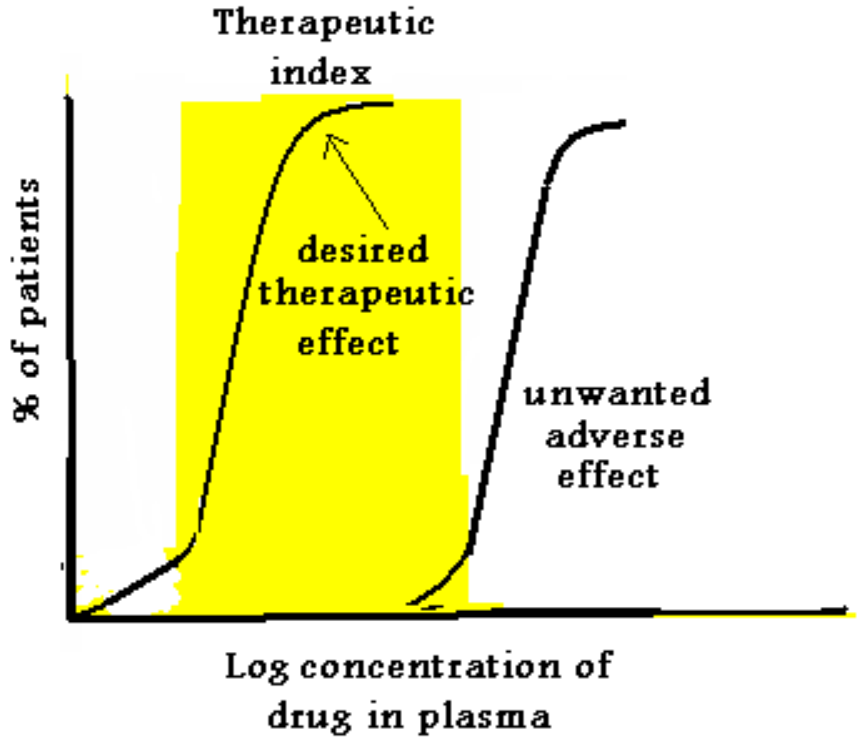
Therapeutic index of a drug is a ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population individuals:

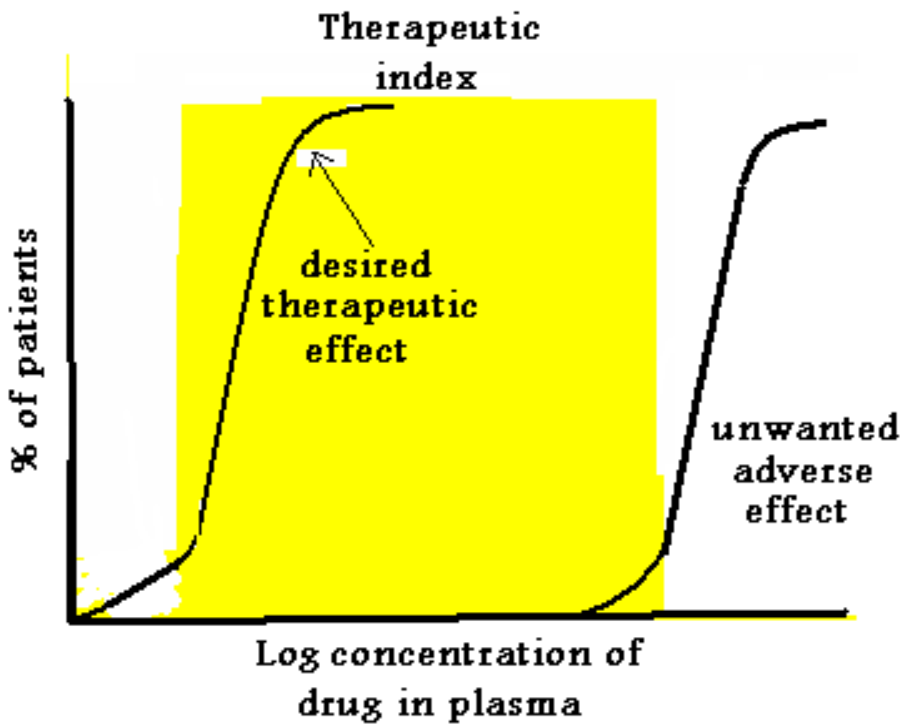
$$TI = \frac{TD_{50}}{ED_{50}}$$

Where TD_{50} is the minimum dose that is lethal or toxic for 50% of the population, and ED_{50} is the minimum dose that is effective for 50% of the population.

Ideally the TD_{50} Should be a much higher dose than the ED_{50} so that the therapeutic index would be large.

Therapeutic index and margin of safety





Properties of an Ideal Drug

- Effective
- Safety
- Selective
- Reversible Action
- Predictable
- Freedom from drug interactions
- Low cost
- Chemically stable