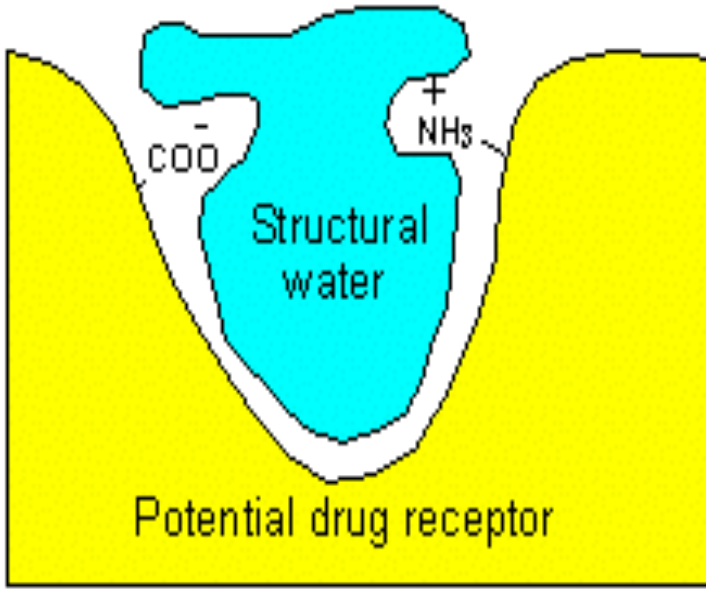
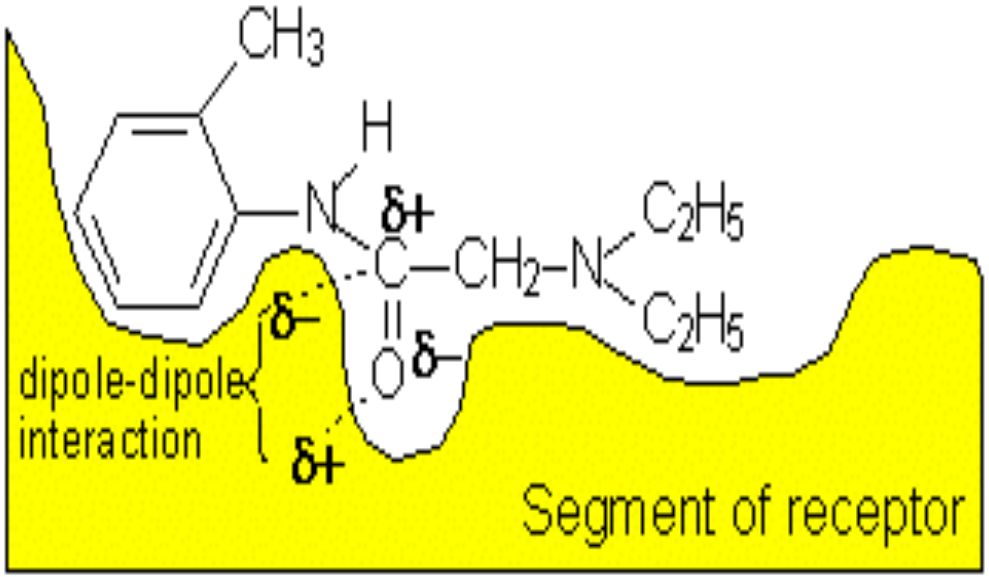
Pharmacodynamics

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: Only a subset of receptors will be targets
- Selectivity: Since receptors are coupled to specific signaling pathways
- Sensitivity: Receptor binding events are amplified intracellularly

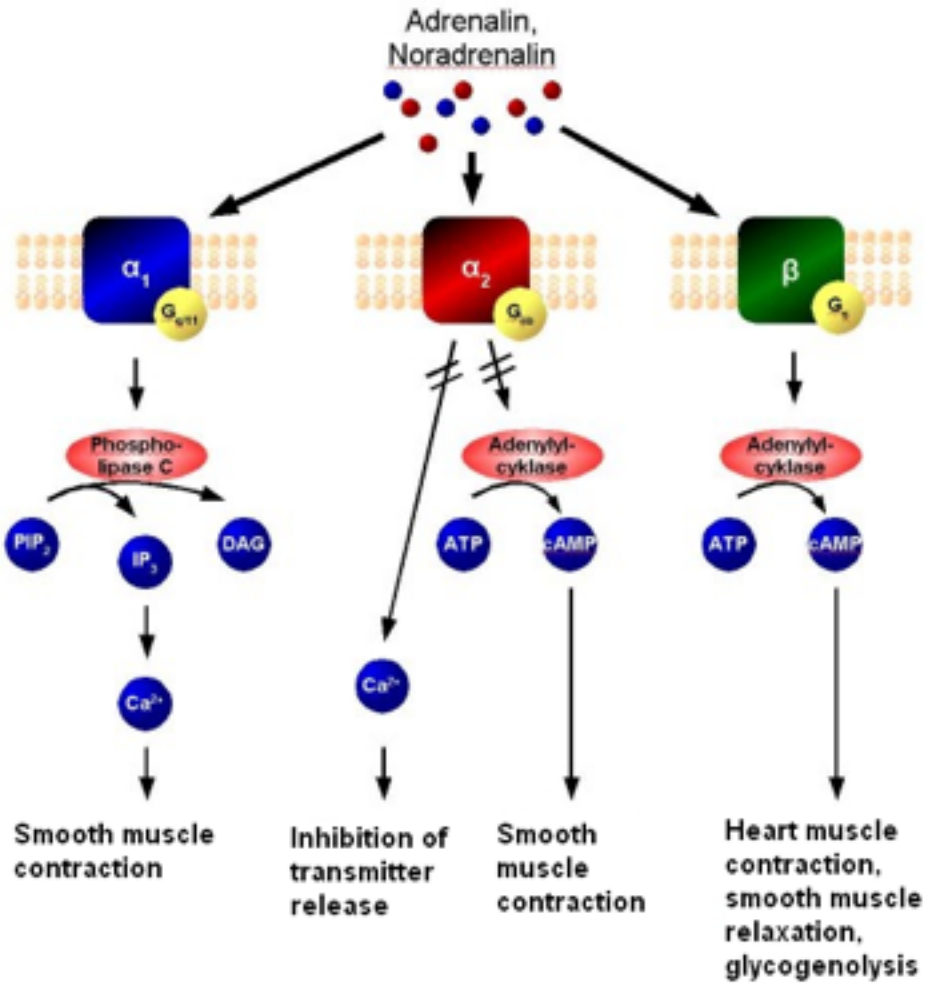
Specificity: Lock and key

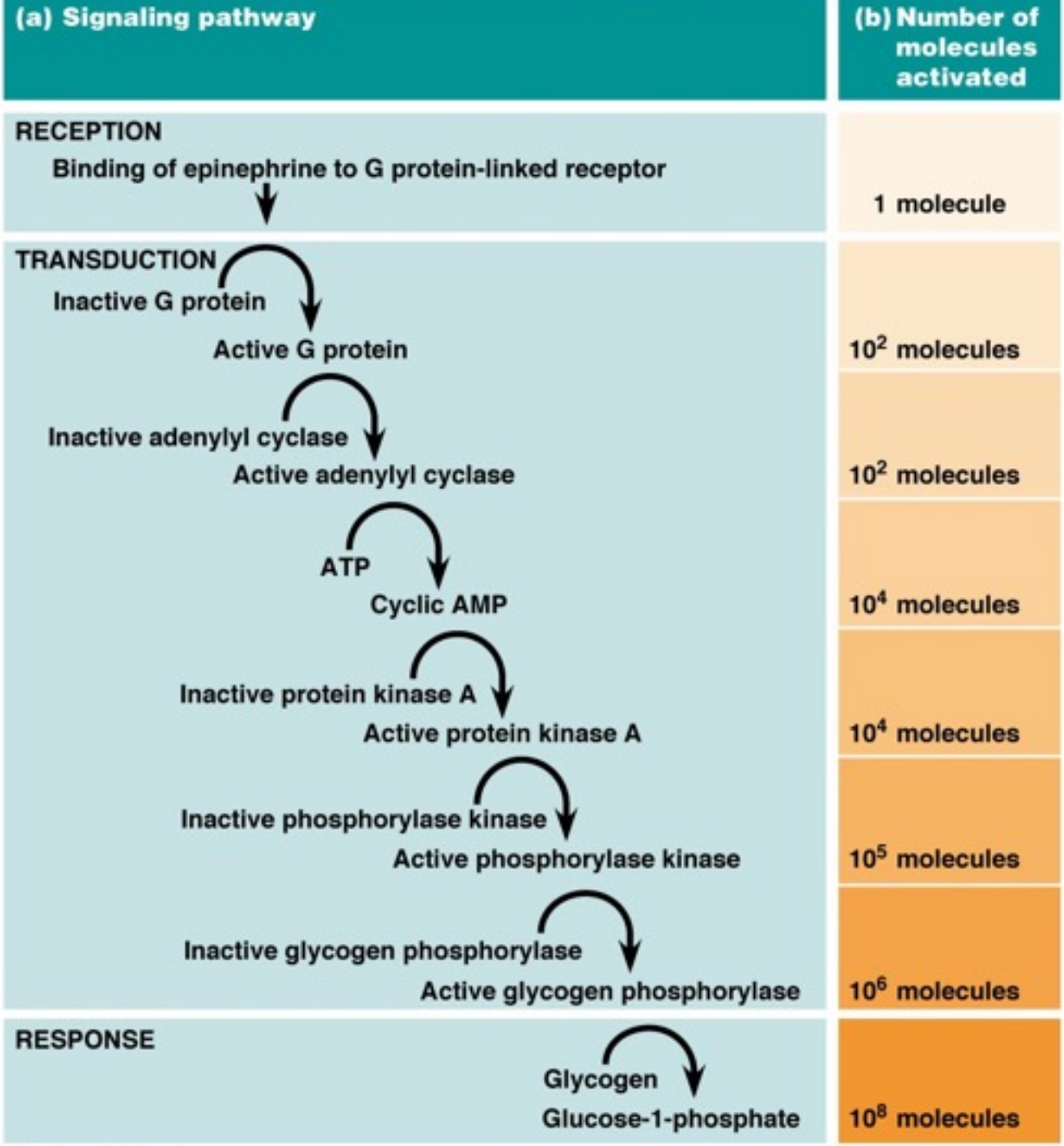




The precise fit required of the ligand ……”**KEY**
The activation of the receptors…….The opening of the “**LOCK**”

This interaction shows high degree of **specificity**


Adrenalin,
Noradrenalin
α1
α2
β
Phospho-
lipase C
PIP2
IP3
DAG
Ca2+
Adenylyl-
cyklase
ATP
cAMP
Adenylyl-
cyklase
ATP
cAMP
Ca2+
Smooth muscle
contraction
Inhibition of
transmitter
release
Smooth
muscle
contraction
Heart muscle
contraction,
smooth muscle
relaxation,
glycogenolysis



Signal Amplification

- Receptor binding are amplification terms of duration and intensity
- Example: G-protein coupled receptors
- Phenomena that account for the amplification:

1. The receptor drug-complex can interact with many G proteins thereby multiplying the organ signal many folds.
2. The activated G-protein persists for longer duration than the original receptor-drug complex

Drug Receptors & Pharmacodynamics

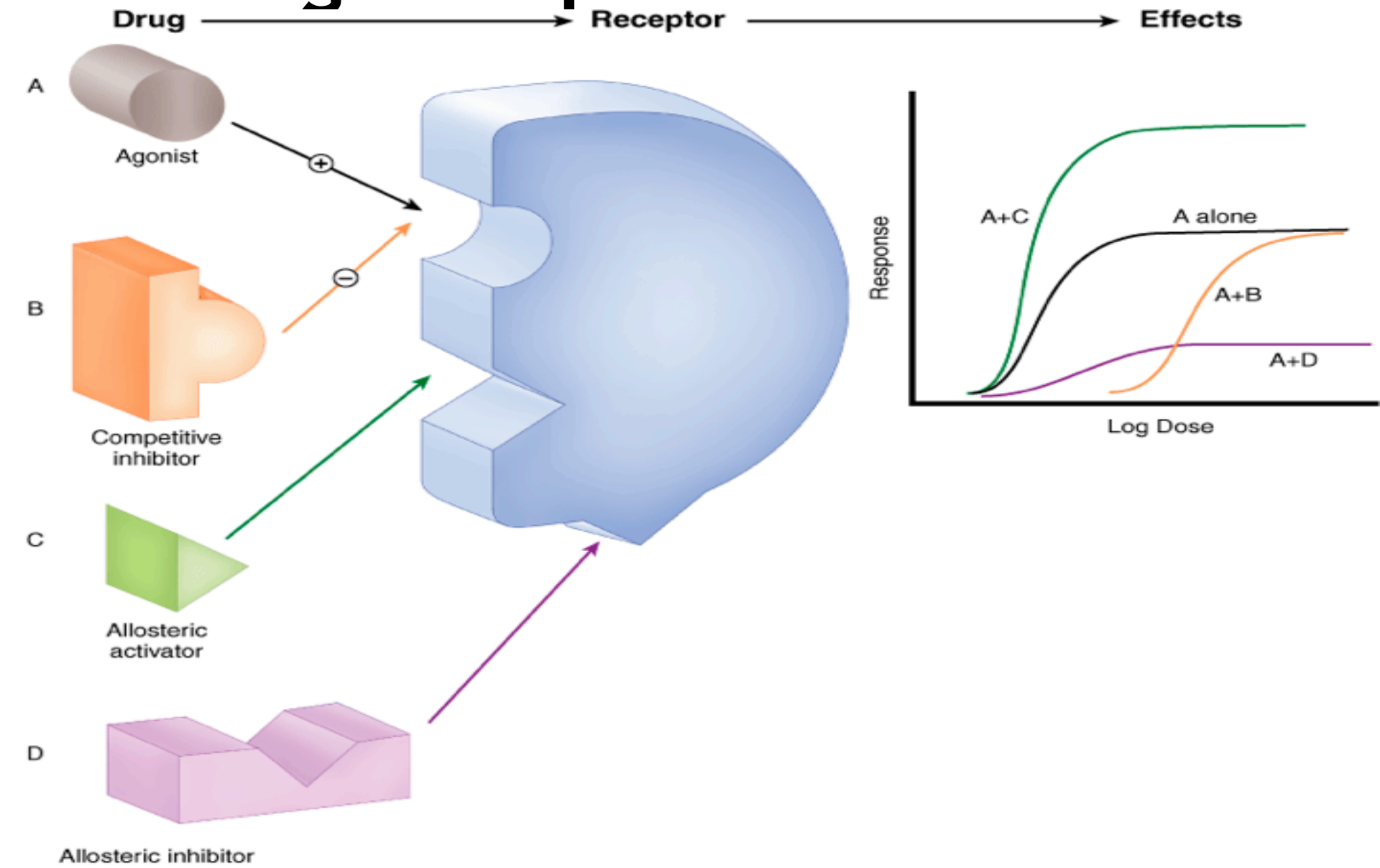
Receptors largely determine the quantitative relations between dose (or concentration) of the drug and pharmacologic effects.

- **The receptor's affinity for binding a drug determines the concentration of drug required to form a significant number of drug-receptor complexes,**
- **The total number of receptors limits the maximal effect a drug can produce.**

Pharmacodynamics

- The molecular mechanisms of action of many drugs have now been identified, and numerous receptors have been isolated, structurally characterized, and cloned.
- In fact, the use of receptor identification methods has led to the discovery of many Orphan Receptors for which no ligand has been discovered and whose function can only be hypothesized.

Drug Receptor Interactions



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Drug Receptor Interactions

- Agonists bind to the agonist binding site and produce an action.
- Competitive inhibitors bind to the same site, to prevent the binding of the agonist, and produce no action.
- Allosteric activators act at separate sites to increase the efficacy of the agonist or its binding affinity.
- Allosteric Inhibitors act at separate sites to decrease the efficacy of the agonist or its binding affinity

Drug Receptors & Pharmacodynamics

Receptor interactions determine the quantitative relations between concentration of drug and pharmacologic effects.

- The receptor's affinity for binding a drug determines the concentration of the drug required to form a significant number of drug-receptor complexes,
- The total number of receptors is usually much smaller than the number of drug molecules.
- This will limit the maximal effect a drug may produce.

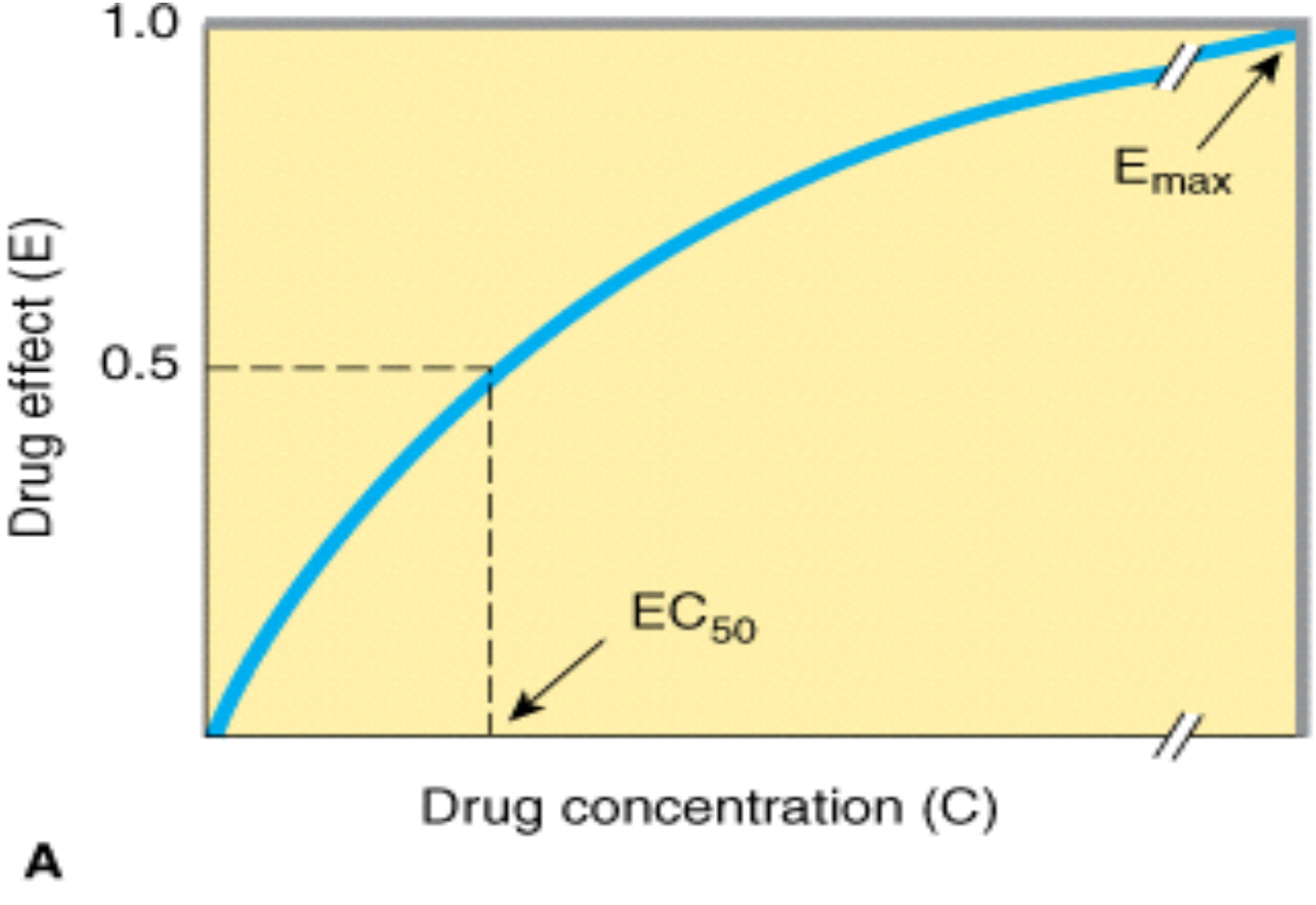
Dose response relationships

- Graded 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.

Relations between drug concentration and drug effect



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As doses increase…….the response increment diminishes

The relation between drug concentration and effect is described by a hyperbolic curve

$$E = \frac{E_{max} \times C}{C + EC_{50}}$$

E = the effect observed at concentration C
E max =the maximal response that can be produced by the drug
EC 50 = the concentration of drug that produces 50% of maximal effect.

mass action law:

which describes association between two molecules of a given **affinity.**

This resemblance suggests that drug agonists act by binding to ("occupying") a distinct class of biologic molecules with a characteristic affinity for the drug receptor.

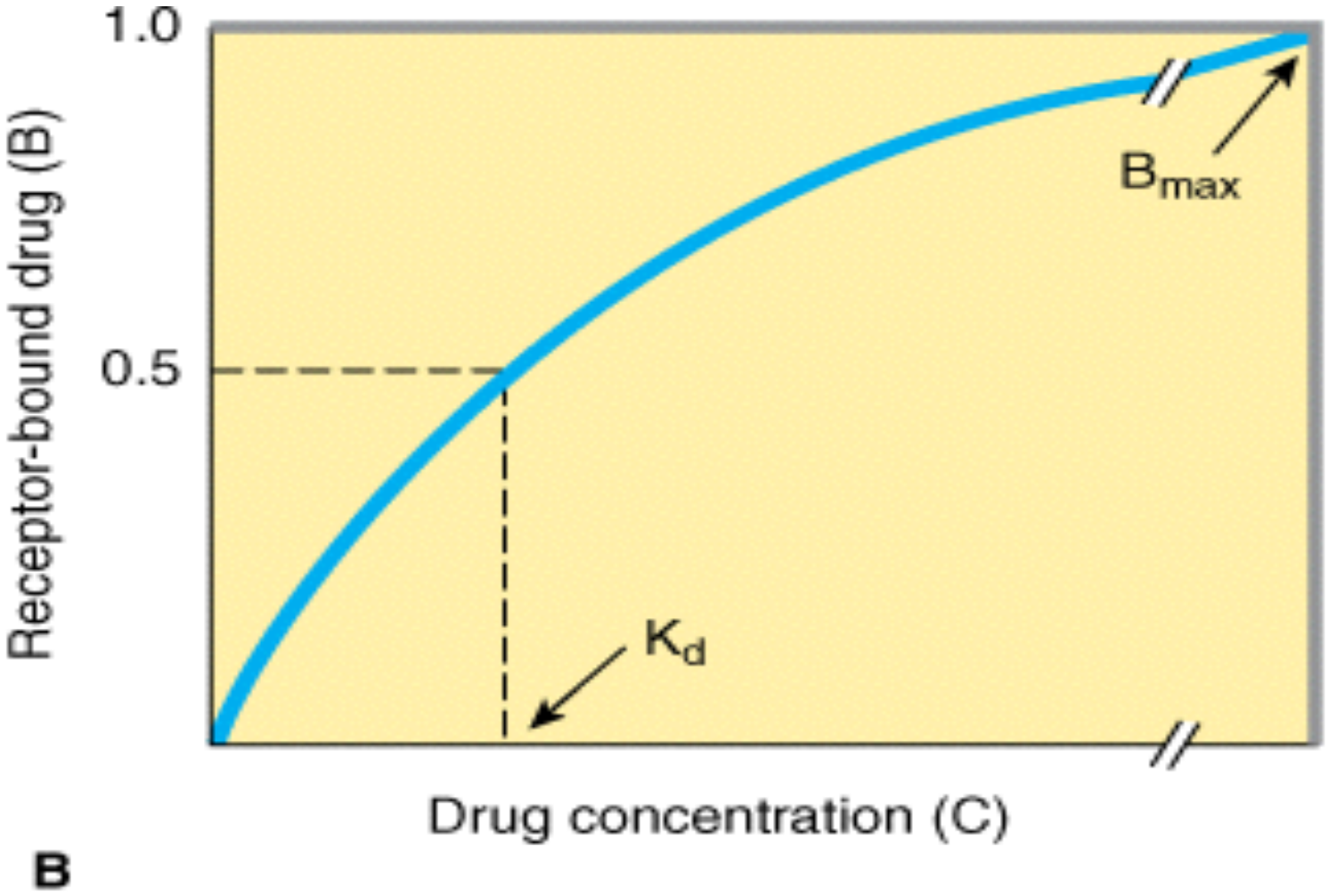
$$B = \frac{B_{max} \times C}{C + K_d}$$

In these systems, drug bound to receptors (B) relates to the concentration of free (unbound) drug (C)

B max = the total concentration of receptor sites

K_d = the equilibrium dissociation constant.

Relations between drug concentration and receptor-bound drug



B

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

K_d (the equilibrium dissociation constant)

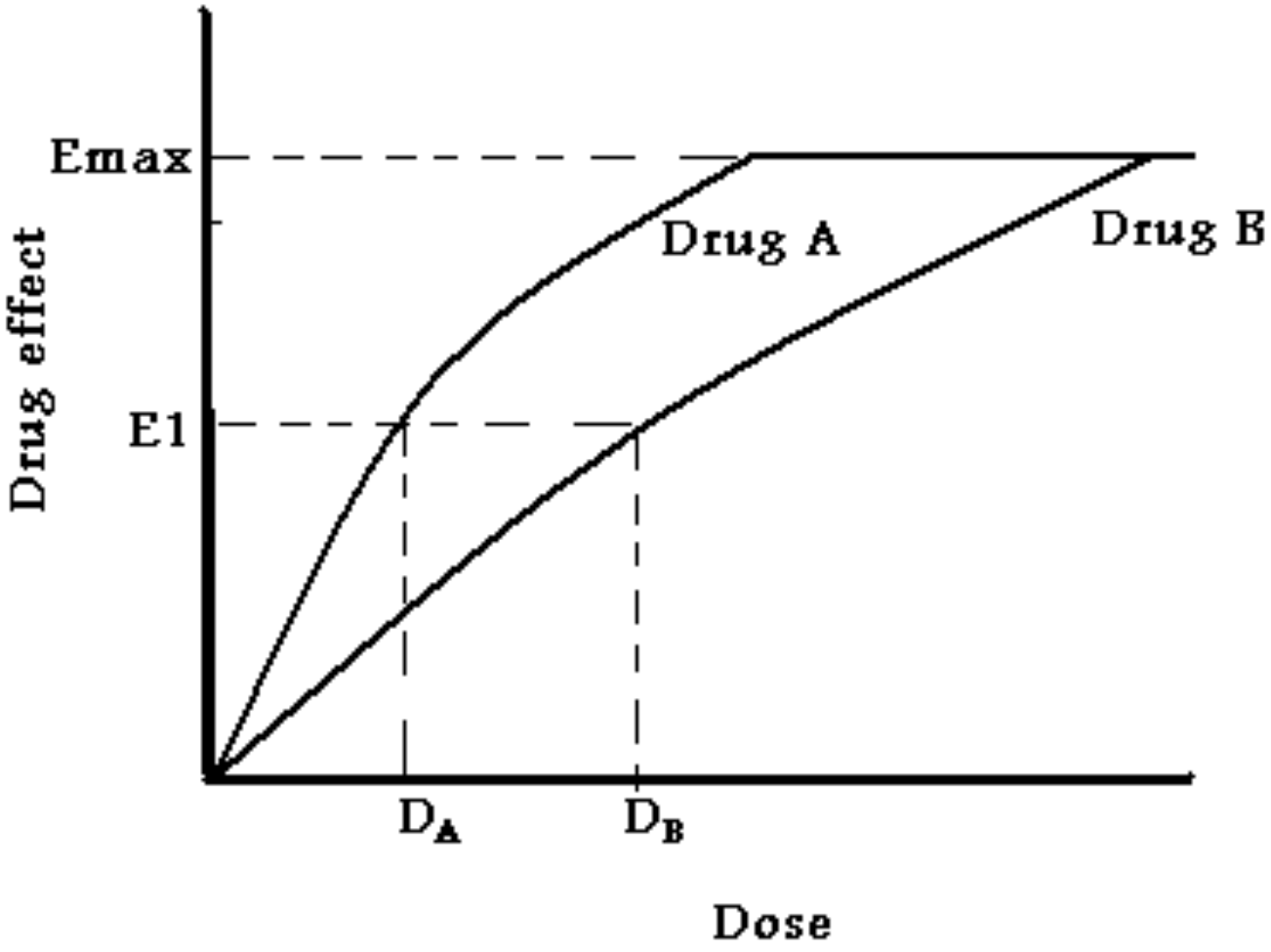
represents the concetration of free drug at which half-maximal binding is observed.
This constant characterizes the receptor's affinity for binding the drug in a reciprocal fashion:
If the K_d is low, binding affinity is high

If K_d is High , binding affinity is low versa.
The EC 50 and K d may be identical,
But not necessarily .

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.
- 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.

Receptor-effector Coupling

When a receptor is occupied by an agonist ———— A conformational change occurs.

The transduction process that links drug occupancy of receptors and pharmacologic response is often termed **coupling.**

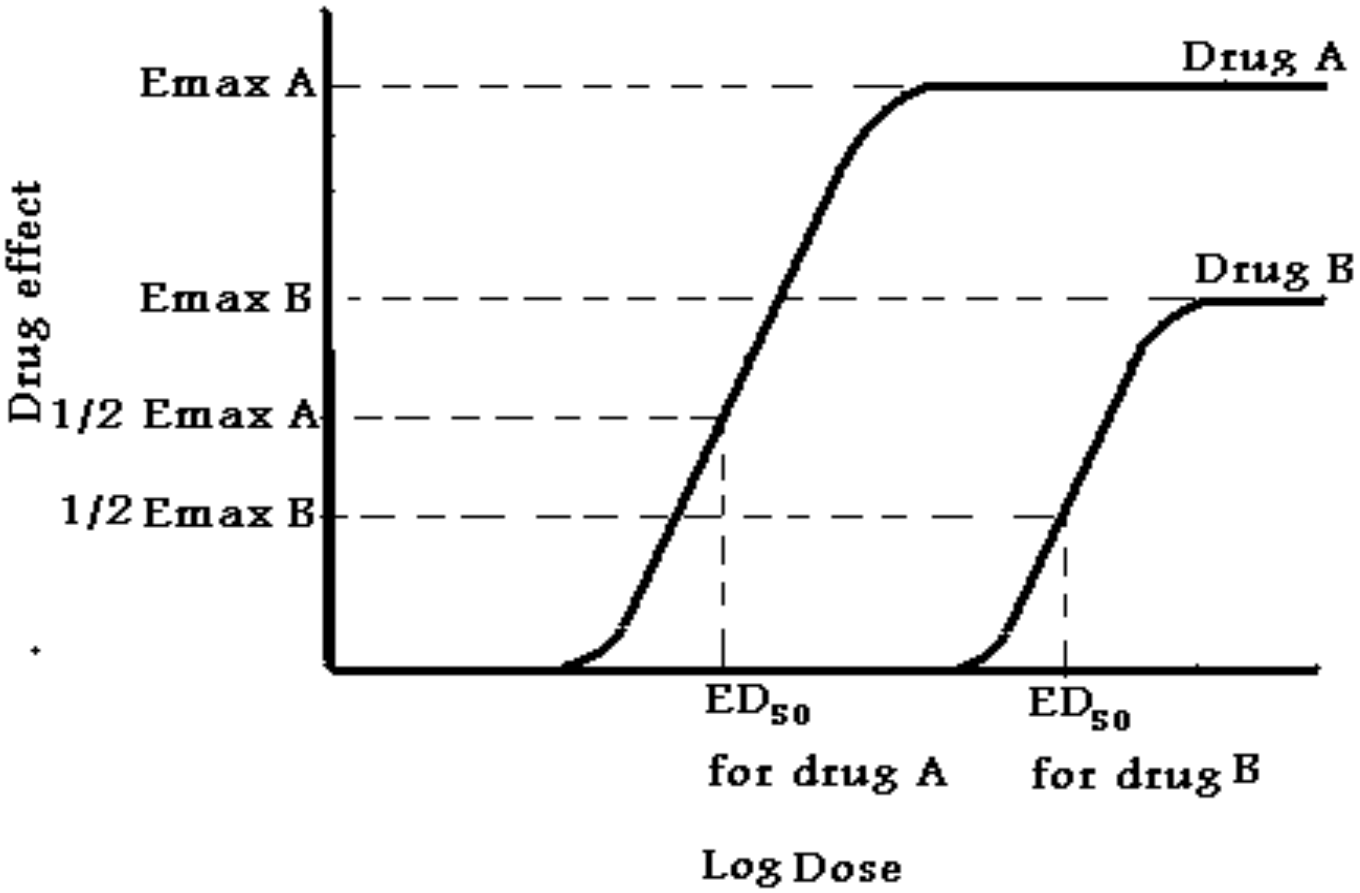
Receptor-effector Coupling

The relative efficiency of occupancy-response coupling is partially determined by the initial conformational change in the receptor.

Coupling efficiency is also determined by the biochemical events that transduce receptor occupancy into cellular response.

Full agonists can be considered more efficiently coupled to receptor occupancy than can the effects of partial agonists

Log dose response curve



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

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

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

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

Hill-Langmuir equation

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

Spare receptors

Only a fraction of total receptors for a specific ligand may need to be occupied to elicit a maximum response.

Examples:

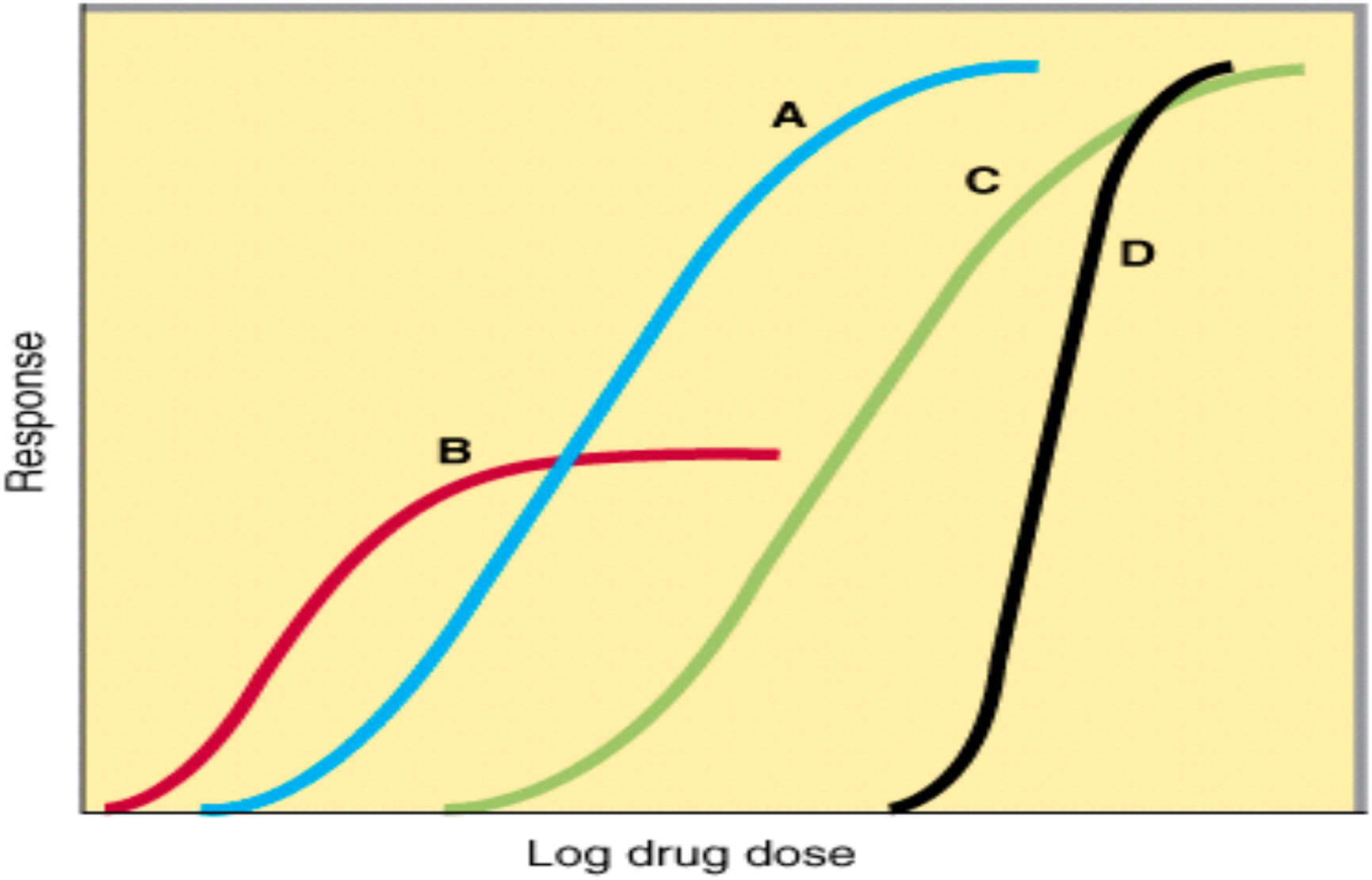
- Insulin receptors are estimated to have 99% of the receptors as spare receptors…….. large functional reserve to ensure adequate control of glucose uptake.

- Only 5-10% of beta adrenoceptors are space……..little functional reserve exist in the failing heart. So most receptors need to be occupied for a maximum effect

Drug Receptors & Pharmacodynamics

Receptors mediate the actions of pharmacologic agonists and antagonists

Graded Dose-Response Curves



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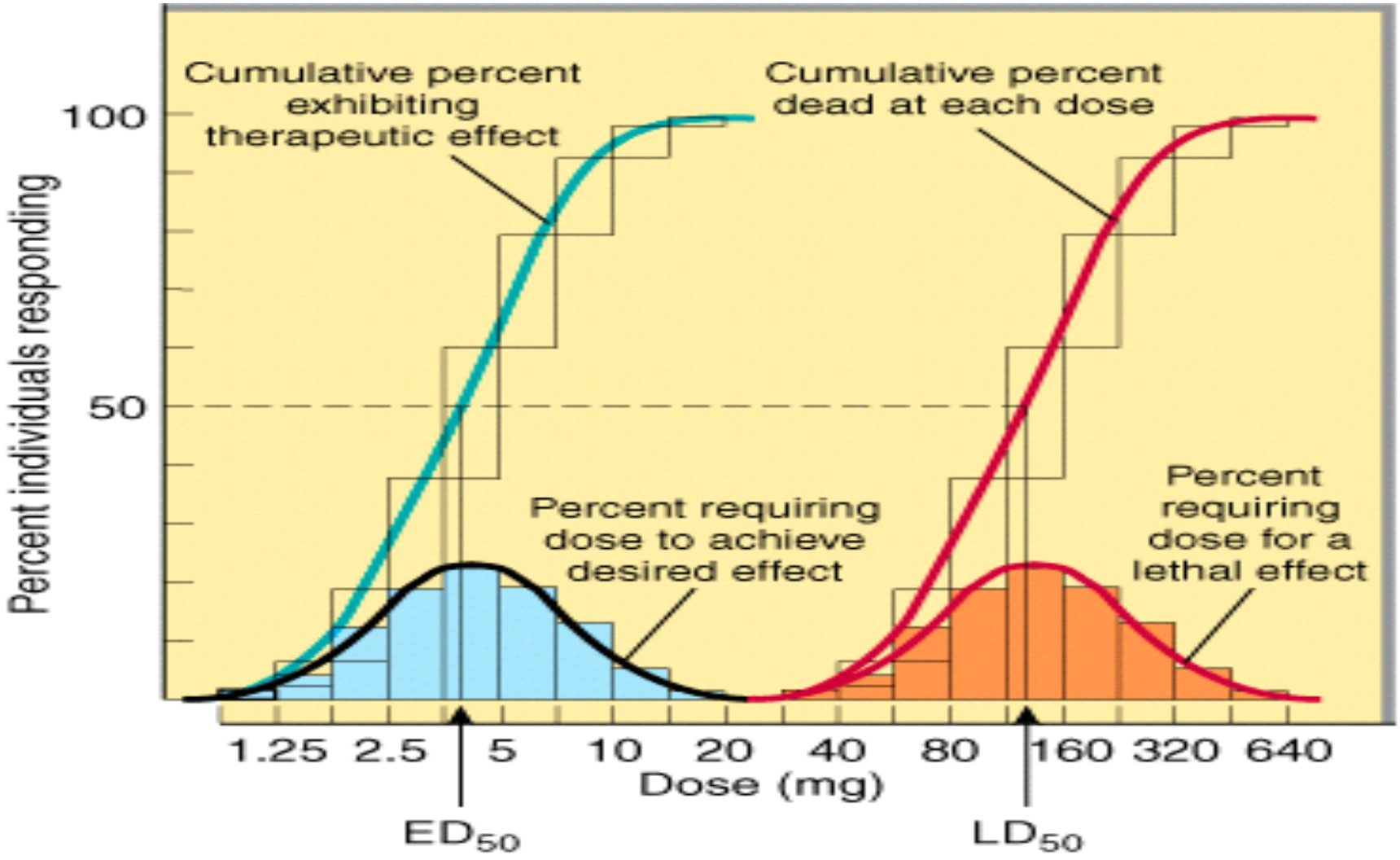
Quantal Dose-Response Curves



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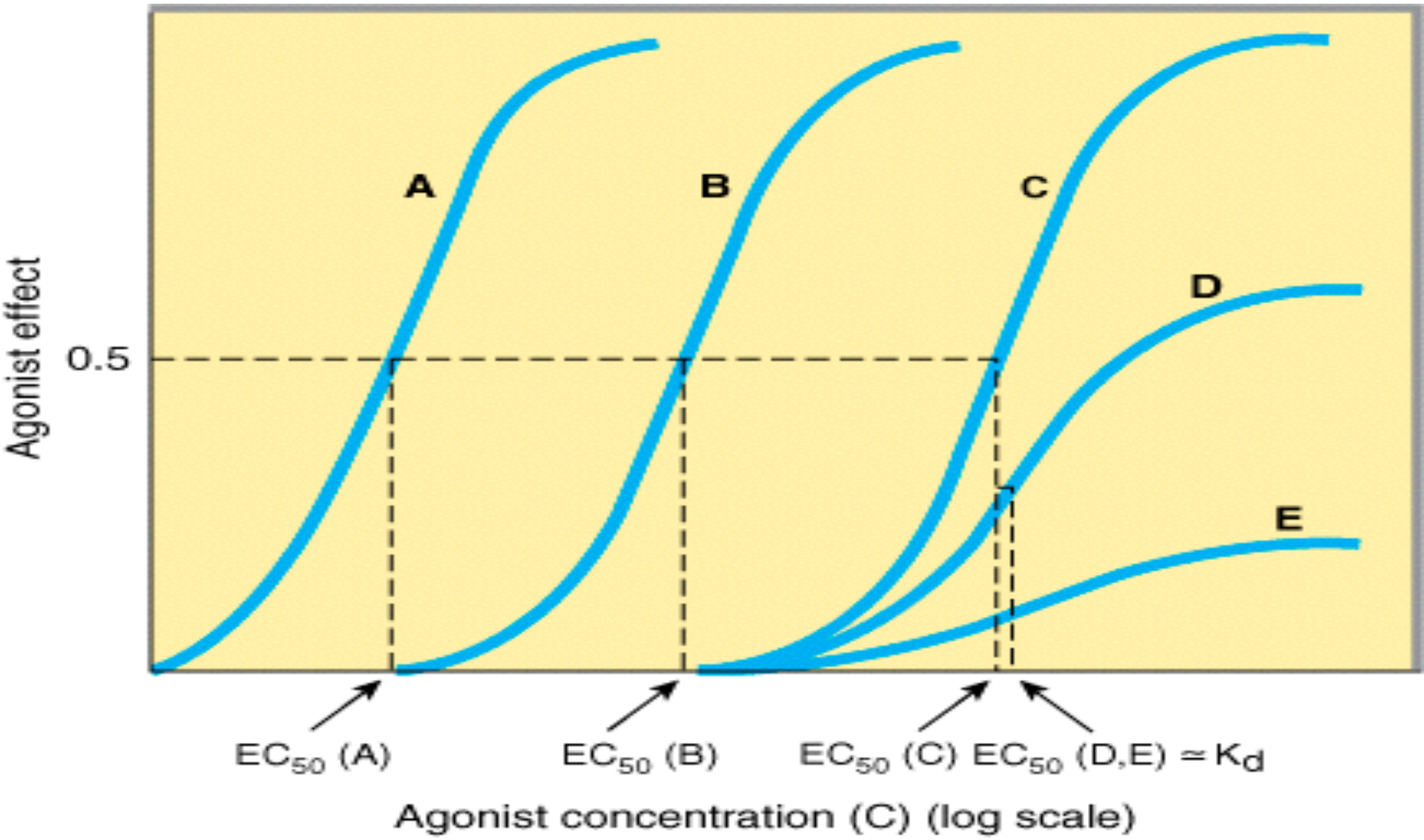
Quantal Dose-Effect Curves

- **Effective Dose (ED50):** is the dose at which 50% of individuals exhibit the specified quantal effect.
- **Toxic Dose (TD50):** is the dose required to produce a particular toxic effect in 50% of animals.
- **Lethal Dose (LD50):** is the dose required to produce death in 50% of the of the animals.

Types of Drug Receptor Interactions

- **Agonist.**
- **Antagonist.**
- **Partial Agonist = Partial Antagonist**

Types of Drug Receptor Interactions



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Possibilities of Drug Combinations

- Antagonistic Effects
- Additive Effects.
- Synergistic Effects.
- No effect.

Drug Antagonism

- **Pharmacologic Antagonism:**
  - Competitive Antagonism
  - Noncompetitive antagonism

- **Physiologic Antagonism:**
  - Epinephrine in Anaphylaxis

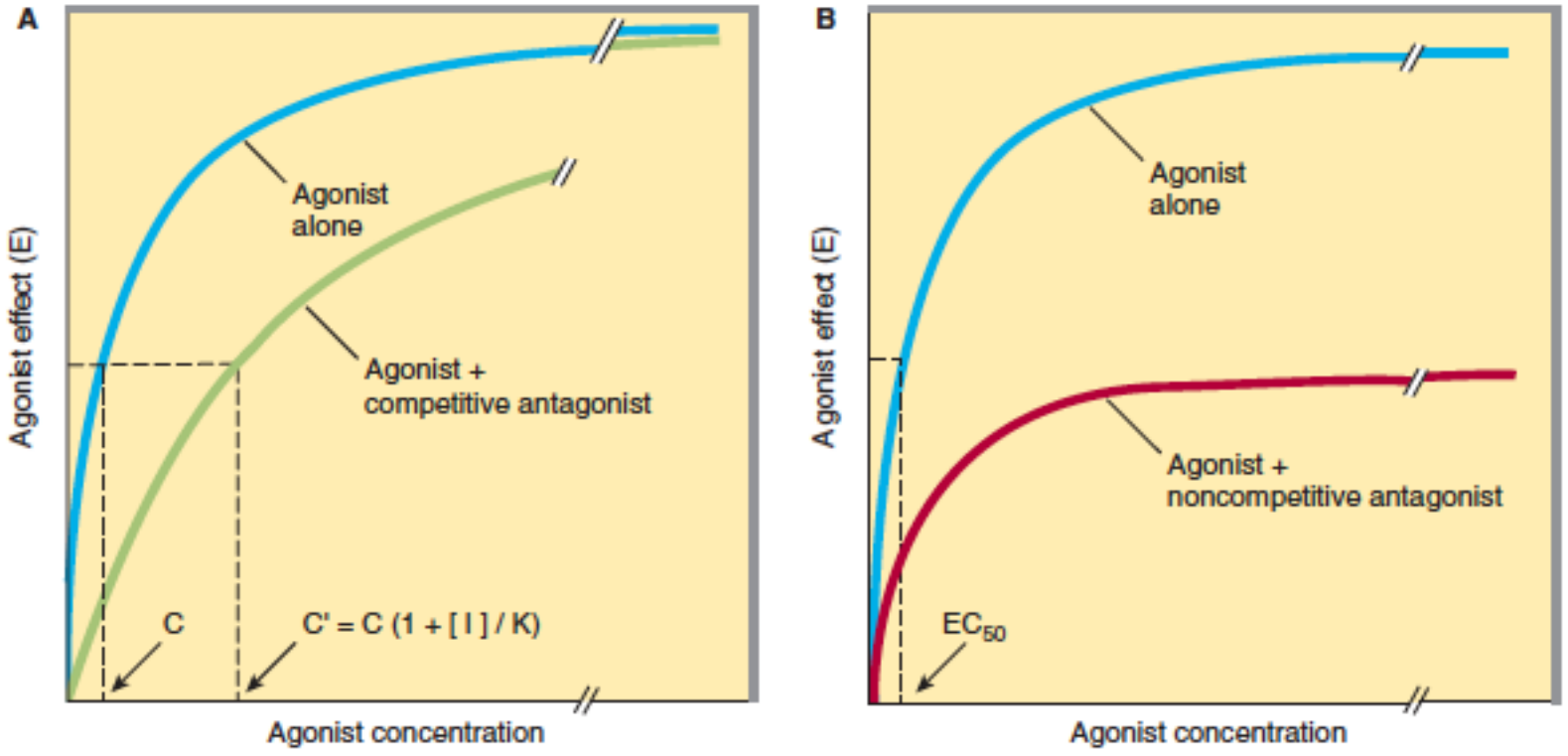
- **Chemical Antagonism:**
  - Antacids in heartburn.

Pharmacologic Antagonism

- **Competitive Antagonism:**
  - **Antagonist binds to the same site of agonist binding and prevents its binding and consequently its effects.**
- **Noncompetitive antagonism:**
  - **Antagonist binds to a site on the receptor separate from the agonist binding site and prevents receptor activation without blocking agonist binding.**

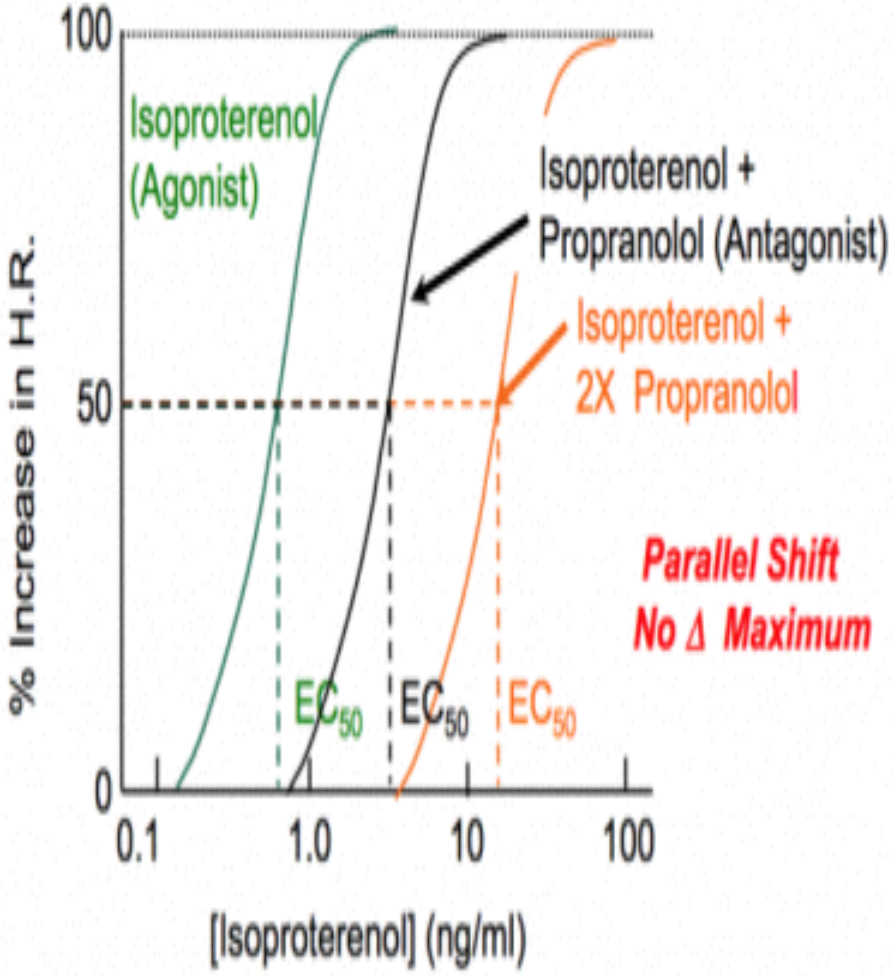
Agonist-Antagonist Relationships

- **Competitive antagonist, higher concentrations of agonist are required to produce a given effect. High agonist concentrations can overcome inhibition by a competitive antagonist.**
- **Irreversible (or noncompetitive) antagonist, reduces the maximal effect the agonist can achieve, although it may not change its EC50.**


A
Agonist effect (E)
Agonist alone
Agonist + competitive antagonist
C
C' = C (1 + [I] / K)
Agonist concentration
B
Agonist effect (E)
Agonist alone
Agonist + noncompetitive antagonist
EC50
Agonist concentration

A

Competitive Inhibition



B

Noncompetitive Inhibition