Pharmacodynamics-2

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Receptor Occupancy Theory

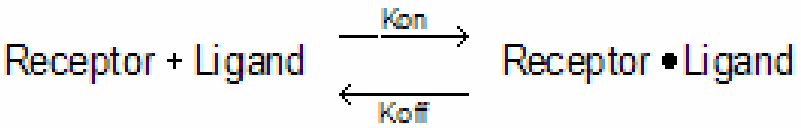
The “Law” of Mass Action

- **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

Law of Mass Action

(a model to explain ligand-receptor binding)

- When a drug combines with a receptor, it does so at a rate which is dependent on the concentration of the drug and of the receptor
- Assumes it's a reversible reaction



- Equilibrium dissociation (Kd) and association/affinity (Ka) constants
  - K_d = Kon/Koff = [D][R]/[DR]
  - K_a = 1/Kd = Koff/Kon = [DR]/[D][R]

Drug-receptor binding

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

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

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

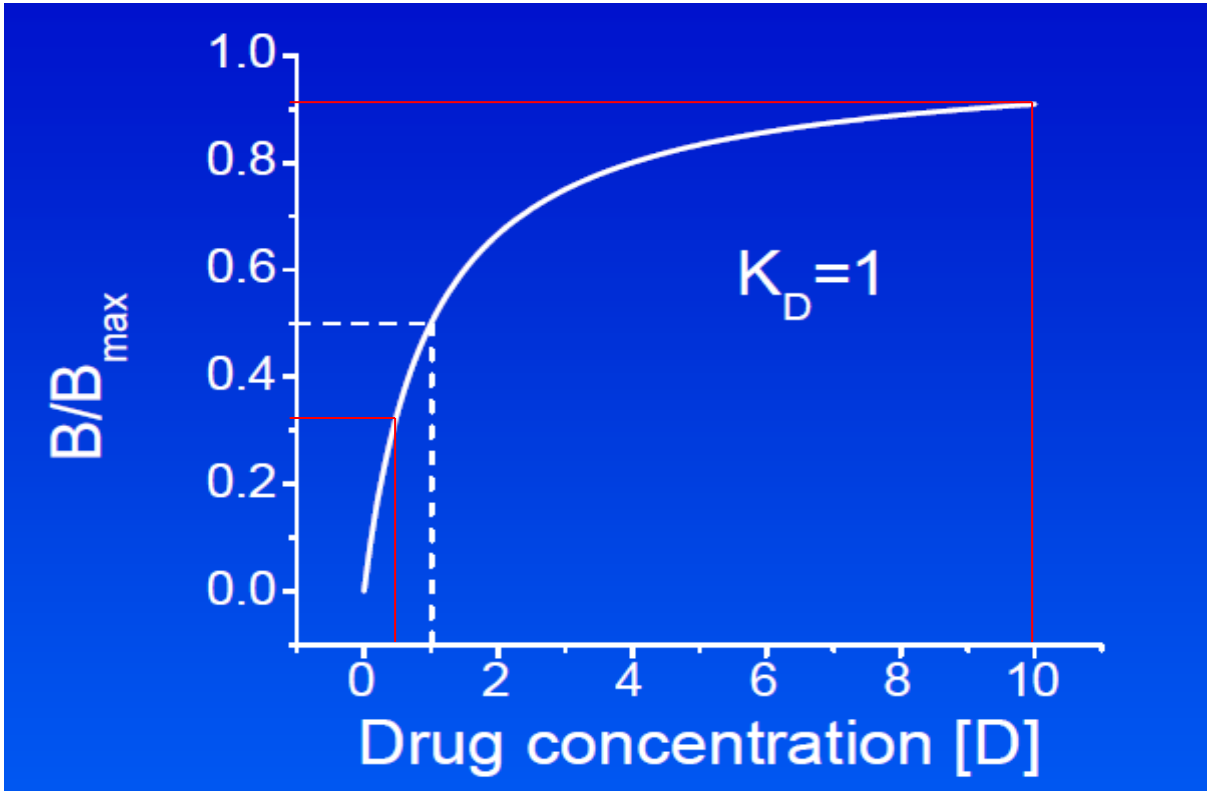
$$\frac{\text{sec}^{-1}}{M^{-1}\,\text{sec}^{-1}} = M$$

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

- **This dissociation constant, Kd, indicates the strength of binding between R and D in terms of how easy it is to separate the complex DR**

Hill-Langmuir equation

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



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

Affinity 1/Kd

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.**

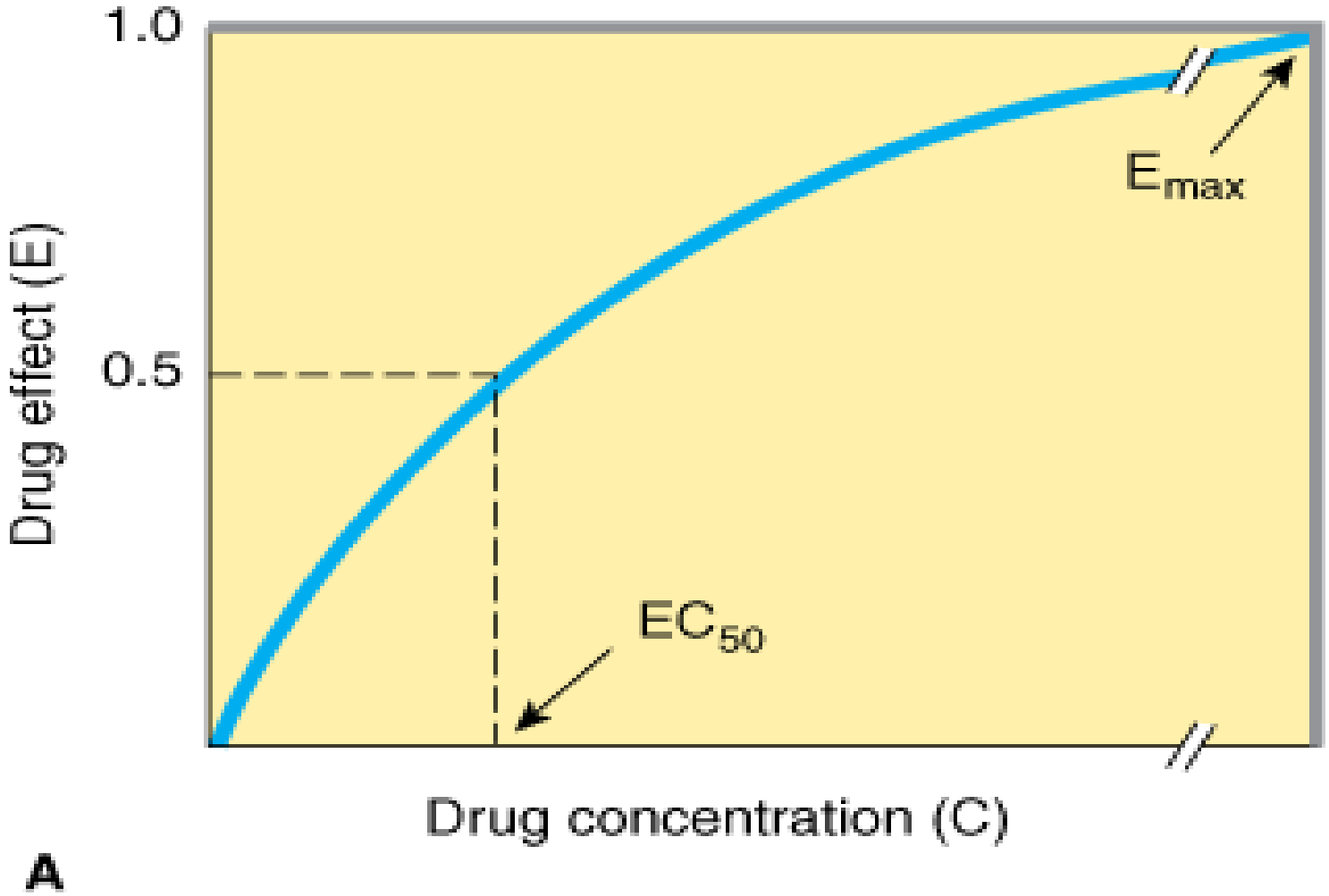
Dose response relationships

» Graduate dose-response relations

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

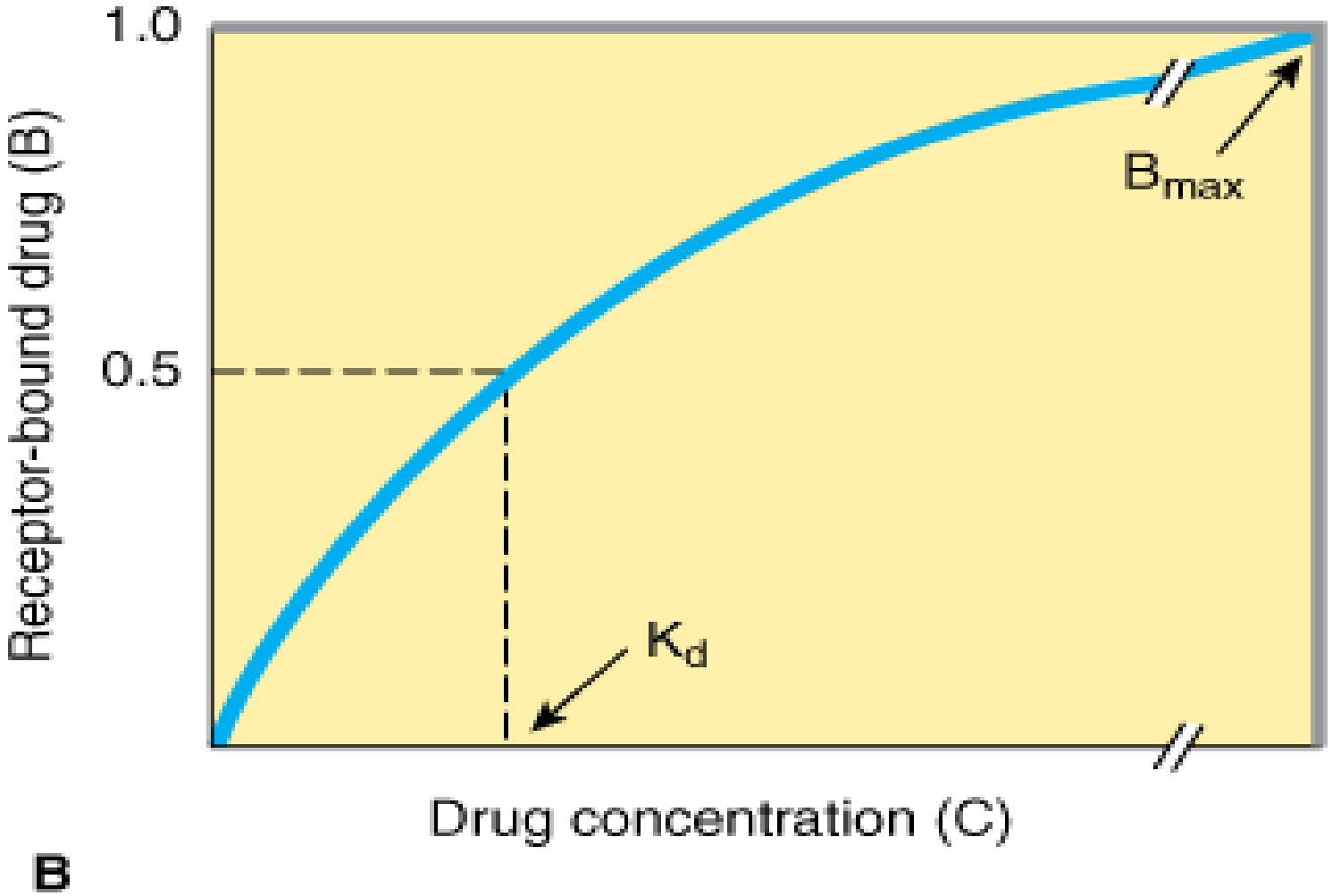
At a certain dose, the effect will reach a maximum level, which is called the ceiling effect or Emax.

Relations between drug concentration and drug effect



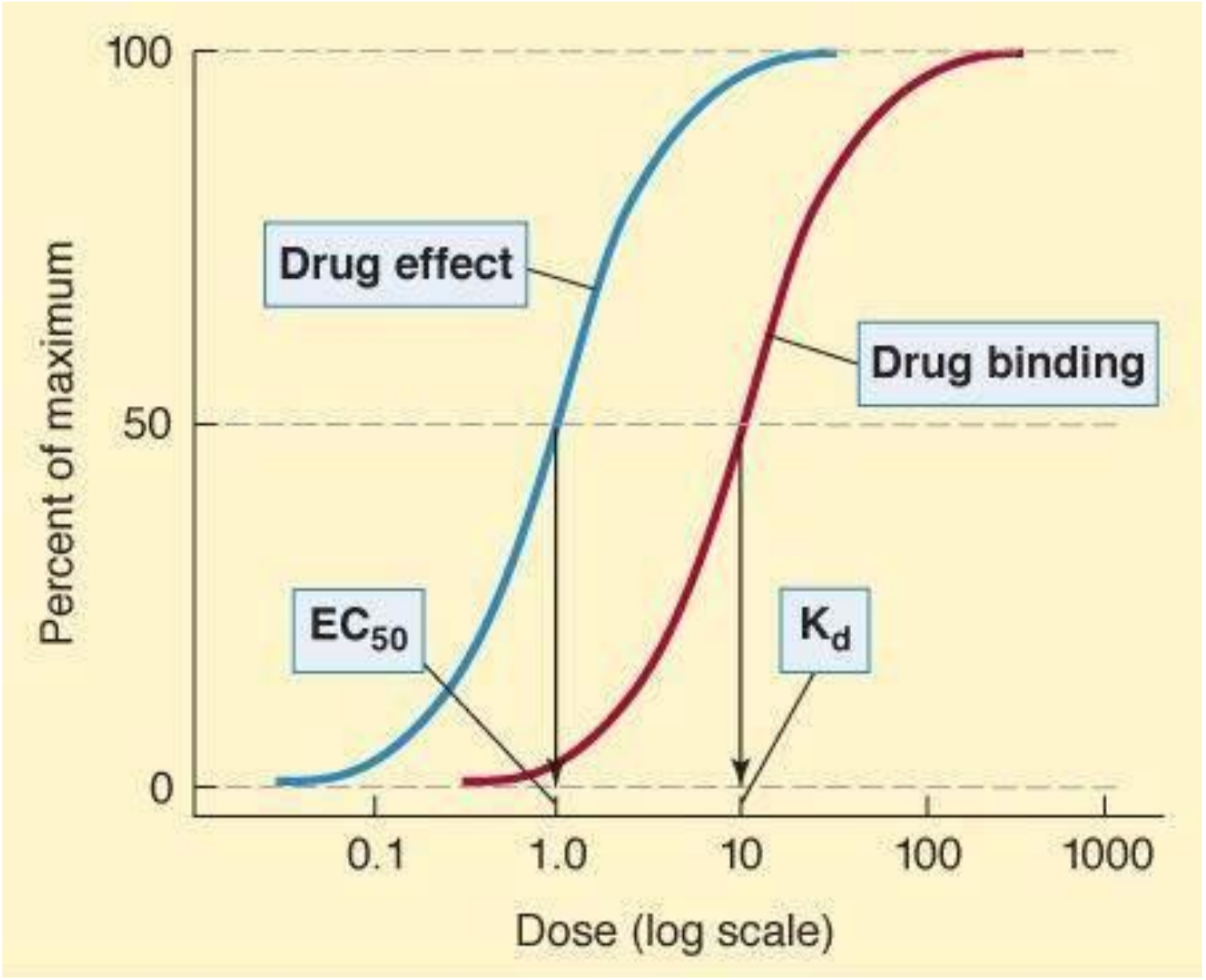
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

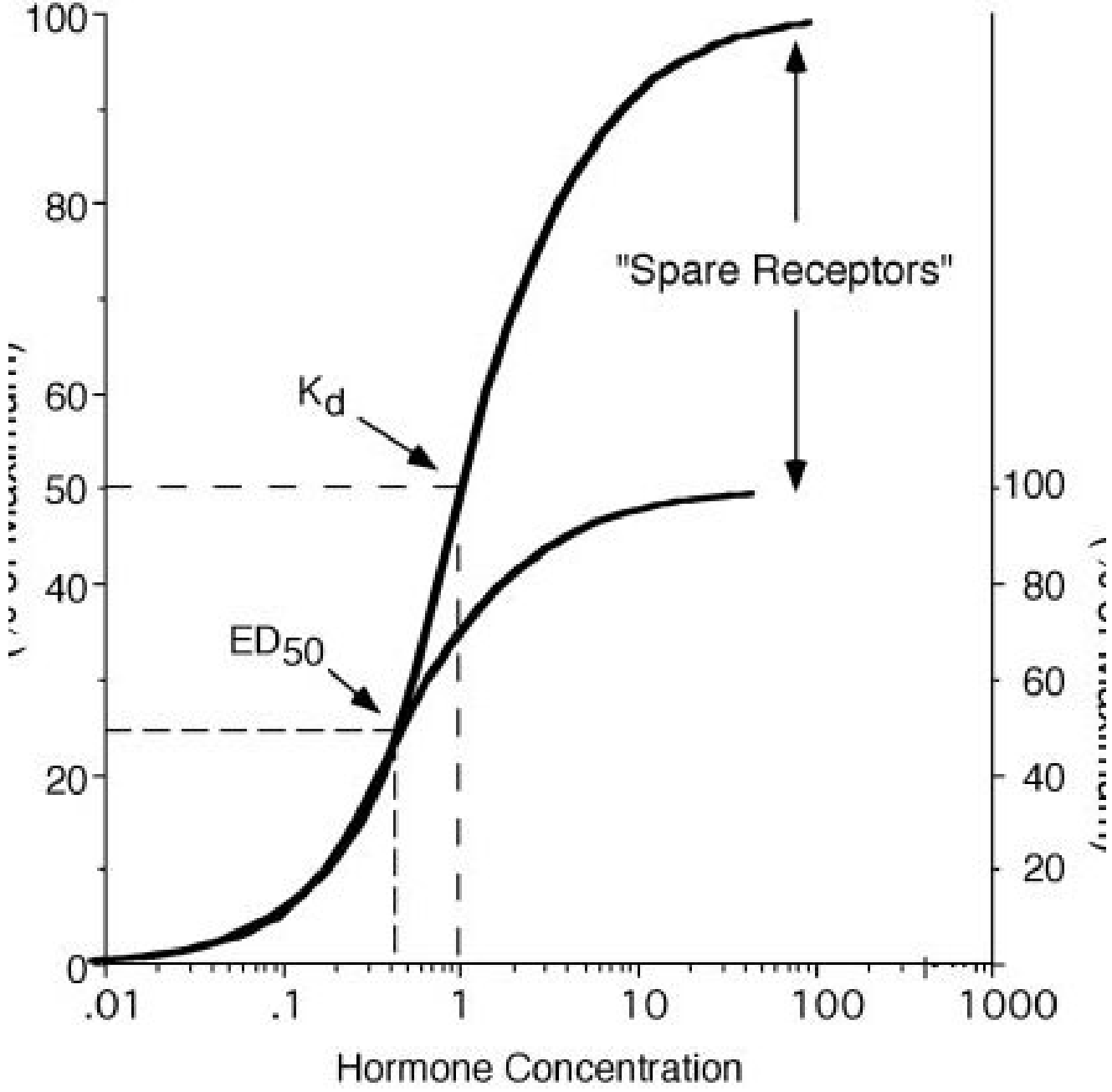
Relations between drug concentration and receptor-bound drug



B

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


100
50
0
Percent of maximum
Drug effect
Drug binding
EC50
Kd
0.1
1.0
10
100
1000
Dose (log scale)


100
80
60
50
40
20
0
"Spare Receptors"
K_d
ED_{50}
100
80
60
40
20
.01
.1
1
10
100
1000
Hormone Concentration

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

So what are the consequences of this amplification????

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 spare…….little functional reserve exist in the failing heart. So most receptors need to be occupied for a maximum effect

Drug Receptors & Pharmacodynamics

Receptors are responsible for selectivity of drug action .

- **The molecular size, shape, and electrical charge of a drug determine how it will bind to a particular receptor.**
- **Accordingly, modifications in the chemical structure of a drug can dramatically increase or decrease a drug's affinities for different classes of receptors, with resulting alterations in therapeutic and toxic effects.**

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.

Potency:

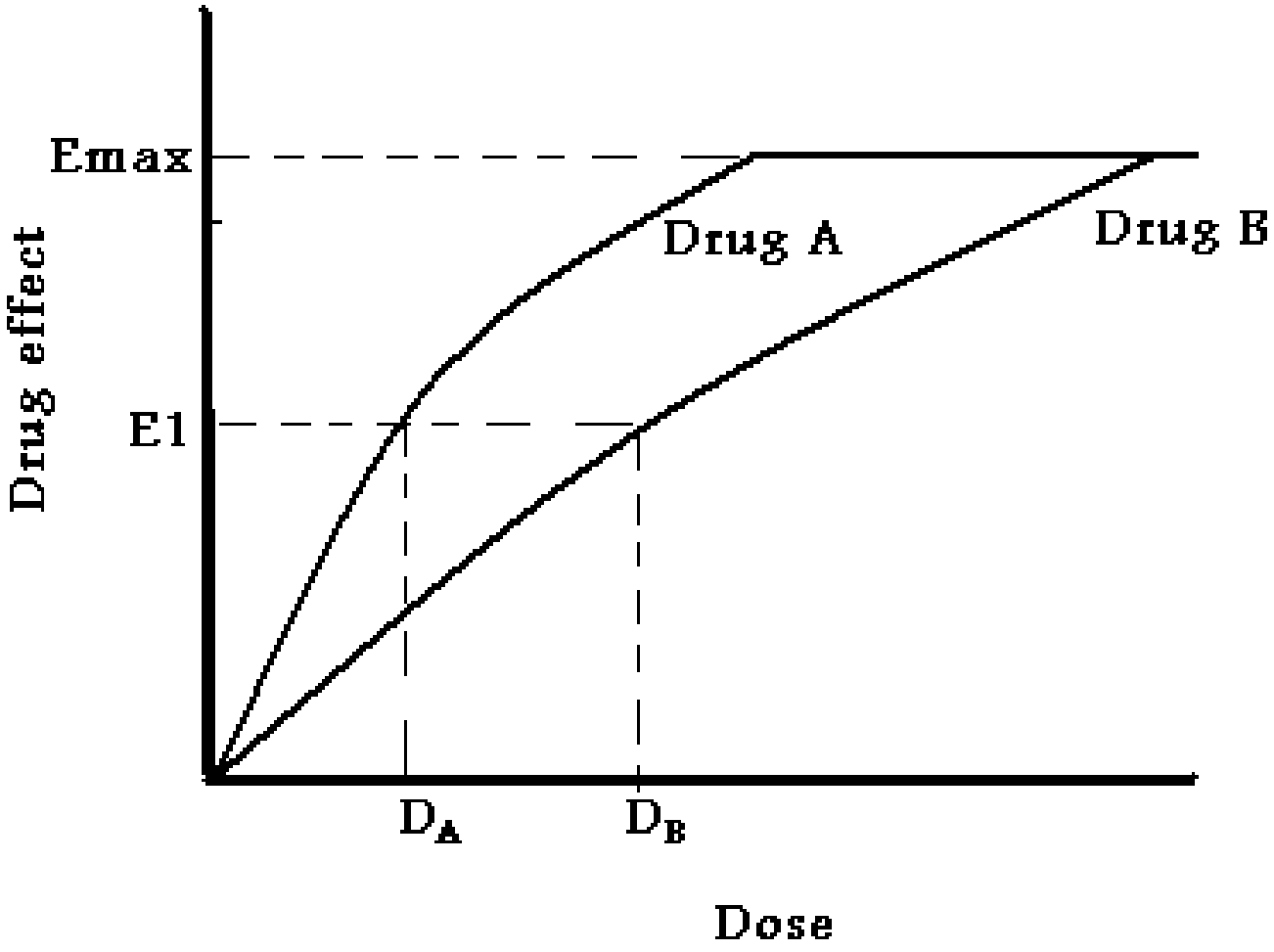
A term used whenever we compare the activity of two drugs producing the same effect

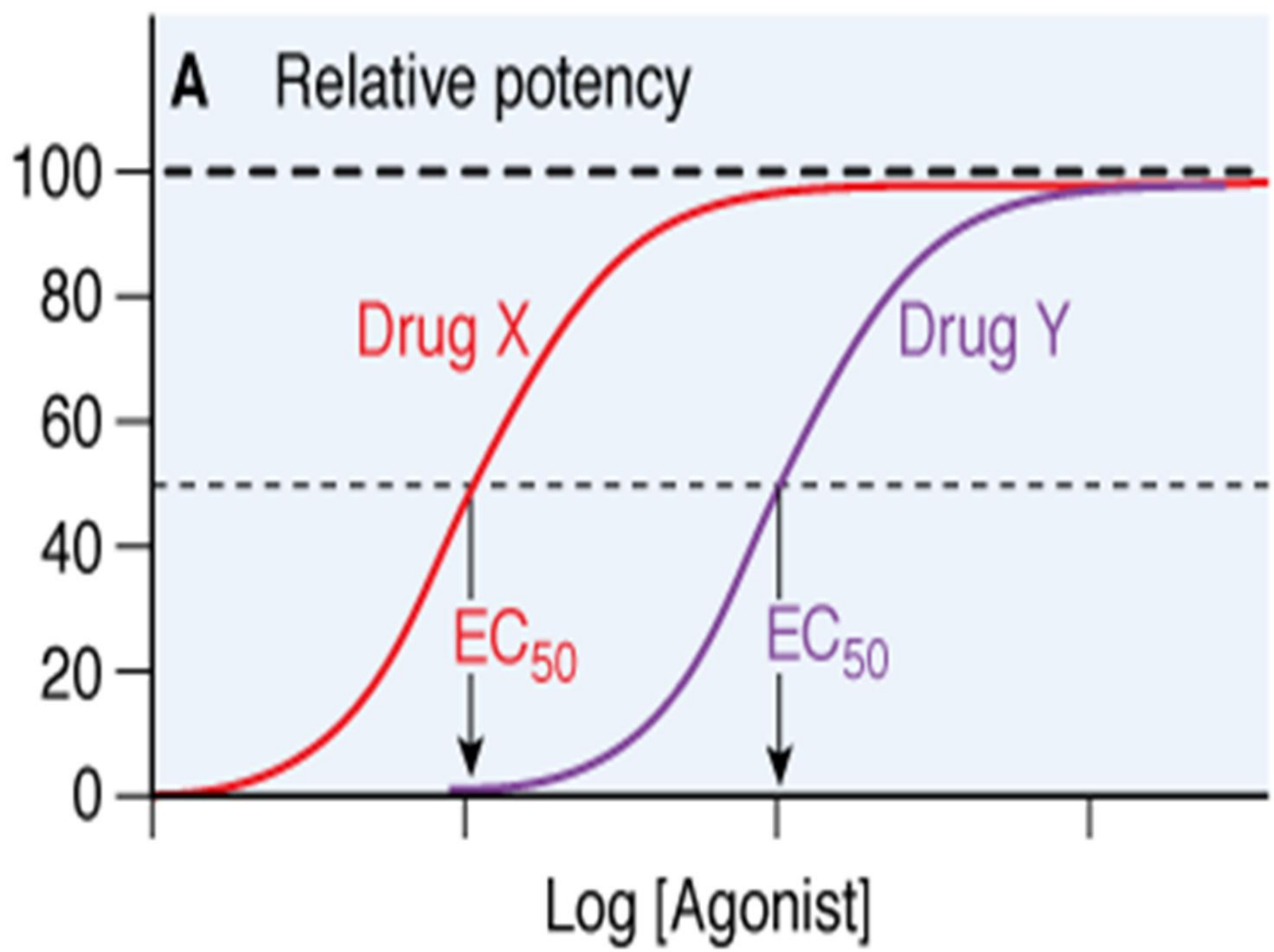
Defined as the dose of one drug necessary to produce a specific response as compared to a second drug producing the same effect

- Affinity:

The ability of a drug to form a stable complex with the receptor

Graduate dose-response curve




A Relative potency
100
80
60
40
20
0
Drug X
Drug Y
EC50
EC50
Log [Agonist]

efficacy

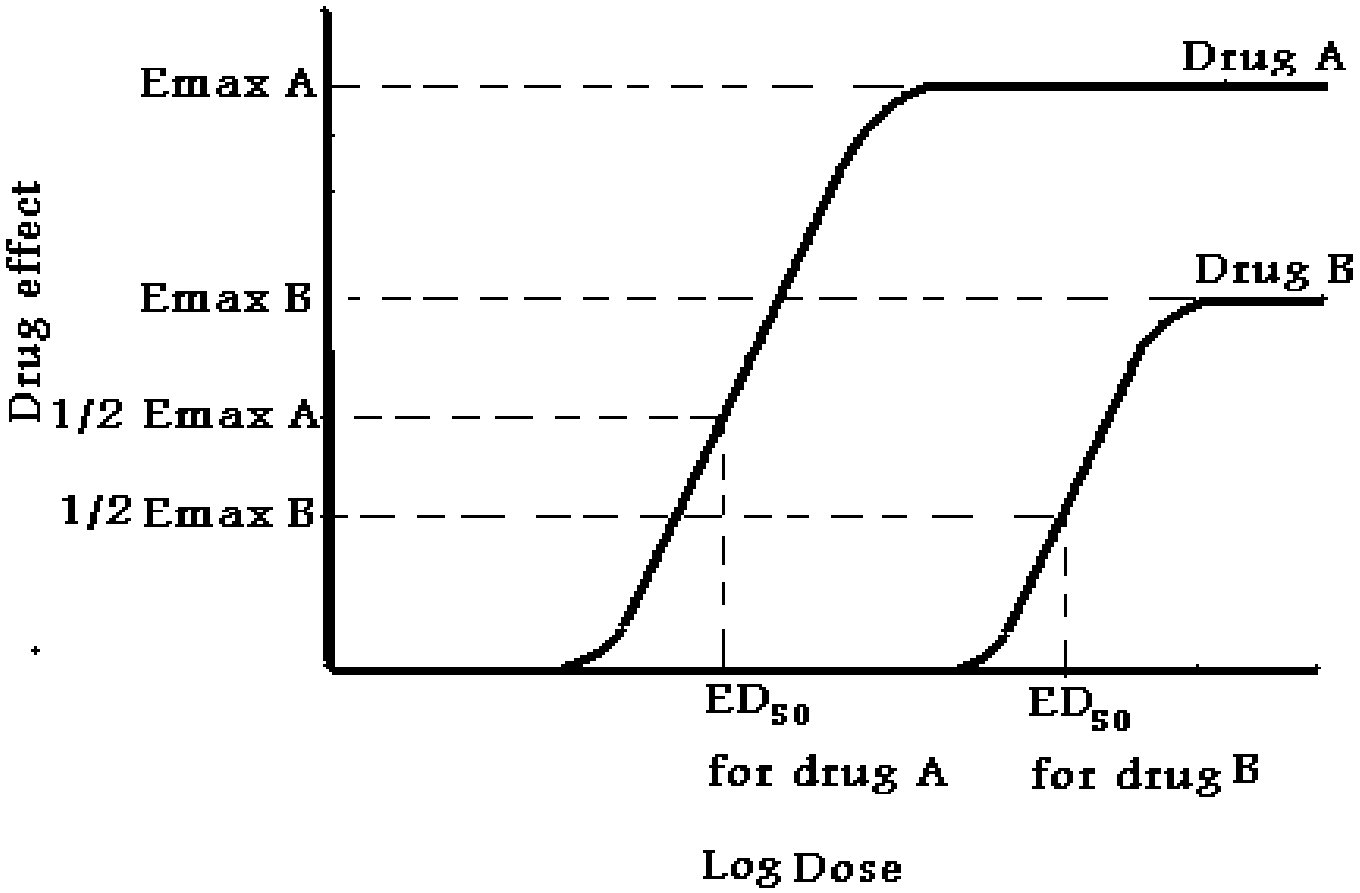
- Efficacy is the maximum effect of a drug, Emax, and does depend on the number of drug-receptor complexes formed, and also on the efficiency of the of coupling of receptor activation to cellular responses.

- 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

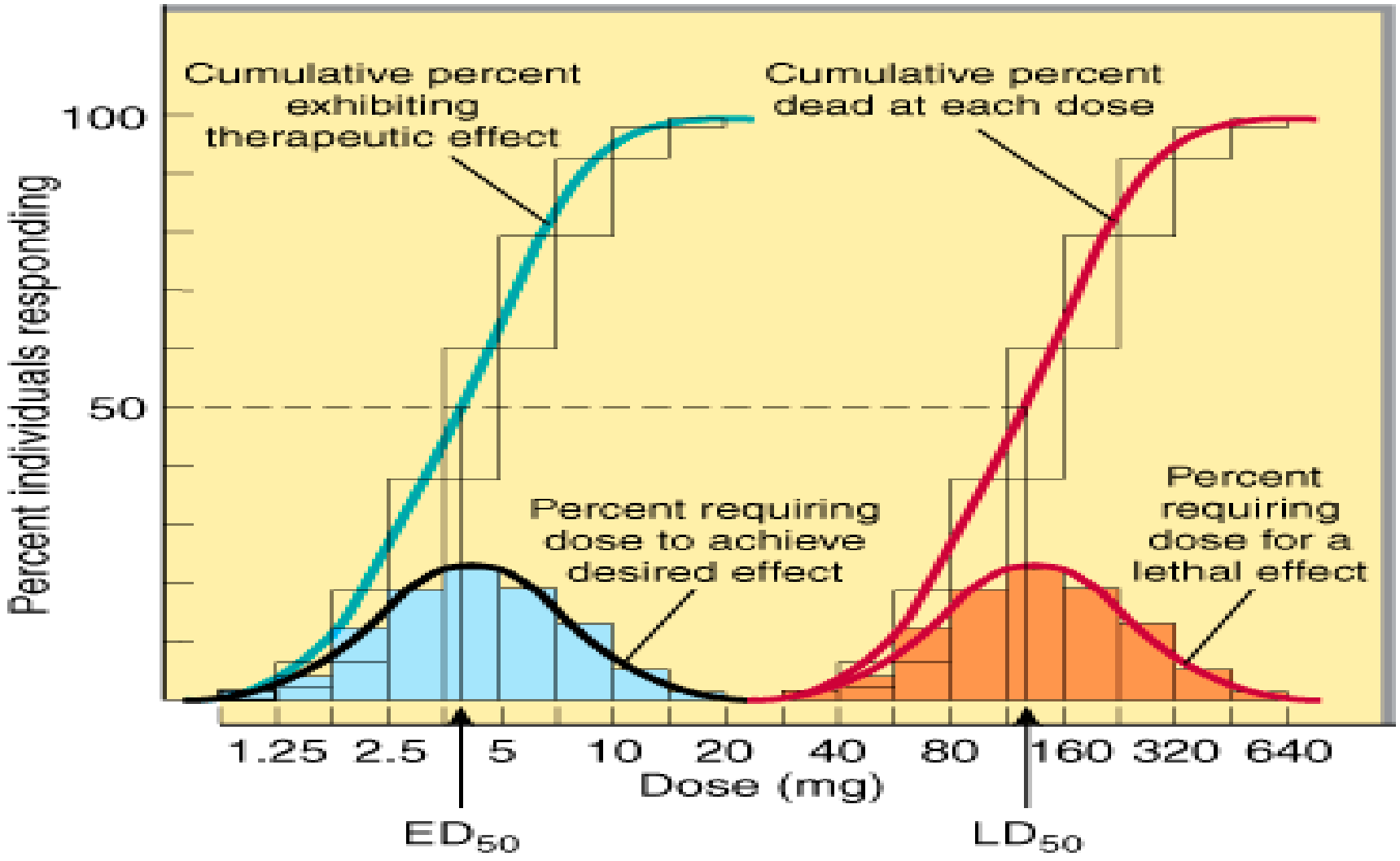
Antagonism between drugs

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.

Quantal Dose-Response Curves



Features of Quantal Dose-Effect Curves

- Involves all or non responses.
- Obeys Normal Frequency Distribution.
- When transformed into cumulative, will result in a sigmoid curve.
  - Straight line for most of the line .
- Can calculate Therapeutic Index= LD50/ED50

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.**

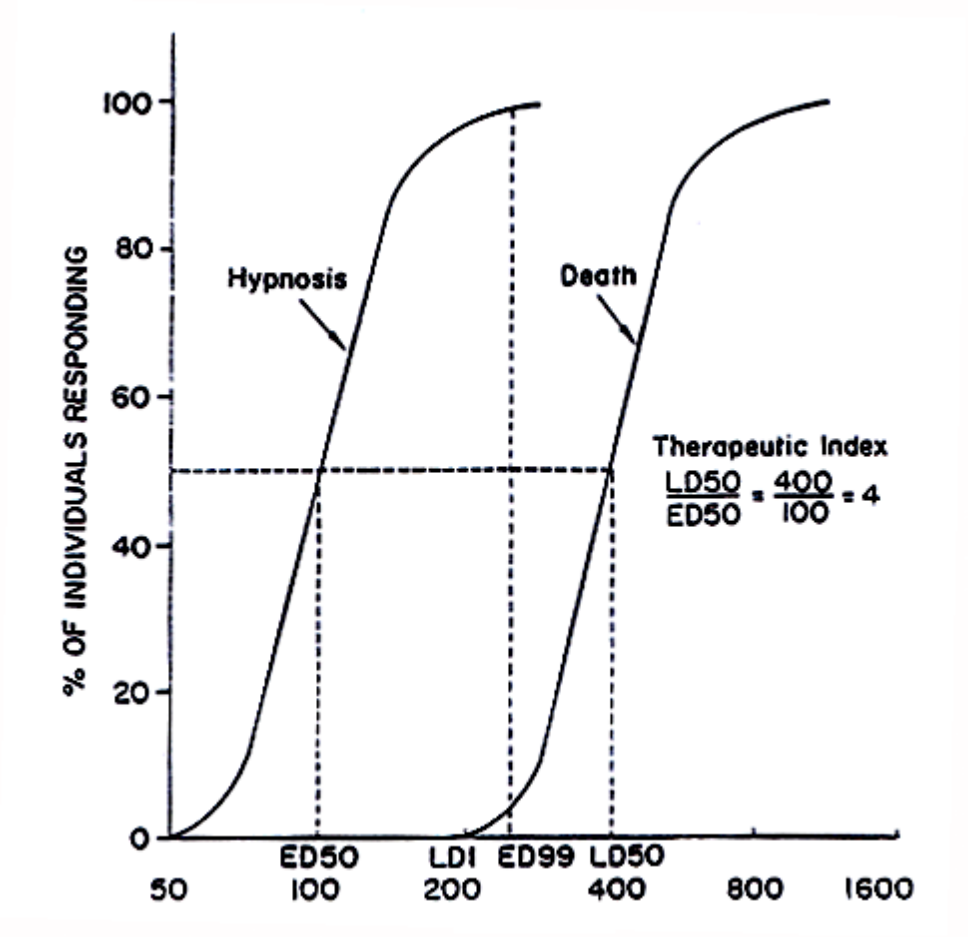
Therapeutic index and margin of safety

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:

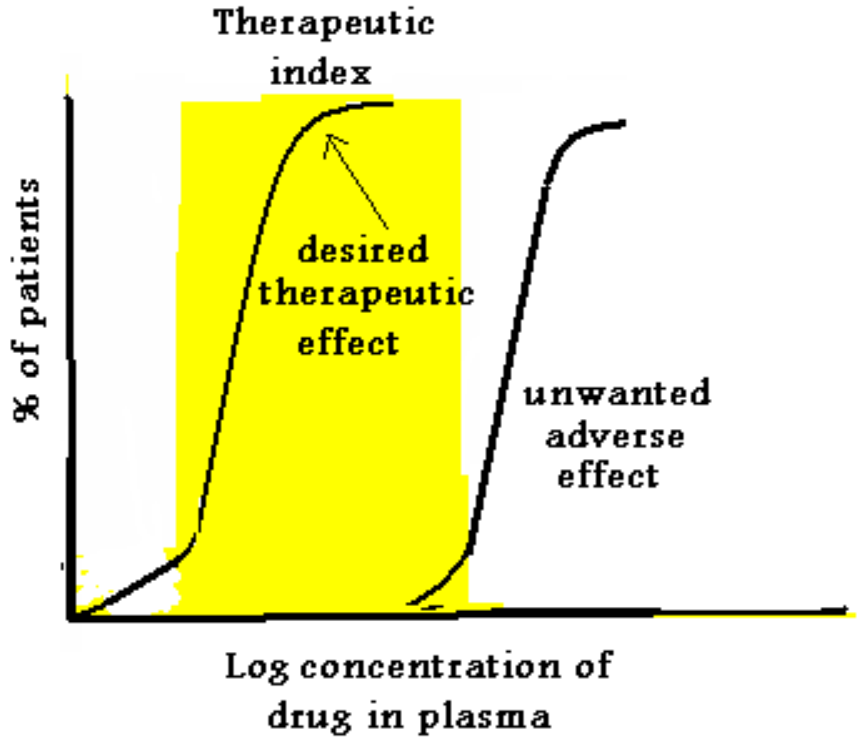
$$TI = \frac{TD_{50}}{ED_{50}}$$

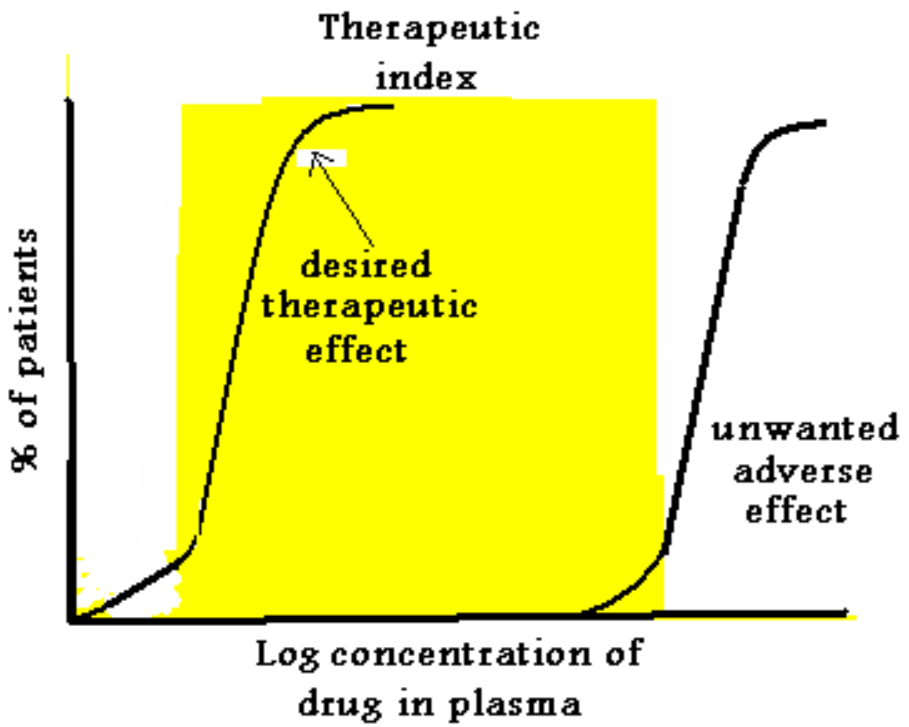
Where TD_{50} is the minimum dose that is lethal or toxic for 50% of the population, and ED_{50} is the minimum dose that is effective for 50% of the population.

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


100
80
60
40
20
0
% OF INDIVIDUALS RESPONDING
Hypnosis
Death
Therapeutic Index
LD50/ED50 = 400/100 = 4
ED50
LD1
ED99
LD50
50
100
200
400
800
1600

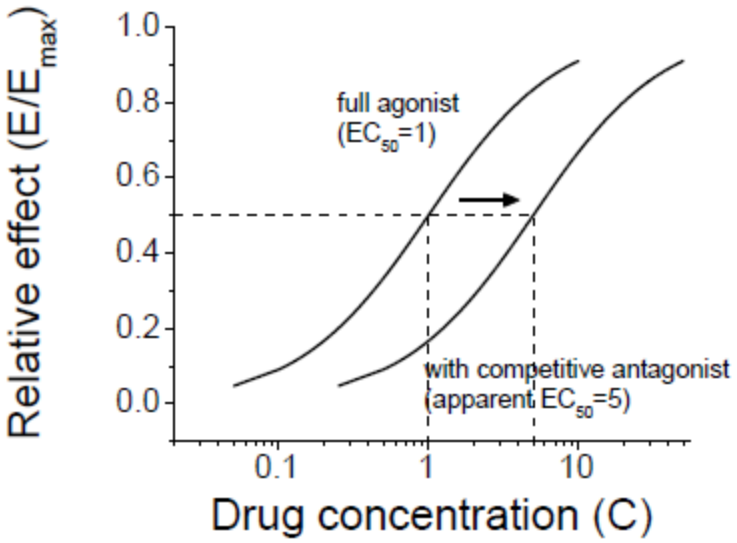
Therapeutic index and margin of safety





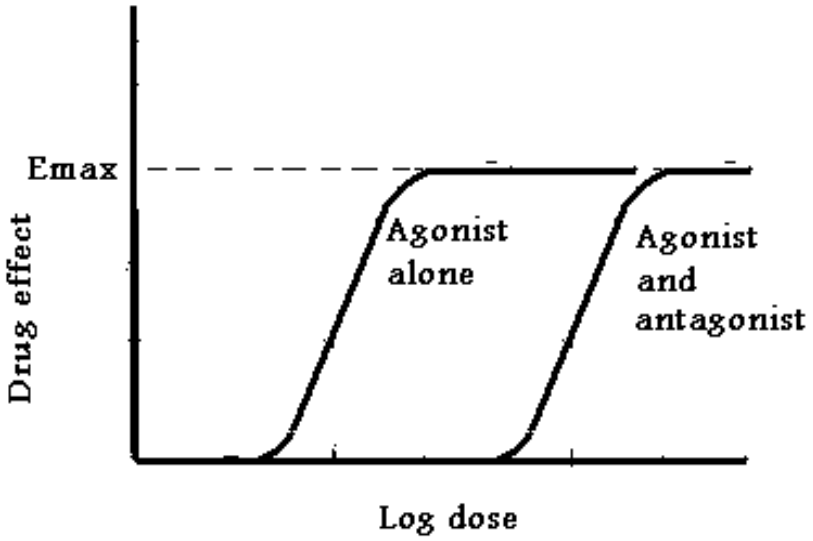
Competitive antagonists

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

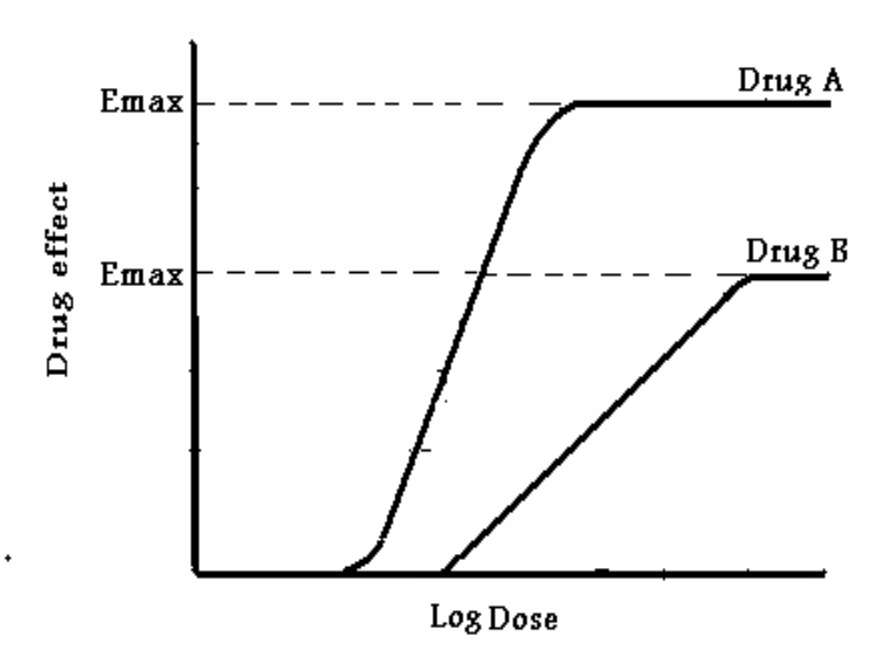


Shift in the log-dose response

Competitive antagonist

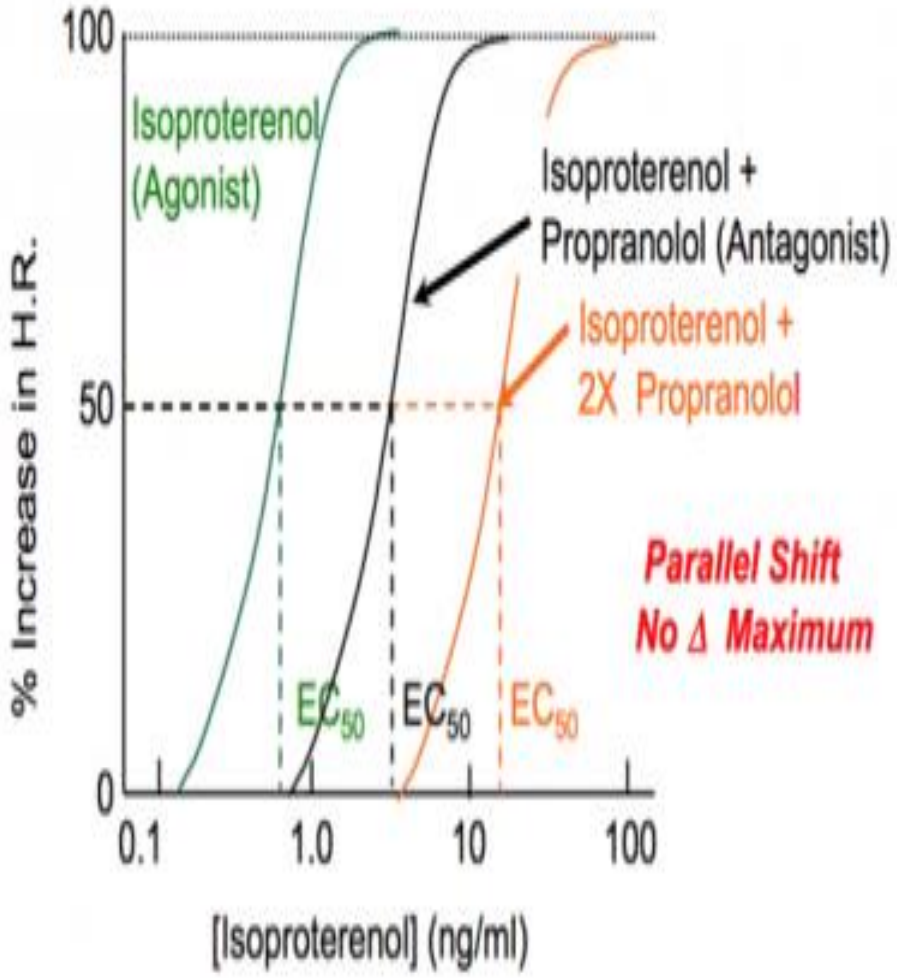


Noncompetitive antagonist



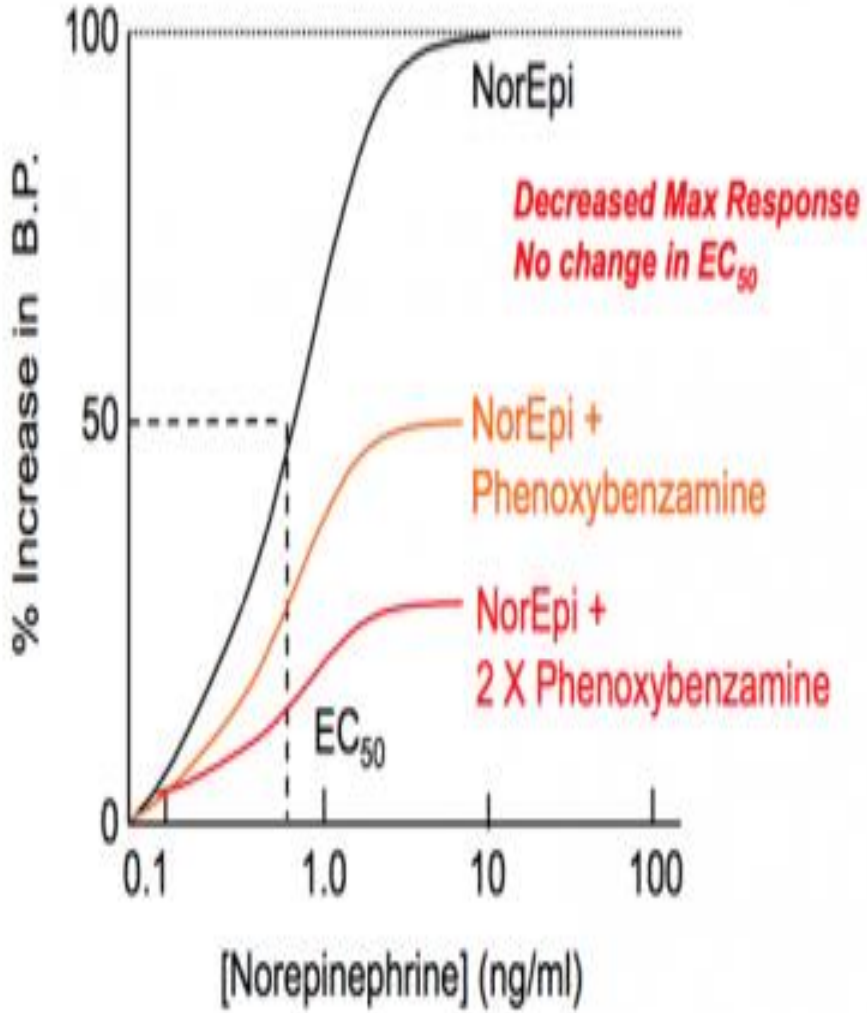
A

Competitive Inhibition



B

Noncompetitive Inhibition



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.

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

Receptor Regulation

- **Sensitization or Up-regulation**

.1Prolonged/continuous use of receptor blocker

.2Inhibition of synthesis or release of hormone/neurotransmitter - Denervation

- **Desensitization or Down-regulation**

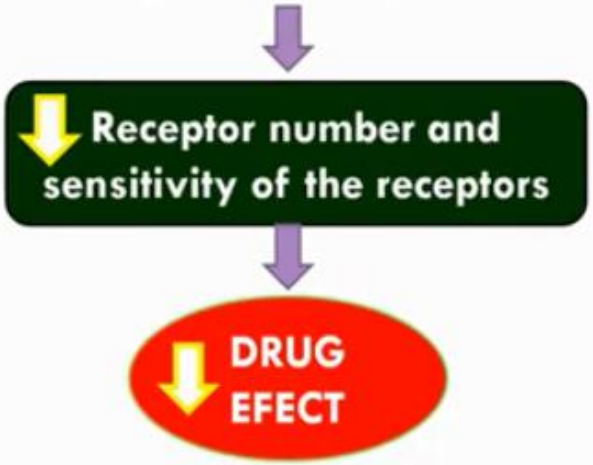
.1Prolonged/continuous use of agonist

.2Inhibition of degradation or uptake of agonist

REGULATION OF RECEPTOR

RECEPTOR -DOWN REGULATION

Prolonged used of agonists

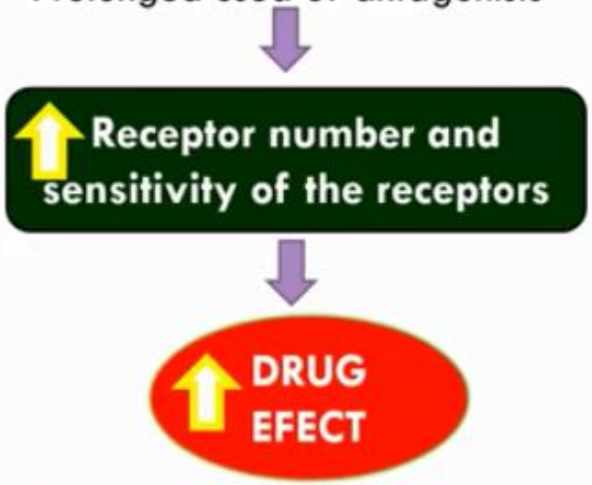


Example: Chronic use of salbutamol

Repeated admn. – adrenergic agonists(salbutamol;) in asthma----→down regulate β-receptors
(responsible for decreased effect of salbutamol in asthmatics)

RECEPTOR - UP REGULATION

Prolonged used of antagonists



Example: sudden withdrawal of β Blocker (propranolol)

When propranolol is stopped after prolonged use, some pts experiences withdrawal syndrome such as anxiety, palpitation, tachycardia, rise BP etc.
This is due to upregulation/supersensitivity of the receptors.

Two-state model of drug-receptor interaction

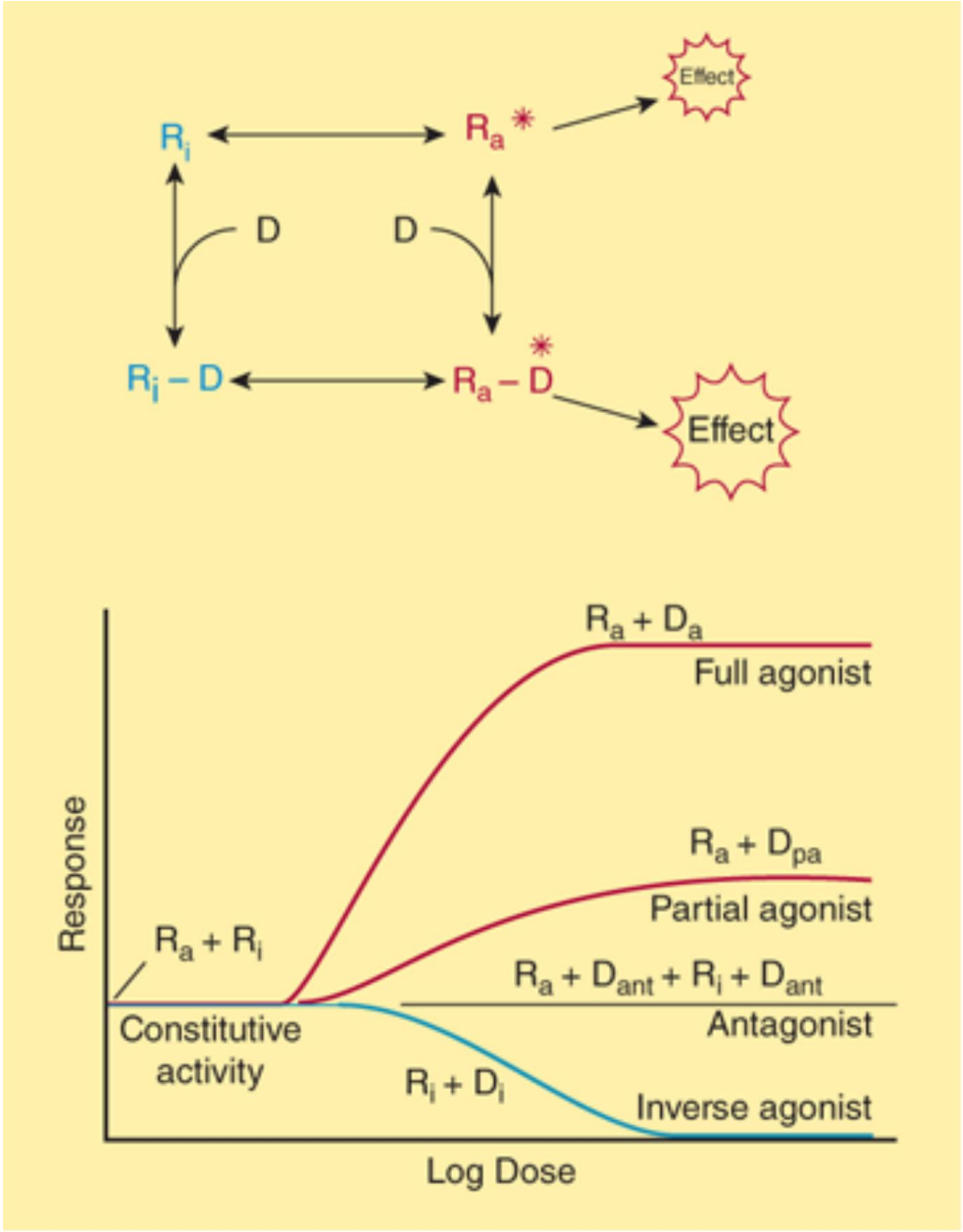
- Full agonists shift equilibrium “fully” towards the active conformation
- Partial agonists shift equilibrium “partially” towards the active conformation
- Sub-maximal effect with receptors completely occupied

Two-state model of drug-receptor interaction

- The receptor is postulated to exist in the inactive, nonfunctional form (Ri) and in the activated form (Ra.(
-
- Thermodynamic considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the Ra form some of the time and may produce the same physiologic effect as agonist-induced activity .
- Agonists have a much higher affinity for the Ra configuration and stabilize it, so that a large percentage of the total pool resides in the Ra–D fraction and a large effect is produced

Constitutive Activity

- The effect of receptors, occurring in the absence of agonist, is termed constitutive activity .
- The recognition of constitutive activity may depend on the receptor density, the concentration of coupling molecules (if a coupled system), and the number of effectors in the system.

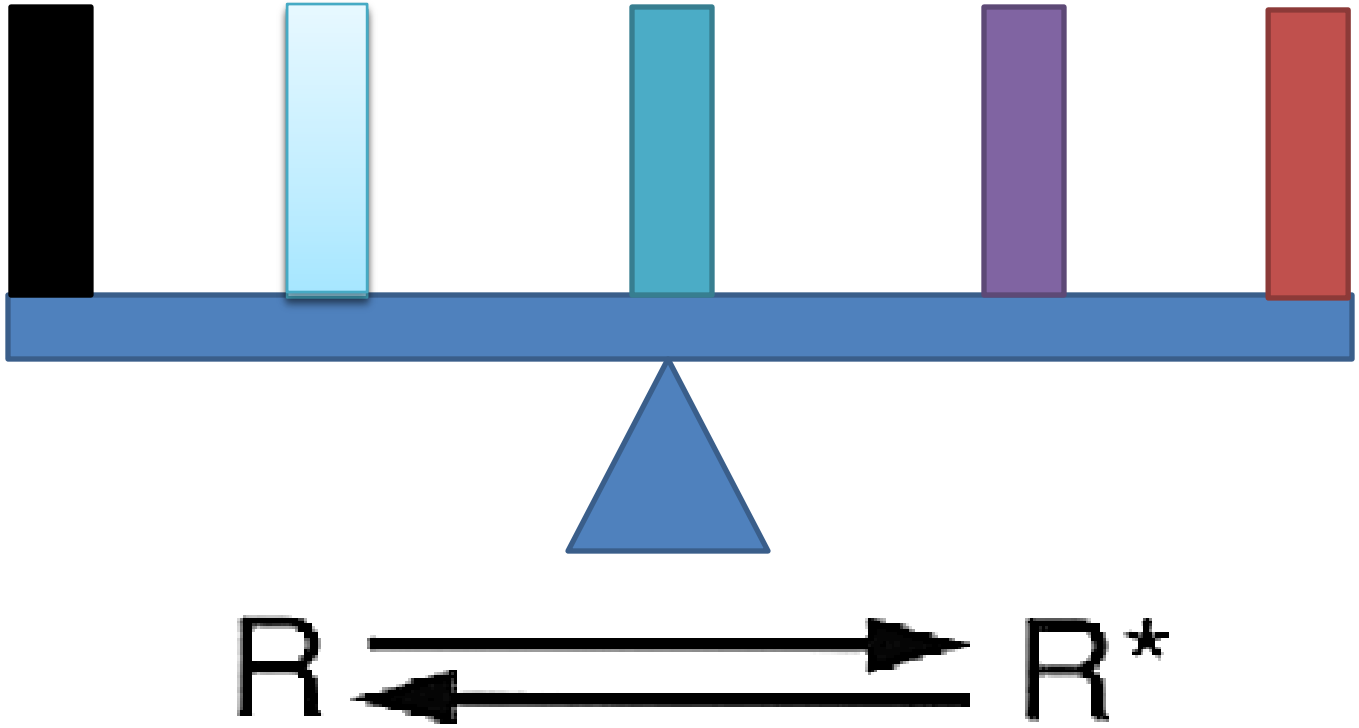


Inverse agonists:

While antagonists are traditionally thought to have no functional effect in the absence of an agonist, some antagonists exhibit “inverse agonist” activity because they also reduce receptor activity below basal levels observed in the absence of any agonist at all.

Competitive & Irreversible Antagonists

- Receptor antagonists bind to receptors but do not activate them
- The primary action of antagonists is to reduce the effects of agonists (other drugs or endogenous regulatory molecules) that normally activate receptors.
- Inverse agonists shift equilibrium towards the inactive conformation
- Effect obvious *if* much constitutive activity



Full agonist

Partial agonist

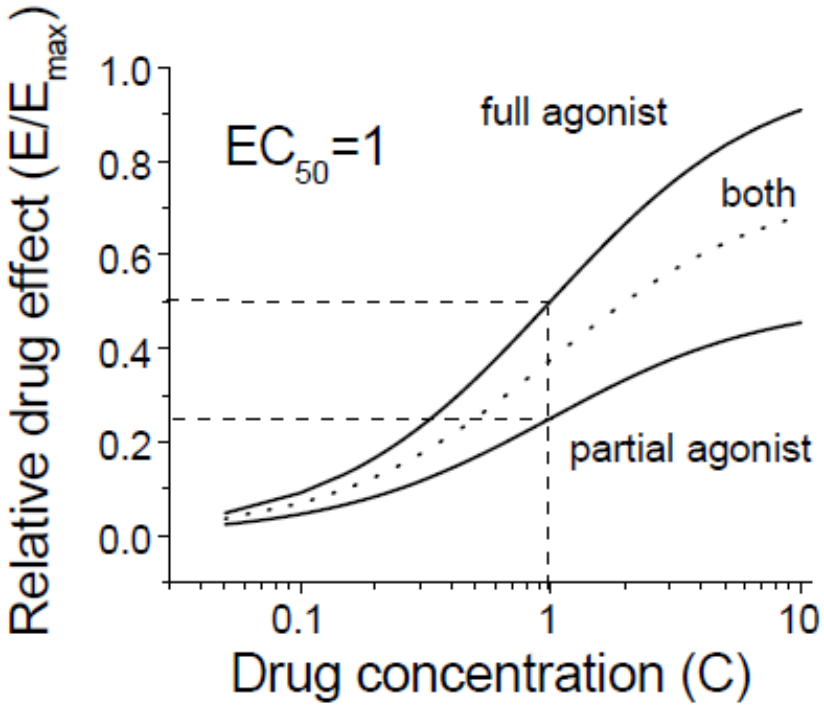
Antagonist

Partial inverse agonist

Full inverse agonist

Inverse agonists

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



Varenicline