Design and optimization of dosage regimen

- To initiate drug therapy a dosage regimen is administered either by continuous infusion or in intervals of time and dose
- The regimen depends on various drug and patient factors including how rapidly a steady state must be achieved
  - Steady state: The state at which the rate of administration equals that of elimination
- The regimen is refined to achieve maximum benefit with minimum adverse effects

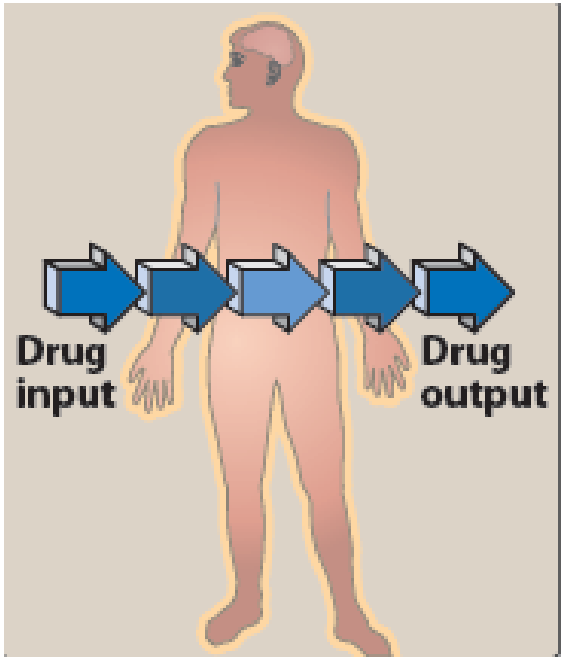
- Drug administration
  - Single dose
  - Continuous administration
    - IV infusion
    - Fixed-dose/fixed time interval regimens

Dosage Regimens

- IV infusion or oral fixed-dose/fixed time interval regimens
- The drug accumulates until a steady state occurs
- At steady state the amount of drug administered equals the amount being eliminated
- At steady state
  - The plasma and tissue levels remain constant with IV infusion and fluctuate around a mean in oral fixed dosage

Plasma concentration of a drug following IV infusion

- Following initiation of IV infusion the plasma concentration of drug rises until the rate of drug eliminated from the body balances the input rate

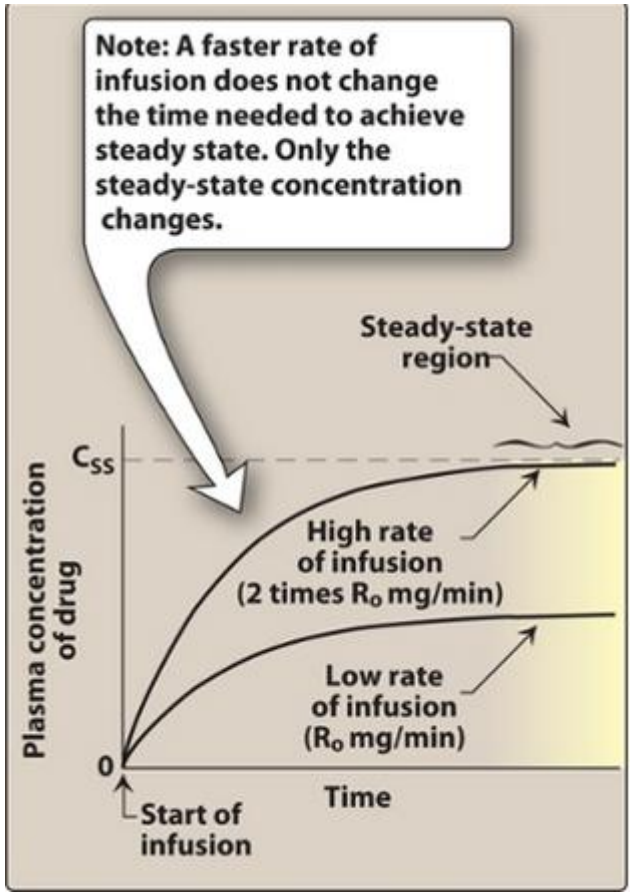


⇒ Steady state is achieved

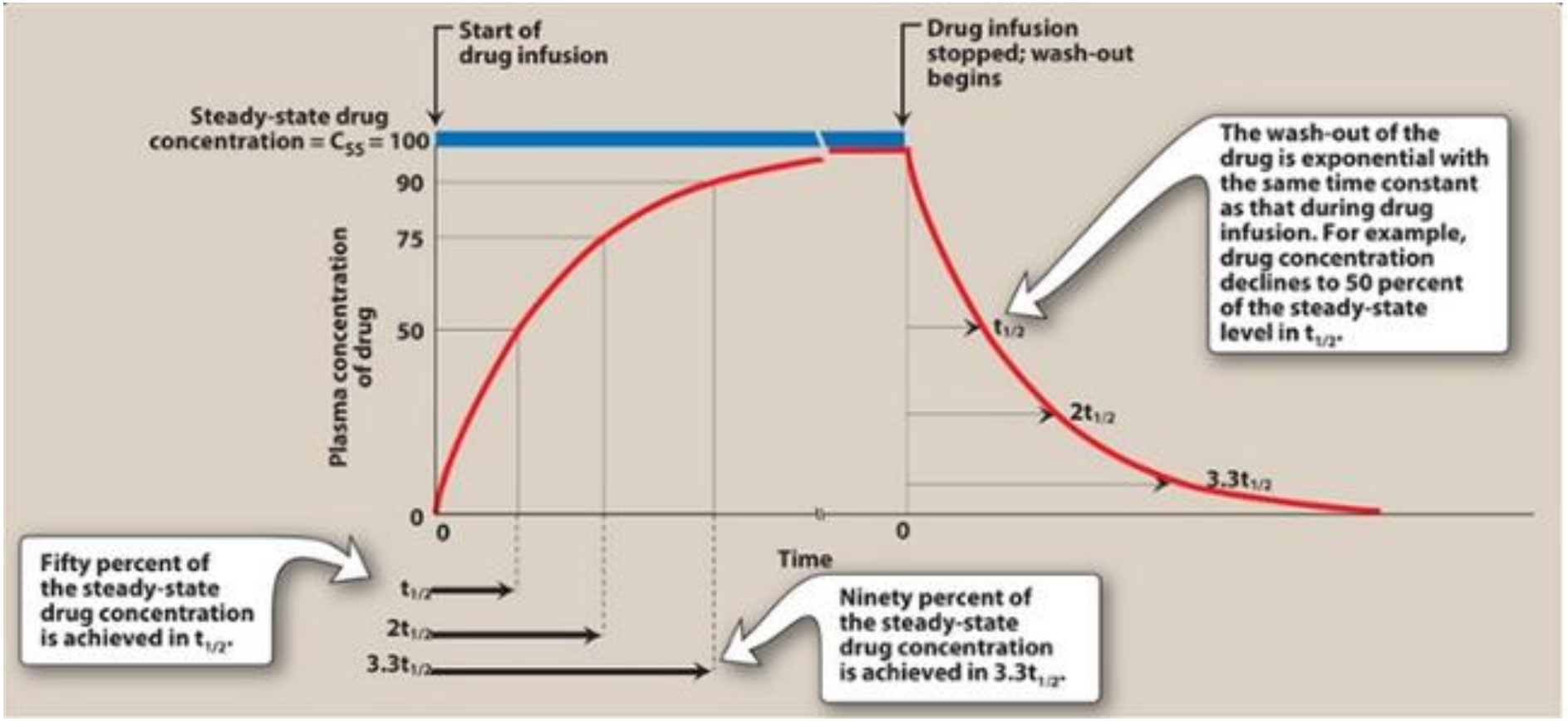
(The plasma concentration of the drug remains constant)
Assuming the drug elimination is first order

Plasma concentration of a drug following IV infusion

- The steady state plasma concentration is directly proportional to the infusion rate
- The steady state concentration is inversely proportional to the clearance of the drug
  - Hepatic or renal disease can increase Css
  - Increased metabolism reduces Css



Time required to reach Css



Fixed dose/Fixed time Regimen

- Administration of drug by fixed doses is more convenient than continuous infusion
- Fixed doses administered by fixed time intervals results in fluctuations in drug levels
- Fixed dose regimens
  - Multiple IV injections
  - Multiple oral administrations

Multiple IV injections

- Following administration of a drug at repeated intervals the plasma concentration increases until steady state is reached
- Using smaller doses at shorter intervals does not does not change the rate at which the steady state is approached or the Css
- 90% of steady state value is reached in $3.3t_{1/2}$

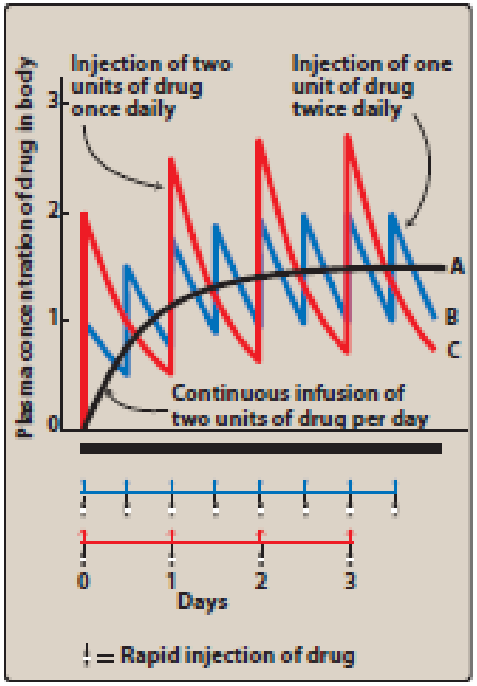
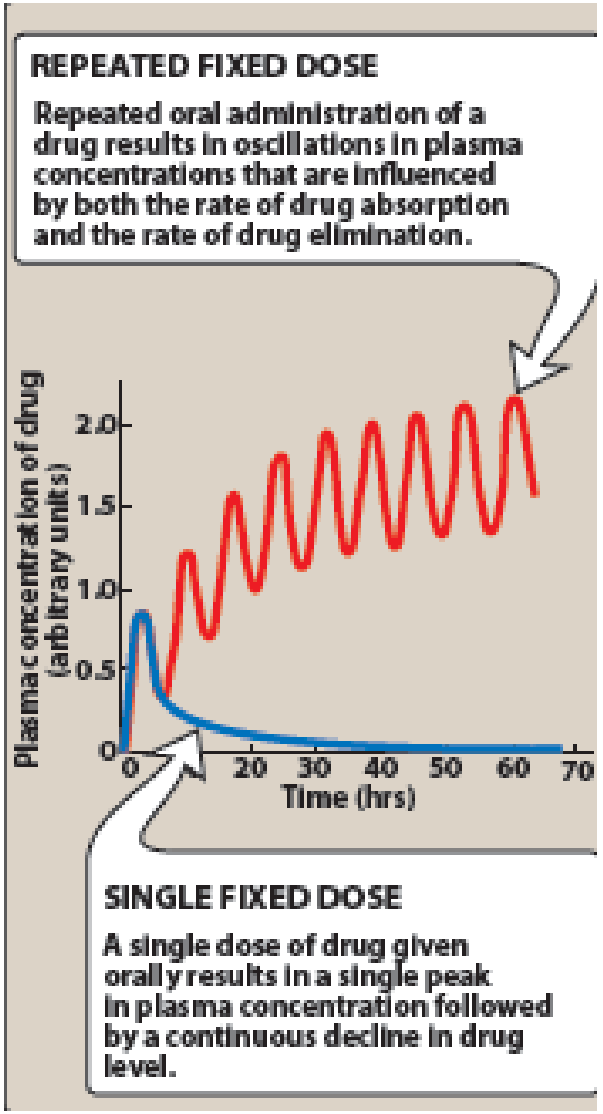


Figure 1.23
Predicted plasma concentrations of a drug given by infusion (**A**), twice-daily injection (**B**), or once-daily injection (**C**). Model assumes rapid mixing in a single body compartment and a half-life of 12 hours.

Multiple oral administration

- Might be absorbed slowly
- Plasma concentration is influenced by
  - the rate of absorption
  - the rate of elimination



Optimization of dose

- The goal of drug administration is to achieve and maintain therapeutic response with minimal toxicity or side effects

- Loading dose: a higher dose or series of doses administered to achieve the desired plasma level rapidly.

- Loading dose is followed by lower multiple doses (Maintenance dose)

- Loading dose = (V_d)(desired Css)/F
- For IV
  Loading dose = (V_d)(desired Css)
- Loading dose might be associated with risk of drug toxicity
- Loading dose is useful for drugs eliminated from the body slowly, and hence require lower maintenance dose to keep the drug at a therapeutic concentration
- Without an initial higher dose, it would take longer to reach Css

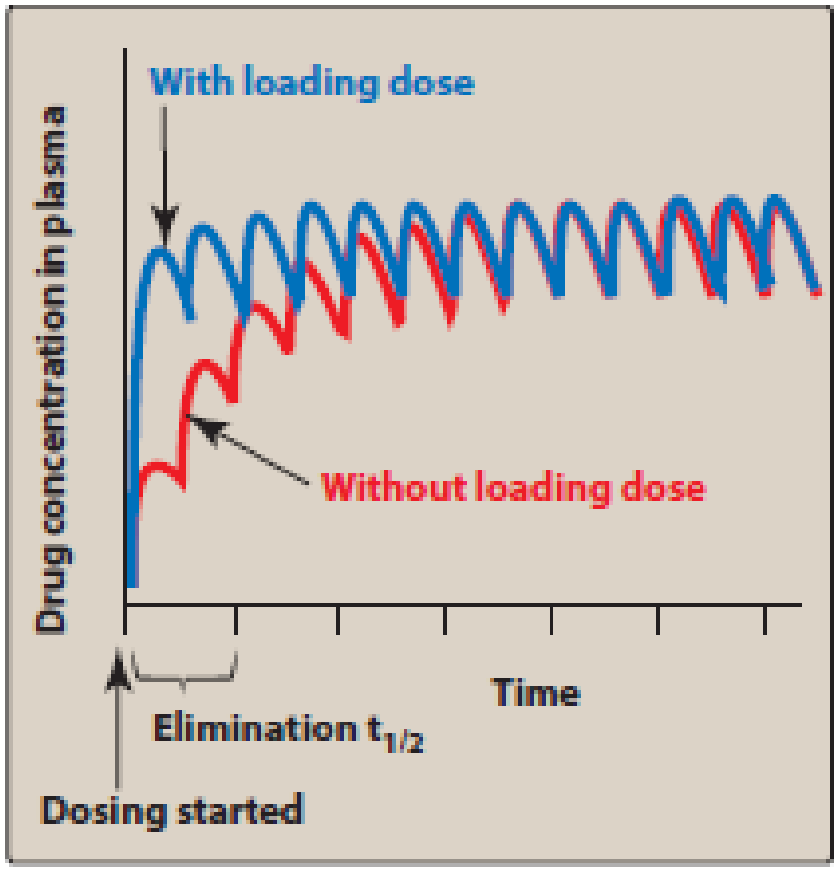


Figure 1.25
Accumulation of drug administered orally without a loading dose and with a single oral loading dose administered at t = 0.

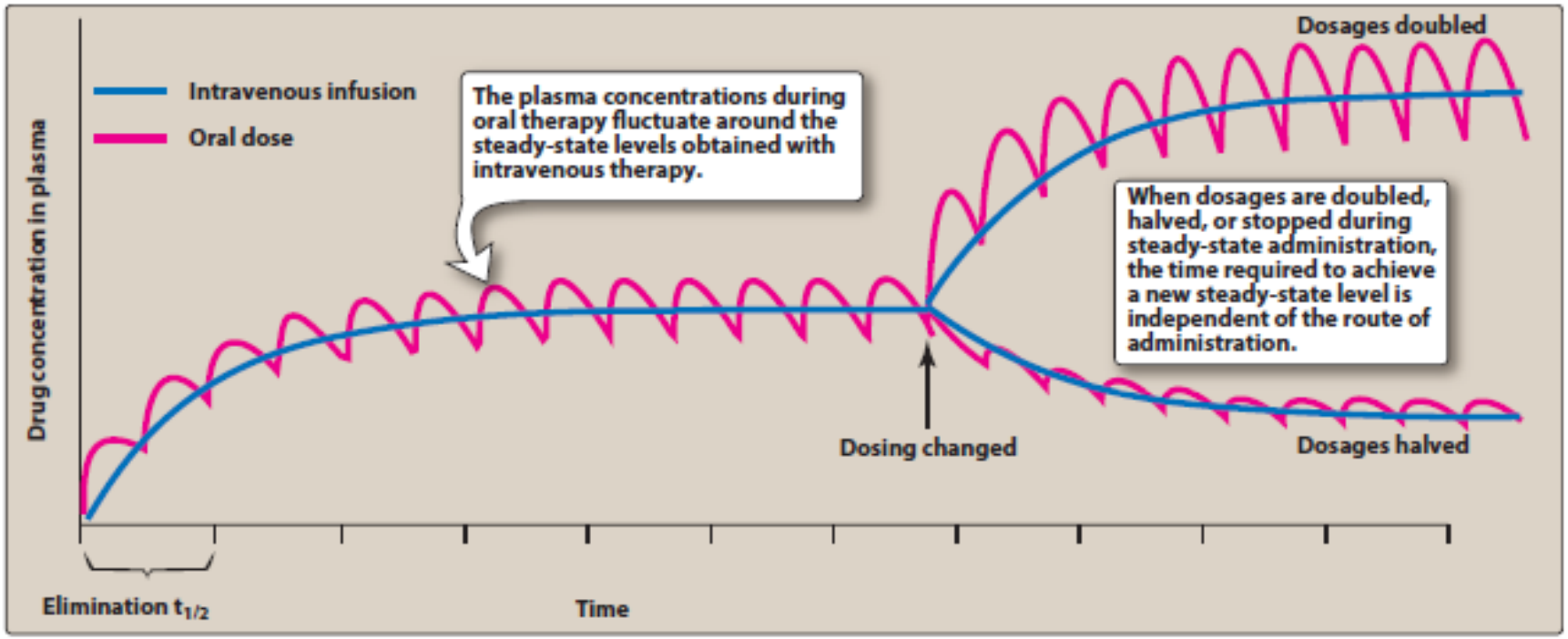


Figure 1.26

Accumulation of drug following sustained administration and following changes in dosing. Oral dosing was at intervals of 50% of $t_{1/2}$.

Dose adjustment

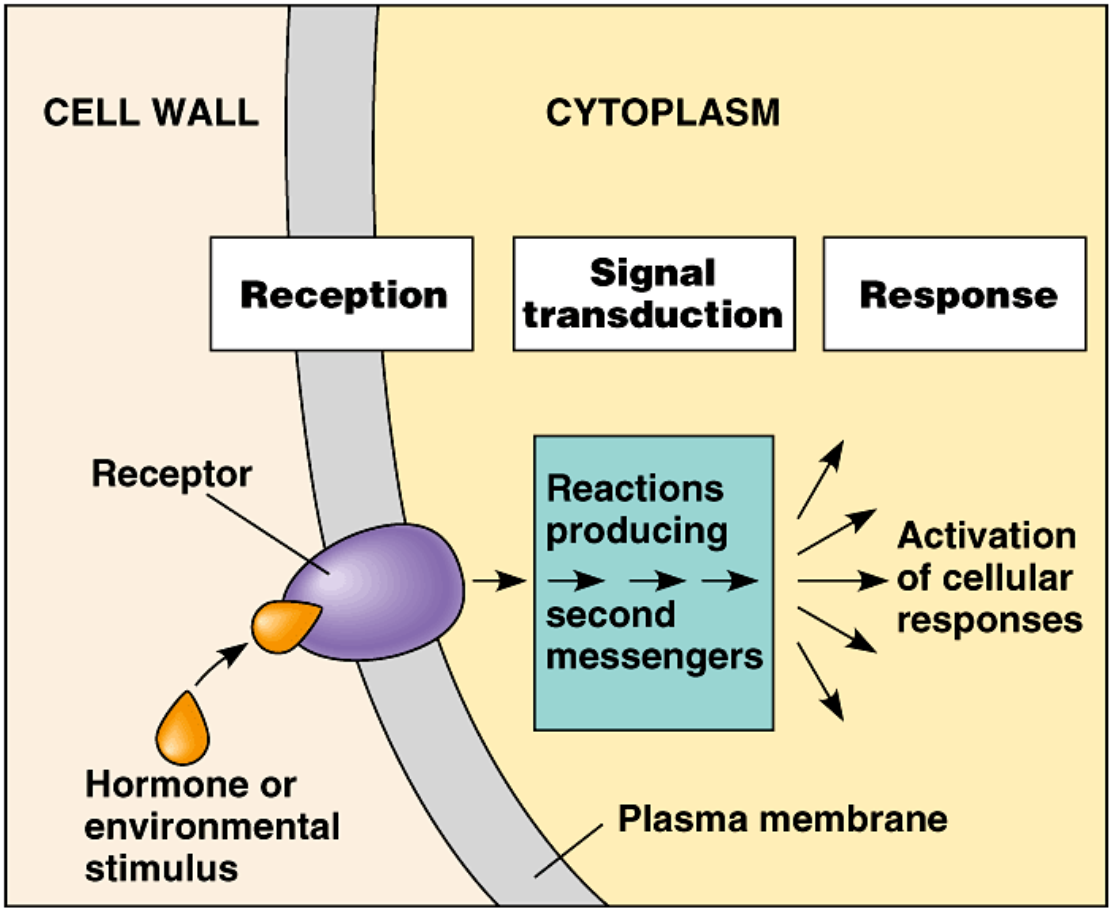
- The amount of drug administered is optimized for the patient taking into account:
  - Interpatient variability
  - Pharmacokinetic factors

- Individualized therapy

Pharmacodynamics

- Pharmacodynamics: describes the action of the drug on the body and the influence of drug concentration on the magnitude of the response

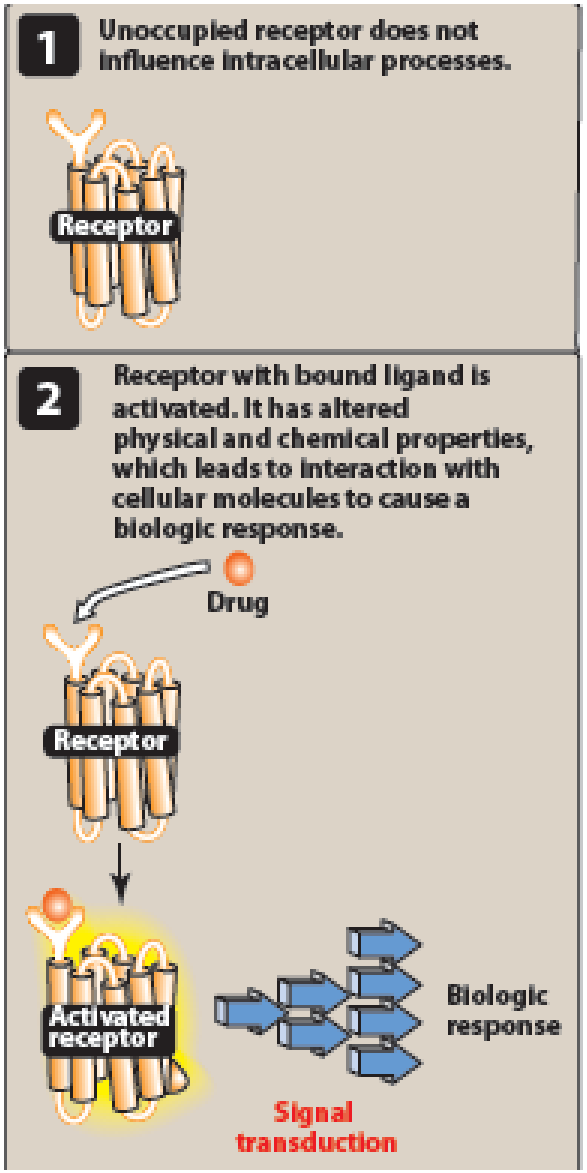
- Drugs cause their therapeutic or toxic effects by interacting with specialized target molecules on the surface of cells or inside cells (e.g. receptors)



- Receptor: any biologic molecule to which a drug binds and produces a measurable response
  - Examples: enzymes, nucleic acids, structural proteins
- Second messenger (effector molecules): part of the cascade of events that translate ligand binding into a cellular response
- Ligand: a small molecule that binds to a site on a target protein
- Affinity: the strength of the interaction (binding) between a ligand and its receptor

Signal transduction

- The process by which the drug receptor complex initiates alterations in biochemical or molecular activity of a cell



Drug receptor complex:

$$\text{Drug} + \text{Receptor} \rightleftarrows \text{Drug–receptor complex} \rightarrow \text{Biologic effect}$$

- Receptors are specific for the ligands they bind to

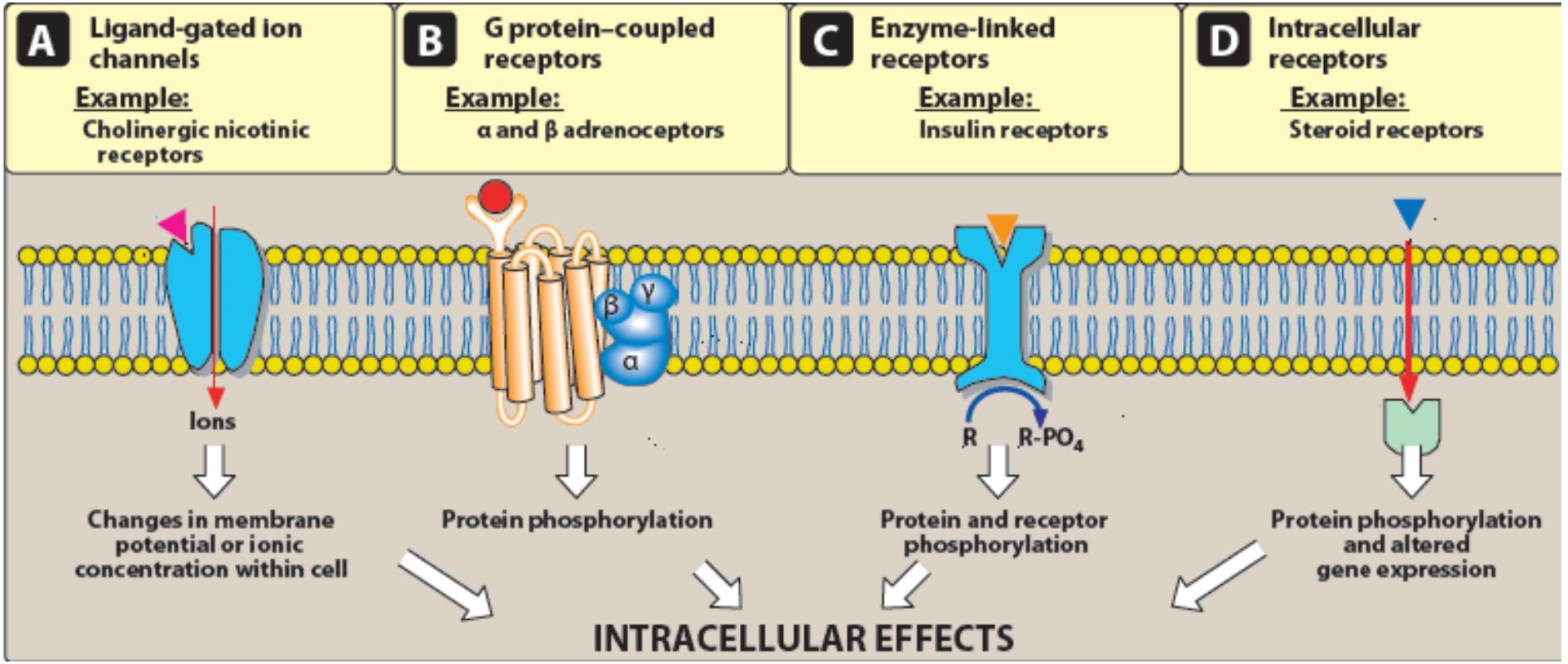
Receptor states:

- Receptors exist in either an inactive state (R) or activated state (R*)
- Binding of a ligand to a receptor can cause the receptor to change from an inactive state (R) to an activated state (R*)
- The activated receptor interacts with other molecules to produce a biologic effect

Major receptor families:

1. Ligand-gated ion channels
2. G protein-coupled receptors
3. Enzyme linked receptors
4. Intracellular receptors

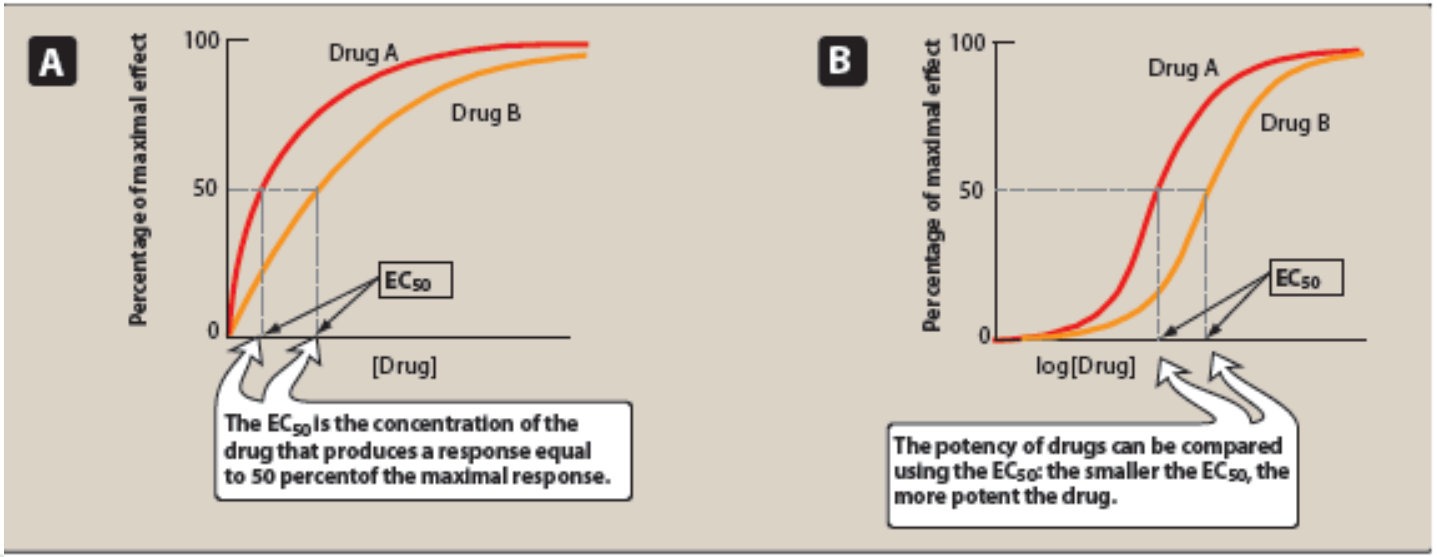
The type of receptor a ligand interacts with depends on the ligand's chemical nature


A
Ligand-gated ion channels
Example:
Cholinergic nicotinic receptors
B
G protein–coupled receptors
Example:
α and β adrenoceptors
C
Enzyme-linked receptors
Example:
Insulin receptors
D
Intracellular receptors
Example:
Steroid receptors
Ions
β
γ
α
R
R-PO4
Changes in membrane potential or ionic concentration within cell
Protein phosphorylation
Protein and receptor phosphorylation
Protein phosphorylation and altered gene expression
INTRACELLULAR EFFECTS

Dose response relationships

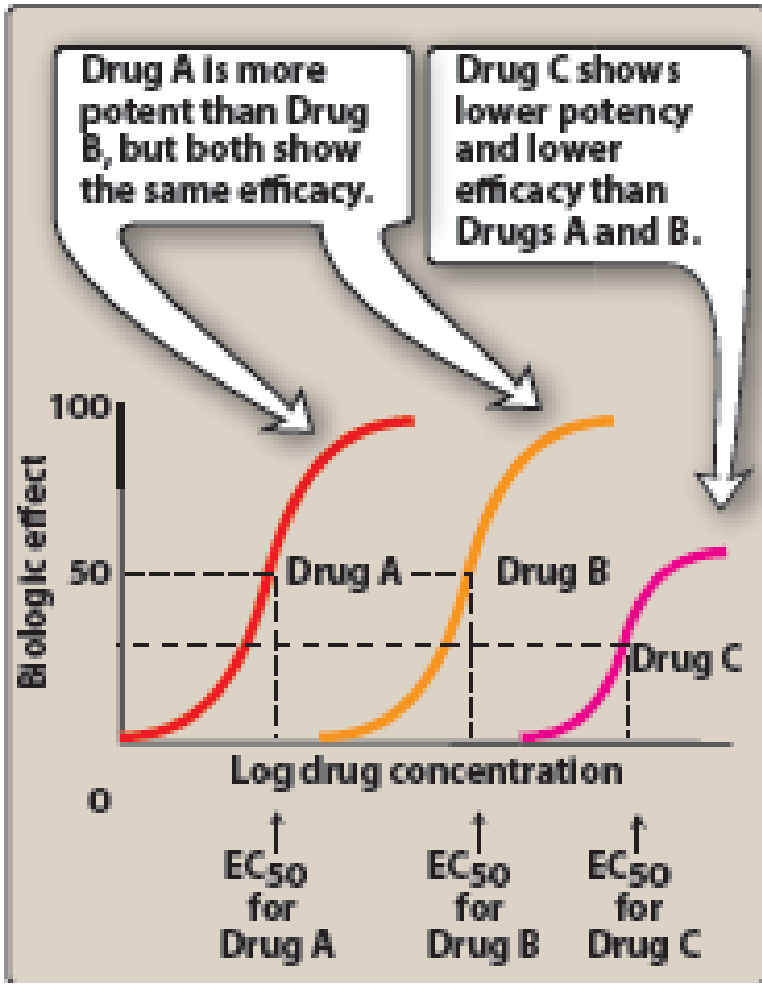
Graded dose-response relationship

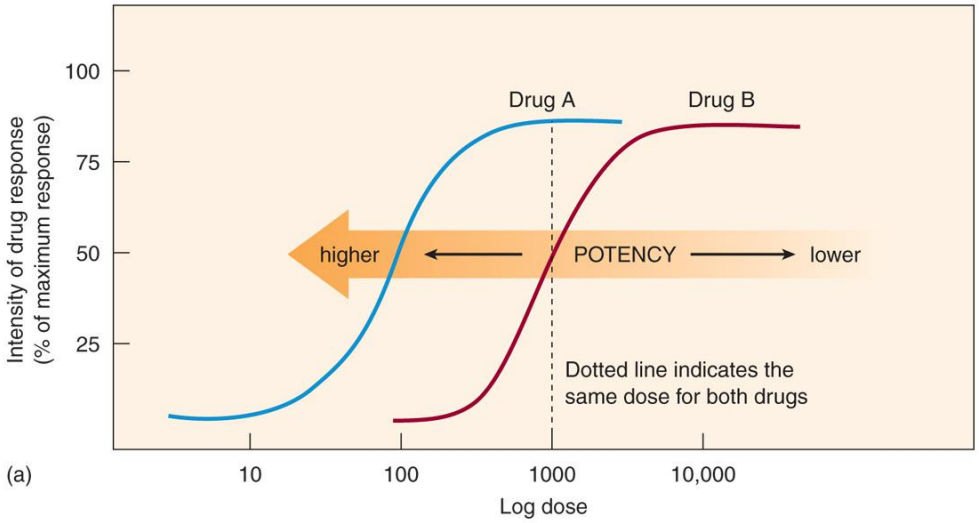
- As the concentration of a drug increases, its pharmacologic effect also increases
- The response is gradual and continuous

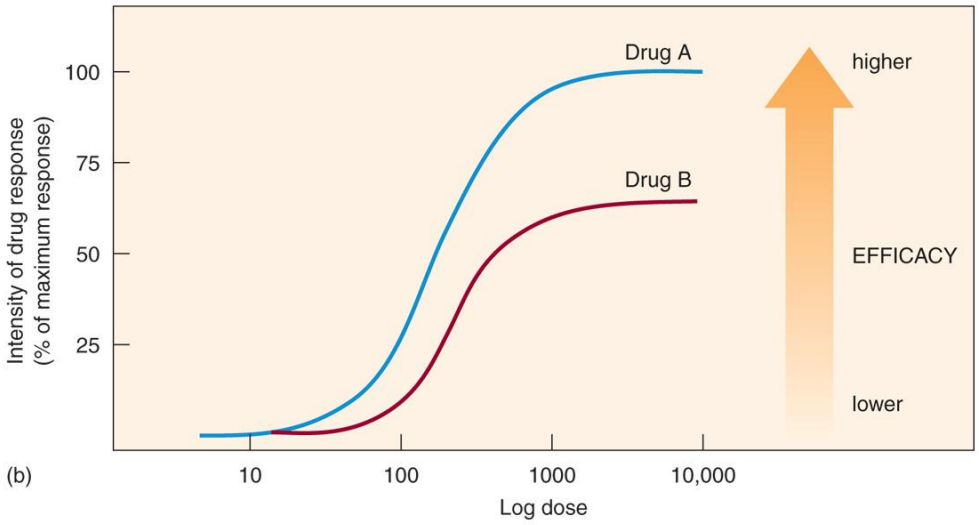


Potency vs Efficacy

- Potency: A measure of the amount of a drug needed to produce an effect of a given magnitude
- EC_{50}: The drug concentration that shows 50% of maximal response
- Efficacy: The ability of a drug to produce a response when it interacts with a receptor




100
75
50
25
Intensity of drug response
(% of maximum response)
Drug A
Drug B
higher
POTENCY
lower
Dotted line indicates the
same dose for both drugs
(a)
10
100
1000
10,000
Log dose


100
75
50
25
Intensity of drug response
(% of maximum response)
Drug A
Drug B
higher
EFFICACY
lower
(b)
10
100
1000
10,000
Log dose

- Agonist: an agent that can bind to a receptor and produce a biologic response

- Agonists usually mimic the actions of the original endogenous ligand on the receptor

(e.g. Norepinephrine on β1 receptor of the heart)

- Agonists stabilize the receptors in their active state

- The magnitude of the drug effect depends on:
  - The concentration of the drug at the receptor site which depends on:
    - The dose of the drug administered
    - The rate of the drug's ADME

Agonists

- Full agonist
- Partial agonists
- Inverse Agonists

Full agonists

- Full agonist: A drug that binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand

- A full agonist has a strong affinity to the receptor and good efficacy

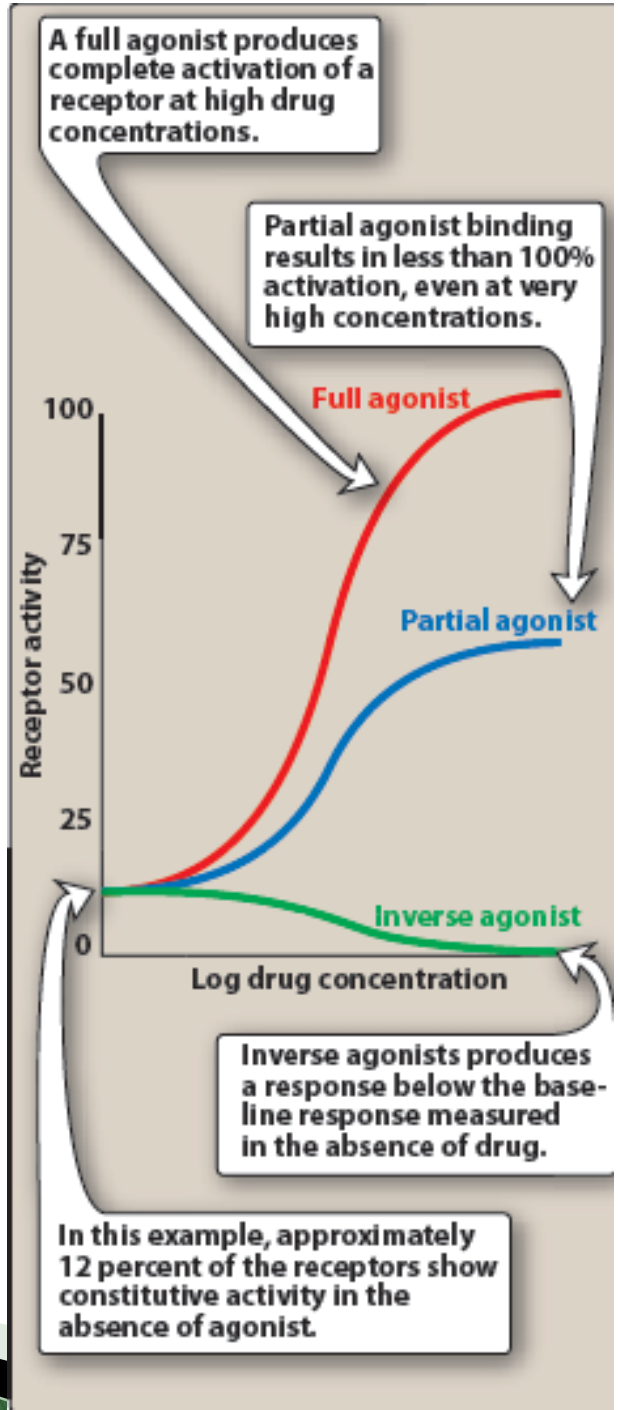
Partial agonists

- Partial agonists have efficacies greater than zero but less than that of a full agonist
- A partial agonist can not produce an Emax of as great a magnitude as a full agonist
- The affinity of a partial agonist might be greater than, less than or equal to a full agonist
- A partial agonist may act as an antagonist of a full agonist

Inverse Agonists

- Stabilize the inactive receptor state
- This decreases the number of activated receptors below that in the absence of the drug
- Inverse agonists reverse the activity of receptors and produce the opposite pharmacological effects of a full agonist

Agonists


A full agonist produces complete activation of a receptor at high drug concentrations.
Partial agonist binding results in less than 100% activation, even at very high concentrations.
Full agonist
Partial agonist
Inverse agonist
100
75
50
25
0
Receptor activity
Log drug concentration
Inverse agonists produces a response below the base-line response measured in the absence of drug.
In this example, approximately 12 percent of the receptors show constitutive activity in the absence of agonist.

Antagonists

- Antagonist: An agent (drug) that decreases or opposes the actions of another drug or endogenous ligand

- An antagonist binds to a receptor and blocks its physiologic response
  (e.g. Antihistamine, used for allergy)

- 2 types of antagonists
  - Competitive antagonists
  - Irreversible antagonists

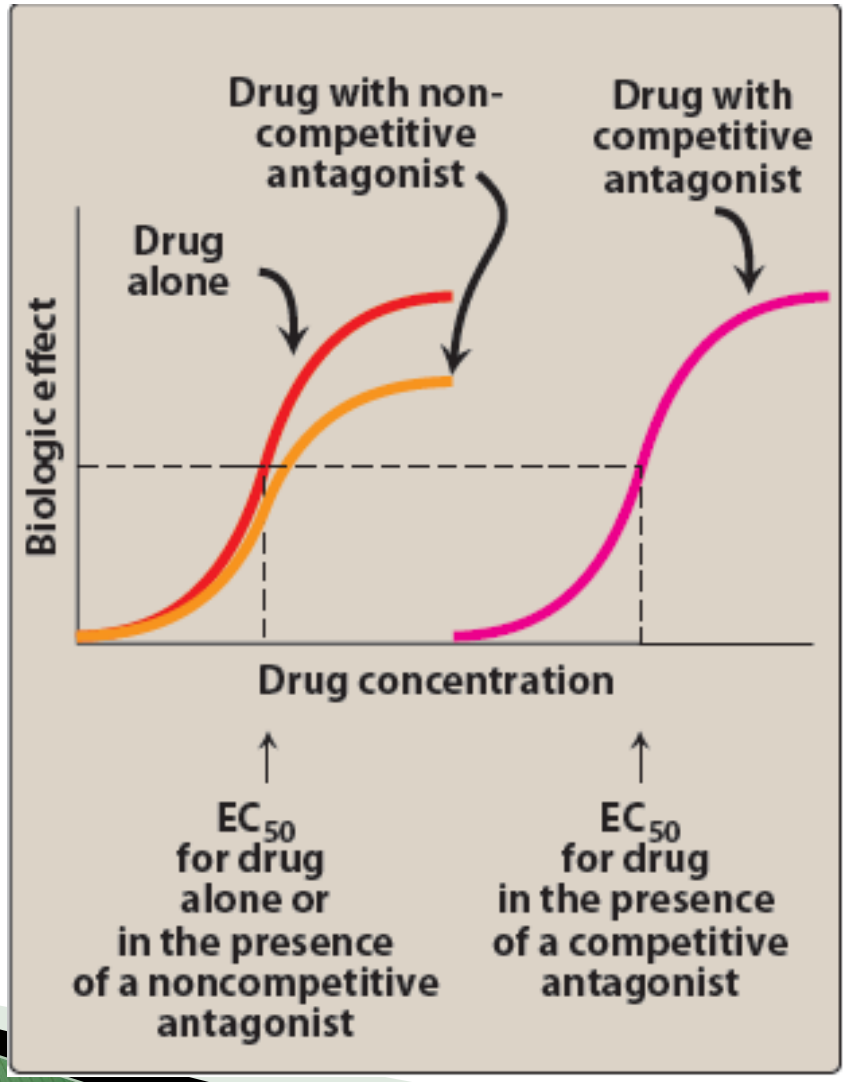
Competitive antagonist

- An antagonist that binds to the same site on the receptor as the agonist
- Prevents an agonist from binding to its receptor and maintains the receptor in its inactive state
- The effect can be overcome by adding more agonist
- Increase EC_{50}

Irreversible antagonists

- Non-competitive
- Cannot be overcome by adding more agonists
- Mechanism:
  - The antagonist binds covalently or with high affinity to the active site of the receptor reducing the amount of the receptor available to the agonist
  - The antagonist binds to a site (allosteric site) preventing the receptor from being activated even when the agonist binds to the active site

Competitive vs non-competitive antagonism



- Functional antagonist
  - Causing effects functionally opposite than those of the agonist while acting at a completely separate receptor than the agonist
- Chemical antagonist
  - Prevents the actions of an agonist by modifying or sequestering the agonist so it is incapable of binding to and activating the receptor
- Pharmacokinetic antagonist
  - Reducing the active drug concentration for example when the drug absorption is decreased or the metabolism and renal excretion are increased

Therapeutic index

- **Therapeutic index** of a drug: the ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in 50% of the population

- Therapeutic index $= \frac{TD_{50}}{ED_{50}}$

TD_{50}: the drug dose the produces a toxic effect in 50% of the population

ED_{50}: the drug dose the produces a therapeutic effect in 50% of the population

- Therapeutic index is a measure of drug safety
- A narrow therapeutic index drug
  (e.g. warfarin, digoxin)
- A large therapeutic index drug
  - more safe to use
  - (e.g. penicillin)