Drug–Receptor Interactions and Pharmacodynamics

*Pharmacodynamics describes the actions of a drug on the body

*Most drugs exert their effects,both beneficial and harmful, by interacting with receptor

*Receptors: is, specialized target macromolecules) present on the cell surface or within the cell

*The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction

Signal Transduction:

Drugs act as signals, and receptors act as signal detectors. A drug is termed an

"agonist' if it binds to a site on a receptor protein and activates it to initiate a series of

reactions that ultimately result in a specific intracellular response

**Second messenger'' or effector molecules are part of the cascade of events that translates agonist binding into a cellular response.

A.The drug-receptor complex

Cells have many different types of receptors, each of which is specific for a particular agonist and produces a unique response

****it is important to know that not all drugs exert effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing stomach upset.

B.Receptor states

Receptors exist in at least two states, inactive (R) and active (R*), that are in reversible equilibrium with one another, usually favoring the inactive state. Binding of agonists causes the equilibrium to shift from R to R* to produce a biologic effect. Antagonists are drugs that bind to the receptor but do not increase the fraction of R*, instead stabilizing the fraction of R.

**Some drugs (partial agonists) shift the equilibrium from R to R*, but the fraction of R* is less than that caused by an agonist

***agonists, antagonists, and partial agonists are examples of molecules or ligands thatbind to the activation site on the receptor and can affect the fraction of R*.

C. Major receptor families

A receptor is defined as any biologic molecule to which a drug binds and produces a measurable response

receptors may be divided into four families:

1) ligand-gated ion channels: These receptors allow ions to pass across cell membranes when activated For example, stimulation of the nicotinic receptor by acetylcholine results in sodium influx and potassium outflux, generating an action potential in a neuron or contraction in skeletal muscle.

***duration few millisecond

2) G protein-coupled receptors

GPCRs activate intracellular signaling pathways. Example: adrenergic receptor

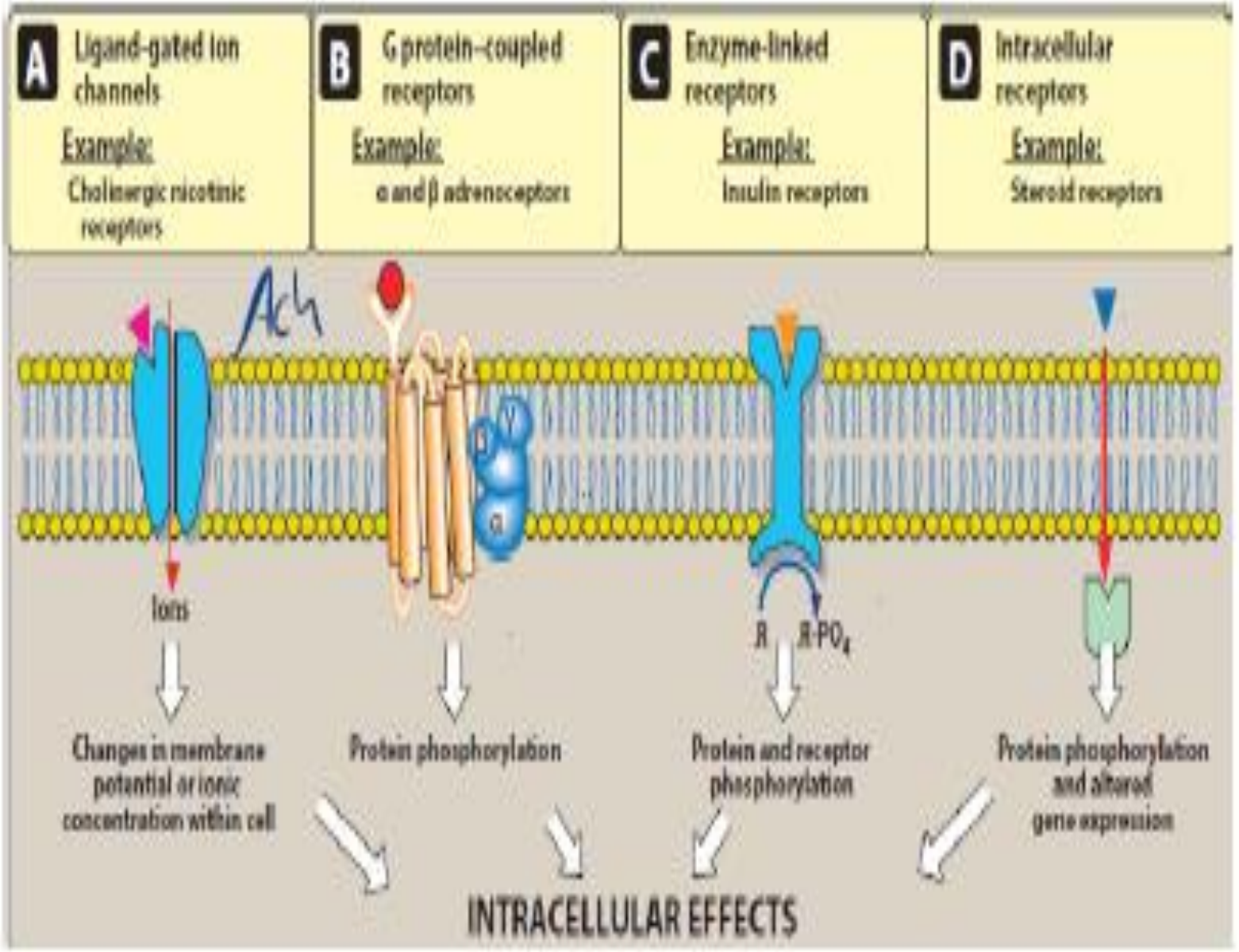
Duration second to minutes

3) enzyme-linked receptors. These receptors, when activated, initiate intracellular enzymatic activity. Example :insulin receptor.**duration minutes to hours

4) intracellular receptor.

Intracellular receptors are located inside the cell and are involved in regulating gene expression. Example: steroid hormone receptors

***Duration hours to days


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
Ach
Ions
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 Relationship

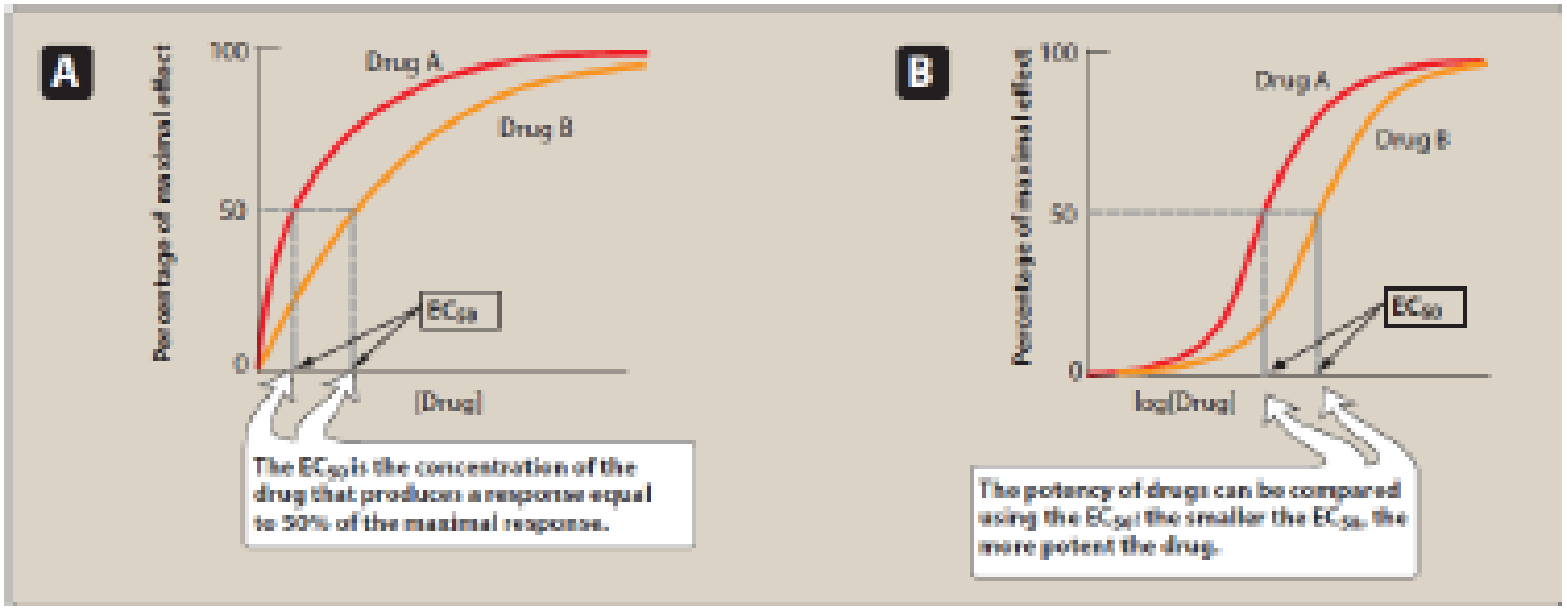
This relationship defines how a drug's effect changes with different doses.

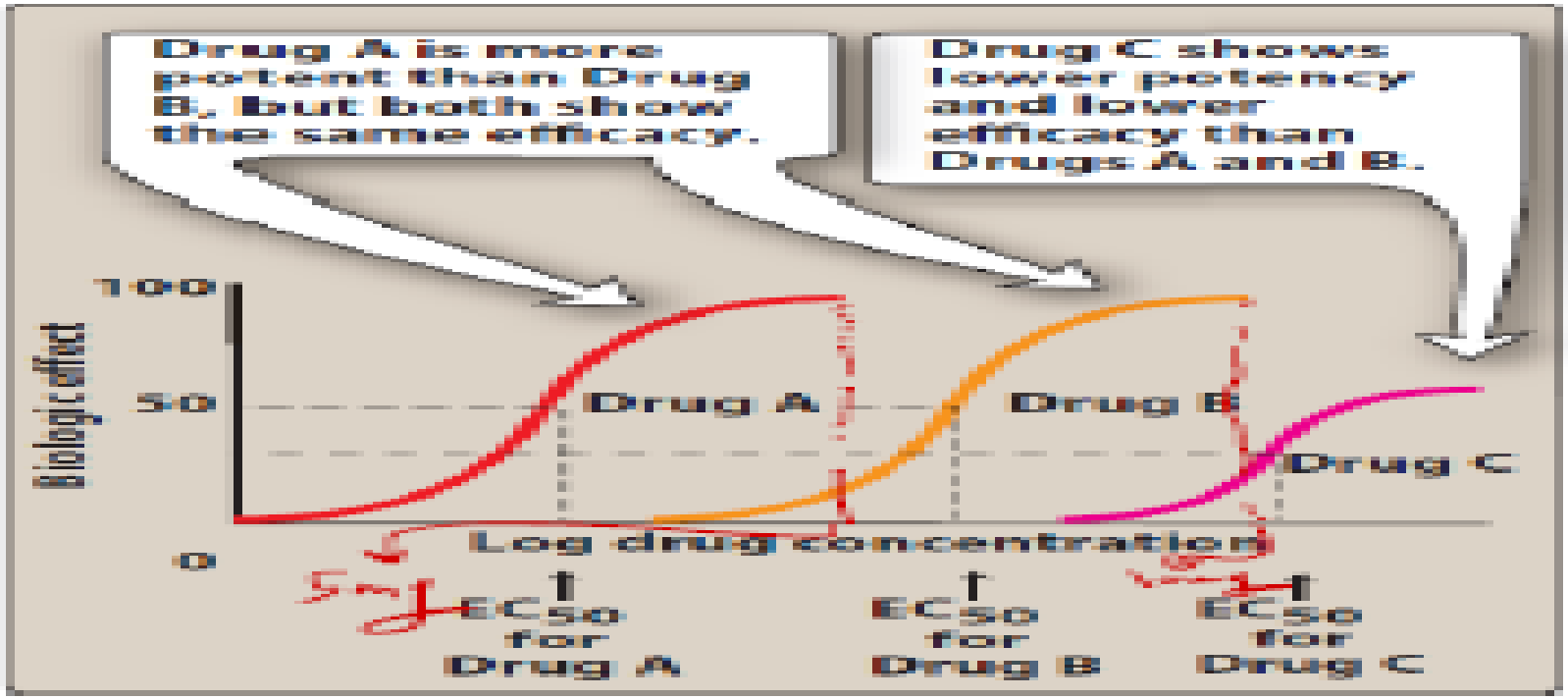
Potency: Potency is a measure of the amount of drug necessary to produce an effect.

**The concentration of drug producing 50% of the maximum effect (EC50) is often used to determine potency.

.Efficacy: The maximum effect a drug can produce.

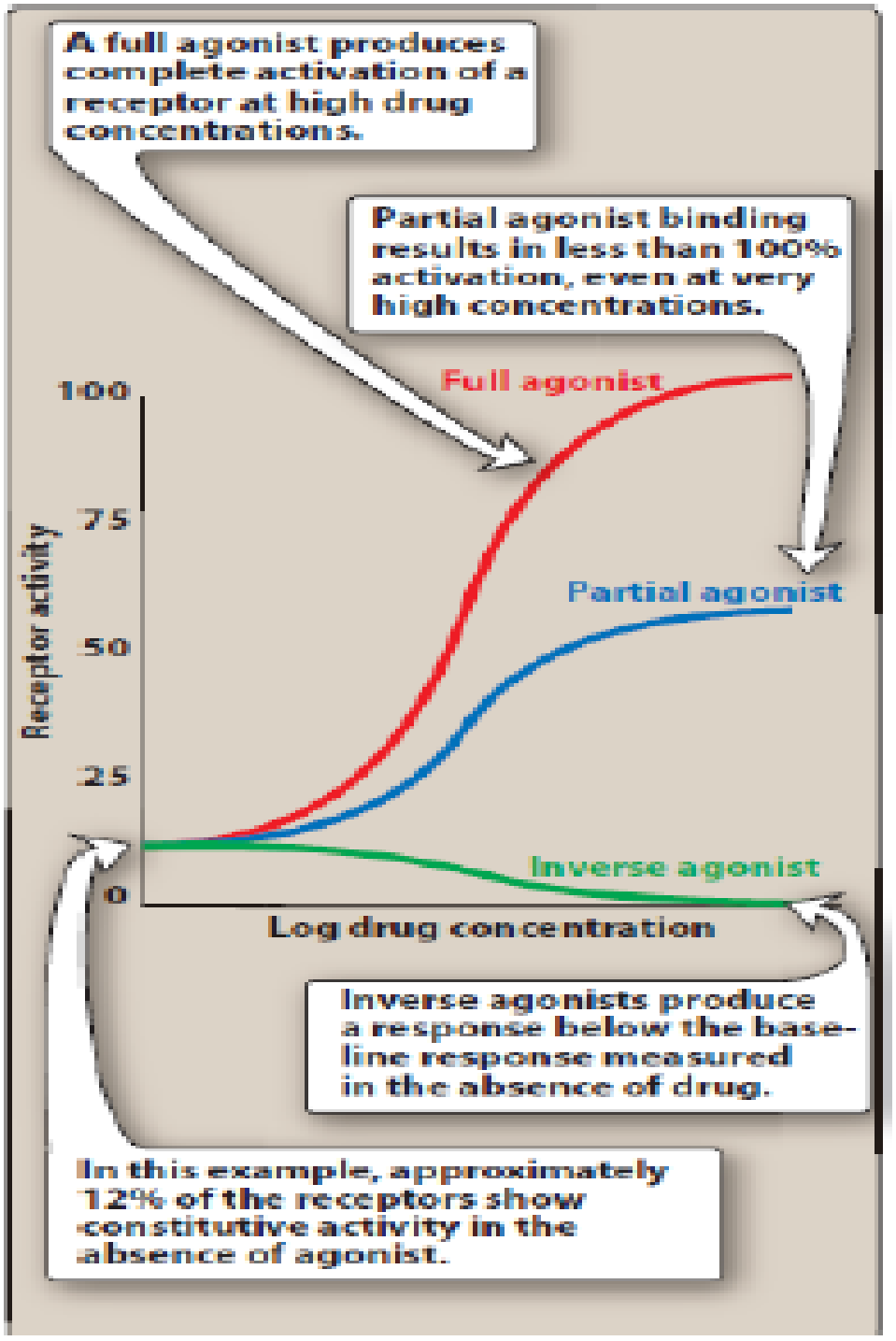
**** Efficacy is a more clinically useful characteristic than potency, since a drug with greater efficacy is more therapeutically beneficial than one that is more potent


A
Percentage of maximal effect
100
50
0
Drug A
Drug B
EC50
[Drug]
The EC50 is the concentration of the drug that produces a response equal to 50% of the maximal response.
B
Percentage of maximal effect
100
50
0
Drug A
Drug B
EC50
log[Drug]
The potency of drugs can be compared using the EC50: the smaller the EC50, the more potent the drug.


Drug A is more potent than Drug B, but both show the same efficacy.
Drug C shows lower potency and lower efficacy than Drugs A and B.
Biologic effect
100
50
0
Drug A
Drug B
Drug C
Log drug concentration
5 mg
EC50 for Drug A
EC50 for Drug B
EC50 for Drug C

Drug-Receptor Interactions

- Drugs can act as agonists or antagonists at receptor sites, affecting receptor function.
- Agonists :are drugs that activate receptors to produce a biological response. Full agonists: produce the maximum response, while partial agonists produce a weaker response.
- Antagonists block receptors and inhibit the action of agonists. They can be competitive or non-competitive

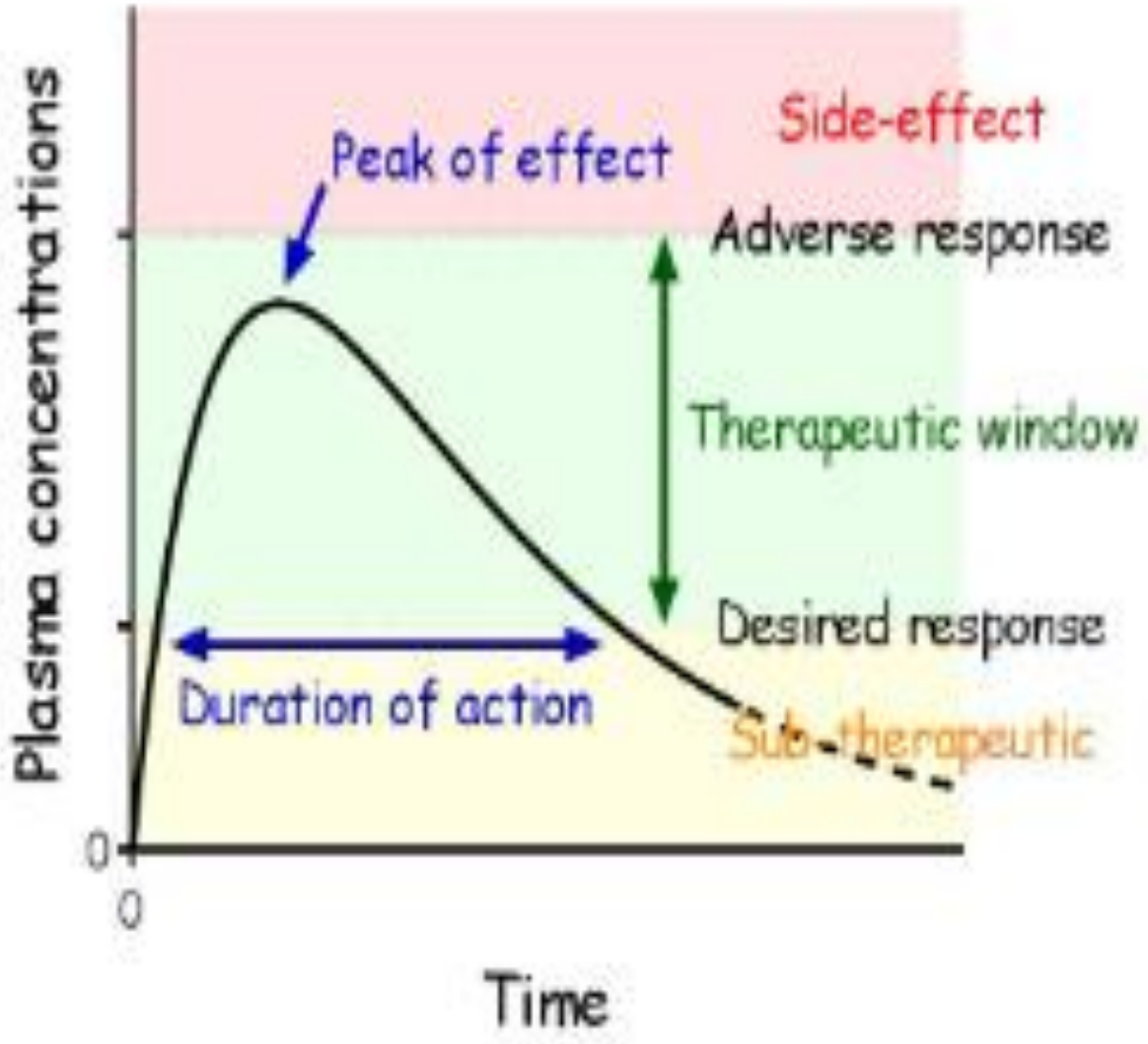

A full agonist produces complete activation of a receptor at high drug concentrations.
Partial agonist binding results in less than 100% activation, even at very high concentrations.
Full agonist
Partial agonist
Inverse agonist
100
75
50
25
0
Receptor activity
Log drug concentration
Inverse agonists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

Therapeutic index

The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in

half the population (TD50) to the dose that produces a clinically desired or effective

response (ED50) in half the population


Plasma concentrations
Peak of effect
Side-effect
Adverse response
Therapeutic window
Desired response
Duration of action
Sub-therapeutic
0
0
Time