4. Intracellular receptors

- The ligand must diffuse into the cell to interact with the receptor
- Drug factors are crucial
- Upon binding its target, the drug-receptor complex stimulate a transcriptional factor to induce certain genes.
- Response occurs in hours to days
- Example : Steroids

Signal transduction

- **Signal amplification :**

  - More than one G-protein may be activated

  - Secondary messenger activation lasts for long time

  The end result is an amplified response

- **Desensitization and down-regulation of receptors**

  - Chronic exposure of the ligand to the receptor leads to its downregulation (as a protective mechanism).

  - Receptor expression may be reduced or it may be engulfed by endocytosis.

Receptor desensitization

- Also termed as down regulation
- Prolonged exposure of receptors to agonists
- Common consequence in clinical practice
- May occur only for a particular agonist (homologus desensitization) or
- To more than one agonist (Heterogenous Desensitization)
- Associated with tolerance to drugs : as in BDZ and morphine

Agonist/ Antagonist

- “Drugs that bind to physiological receptors and mimic the regulatory effects of the endogenous signaling compounds are termed ***agonists***”

- “Drugs bind to receptors without regulatory effect, but their binding blocks the binding of the endogenous agonist are termed ***antagonists”***

Partial Agonist/Inverse Agonist

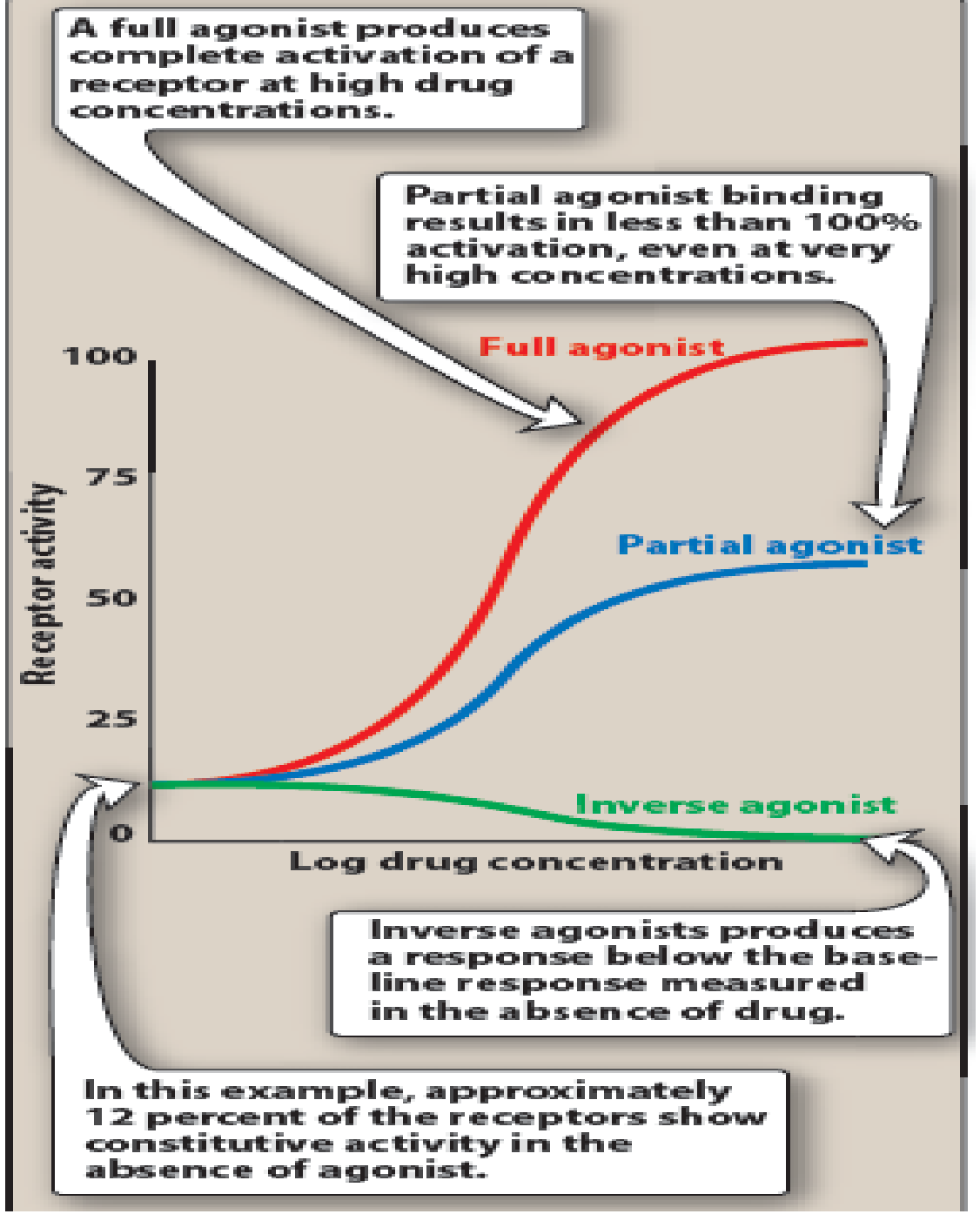
- Agents that are only partly as effective as agonists no matter the amount employed are termed ***partial agonists***

- and those which stabilize the receptor in its inactive conformation are termed ***inverse agonists***

Partial Agonist

- combine with receptors and activate them, but are incapable of eliciting a maximal response, no matter how high their concentration may be.(low efficacy)
- Ex: **buprenorphine (a partial agonist** at morphine mu-receptors)
- partial agonists antagonize the effect of a full agonist

sine they both compete for the same receptor


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.

Antagonism

Competitive Antagonist

- Compete with Agonist on the same receptor (reversible)

Examples : Famotidine Vs hitamine on H2 receptors

- Increasing Comp. Agonist dose decreases Antagonist effect

Non competitive Antagonist

- Does not compete with Agonist
- Bind irreversibly, to receptor

Example : phenoxybenzamine on adrenaline receptors

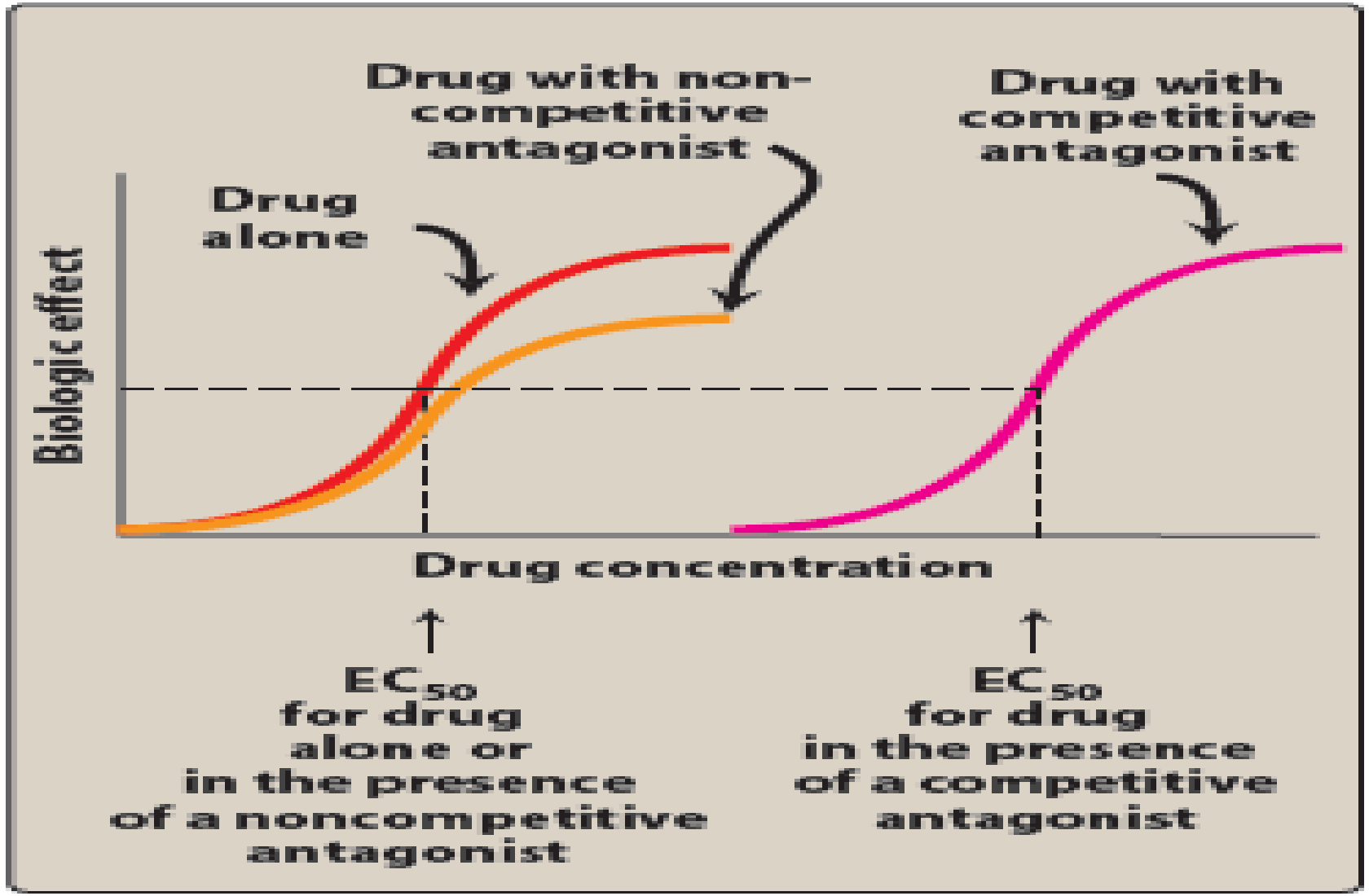
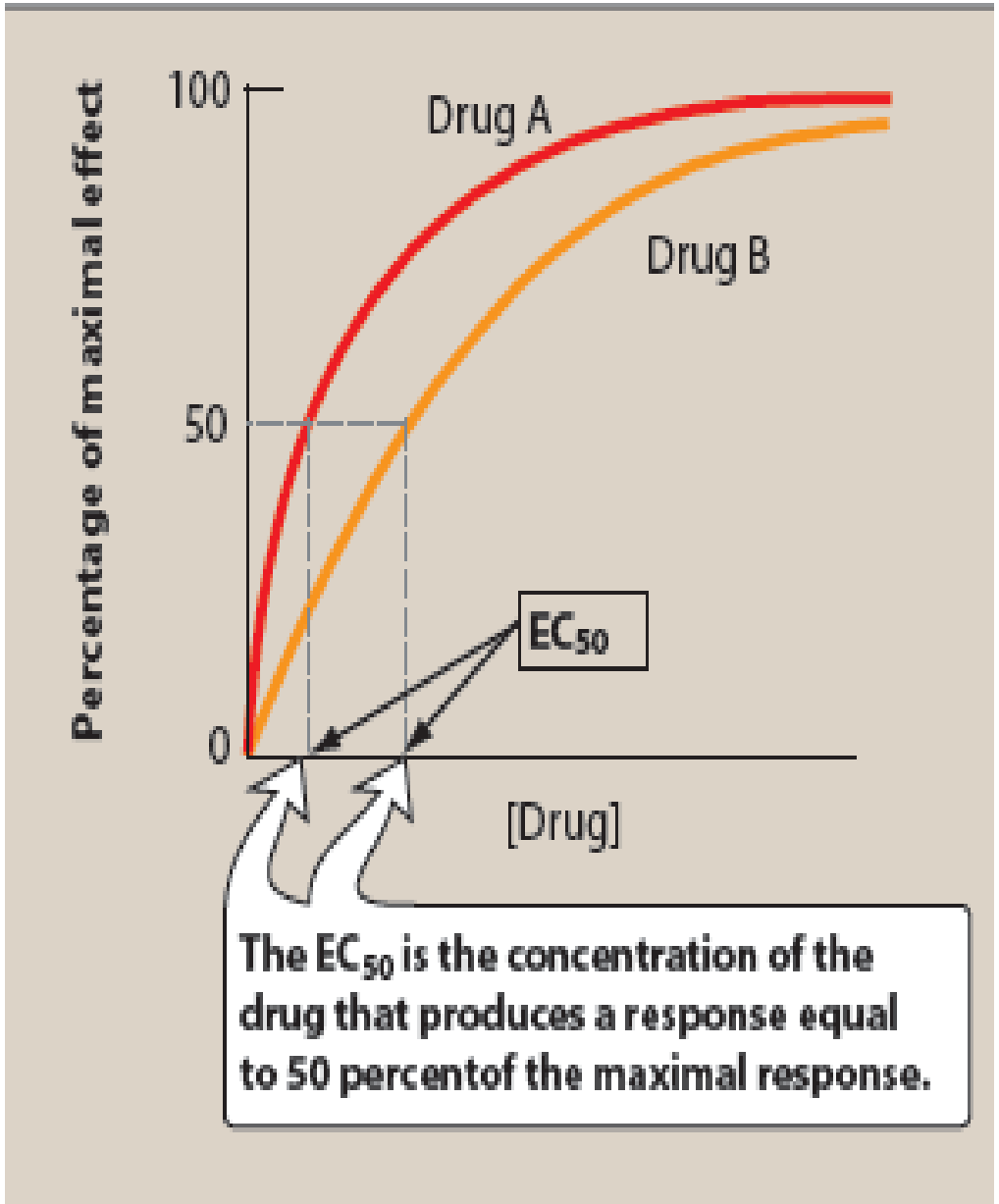


Figure 2.12
Effects of drug antagonists. EC_{50} = drug dose that shows 50 percent of maximal response.

DOSE–RESPONSE RELATIONSHIPS

1. **Graded dose–response relations**

- As the concentration of a drug increases, the magnitude of its pharmacologic effect also increases
- The response is continuous and gradual
- A graded dose–response curves can be used to determine :
  - **Drug Potency**
  - **Drug Efficacy**

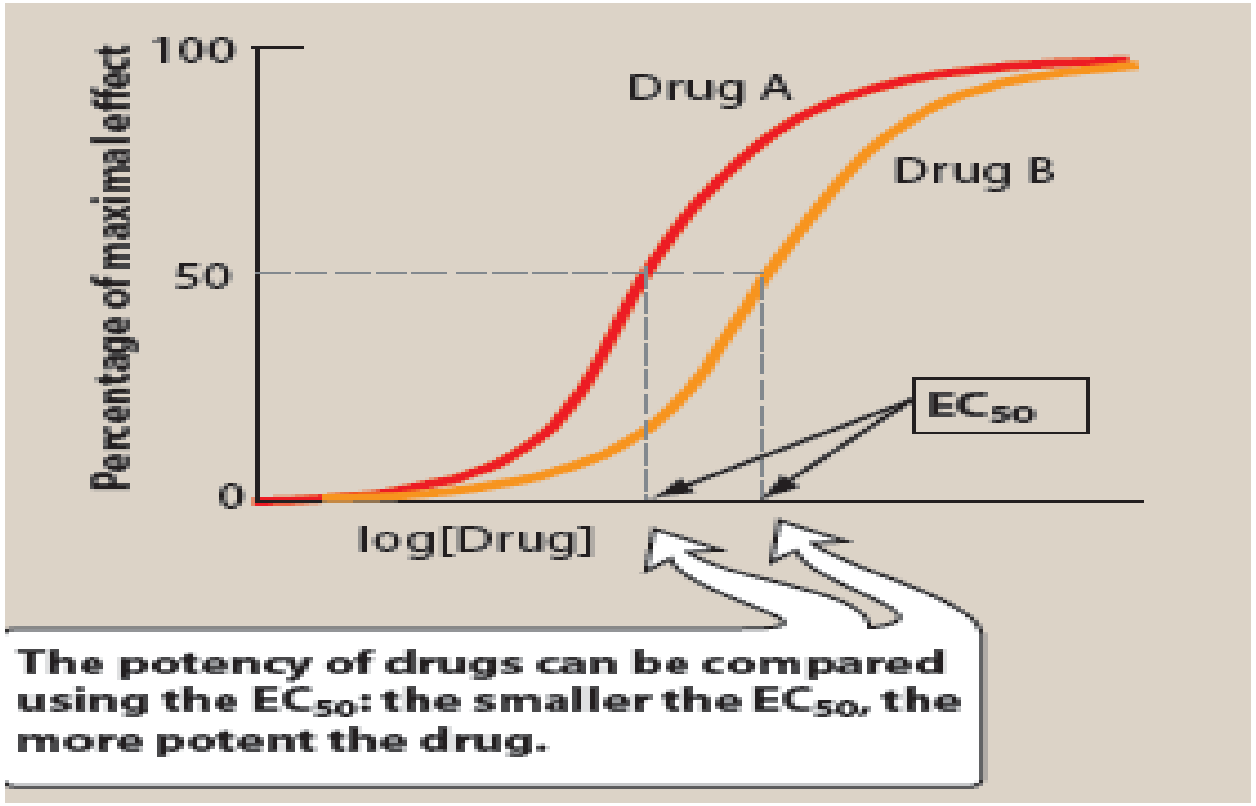


Graded dose-response curve:

- Shows gradual increase
-EC50 can be determined (potency)
- Also Efficacy can be determined

Potency

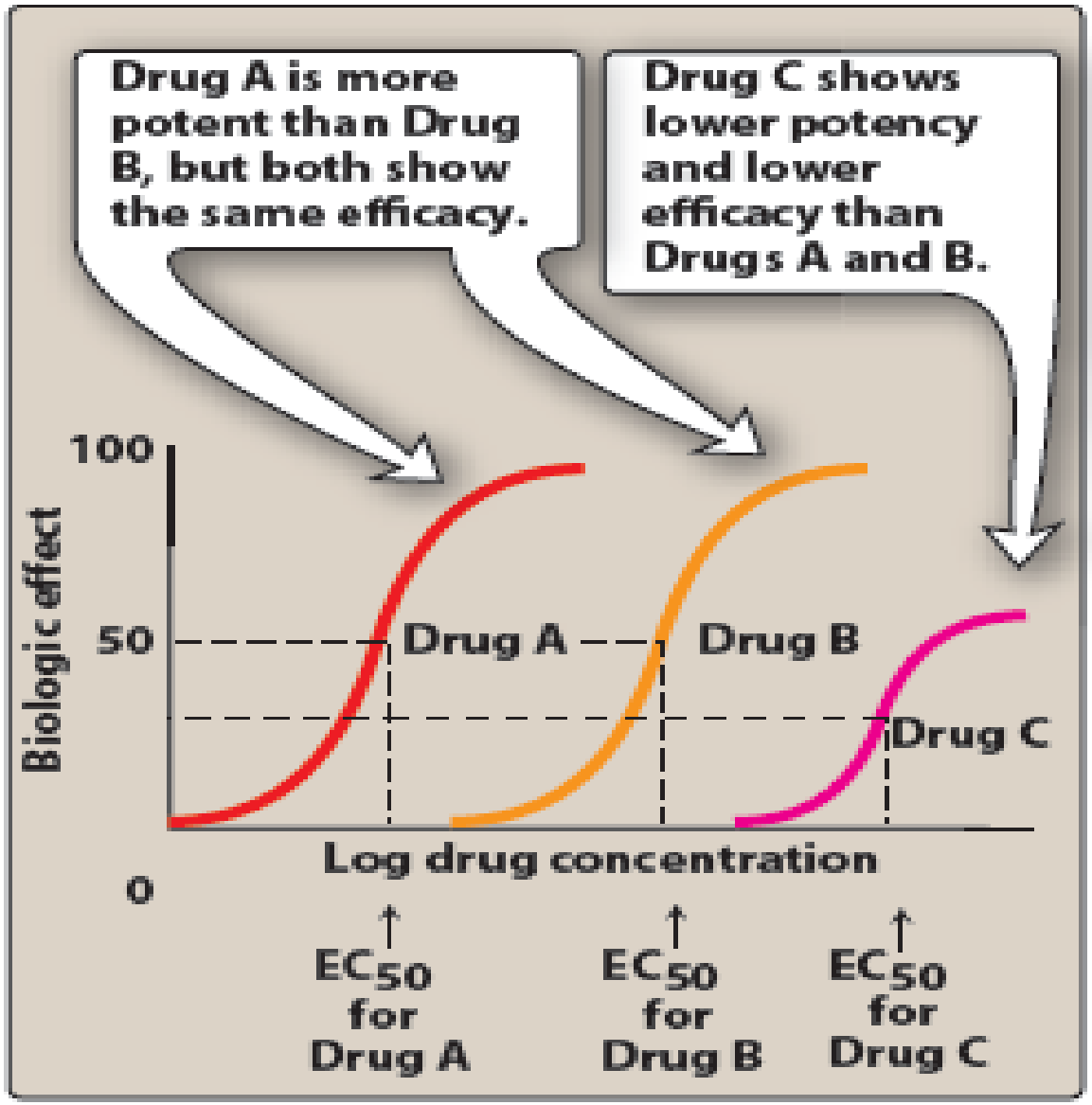
- “A measure of the **amount of drug** necessary to produce an effect of a given magnitude.”
- The concentration of drug producing an effect that is 50 percent of the maximum is used to determine potency and is commonly designated as the EC50


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.

Efficacy

- “The ability of a drug to elicit a **response** when it interacts with a receptor”
- Efficacy, is more important than drug potency. A drug with greater efficacy is more therapeutically beneficial than one that is more potent.

- Efficacy deals with drug ability to bind receptor and exert a clinical response



Efficacy(E_{max})

Non receptor mechanisms

- No specific biological receptor
- Based on properties of the drug(chemical)
- EX :antiacids, osmotic diuretics