Introduction

- Pharmacology is the study of the biochemical and physiological aspects of the drug effects including absorption, distribution, metabolism, elimination, toxicity and specific mechanism of action.

- The main areas of pharmacology are:

  A. Pharmacokinatics: the way the body handle drug absorption, distribution, biotransformation, and excretion.

  B. Pharmacodynamics: the study of the biochemical and physiological effect of the drugs and their mechanism of action.

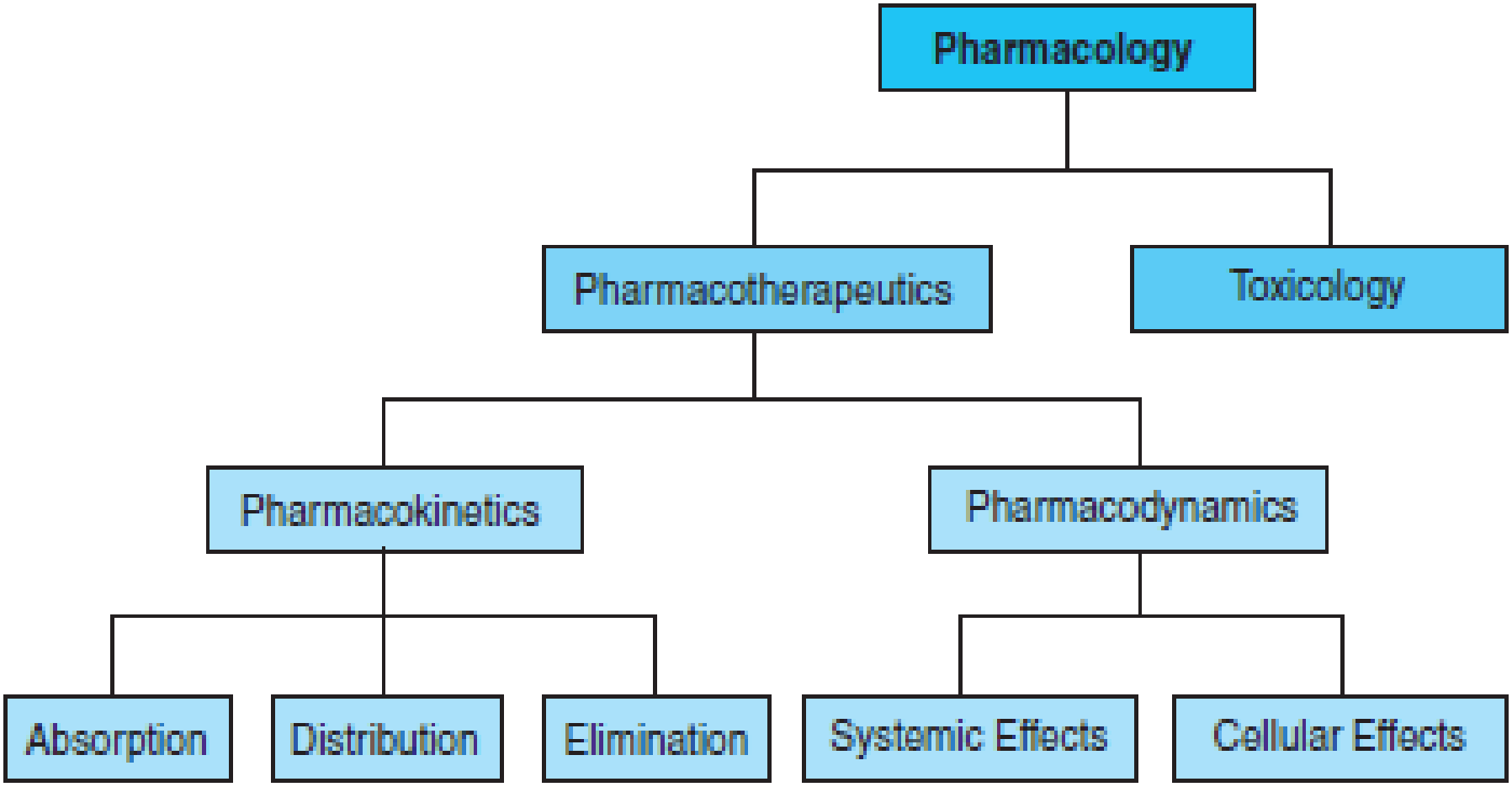


FIGURE 1–1 ▼ Areas of study within pharmacology.

Drug Naming

- **Chemical Name** - describe chemical structure (rarely seen in medical literature)
- **Generic Name** - a name assigned to drug that can be used by anyone (not proprietary)
- **Trade Name** - Proprietary name given to the drug by the manufacturer

Table 1–1 EXAMPLES OF DRUG NOMENCLATURE

Chemical	Generic (Nonproprietary)	Trade/Brand-Name (Proprietary)
N-Acetyl-*p*-aminophenol	Acetaminophen	Tylenol, Panadol, many others
3,4-Dihydroxyphenyl-L-alanine	Levodopa	Larodopa
5,5-Phenylethylbarbituric acid	Phenobarbital	Luminal, Eskabarb
7-Chloro-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one	Diazepam	Valium

Over the counter????

Mechanism of drug action

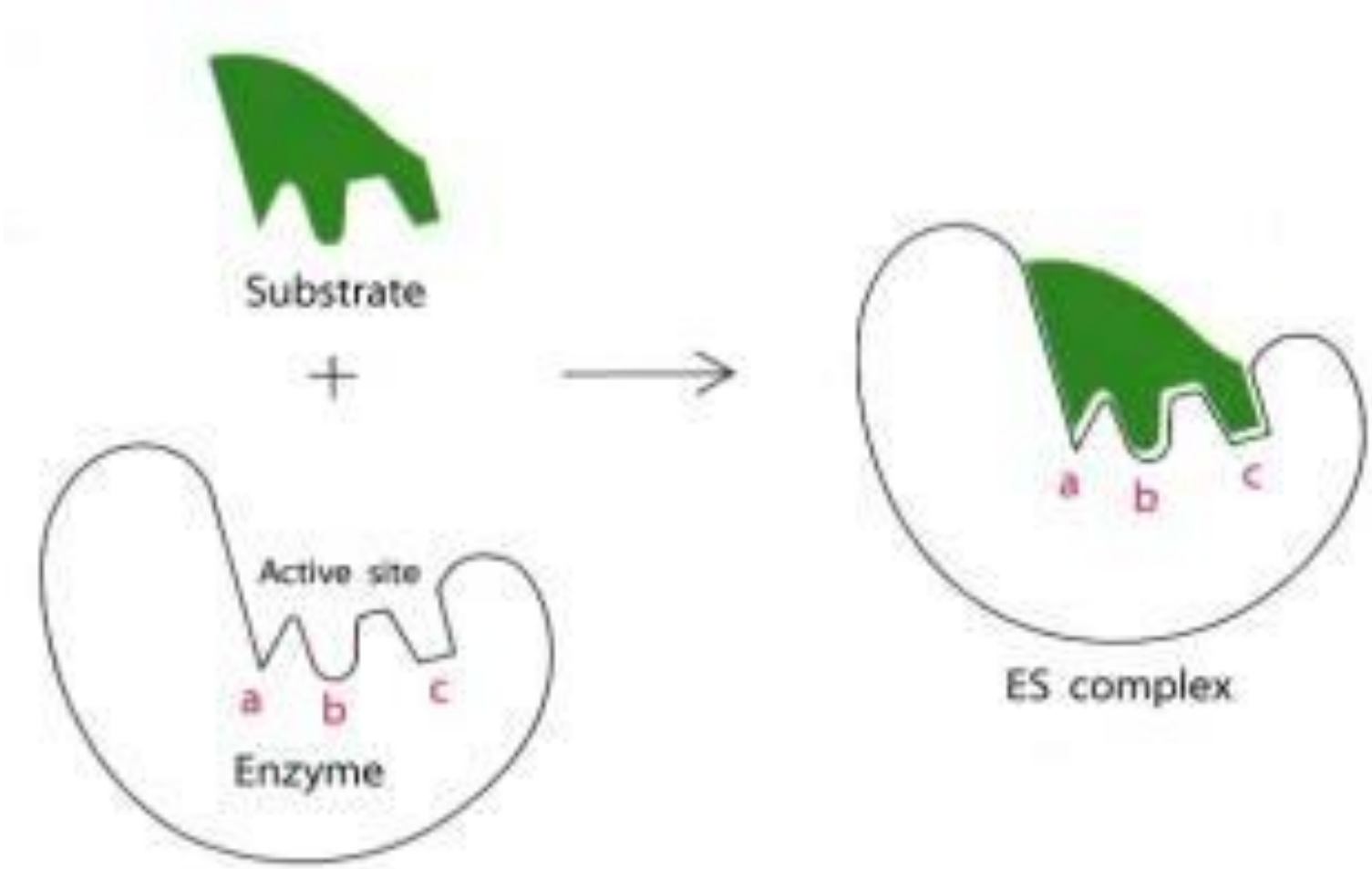
- Most drugs exert their effect by intercting with a specialized target macromolecules, called receptors, present on the cell surface or intracellularly.

- The receptors will transduce the binding into a response by causing a conformational changes or biochemical effect.

- Receptors are large macromolecules with a well-defined 3D shape.

- The two fundamental properties underlying specificity in drug-receptor interactions are complementarity of shape between drug and receptor, and complementarity between the electrostatic, hydrophobic, and hydrogen bonding surfaces of each component.

Model of Drug/Receptor Binding



Receptors properties

- differentiated activity of the target cell.

  Example: adrenergic receptors

  ➢enhances cardiac contractility

  ➢ relaxation of smooth muscle cells

Why and How???????????

- capacity to significantly amplify a physiological signal.

How

Major receptor families

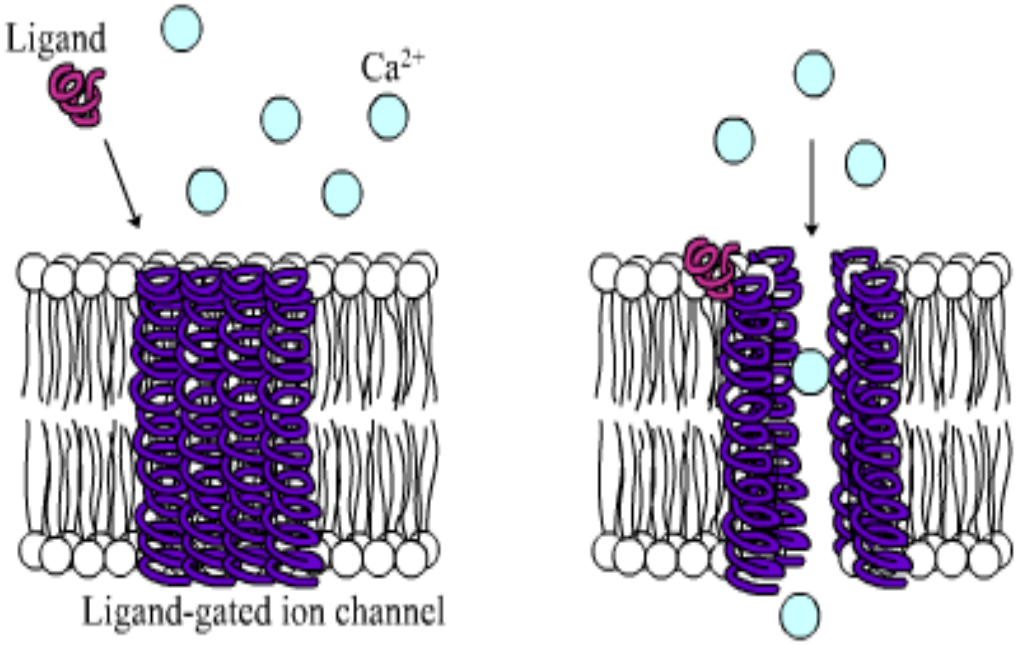
- **Ligand-gated ion channels**
- **G protein-coupled receptors**
- **Enzyme-linked receptors**
- **Intercellular receptors**

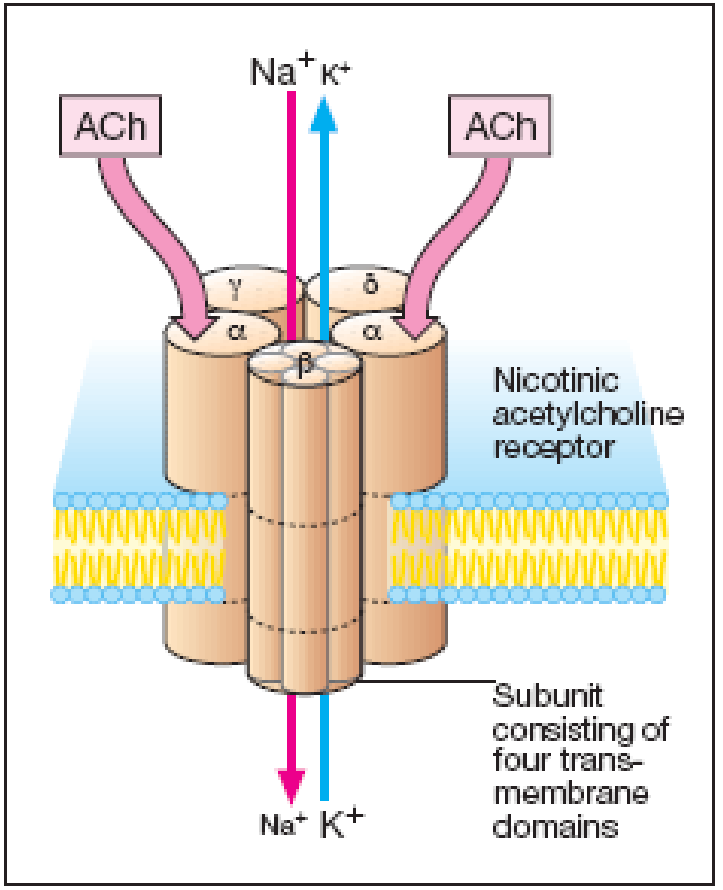
Ligand-gated ion channels

- Responsible for regulation of the flow of ions channels across cell membranes.

- Regulated by binding of a ligand to the channels.

- The best example being the nicotinic receptor, in which the binding of the acetylcholine results in sodium influx and the activation of contraction in skeletal muscle



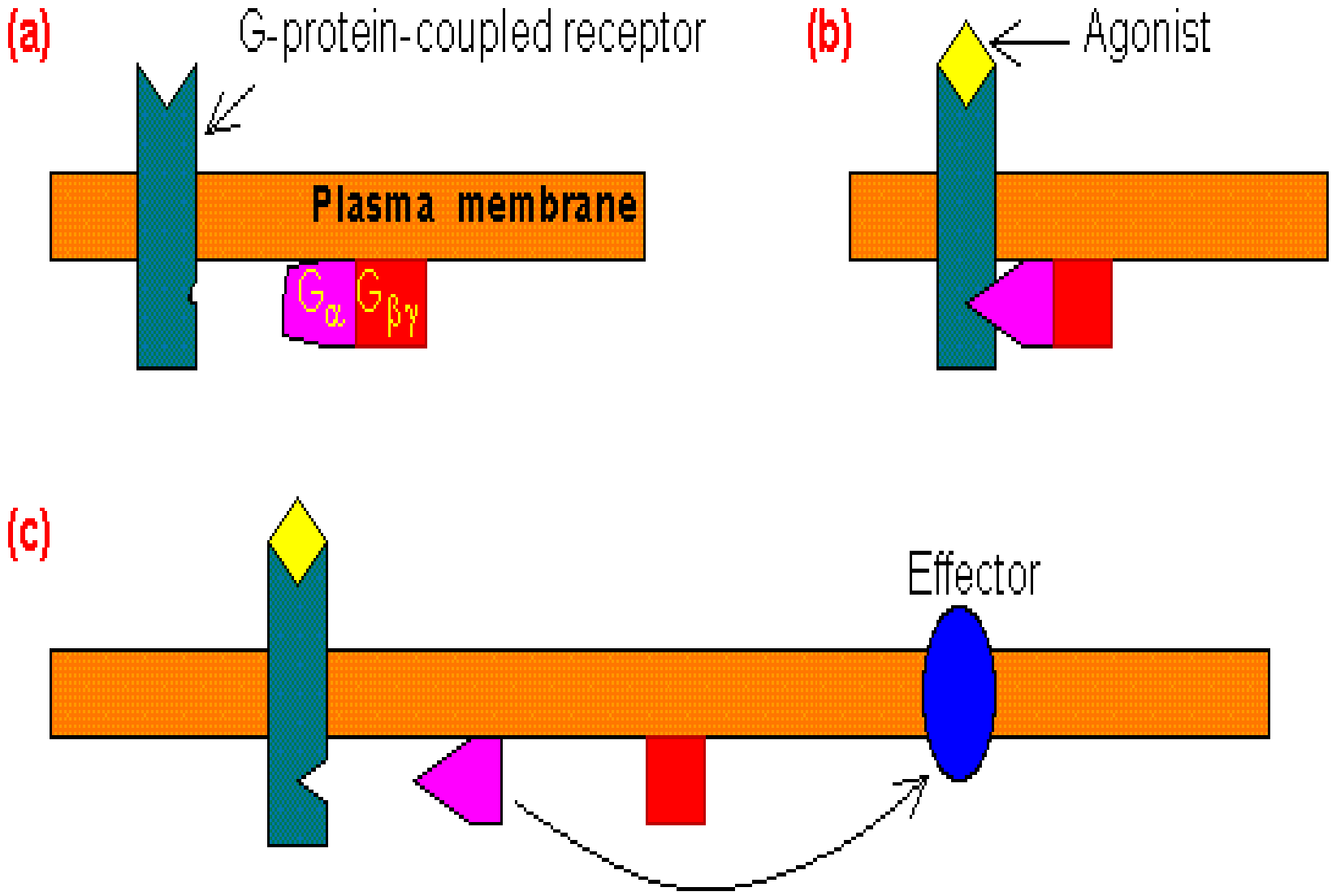


B. Ligand-gated ion channel

G protein-coupled receptors

- Receptors on the inner face of the plasma membrane regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as G proteins.

- Some hormones peptide receptors and neurotransmitter receptors (e.g., adrenergic and moscarinic receptors depend n the G proteins) mediate their action on cells.


(a)
G-protein-coupled receptor
Plasma membrane
G_α $G_{\beta\gamma}$
(b)
Agonist
(c)
Effector

Enzyme-linked receptors

- Binding of the ligand to the extra cellular domain activates or inhibits the related cytosolic enzyme.

- The most common are the receptors that have a tyrosine kinase activity as part of their structure, in which the binding results in the phosphorylation of tyrosine residues of specific protein.

- The addition of phosphate group can modify the three-dimensional structure of the target protein, and so resulting in molecular switch.

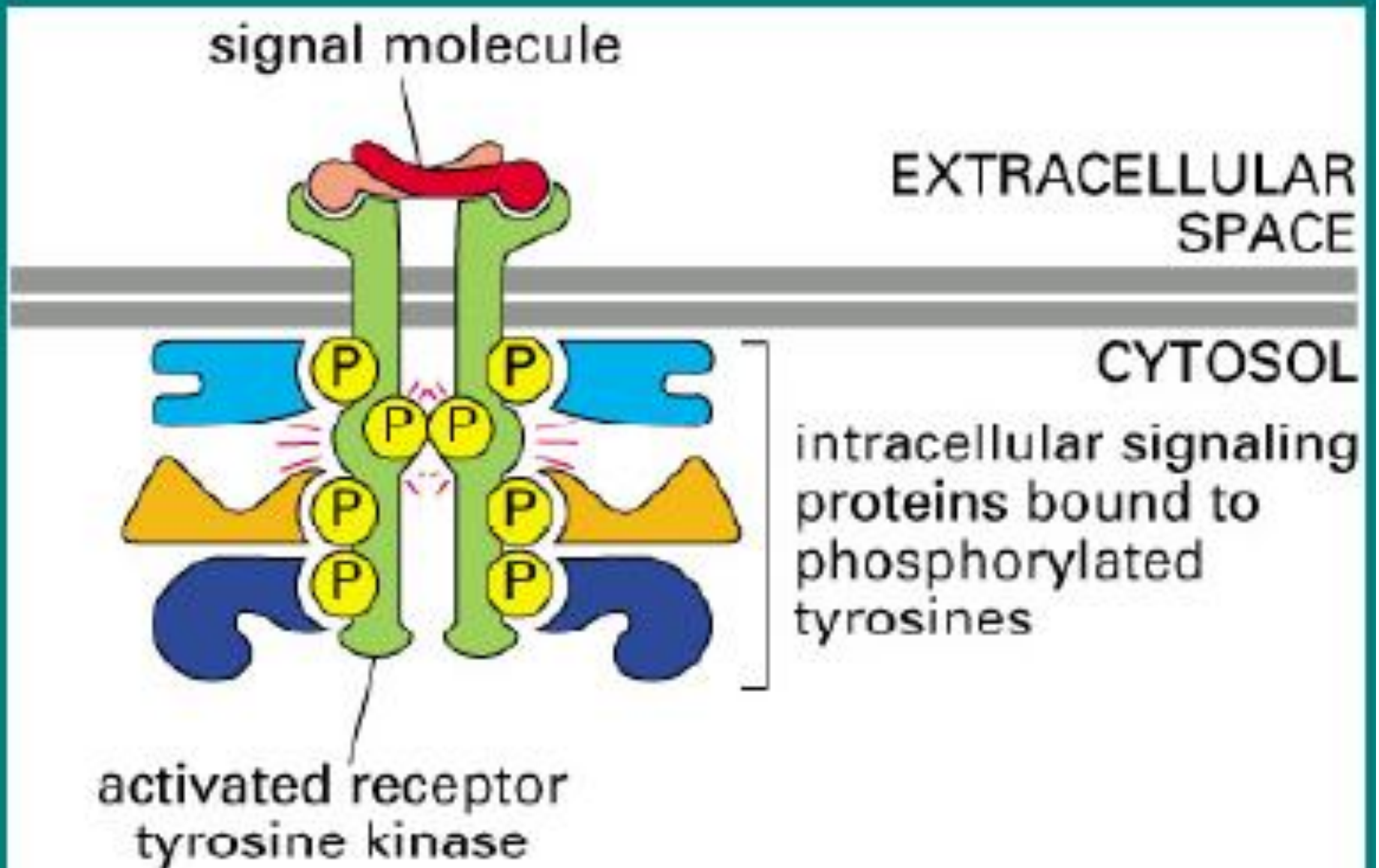
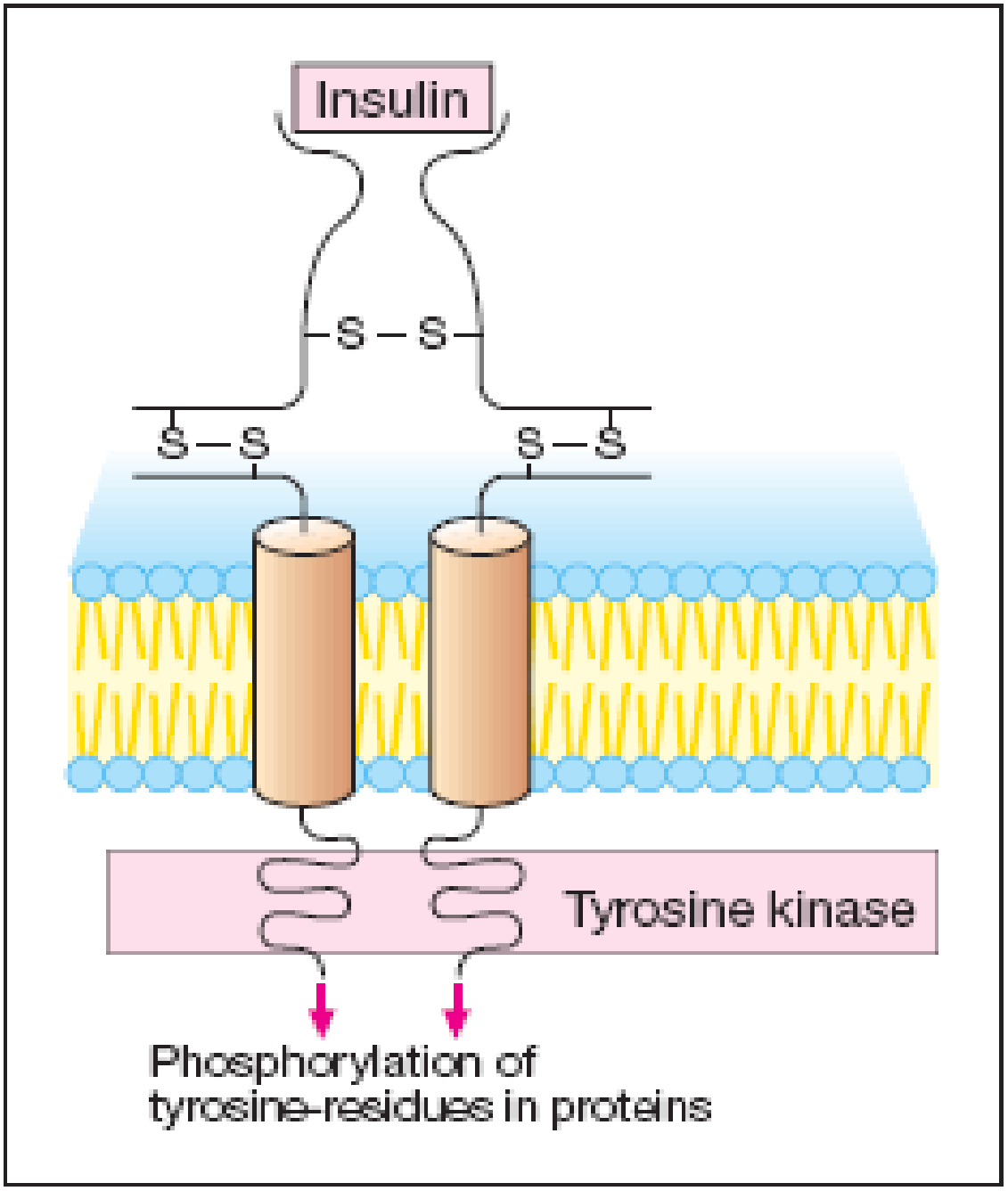


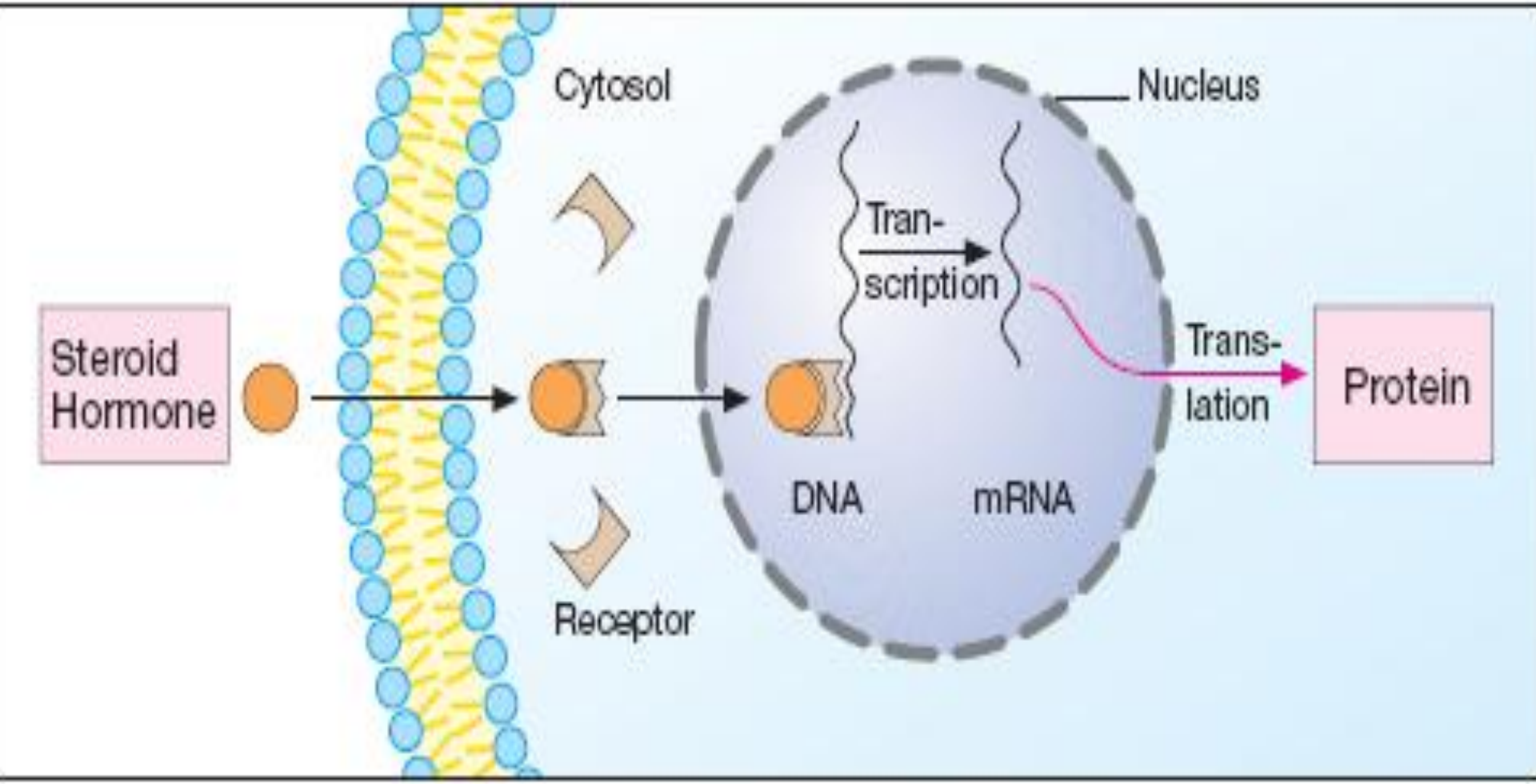
Figure 15–52. Molecular Biology of the Cell, 4th Edition.



C. Ligand-regulated enzyme

Intercellular receptors

- In this family the ligand must diffuse into the cell to interact with the receptors.
- Therefore the ligand must have sufficient lipid solubilities to be able to move across the target cell membranes.
- The best example being the steroids hormones. In which the activated ligand-receptor complex migrate to the nucleus, where it bind to a specific DNA sequences, resulting in regulation of the gene expression.



D. Protein synthesis-regulating receptor

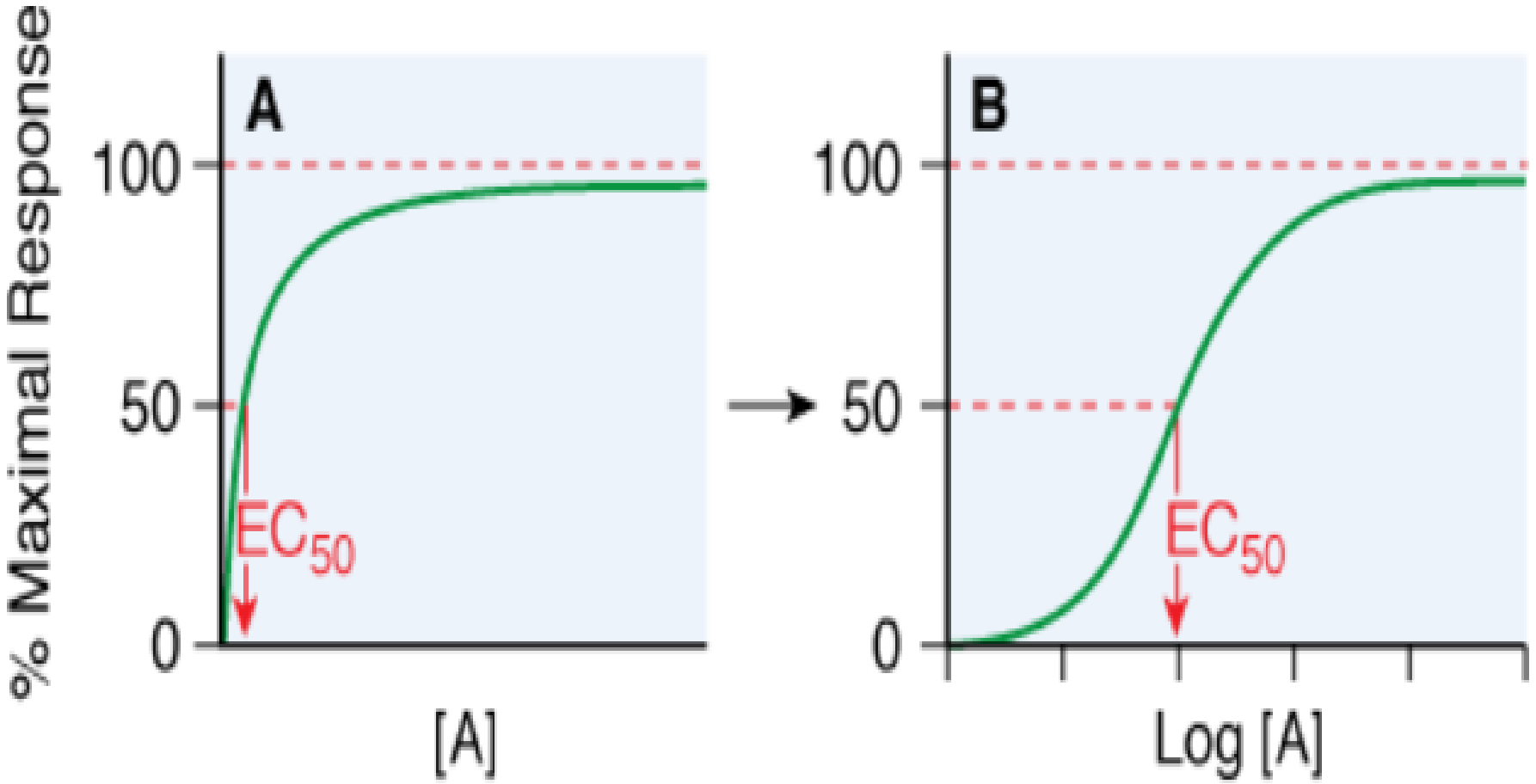
Dose response relationships

- Graduate dose-response relations

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

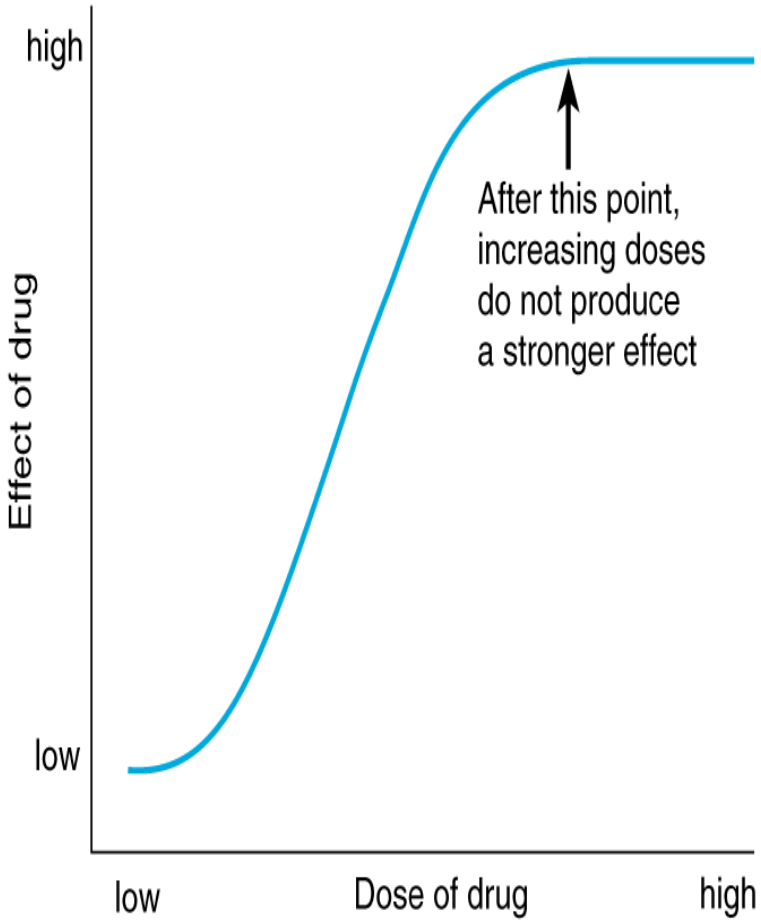
At a certain dose, the effect will reach a maximum level, which is called the ceiling effect or Emax.

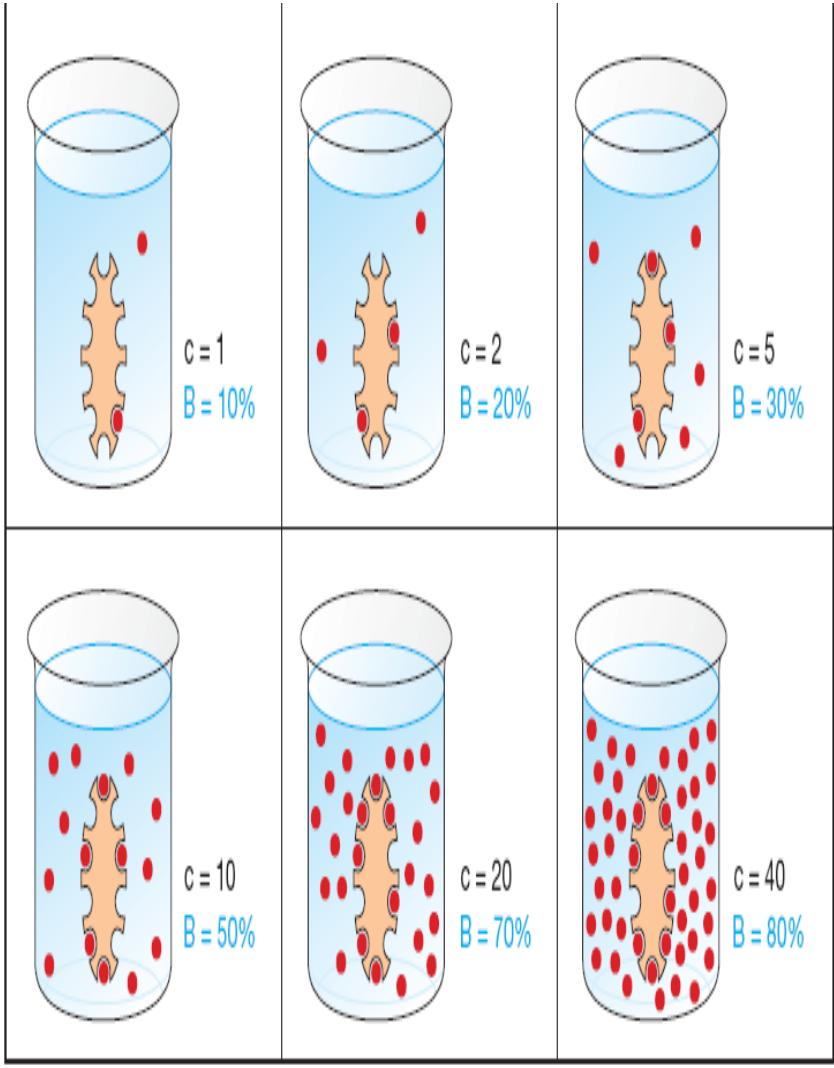
Graduate dose-response curve



Graduate dose-response curve

▶ Dose-Response Curve





Potency and efficacy

- Potency is a measure of the amount of drug necessary to produce an effect of a given magnitude.

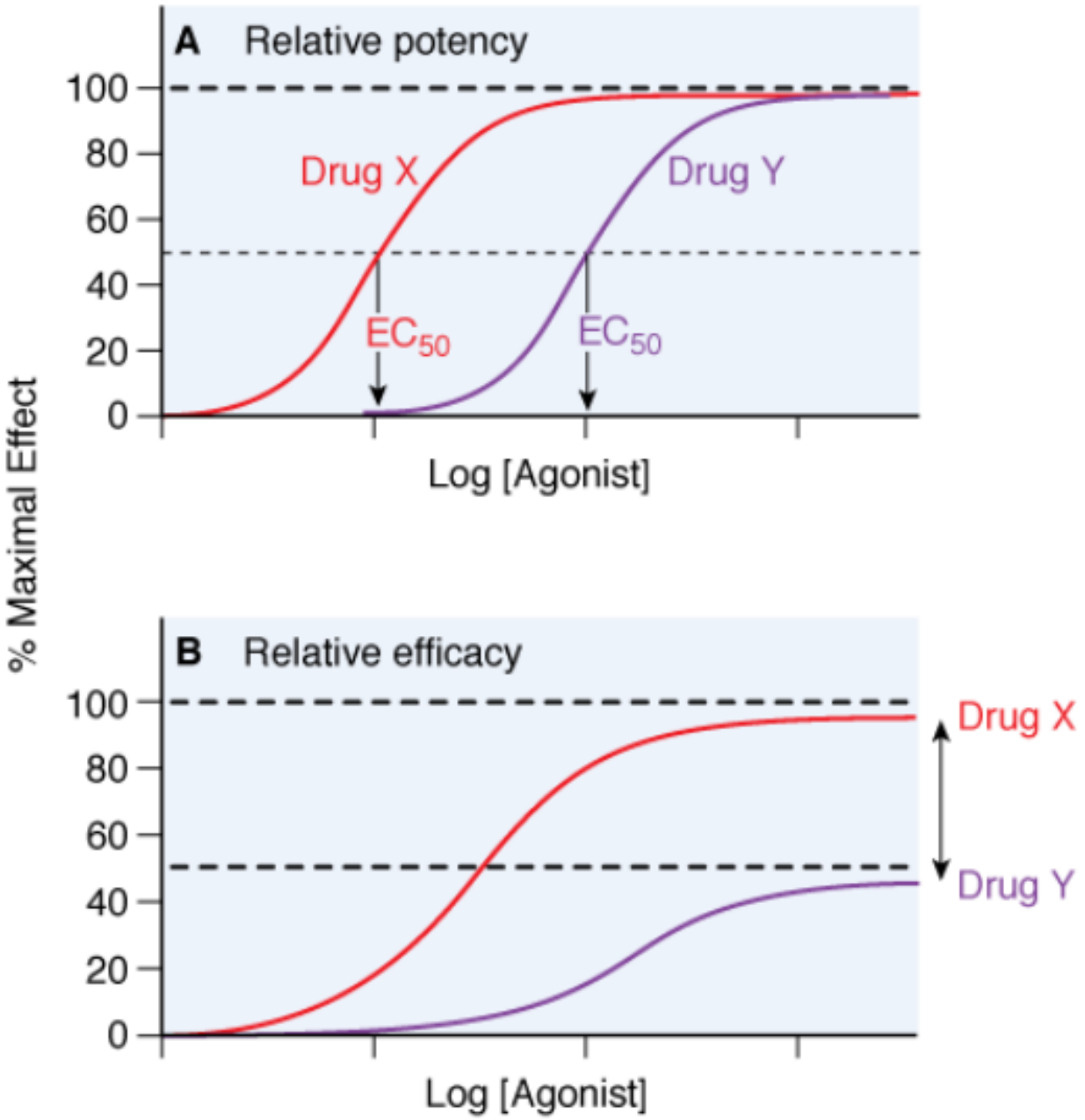
- The concentration producing an effect that is the fifty percent of the maximum is used to determine potency (EC_{50}).

- Efficacy is the maximum effect of a drug, E_{max}, 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.

Log dose response curve

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



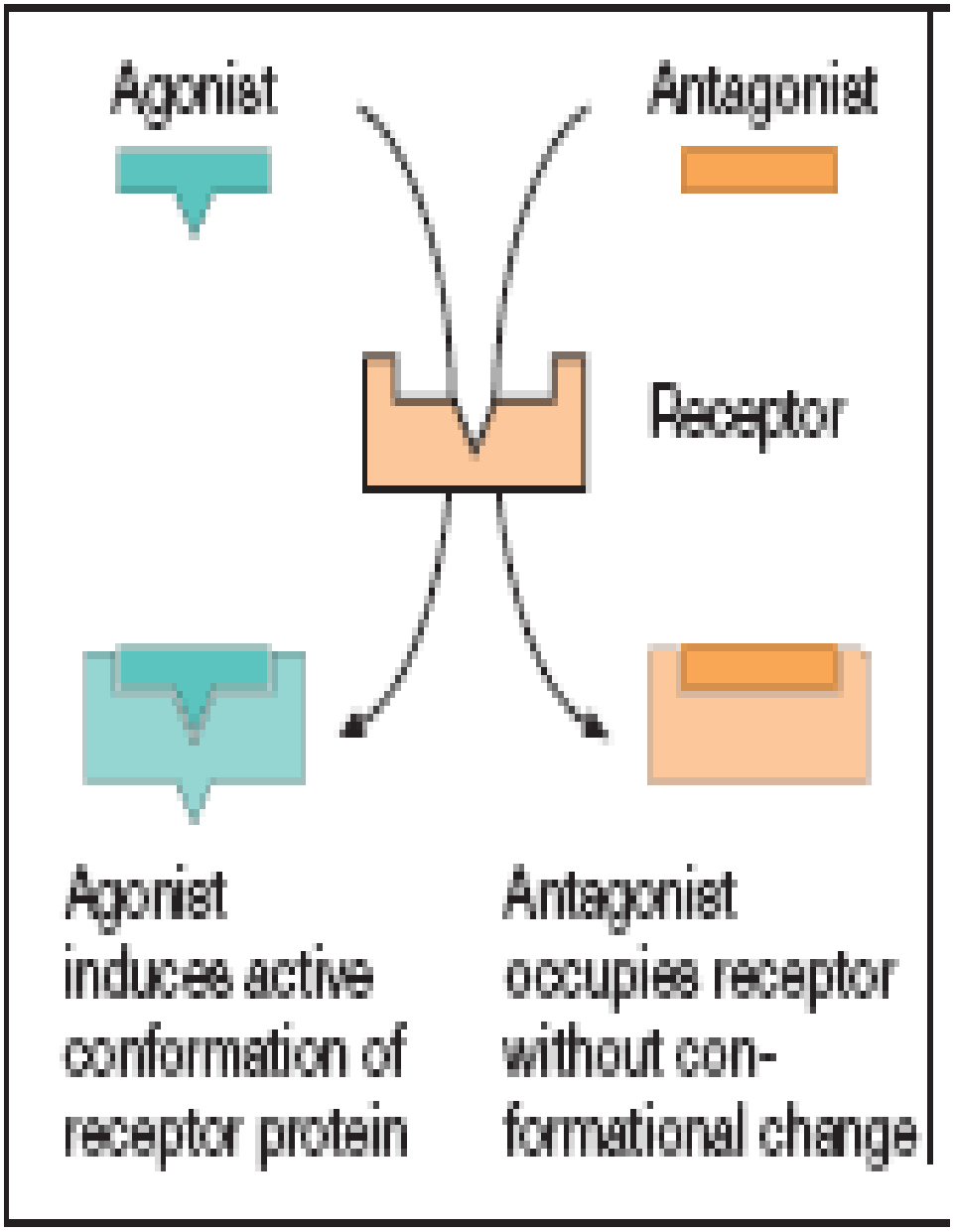
Agonist and antagonist

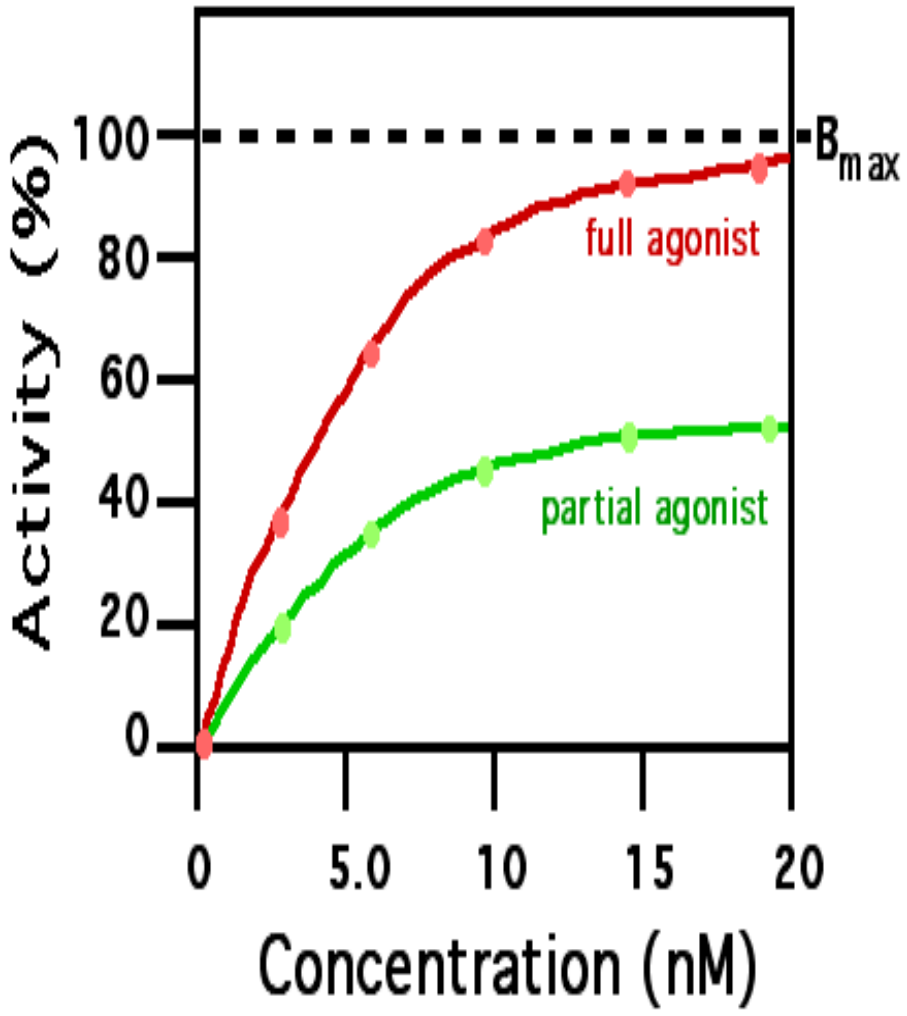
- drugs can either mimic physiological activity of the body's own molecules or Block the physiological activity of the body's own molecules.

- If the drug bind to a receptor and produces a biological effect that mimics the response to the endogenous ligand, it is known as an agonist.

- Antagonists are the drugs that decrease the action of another drug or endogenous ligand.

- **Partial agonists**: bind and activate a given receptor, but have only partial efficacy at the receptor relative to a full agonist.


Agonist
Antagonist
Receptor
Agonist induces active conformation of receptor protein
Antagonist occupies receptor without conformational change


Activity (%)
100
80
60
40
20
0
B_{max}
full agonist
partial agonist
0
5.0
10
15
20
Concentration (nM)

Antagonism between drugs

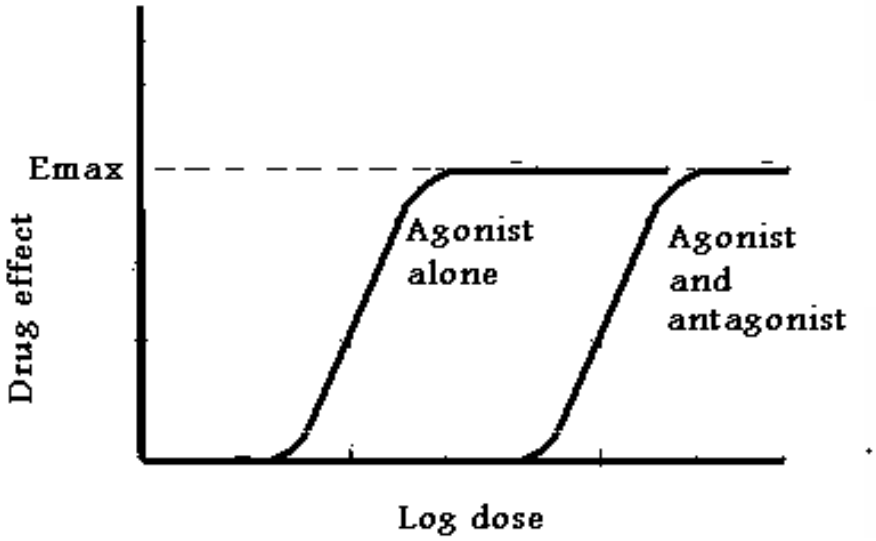
A. Pharmacologic antagonism: occurs when an antagonist prevent an agonist from interacting with its receptors to produce an effect, and it can be either competitive or noncompetitive.

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.

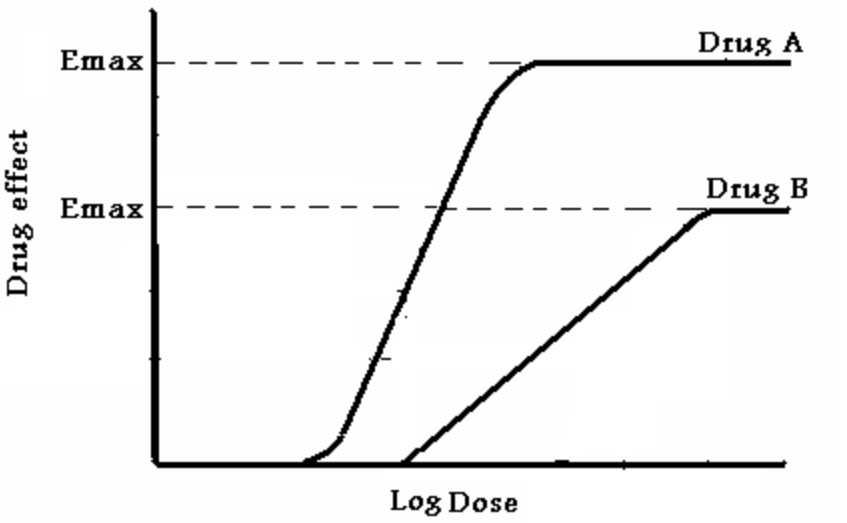
Noncompetitive antagonist binds irreversibly to the receptors site or to another side that inhibit the response to the agonist. And no matter how much agonist is given, the action of the antagonist can not overcome. The shift in the log response curve in this case is a nonparallel shift.

Shift in the log-dose response

Competitive antagonist



Noncompetitive antagonist



Antagonism between drugs

B. Physiologic Antagonist: here the drugs act independently on two different receptors, and exemplified by one drug acting on the sympathetic nervous system causing the heart rate to increase and causing vasoconstruction; while another drug acting on the parasympathetic nervous system decrease the heart rate and causes vasodilation.

C. Chemical antagonist (Antagonism by neutralization):

Occurs when two drugs combine with one another to form an inactive compound, and the best example being the drugs containing sulfhydryl (SH) groups, when combine with mercury or arsenic.

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.

$E_{AB} > E_A + E_B$ $\qquad$ $0 + 1 > 2$

Receptor are in dynamic state

- The affinity of the response to drugs is not fixed. It alters according to situation.

- Receptor down regulation:

Prolonged use of agonist

↓

↓↓Receptor number and sensitivity

↓

↓↓Drug effect

Ex: Chronic use of salbutamol down regulates $ß_2$ adrenergic receptors.

- Receptor up regulation:

Prolonged use of antagonist

↓

↑↑Receptor number and sensitivity

↓

↑↑Drug effect

- Ex:- propranolol is stopped after prolong use, produce withdrawal symptoms. Rise BP, induce of angina.

Therapeutic index and margin of safety

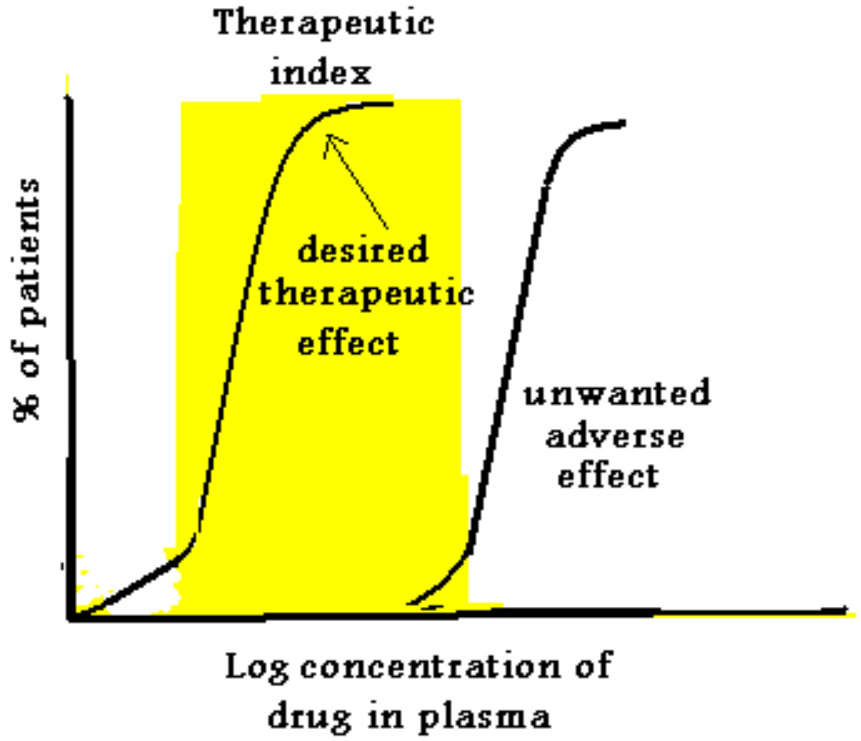
Therapeutic index of a drug is a ratio of the dose that produces toxicity to the dose that produces a clinically desired or effective response in a population individuals:

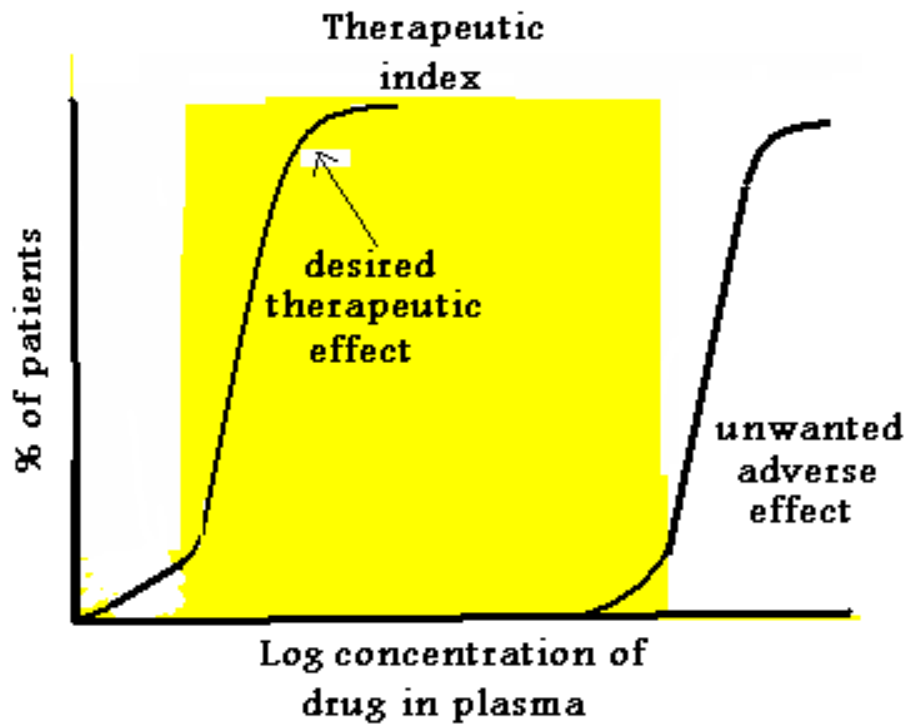
$$TI = \frac{TD_{50}}{ED_{50}}$$

Where TD_{50} is the minimum dose that is 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.

Therapeutic index and margin of safety





- Cyclosporine – 100-400ng/ml
- Carbamazapine- 4-10µg/ml
- Digoxin- 0.8-2ng/ml
- Phenotoin – 10-20µg/ml
- Qunindine- 2-6µg/ml

Drug-drug interaction

- When two drugs taken together, there is a possibility that the drugs will interact with each other to cause unanticipated effect. Usually increase or decrease in the desired therapeutic effect.

- Drug-drug interaction can occur in the following sites

1. at the side of absorption, tetracycline is not absorbed from the GI tract if calcium product present in the stomach.

2. during biotransformation (CYP 450).

3. At the site of action, dug antagonism.

Drug-drug interaction

3. During excretion, digoxin and quinidine are both excreted from the same sites in the kidney. The quinidine will be excreted first because it is more competitive for these sites, resulting in increased serum levels of digoxin.

4. During distribution, aspirin competes with methotrexate for protein binding sites, and because aspirine is more competitive for the sites, resulting in increased release of methotrexate and so increase toxicity to tissues.

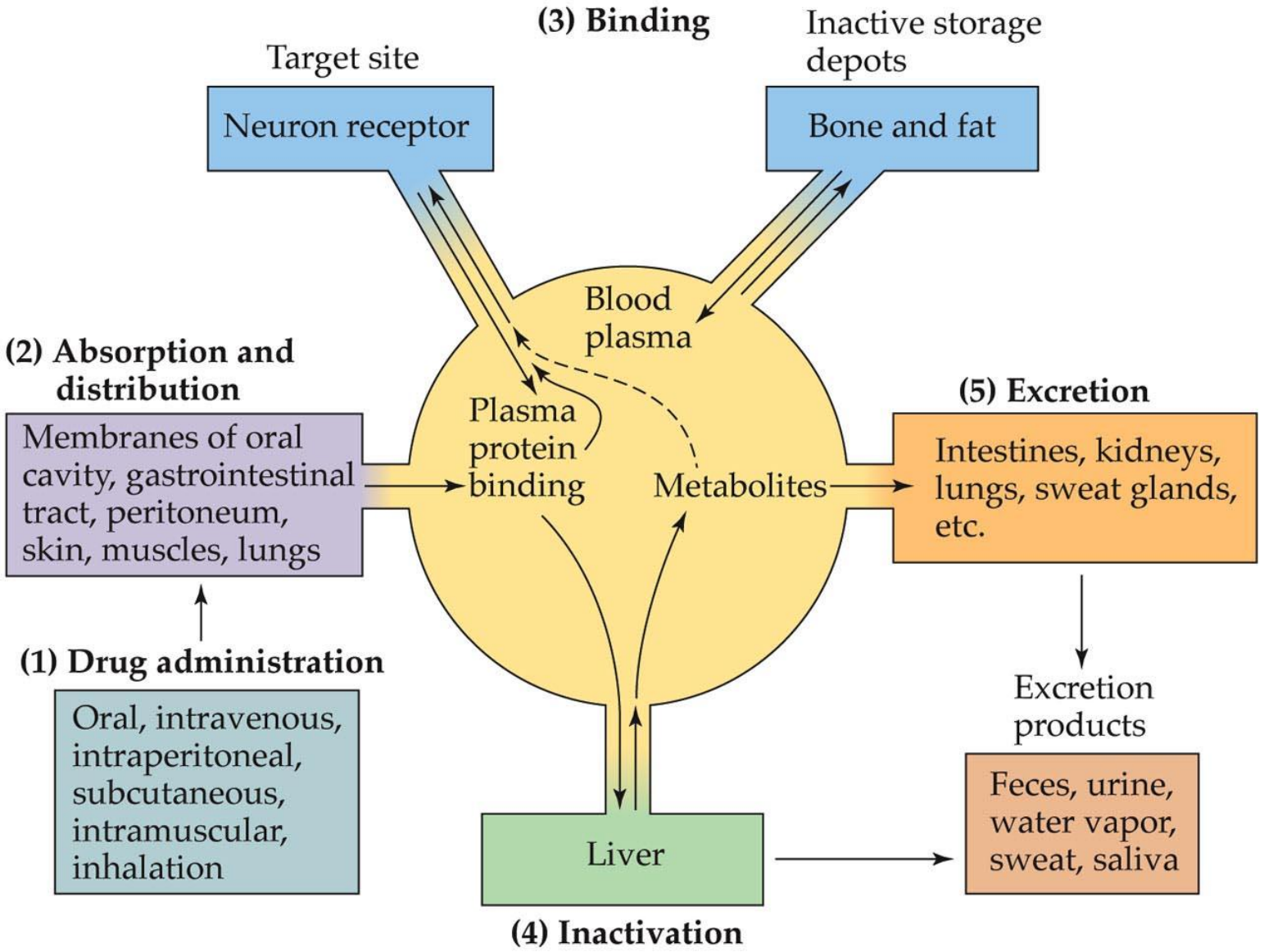
Adverse effect

- Adverse effect are undesired effect that may be unpleasant or even dangerous they can occur for many reasons:

1. The drug may have other effects on the body besides the therapeutic effect.
2. The patient is sensitive to the drug.
3. The patient is taking too much or too little of the drug.

- the nurse, as the most frequently administers medications, must be constantly alert for sign of drug reactions of various types.

Pharmacokinetics



REMEMBER

No drug produces a single effect!!!

Alphabetic classification of types of adverse drug effects

Type	Type of effect	Definition	Examples
A	Augmented pharmacologic effects	Adverse effects that are known to occur from the pharmacology of the drug, and are dose-related. They are seldom fatal and relatively common	Hypoglycemia due to insulin injection Bradycardia due to β adrenoceptor antagonists Hemorrhage due to anticoagulants
B	Bizarre effects	Adverse effects that occur unpredictably and often have a high rate of morbidity and mortality. They are uncommon	Anaphylaxis due to penicillin Acute hepatic necrosis due to halothane Bone marrow suppression by chloramphenicol
C	Chronic effects	Adverse effects that only occur during prolonged treatment and not with single doses	Iatrogenic Cushing's syndrome with prednisolone Orofacial dyskinesia due to phenothiazine tranquilizers Colonic dysfunction due to laxatives
D	Delayed effects	Adverse effects that occur remote from treatment, either in the children of treated patients, or in patients themselves years after treatment	Second cancers in those treated with alkylating agents for Hodgkin's disease Craniofacial malformations in infants whose mothers have taken isotretinoin Clear-cell carcinoma of the vagina in the daughters of women who took diethylstilbestrol during pregnancy
E	End-of-treatment effects	Adverse effects that occur when a drug is stopped, especially when it is stopped suddenly (so-called withdrawal effects)	Unstable angina after β adrenoceptor antagonists are suddenly stopped Adrenocortical insufficiency after glucocorticosteroids such as prednisolone are stopped Withdrawal seizures when anticonvulsants such as phenobarbital or phenytoin are stopped

Fig. 6.4 An alphabetic classification of adverse drug effects.

CYP isoform	Substrates	Inducers	Inhibitors
CYP1A2	**Anti-Alzheimer**: tacrine **Antiasthmatic**: theophylline **Antidepressants**: fluvoxamine, imipramine **Antipsychotics**: clozapine, halperidol	**Antibiotic**: rifampin **Anticonvulsant**: carbamazepine **Foods**: char-grilled meats **Recreational drug**: tobacco	**Antibiotics**: ciprofloxacin, erythromycin, ofloxacin **Antidepressant**: fluvoxamine
CYP2C9	**Angiotensin-2 receptor blockers**: ibresartan, losartan **Anticoagulant**: warfarin **Anticonvulsant**: phenytoin **Hypoglycemics**: glipizide, glyburide, tolbutamide **Non-steroidal anti-inflammatory drugs**: diclofenac, ibuprofen, naproxen	**Antibiotic**: rifampin **Barbiturates**: phenobarbital, secobarbital	**Antibiotic**: metronidazole **Antidepressants**: fluvoxamine, paroxitene, sertraline **Antifungal**: fluconazole
CYP2D6	**Antidepressants**: amitriptyline, desipramine, imipramine, paroxitene **Antipsychotics**: halperidol, risperidone **Beta-blockers**: metoprolol, propranolol, timolol **Narcotic analgesics**: codeine, hydrocodone, tramadol	**Antibiotic**: rifampin **Corticosteroid**: dexamethasone	**Antidepressants**: fluoxetine, paroxitene, sertraline **Antiarrhythmic**: amiodarone **H1 receptor blockers**: hydroxyzine, promethazine
CYP2E1	**Alcohol**: ethanol **General anesthetics**: enflurane, halothane, isoflurane, sevoflurane **Muscle relaxer**: chlorzoxazone **Non-narcotic analgesic**: acetaminophen	**Antibiotic**: isoniazid **Recreational drugs**: ethanol, tobacco	**Alcoholism rehabilitation agent**: disulfiram
CYP3A4	**Antibiotics**: clarithromycin, erythromycin **Anticoagulant**: warfarin **Anticonvulsant**: carbamazepine **Antipsychotics**: haloperidol, pimozide **Benzodiazepines**: alprazolam, diazepam, midazolam, triazolam **Calcium channel blockers**: amlodipine, diltiazem, felodipine, verapamil **Cholesterol-lowering drugs**: atorvastatin, cerivastatin*, lovastatin, simvastatin **Corticosteroids**: hydrocortisone, methylprednisolone **H1 receptor blockers**: astemizole*, terfenadine* **HIV protease inhibitor**: idinavir, nelfinavir,	**Antibiotic**: rifampin **Anticonvulsants**: carbamazepine, phenytoin **Barbiturates**: phenobarbital, secobarbital **Corticosteroids**: dexamethasone, hydrocortisone, prednisolone, methylprednisolone **Herbal remedy**: St John's wort **HIV reverse transcriptase inhibitors**: efavirenz, nevirapine	**Antibiotics**: clarithromycin, erythromycin **Antidepressants**: fluvoxamine, nefazodone **Antifungals**: clotrimazole, fluconazole, itraconazole, ketoconazole **Calcium channel blockers**: diltiazem, verapamil **Foods**: Grapefruit juice, Seville oranges **H2 receptor blocker**: cimetidine **HIV protease inhibitors**: idinavir, nelfinivir, ritonavir, saquinavir

Risk Factors for Adverse Drug Reactions

- Simultaneous use of several different drugs
  - Drug-drug interactions
- Very young, or very old in age
- Pregnancy
- Breast Feeding
- Hereditary Factors
- Disease states which may effect drug absorption, metabolism, and/or elimination

risk: benefit ratio

With every drug use, unwanted effects must be taken into account. Before prescribing a drug, the physician should therefore assess the

risk: benefit ratio.

In this, knowledge of principal and adverseeffects is a prerequisite.

COMMUNICATING WITH THE PATIENT

- SPEAKING CLEARLY AND SLOWLY IS VERY IMPORTANT
- BE AWARE OF THE DIFFFERNT LANGUAGES AND CULTURES.
- PATIENTS WILL SOMETIMES HAVE A DIFFERENT MEANING THAN THE PERSON TEACHING THE INFORMATION.

Hints

- Balance between over-prescription and under-prescription.
- Avoid a pill for every ill.
- Always consider non pharmacological therapy.