Lecture 3

GENERAL PHARMACODYNAMICS

(GENERAL MECHANISMS OF DRUG ACTIONS)

LEARNING OUTCOMES

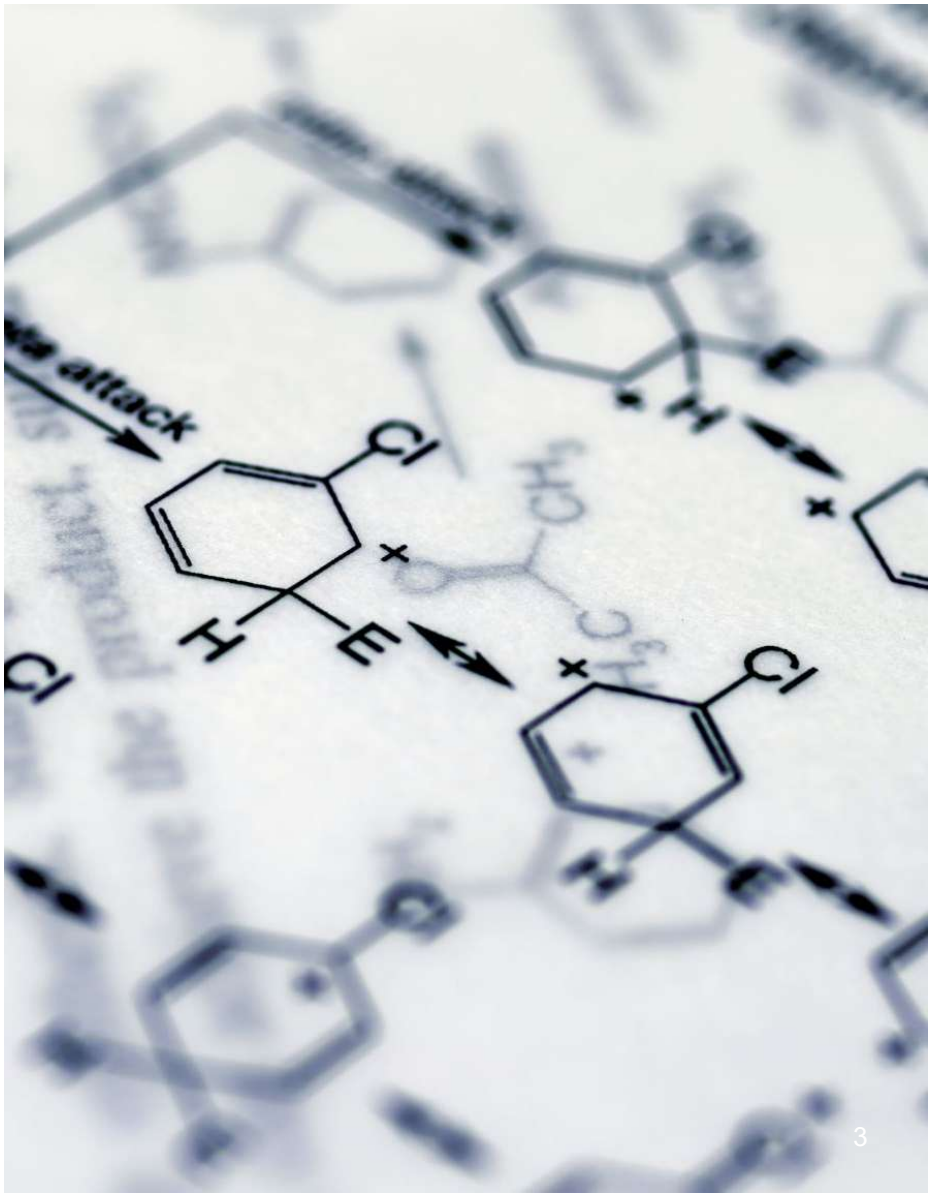
- Define pharmacodynamics
- Outline mechanisms of drug actions
- Recognize dose-response relationship
- Describe drug tolerance

Pharmacodynamics

"Pharmacodynamics is the detailed study of the mode of action of drugs in the body" or how drugs exert their effect at a cellular level

A. Receptors
B. Enzymes
C. Chemotherapy

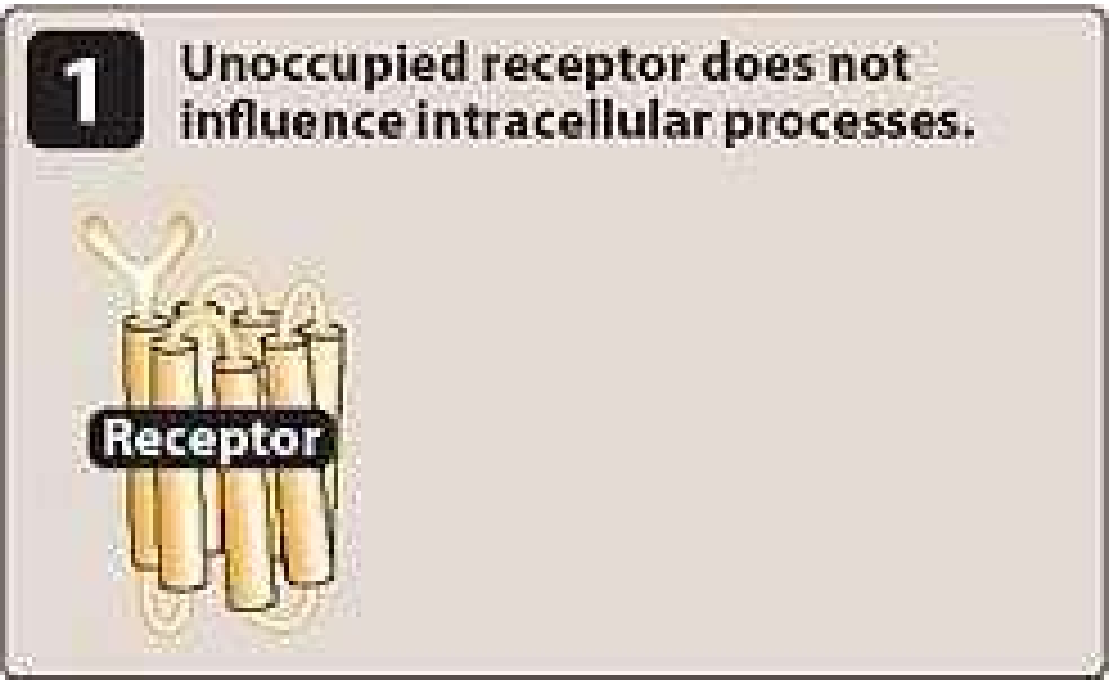
Understanding the pharmacodynamics of drugs will enable you to predict drug interactions and toxicities.

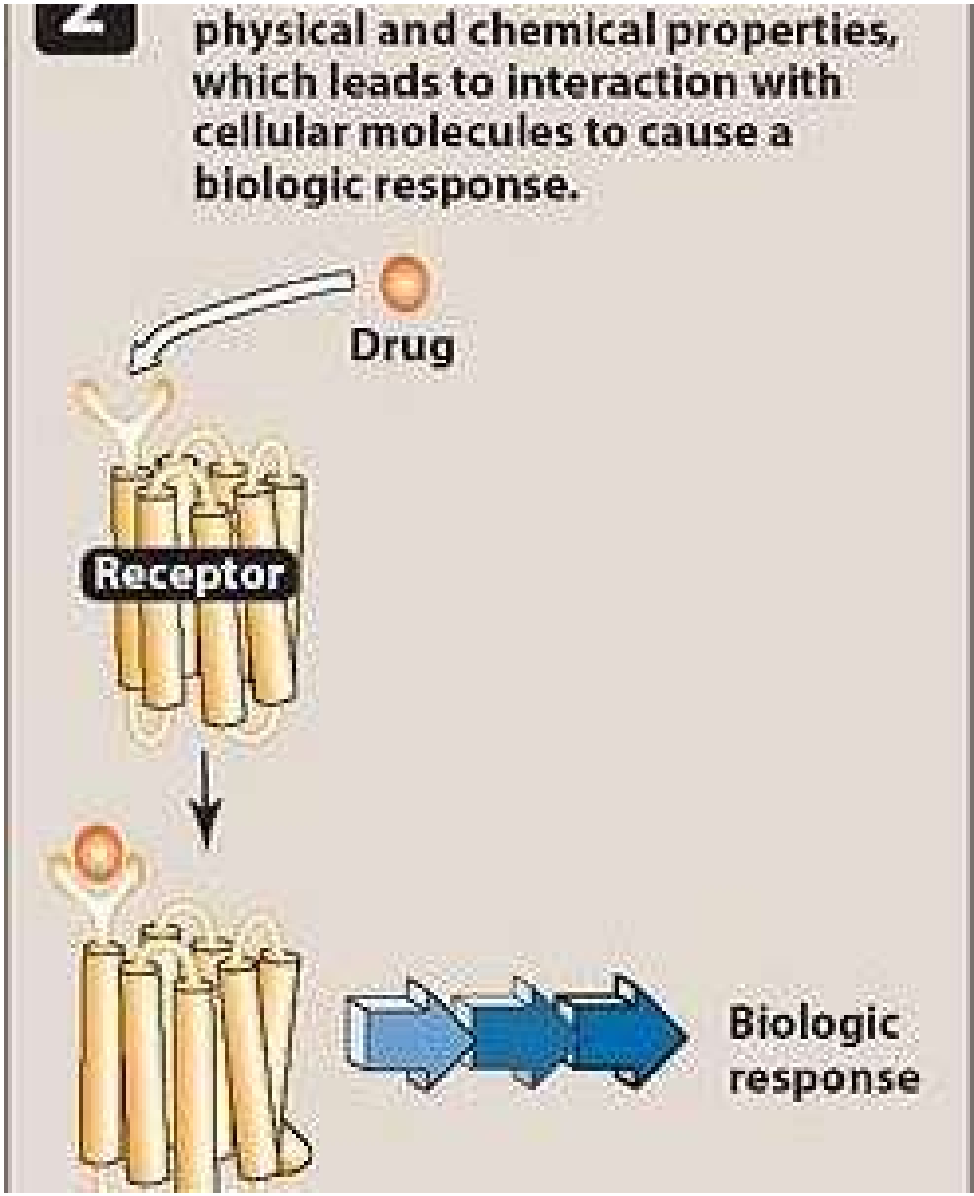


Action of Drugs By Receptors and Enzymes

- Most drugs exert their beneficial and harmful effects by interacting with receptors that are specialized target macromolecules present on the cell surface or intracellularly.
- Receptors bind drugs and initiate events leading to alterations in a cell's activity, and consequently, the function of an organ.
- Drugs may bind to enzymes (e.g., inhibition of dihydrofolate reductase by trimethoprim), nucleic acids (e.g., blockade of transcription by dactinomycin), or membrane receptors (e.g., alteration of membrane permeability by pilocarpine).
- In each case, the formation of the drug receptor complex leads to a biological response.

- **THE RECOGNITION OF A DRUG BY A RECEPTOR TRIGGERS A BIOLOGICAL RESPONSE**





Examples

Most receptors are named to indicate the type of drug/chemical that interacts best with it; **e.g.,** the receptor for histamine is called a histamine receptor.

Cells may also have different types of receptors, each of which is specific to a particular ligand.

On the heart, for example, there are β receptors for **norepinephrine** and muscarinic receptors for **acetylcholine.**

These receptors dynamically interact to control vital functions of the heart

Major Receptor Families

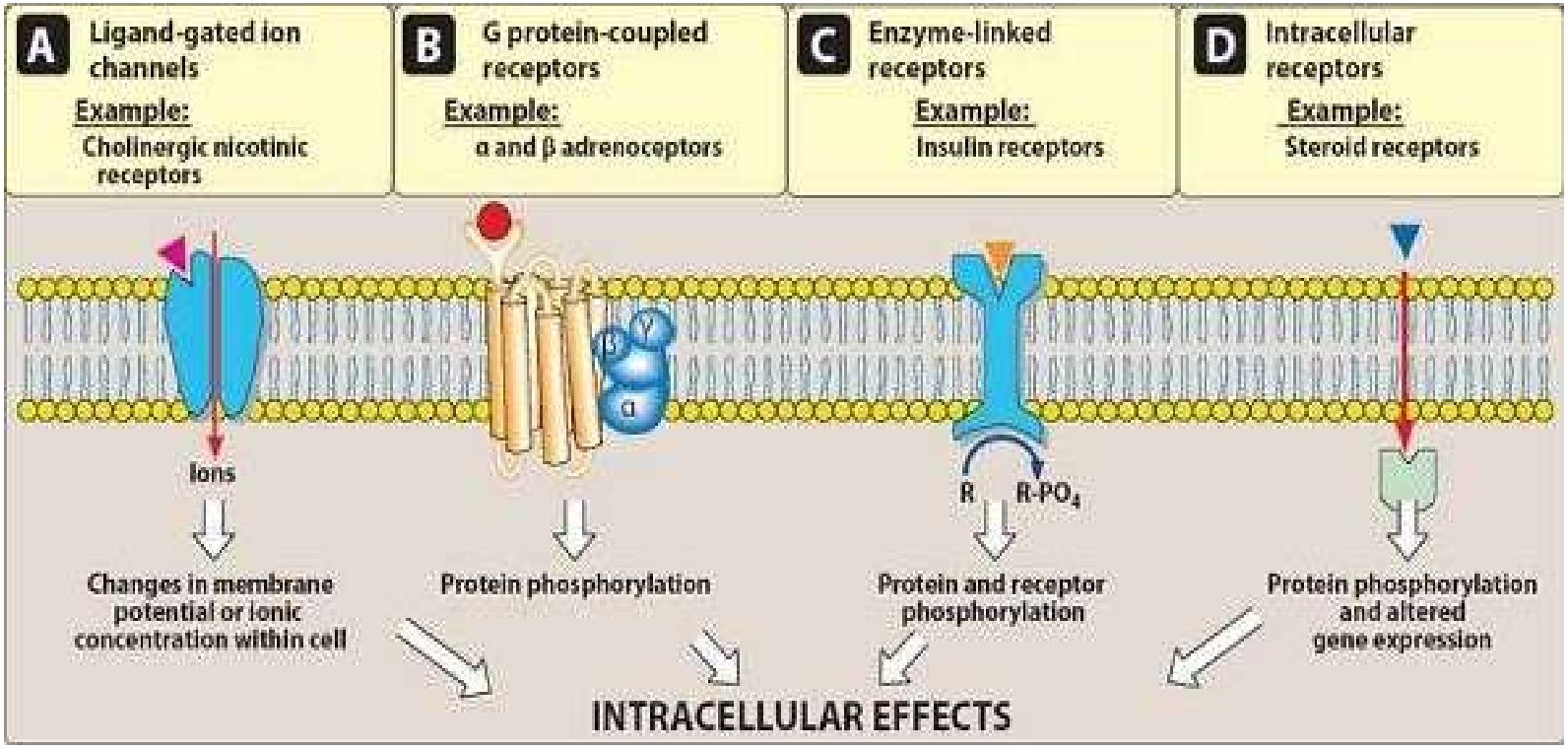
- Pharmacology defines a receptor as any biological molecule to which a drug binds and produces a measurable response.

Enzymes and structural proteins can be considered to be pharmacologic receptors.

The richest sources of therapeutically pharmacologic receptors are proteins that are responsible for transducing extracellular signals into intracellular responses.

These receptors may be divided into four families:
1) Ligand-gated ion channels.
2) G protein-coupled receptors.
3) Enzyme-linked receptors.
4) Intracellular receptors.

The type of receptor that a ligand will interact with, depends on the nature of the ligand.



Transmembrane signalling mechanisms.

A. Ligand binds to the extracellular domain of a ligand-gated channel.

B. Ligand binds to a domain of a serpentine receptor, which is coupled to a G protein.

C. Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme.

D.Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor.

TYPES OF RECEPTORS-Contd’

- G-protein-couple receptors, Work in seconds

e.g. Muscarinic ACh receptors, adrenoceptors, histamine receptors

- Kinase-linked receptors, Takes hours

e.g. Insulin, Growth factor

- Nuclear intracellular receptors, Also takes hours

e.g. steroid, thyroid hormone

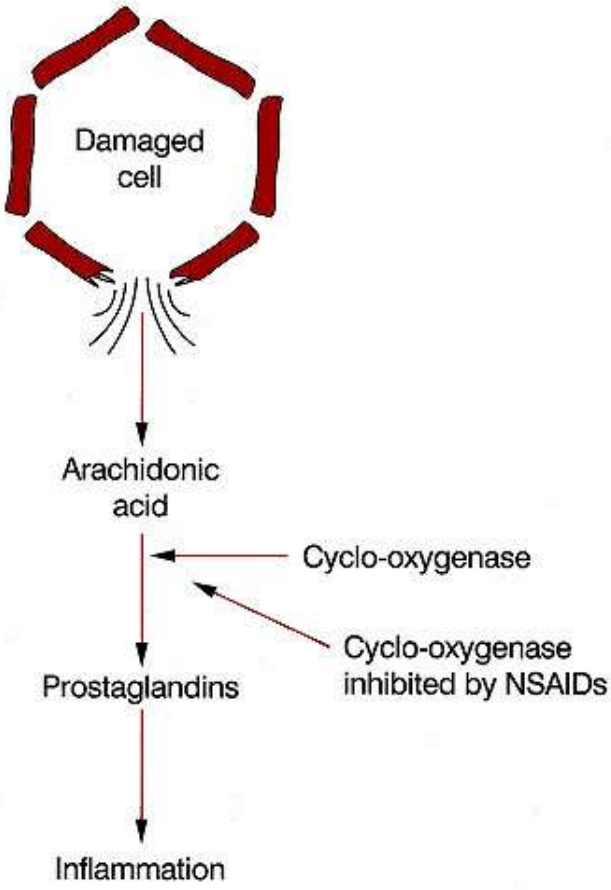
- Ligand-gated ion channels, milliseconds

Example: GABA benzodiazepines, Nicotinic Ach

Enzyme Inhibitors

- **Aspirin mechanism:**

Acts on cyclooxygenase enzyme responsible for the synthesis of prostaglandins.



Chemotherapeutic agents

- Cytotoxic drugs act by interfering with cell growth and division at different stages of the cycle
- Anti-infective drugs

For example:

- Folic acid is required for DNA synthesis. **Methotrexate** inhibits the formation of folic acid
- **Penicillins and cephalosporins** inhibit the synthesis of bacterial cell walls

PHYSIOLOGICAL VARIABILITY

LIVER DISEASE

CHRONIC ALCOHOLISM

RENAL DISEASE

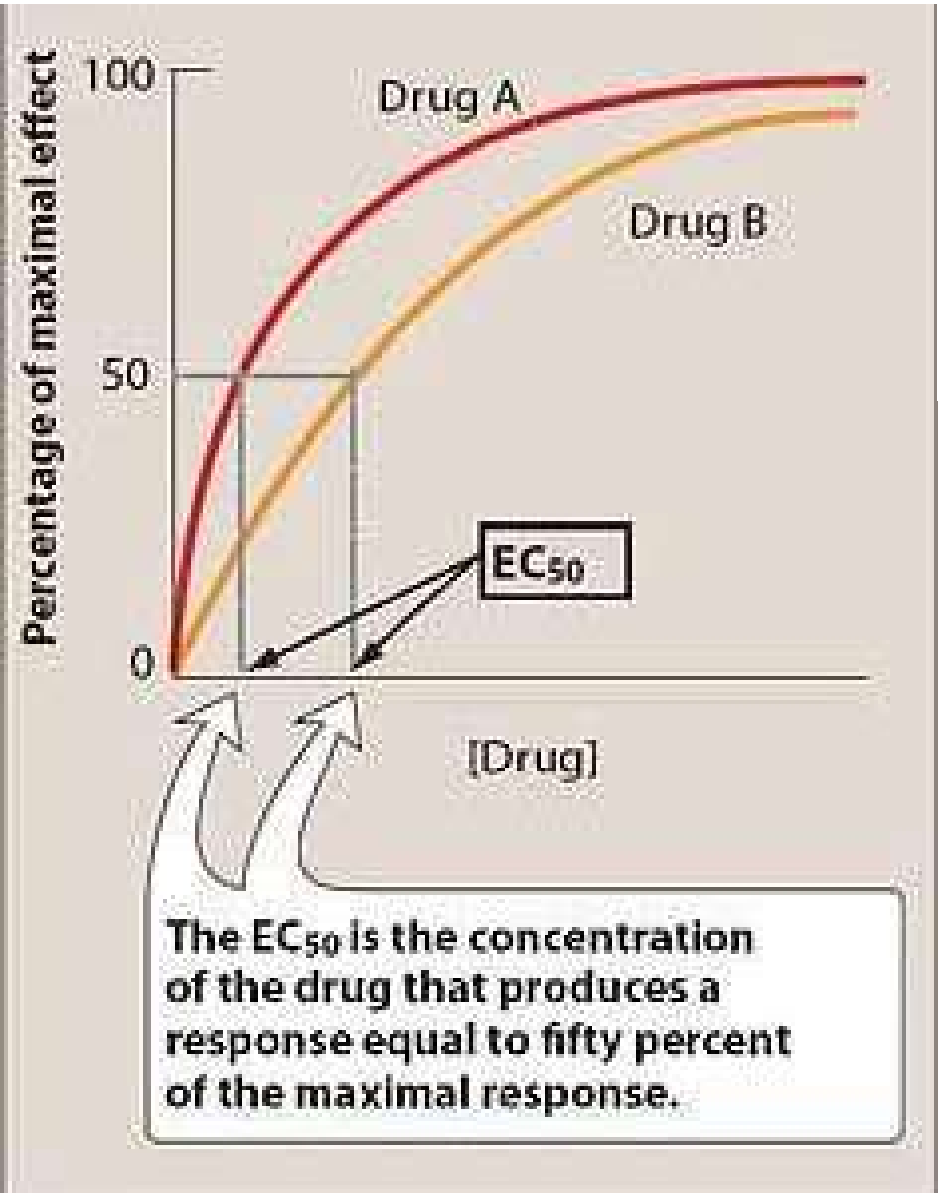
ALLERGY

DOSE-RESPONSE RELATIONSHIPS

The drugs act on receptors and elicit a biological response.

The magnitude of the drug effect depends on the drug concentration at the receptor site, which in turn is determined by the dose of the drug administered and by factors characteristic of the drug pharmacokinetic profile, such as rate of absorption, distribution, and metabolism.

As the concentration of a drug increases, the magnitude of its pharmacologic effect also increases.



- The response is a graded effect, meaning that the response is continuous and gradual.
- Two important properties of drugs can be determined by graded dose-response curves.
- The concentration producing an effect that is fifty per cent of the maximum is used to determine potency; it is commonly designated as the EC_{50}.

DRUG TOLERANCE

Drug tolerance is a pharmacological concept describing subjects' reduced reaction to a drug following its repeated use.

Increasing its dosage may re-amplify the drug's effects; however, this may accelerate tolerance, further reducing the drug's effects.

The process of tolerance development is reversible (e.g., through a drug holiday) and can involve both physiological factors and psychological factors.

Examples of drugs: **Amphetamine and Opiates.**

References

Bart –Jhonson, Frank J. Dowd. ***Pharmacology and Therapeutic for Dentistry***, 6th edition, 2011. Elsevier Publishers,USA

Karen Whalen, Richard Finkel, Thomas A Panavelil. **Lippincott Illustrated Reviews Pharmacology**. 6th ed. 2015. Philadelphia Wolter Kluwer Puplisher.