

# Pharmacodynamics: (Protein Targets for Drug Binding)

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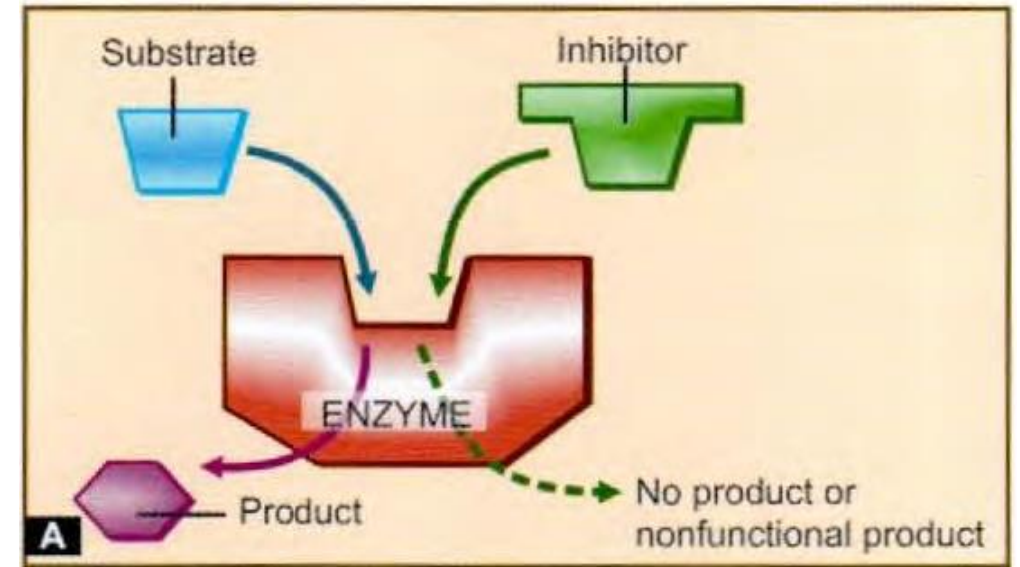
# Protein Targets for Drug Binding

Four main kinds of regulatory proteins are commonly involved as primary drug targets, namely:

- Enzymes
- Ion channels
- Carrier molecules (transporters)
- Receptors

# Enzymes

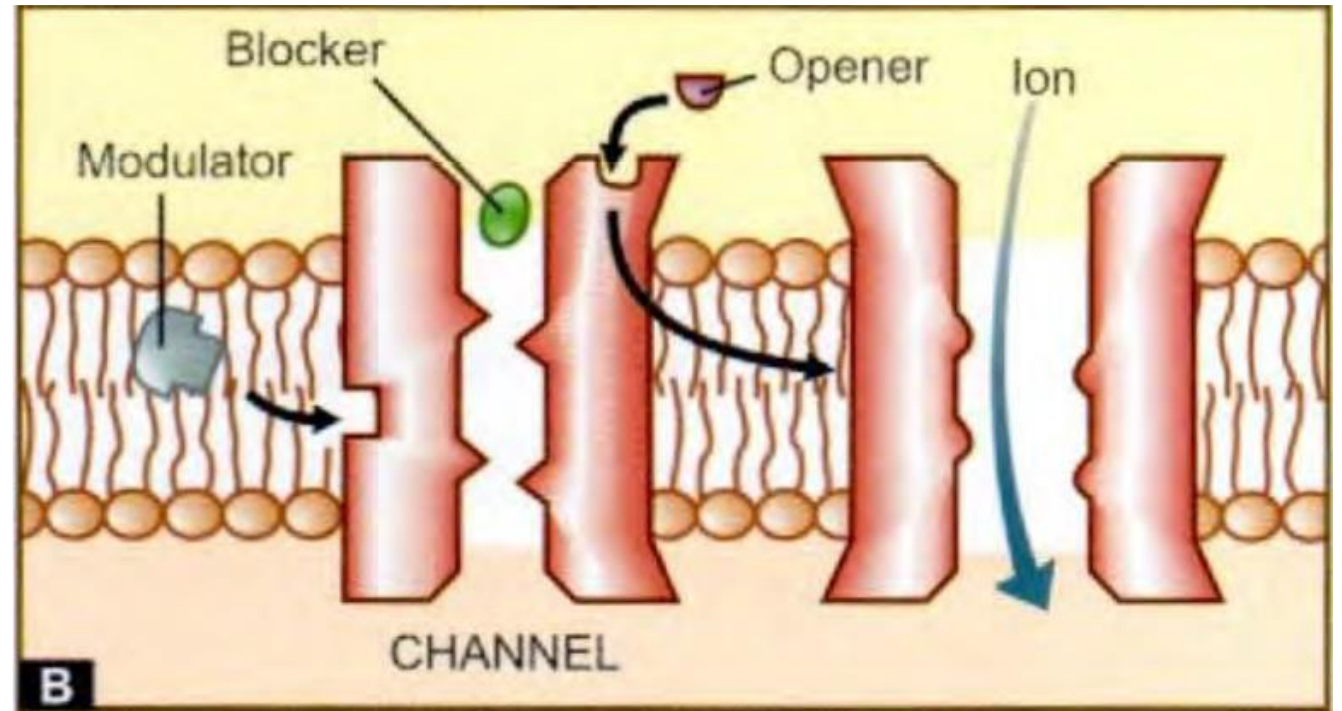
- Almost all biological reactions are carried out under catalytic influence of enzymes; hence, **enzymes are a very important target of drug action.**



- Drugs can either increase or decrease the rate of enzymatically mediated reactions.
- **Enzyme Inhibition:** Non-selective & Selective.
- **Selective enzyme inhibition:** Competitive & Non-competitive.

# Ion Channels

- Some ion channels (known as ligand gated channels) are directly linked to a receptor and they open only when the receptor is occupied by an agonist.



- Ion channels also serve as targets for drug action.

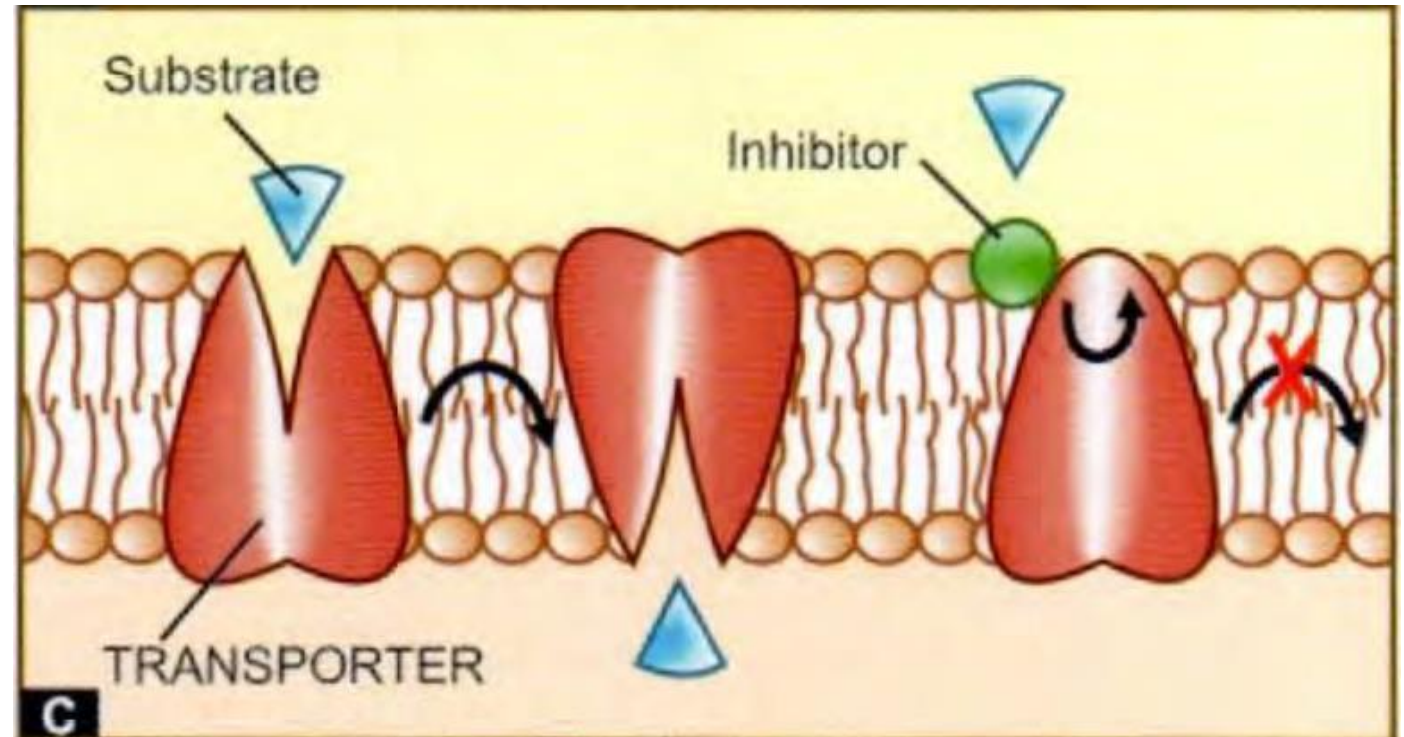
# Ion Channels

contd...

- The simplest type of interaction involves the physical blocking action of local anaesthetics on the voltage-gated sodium channels.
- Ion channel modulation by drugs, acting directly on the channel or indirectly is one of the most important mechanisms by which pharmacological effects are produced at the cellular level.

# Carrier Molecules (Transporters)

- The transport of ions and small organic molecules across cell membranes generally requires a **carrier protein (transporter)**, since the **polar** molecules are often permeating lipid membranes on their own.



# Carrier Molecules (Transporters)

contd...

- Many drug produce their action by directly interacting with the **solute carrier (SLC) class of transporter proteins** to inhibit the ongoing physiological transport of the metabolite/ ion.
- Examples are: Desipramine and cocaine block neuronal reuptake of noradrenaline by interacting with **norepinephrine transporter (NET)**.

# Receptors

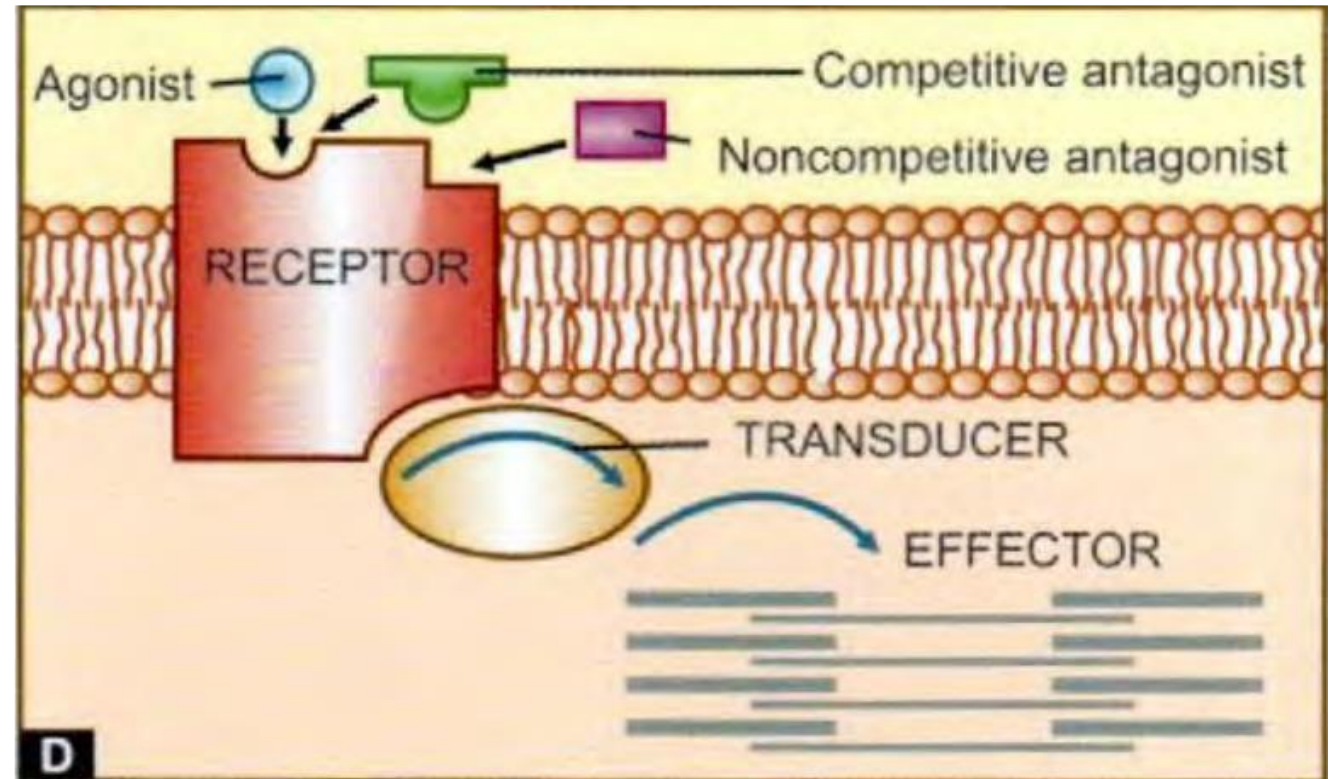
- ✓ **J.N. Langley** (1878) introduced the concept of receptor. He used the term **receptive substance**.
- ✓ The term receptor was first used by **Paul Ehrlich** (1913) to describe the hypothetical specific chemical groupings of "side chains" on cells upon which the chemotherapeutic agents were postulated to act.



# Receptors

contd...

- ✓ Receptors are **sensing elements** in the system of chemical communications that **coordinates the function of different cells** in the body, the chemical messengers being hormones, transmitter substances or other mediators.



# Receptors

contd...

- ✓ Many therapeutically useful synthetic drugs act as **agonists or antagonists** on receptors for known endogenous mediators.
- ✓ Receptors are **macromolecular structures** with which a drug interacts to initiate its pharmacologic effects.
- ✓ Receptors elicit many different types of cellular effect, some of which may be rapid, such as those involved in **synaptic transmission**.

# Receptors

contd...

- ✓ A receptor is often defined in terms of the **endogenous substance or ligand** that produces a given effect upon interaction with a given biological substrate.
- ✓ A number of binding sites exist in biological tissues for drugs and toxins for which there is **no known endogenous ligand**.

# Receptors contd...

- ✓ Binding of drugs to receptors necessarily obeys the **Laws of Mass Action**. At equilibrium, **receptor occupancy** is related to drug concentration.
- ✓ The higher the **affinity of the drug** for the receptor, the lower is the concentration at which it produces a given level of occupancy.
- ✓ The same principles apply when **two or more drugs compete for the same receptors**; each of which has the effect of reducing the apparent affinity for the other.

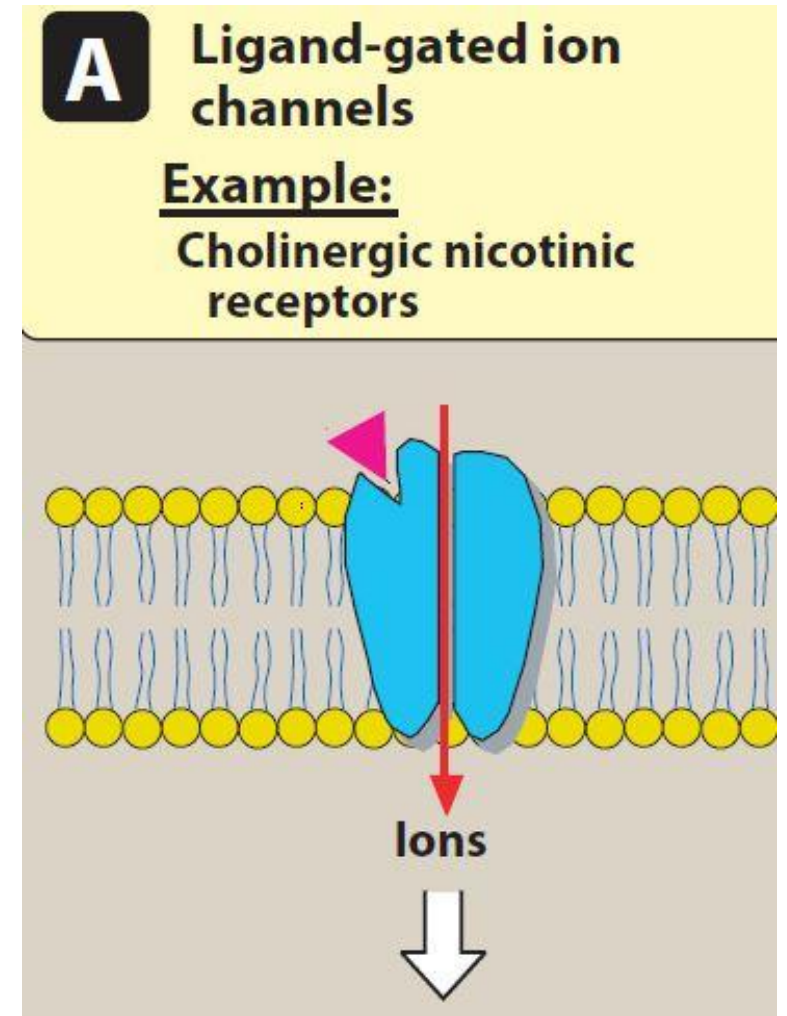
# Properties of Receptors

- Saturability** : A finite number of receptors per cell should be present.
- Specificity** : The drug should be structurally complementary to the receptor.
- Reversibility** : The drug should bind to the receptor and then dissociate in its non-metabolized form.

# Types of Receptors

## [A]. Ligand-gated ion channels (Ionotropic receptors):

- Membrane receptors coupled directly to ion channels and are the receptors on which fast neurotransmitters act.
- *Examples:* the nicotinic acetylcholine receptor;  $GABA_A$  receptor; and glutamate receptors.

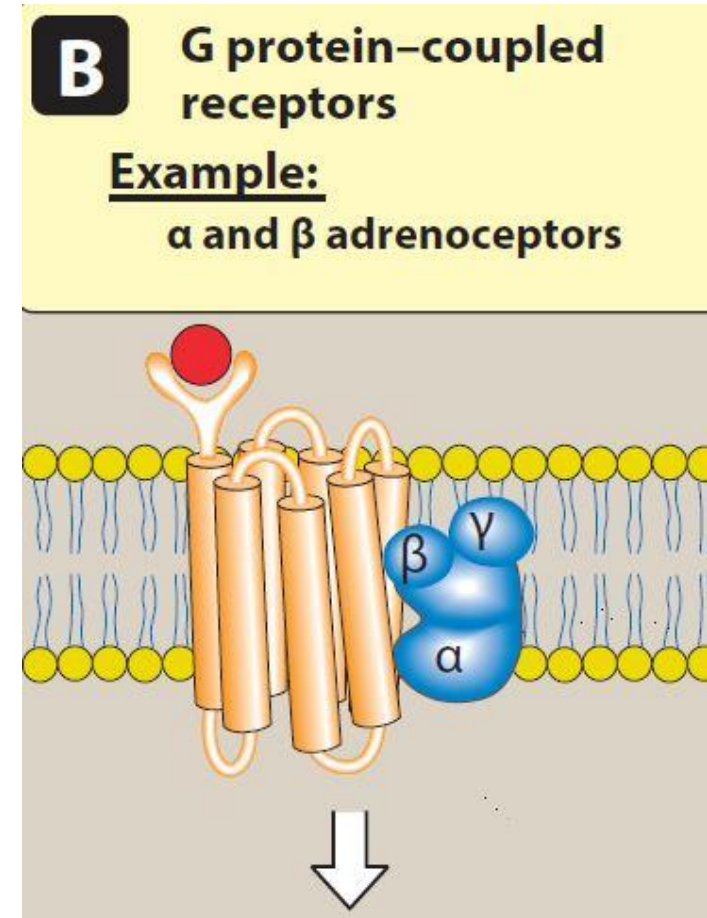


# Types of Receptors

contd...

## [B]. G-protein-coupled receptors (GPCRs):

- Also known as metabotropic receptors or 7-transmembrane-spanning (heptahelical) receptors.
- Are membrane receptors that are coupled to intracellular effector systems via a G-protein.
- Examples: Receptors for many hormones and slow transmitters, e.g. the muscarinic acetylcholine receptor and adrenergic receptors.

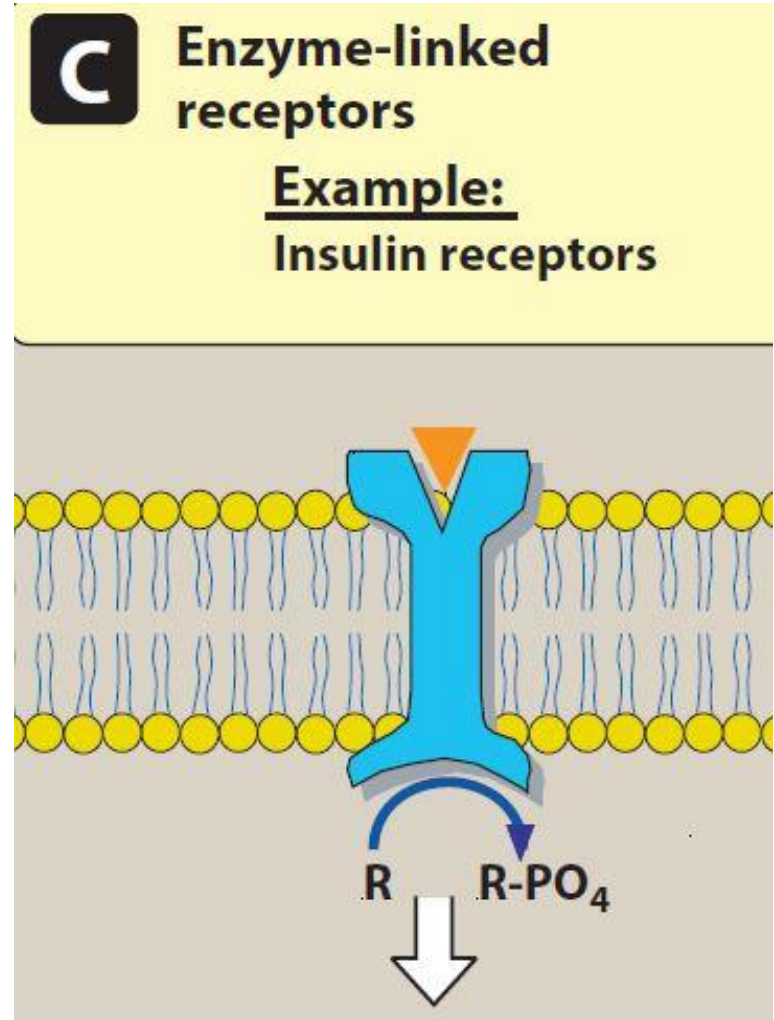


# Types of Receptors

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## [C]. Kinase-linked and related receptors:

- Are membrane receptors that incorporate an intracellular protein kinase domain within their structure.
- They include receptors for insulin, various cytokines and growth factors.



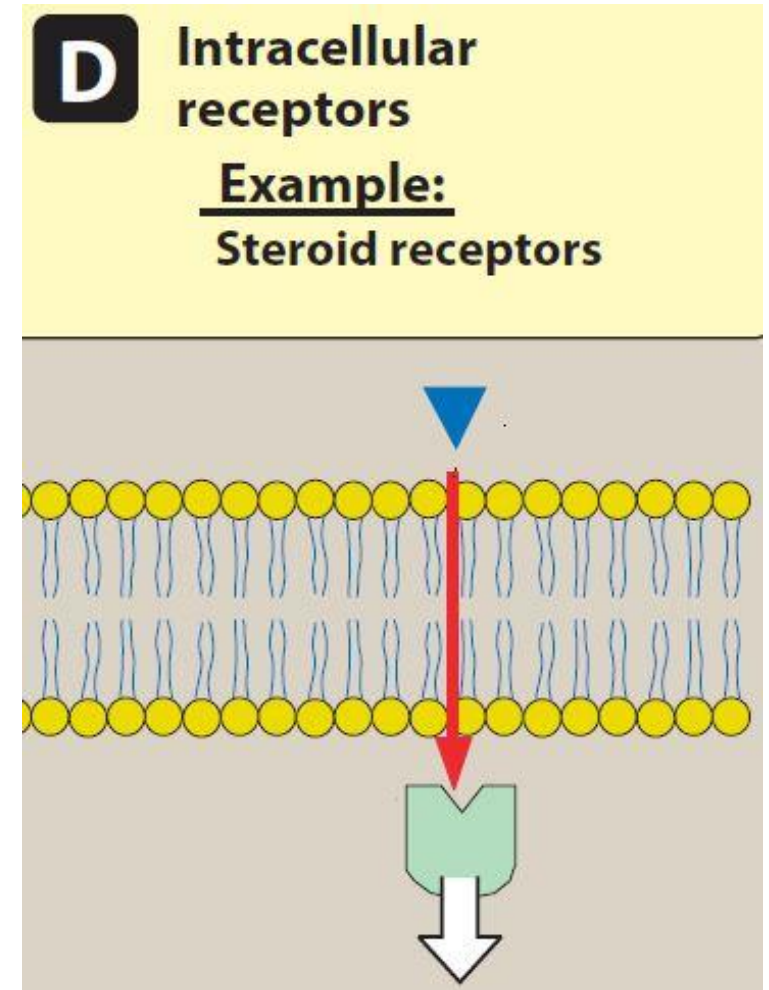


# Types of Receptors

contd...

## [D]. Nuclear receptors:

- These are receptors that regulate gene transcription.
- The term *nuclear receptor* is something of a misnomer, because some are actually located in the cytosol and migrate to the nuclear compartment when a ligand is present.
- They include receptors for steroid hormones, thyroid hormone, and other agents such as retinoic acid and vitamin D.



# Functions of Receptors

- ✓ To propagate regulatory signals from outside to within the effector cell when the molecular species carrying the signal can not itself penetrate the cell membrane.
- ✓ To amplify the signal.
- ✓ To integrate various extra cellular and intracellular regulatory signals.
- ✓ To adopt short term and long term changes in the regulatory milieu and maintain homeostasis.

# Structure Activity Relationship (SAR)

- The ability of a drug to combine with a receptor to produce an effect is dependent on the **three dimensional chemical structure of the drug**.
- Relatively minor **modifications in the drug molecule** may result in major **changes in pharmacological properties**.
- Changes in structure can change the activity of the drug, some actions may be affected while others are not, drug may have lesser toxic side effects with better pharmacokinetic characteristics.

**Thank You**

