

Pharmacodynamics: (Protein Targets for Drug Binding)

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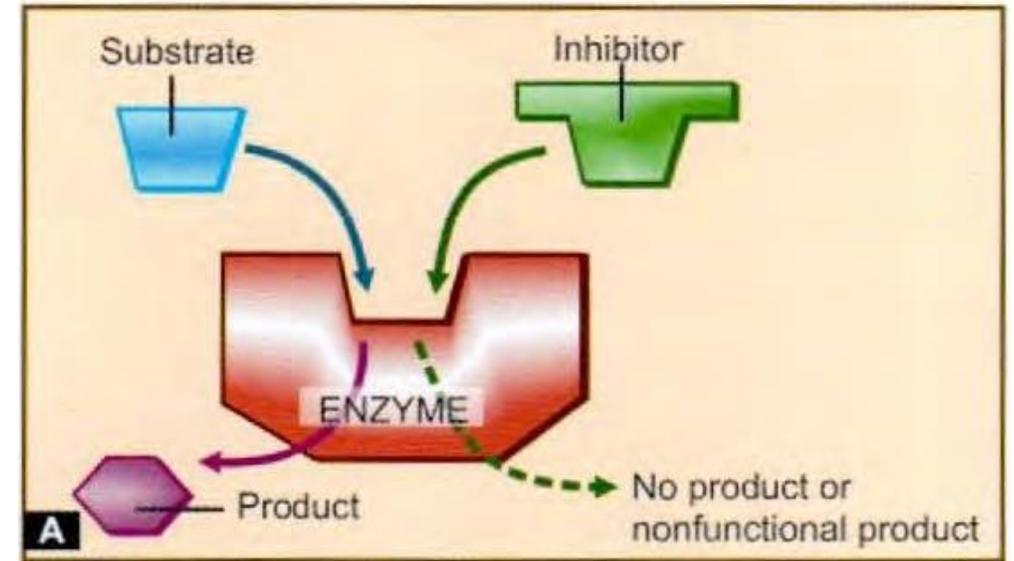
Protein Targets for Drug Binding

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

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

Enzymes

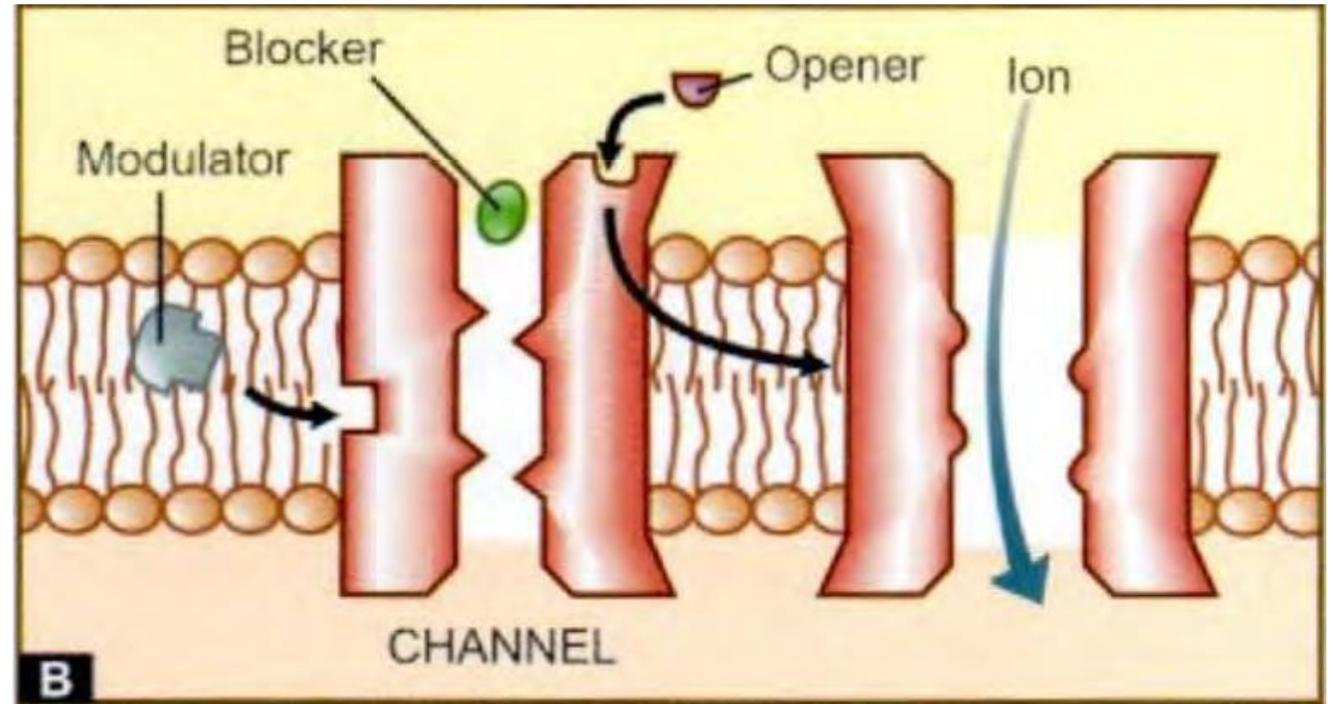
- Almost all biological reactions are carried out under catalytic influence of enzymes; hence, **enzymes are a very important target of drug action.**



- 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.

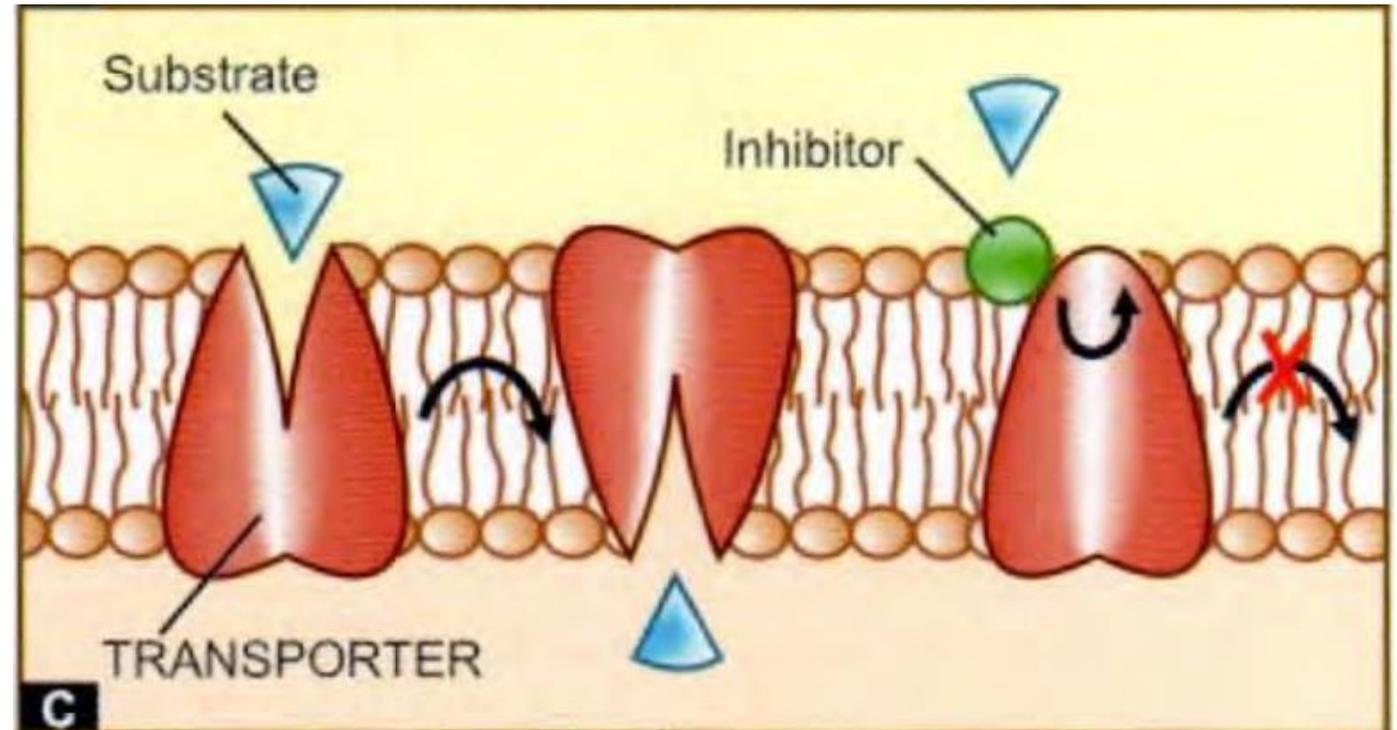
Ion Channels

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- 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)**.

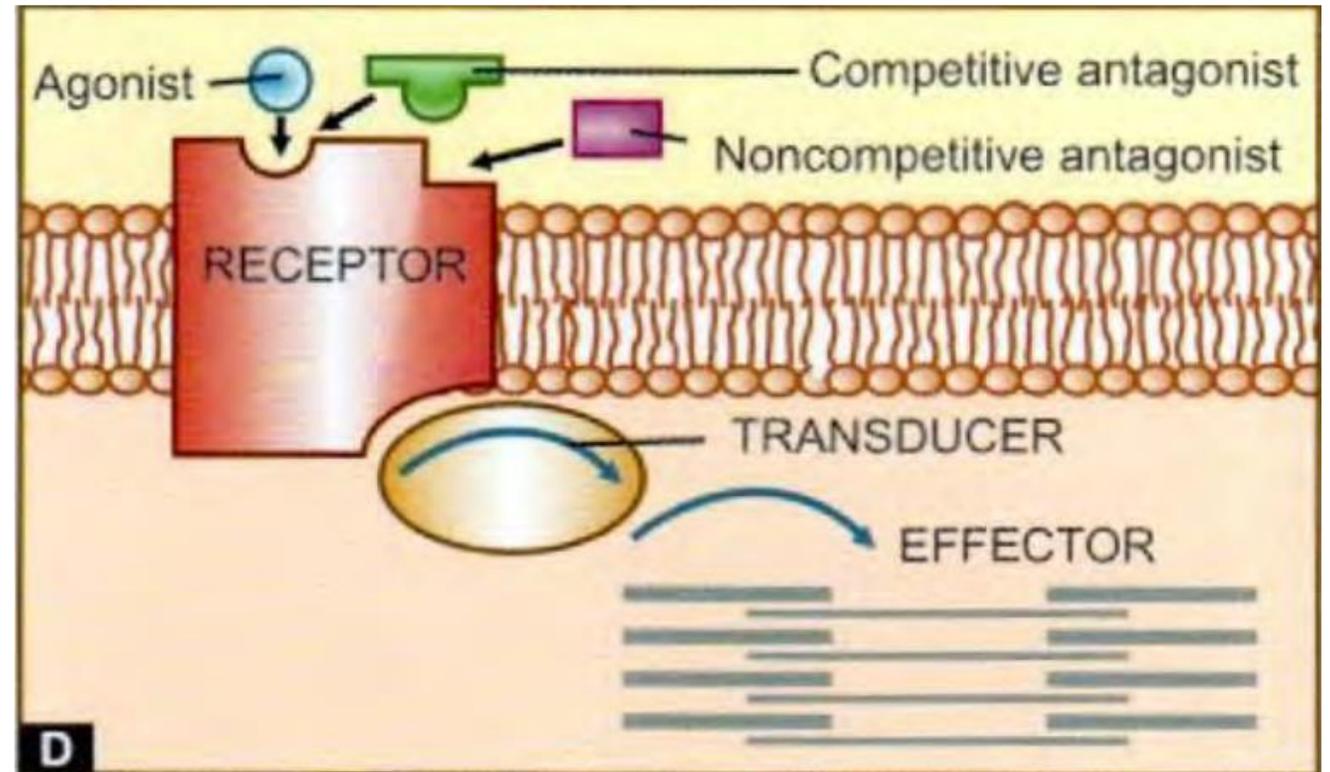
Receptors

- ✓ **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.

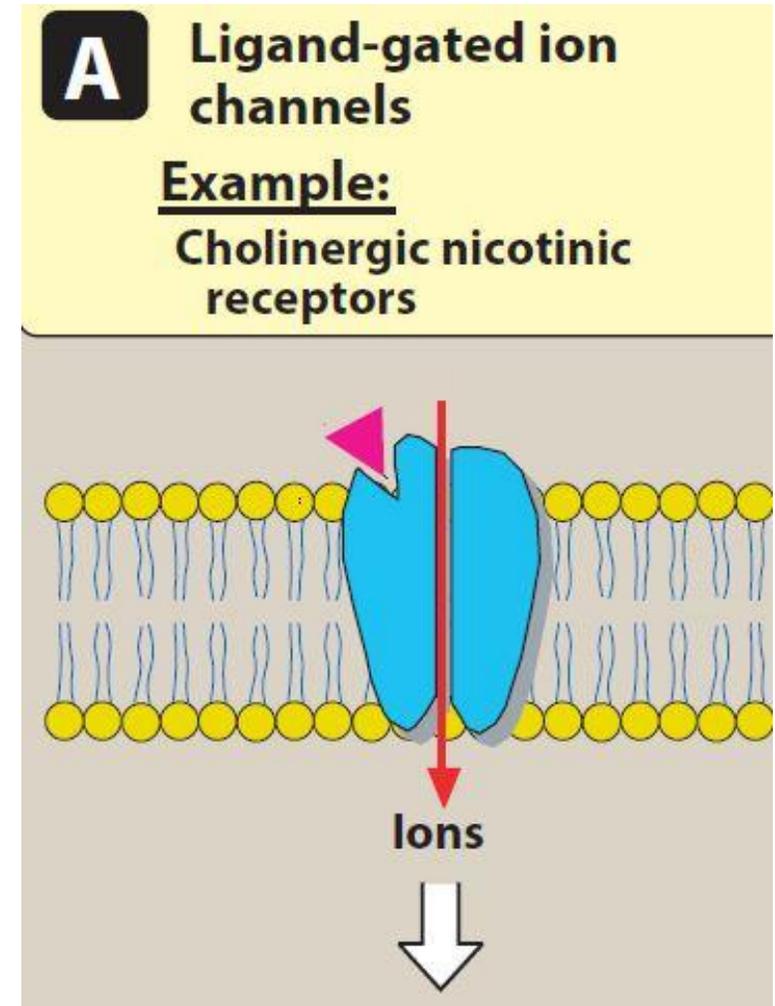
Properties of Receptors

- 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.

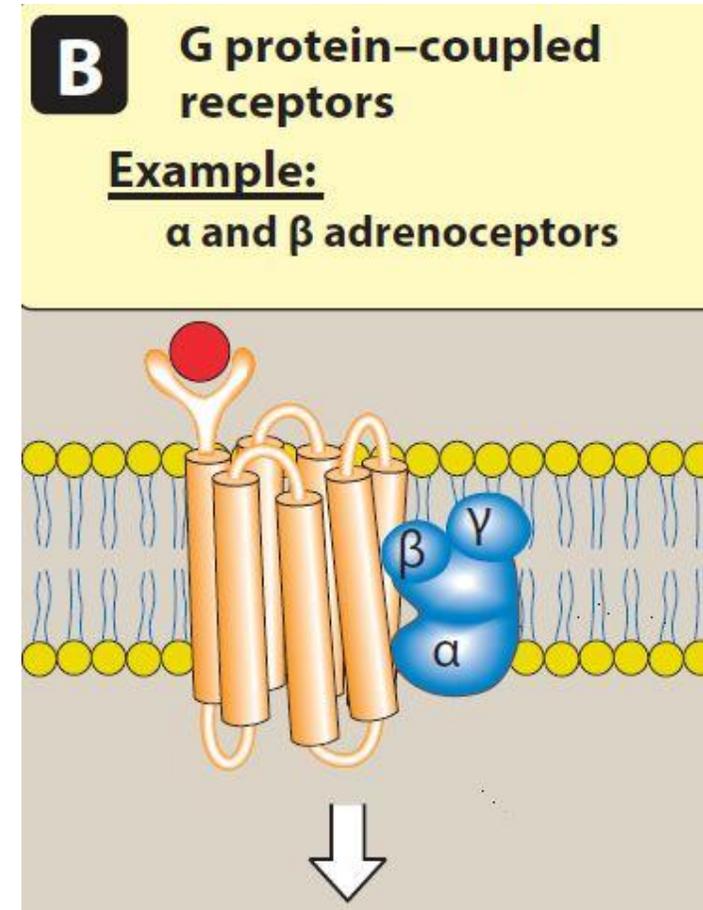


Types of Receptors

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.

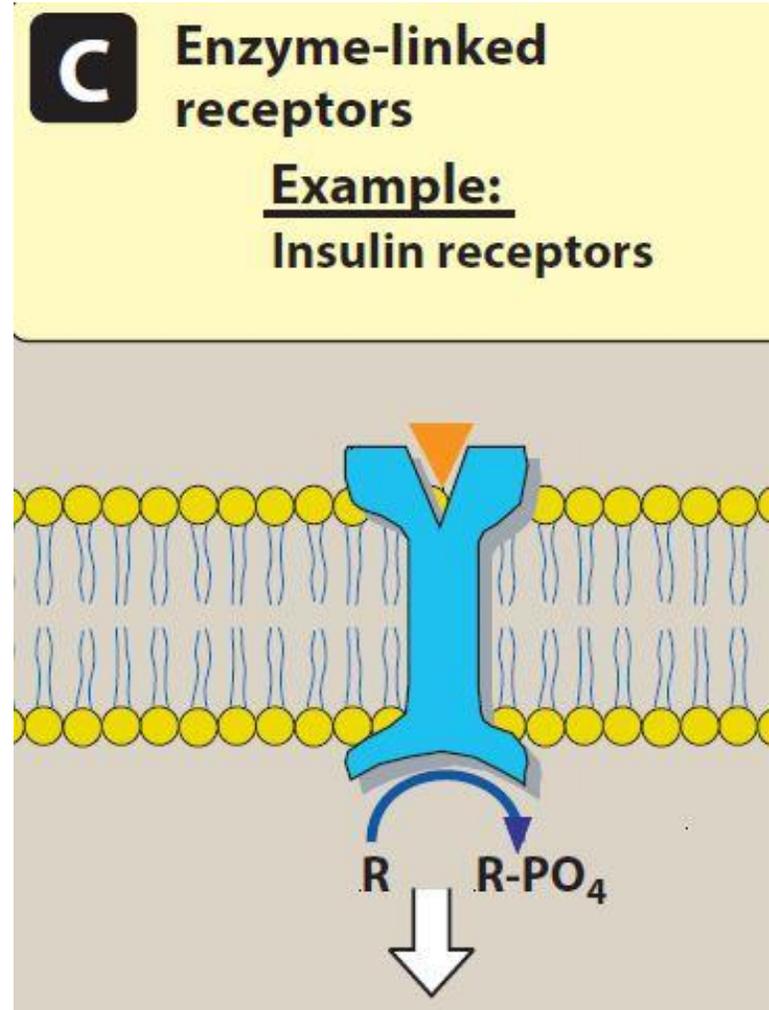


Types of Receptors

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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.

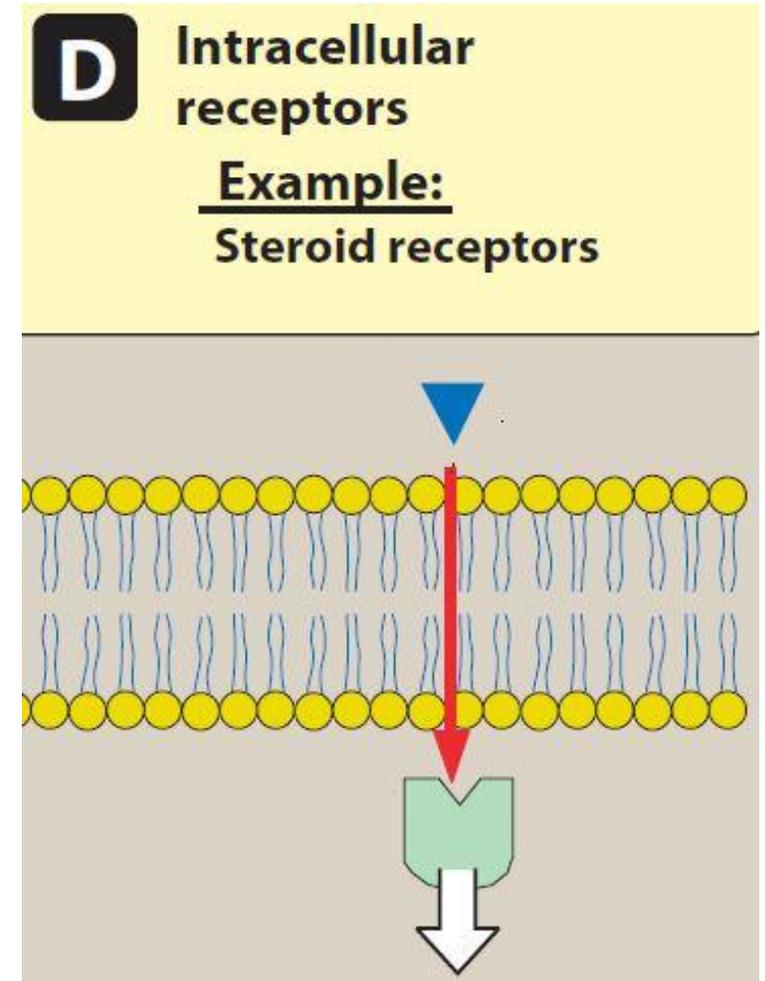


Types of Receptors

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

