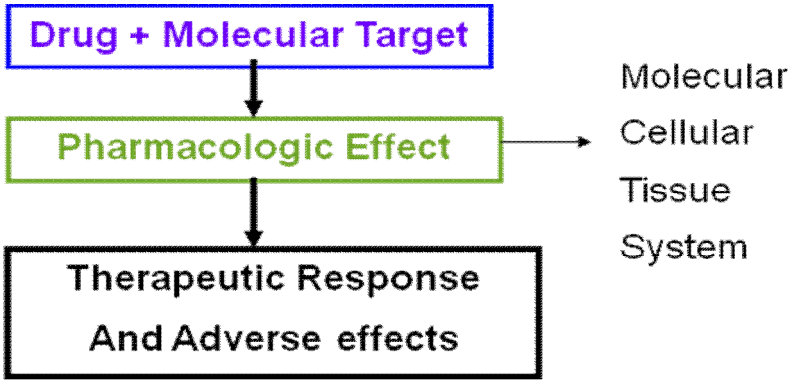
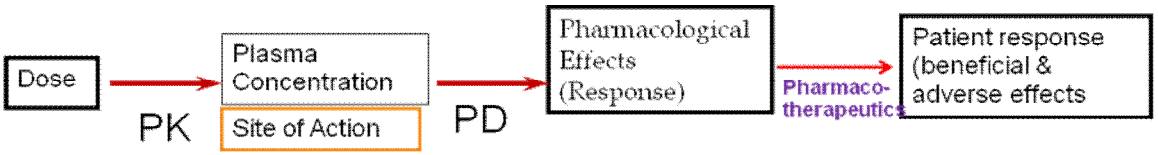
Introduction to Pharmacology

- **Pharmacology:** the science dealing with drug actions.
  - ***Drug action* =**





- **Pharmcokinetics (PK) :** The action of the body on the drug
  - (absorption, distribution and elimination)
- **Pharmacodynamics (PD):** The action of the drug on the body.
  - biochemical and physiological effects of drugs and mechanisms of their action.

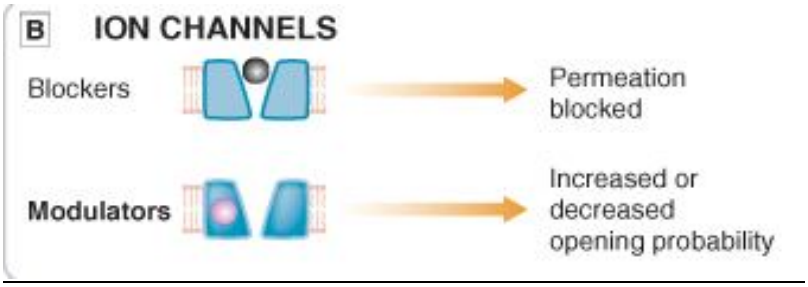
Pharmacodynamics

Targets for Drugs

- There are four molecular protein targets for drugs:
  1. **Ion channels**
  2. **Enzymes**
  3. **Carrier molecules**
  4. **Receptor**
  - Some drugs act on no molecular targets. *Like antiacids*
- Drugs are classified on the type of target they act on, making them 5 classes of drugs *(1 for each target + a class acting on none)*

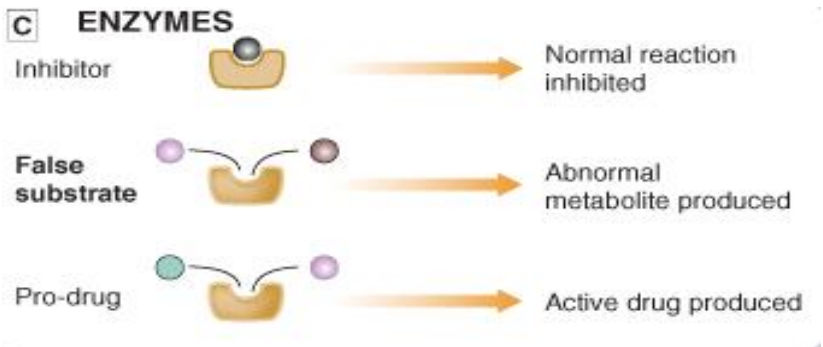
1. Ion Channels

- Ion channels are pores in the cell membrane that allow the passage of ions.
- Drugs can *DIRECTLY* bind to channel proteins leading to alteration of its function.
- It can act either by:
  - *First:* physical blockade of the channel by the drug molecule *(blockers)*
  - *Second mode* is modulation of channel function by drugs that bind to accessory sites on the channel protein (allosteric modulators) → either increase or decrease ion channel function



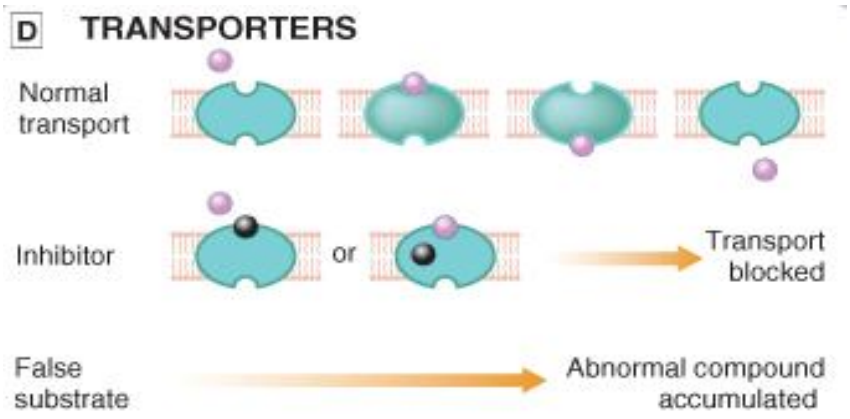
2. Enzymes

- Drugs can either inhibit the normal action of the enzyme or by being a false or a true substrate.
- ***Competitive Inhibitors:*** the drug is a substrate analogue (look like the substrate), so it stays in the binding site, and doesn't allow substrate to bind to enzyme.
  - A drug can be *reversible* or *irreversible*.
- ***False substrates:*** bind to the enzyme binding site and produces an abnormal useless substance.
- ***True substrates:*** bind to the enzyme binding site and produces the active form of the drug. So the drug *(prodrug)* is inactive before binding to the enzyme, and is activated by the enzyme.



3. Carrier proteins

- Carrier protein molecules function to **transport ions & small organic molecules** (too polar to penetrate) across cell membranes
  - ❖ They have **a recognition site** that is specific for a particular substance to be carried.
- Drugs target these recognition sites to block the transport system

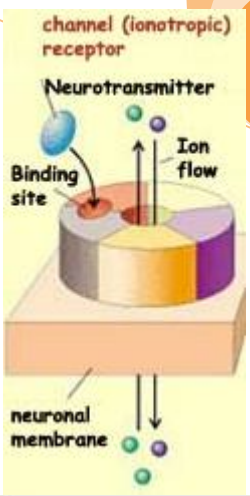


4. Receptors

- **Receptors**: cellular *macromolecular* proteins
  - ❖ located mostly in the cell membrane but can be found less frequently in the cytoplasm
  - ❖ They have **specific recognition sites** that bind selectively with a structurally-related group of synthetic drugs and endogenous mediators (ligands)

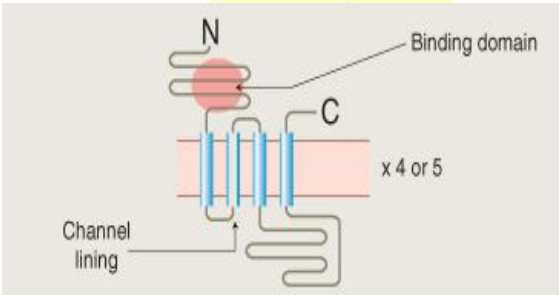
Receptor structure

- Receptors are made up of 3 parts:
  - ❖ one or more than one hydrophobic membrane-spanning α-helical segment
  - ❖ the extracellular ligand-binding domain
  - ❖ the intracellular *transduction domain*
- Receptors are classified into several classes based upon ***molecular structure*** and ***pharmacological functional aspects*** (*recognition* and *transuction* aspects)



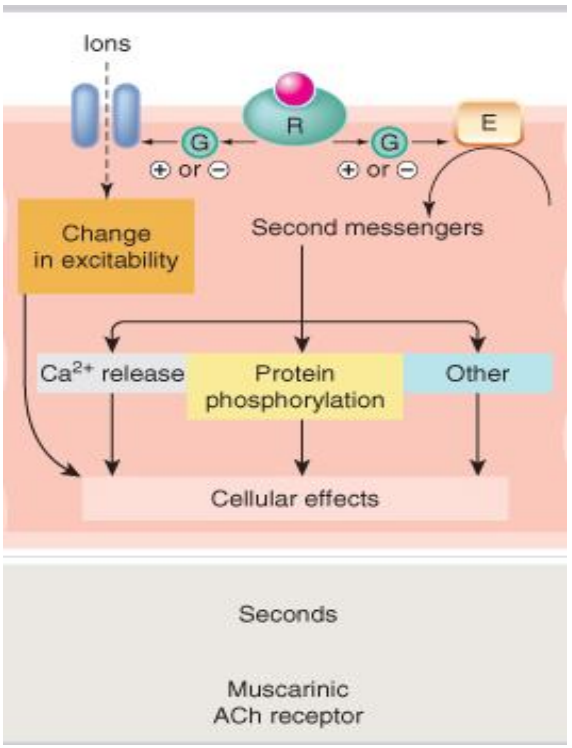
Class 1: Ionotropic Receptor

- The receptor here is an integral part of an ion channel that opens and closes with the control of an agonist binding, mostly a fast neurotransmitter.
- Made up of 4 or 5 subunits
  - The prototype nACh receptor is a pentamer protein ($\alpha_2\beta\gamma\delta$), each of four hydrophobic membrane-spanning helices
  - Each subunit bring one membrane-inserted segment towards the centre of the structure creating the channel pore



Class 2: G-protein coupled (metabotropic) receptors

- Receptors are linked to GTP-binding protein (G-protein)
- G-protein controls the activity of an effector protein; a membrane enzyme or an ion channel
- Activation/inhibition of the effector enzyme increase/decrease the release of a diffusible second messenger such as cAMP or IP3
- A ***single polypeptide chain*** (400-500-amino acid) as **<u>seven transmembrane α-hydrophobic helices</u>**
- Three regions exist:
  - extracellular amino terminus,
  - intracellular carboxy terminus
  - long cytoplasmic loop responsible for interaction with G-protein
- Agonist-binding usually occurs on a hydrophilic domain lying among the helices or on N-terminus



- G-protein exists as different types.. such as:

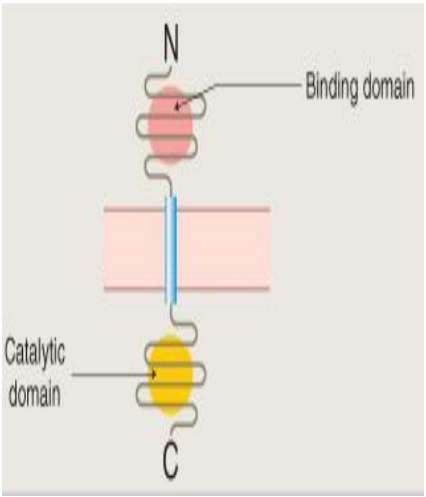
G-Protein	Actions
G-stimulatory (G_s)	Activates Ca^{2+} channels/ adenylyl cyclase
G-inhibitory (G_i)	Activates K^+ channels/ Inhibits adenylyl cyclase
G_0	Inhibits Ca^{2+} channels
G_q	Activates phospholipase C
$G_{12/13}$	Interactions with different ion trasnporters

Targets for G-protein:

- The adenylate cyclase/c-AMP system/PKA cascade
- The phospholipase C (PLC)/ inositol triphosphate (IP_3)-Ca^{2+} release/DAG-PKC system
- G-protein direct regulation of ion channel, e.g., muscarinic ACh receptors stimulate cardiac potassium channels

Class 3: Enzyme-associated receptors

- The receptors functions both as recognition site (receptor) as well as an enzyme usually on the intracellular side, activated upon agonist binding
- They are two main groups
  1. **tyrosine-kinase-linked** receptors such as receptors for insulin, growth factors and many cytokines,
  2. **guanylate cyclase-coupled** receptors for atrial natriuretic peptide (ANP)
- Receptors consist of a single polypeptide chain of 3 parts
  - One hydrophobic *membrane-inserted segment*
  - Extracellular agonist-binding domain
  - Intracellular catalytic (enzyme) domain



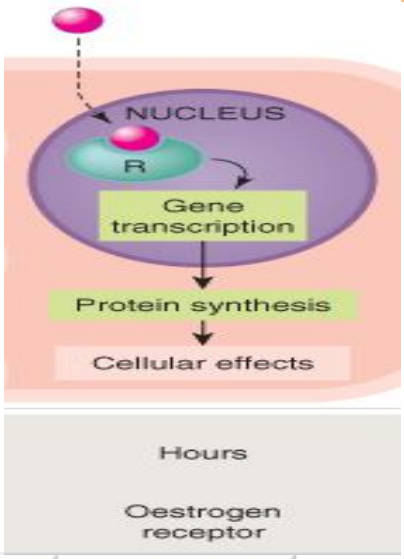
Class 4: Gene Transcription-Regulating Receptor

- **The only intracellular type** *(no membrane segments)*
- Ligands are *lipophilic* molecules that can *readily cross cell membrane*

- A single polypeptide chain located in the **cytoplasm** of 3 main segments
  - ❖ DNA binding domain
  - ❖ Agonist binding domain (C-terminus)
  - ❖ *Gene-transcription domain* (N-terminus) bound to hsp90 protein

STEPS

- Upon receptor-ligand binding, the hsp90 protein is released, uncovering the DNA binding gene-transcription domains
- Followed by stimulation or suppression of a specific m.RNA-protein synthesis cascade



SUMMARY OF RECEPTOR TYPES