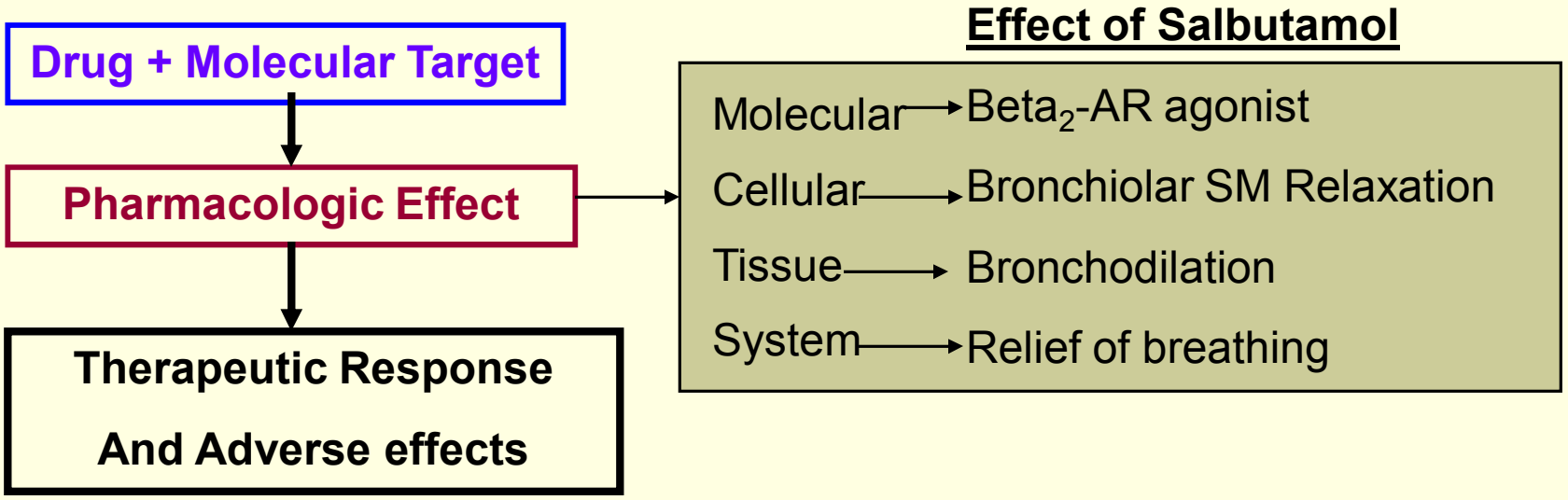
INTRODUCTION TO PHARMACOLOGY

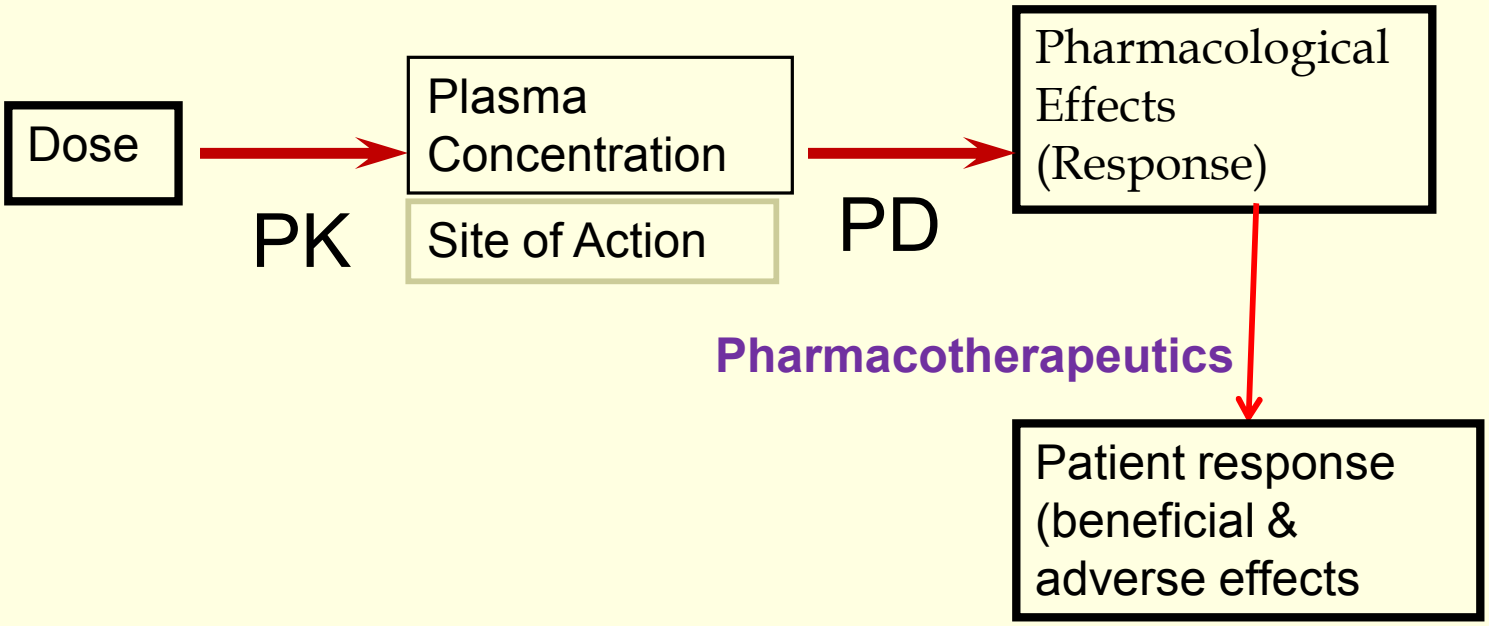
- Marei is a 57-years-old farmer. On several visits over a period of a year you note his blood pressure is 142/97
- He has a history of smoking & has chronic bronchitis He also has elevated lipid and cholesterol levels
- You wish to begin antihypertensive therapy
- Two of the potential choices are prazosin, which is a competitive alpha-receptor blocker, and propranolol, which is a competitive beta-receptor antagonist

Molecular Aspects of Drug Actions

- **Pharmacology is the science dealing with drug actions**



Pharmacokinetics (PK) and Pharmacodynamics (PD)



FOUR MOLECULAR PROTEIN TARGETS FOR DRUGS

I. **Ion Channels**

II. **Enzymes**

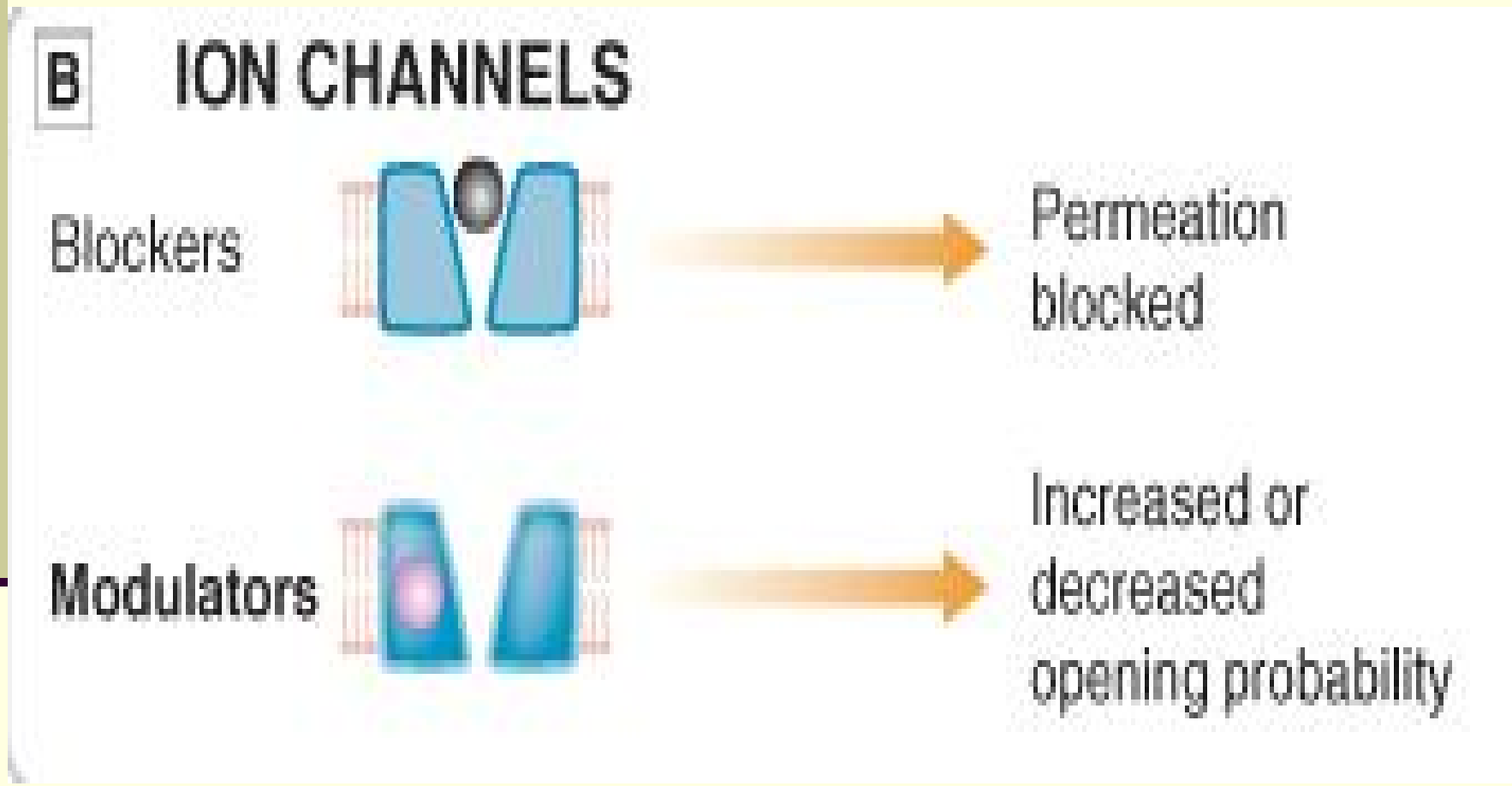
III. **Carrier molecules**

IV. **Receptors**

- **Non drug-target model:**

A fifth class of drug act on NO molecular target

Ion Channels



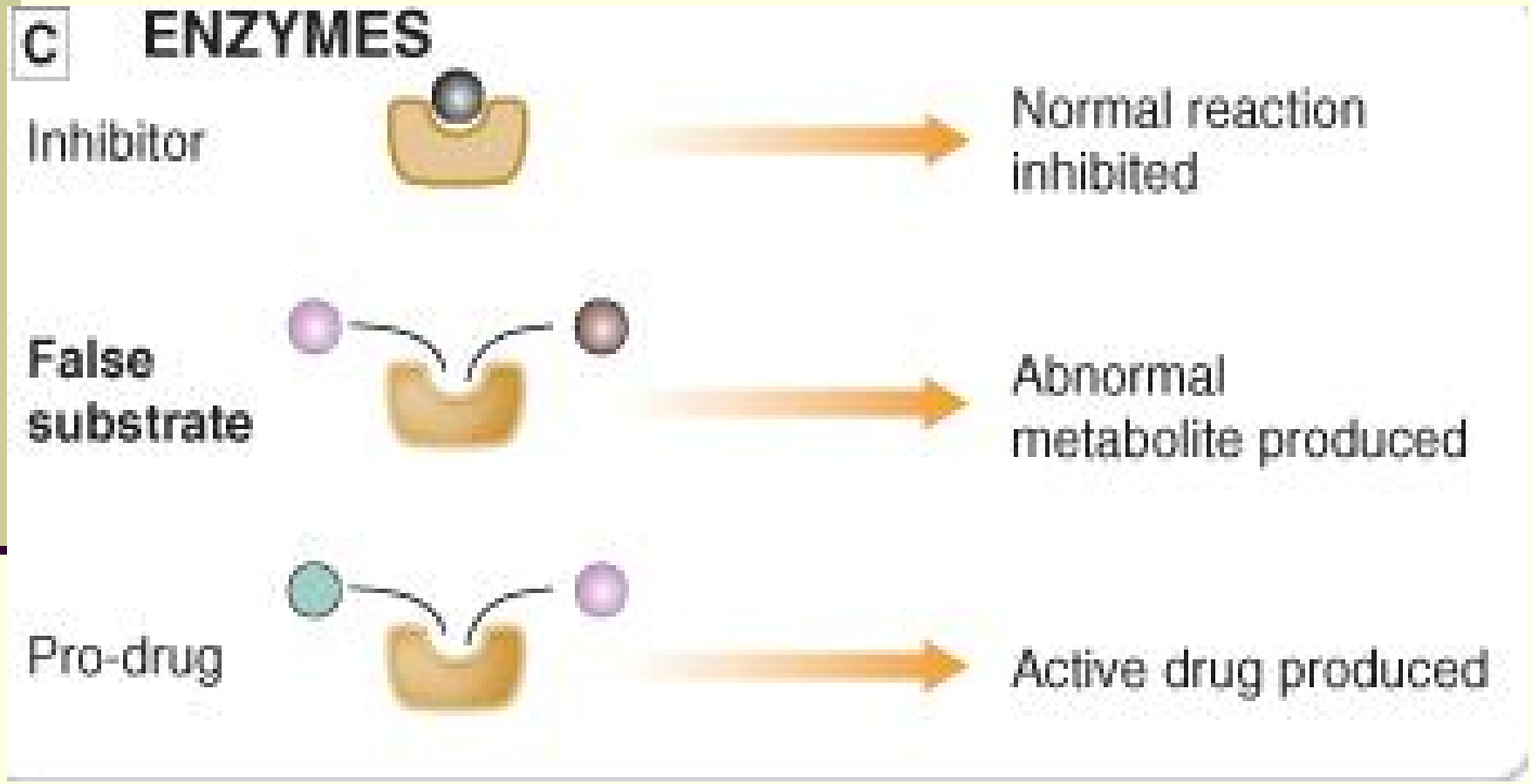
Ion Channels

- Drugs can ***DIRECTLY*** bind to channel proteins leading to alteration of its function
- ***First:*** physical blockade of the channel by the drug molecule
- Example: blocking of neuronal voltage-gated Na^+ channels by local anesthetics and inhibition of Na^+ entry in renal tubules by amiloride diuretic

Ion Channels

- ***Second mode*** **is modulation of channel function by drugs that bind to accessory sites on the channel protein (allosteric modulators)**
  - **Example: The blocking effect of dihydropyrines on voltage-gated calcium channels**

ENZYMES

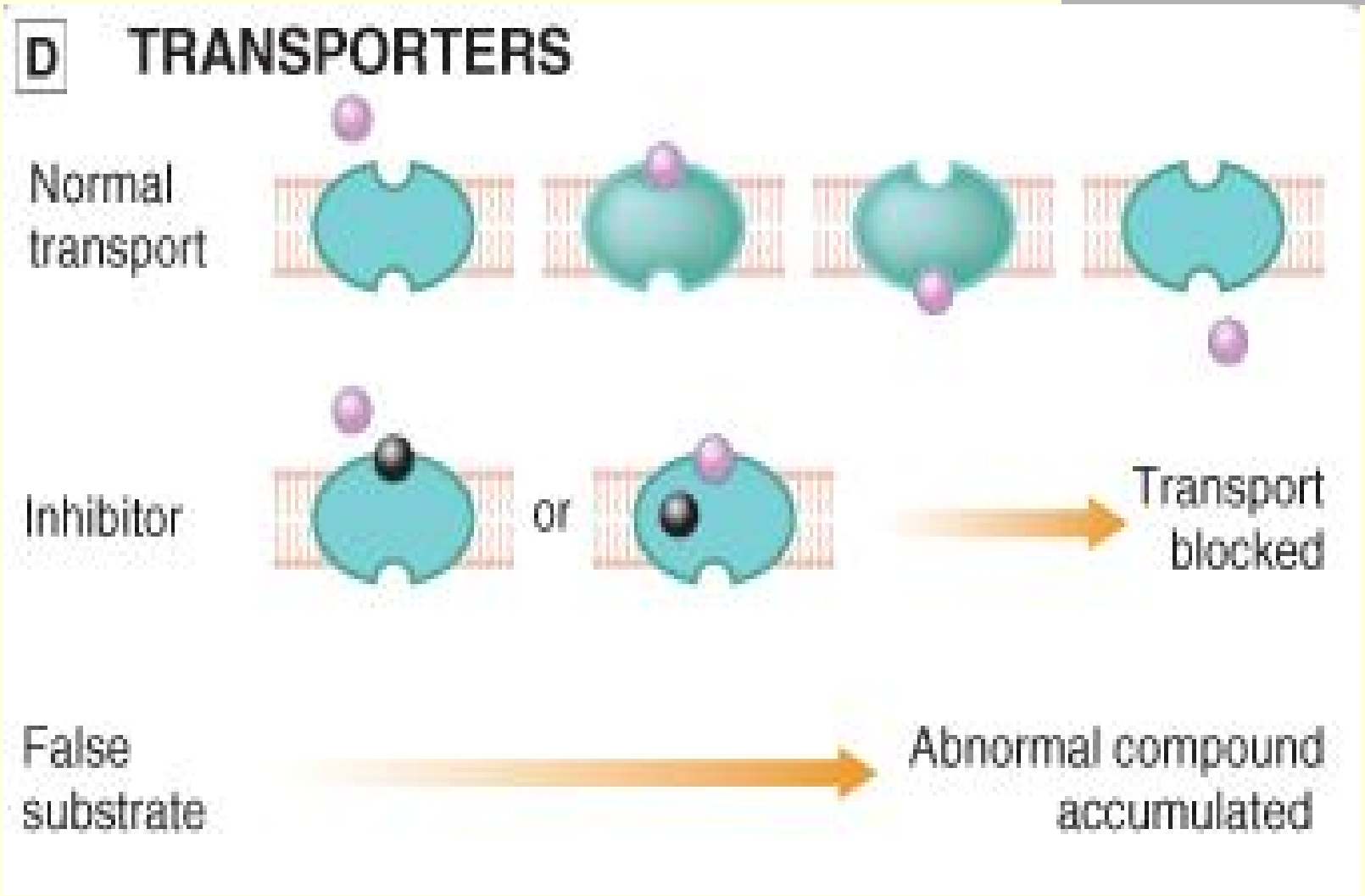

C ENZYMES
Inhibitor
Normal reaction inhibited
False substrate
Abnormal metabolite produced
Pro-drug
Active drug produced

ENZYMES

- *Competitive inhibitor of the enzyme* by being a substrate analogue
- Examples:
  - Irreversible inhibition of cyclo-oxygenase by aspirin
  - reversible inhibition of cholinesterase by neostigmine

- The drug acts as *true/false substrate*
- Examples:
  - L-DOPA converted into dopamine
  - Hemicholinium targeting choline acetyltransferase

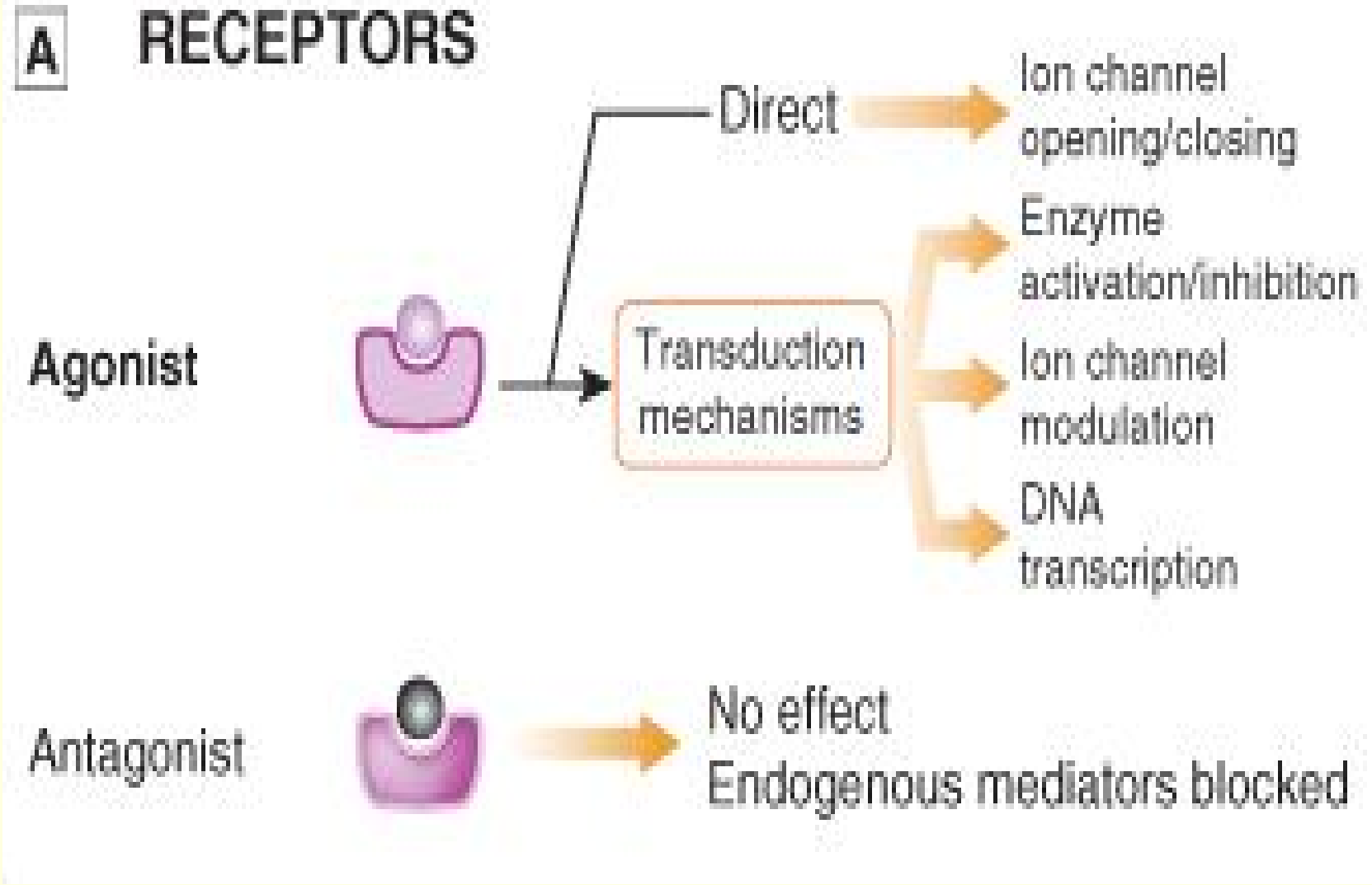
CARRIERS


D TRANSPORTERS
Normal transport
Inhibitor
or
Transport blocked
False substrate
Abnormal compound accumulated

CARRIER MOLECULES

- Carrier protein molecules function to **transport ions & small organic molecules** (too polar to penetrate) across cell membranes
- They possess ***a recognition site*** that confers specificity for a particular carried agent
- Such recognition sites can be targets for drugs where they block the transport system
- An example is the inhibition of **cardiac Na^+K^+-ATPase** by **cardiac glycosides**

RECEPTORS


A
RECEPTORS
Agonist
Direct
Ion channel opening/closing
Transduction mechanisms
Enzyme activation/inhibition
Ion channel modulation
DNA transcription
Antagonist
No effect
Endogenous mediators blocked

RECEPTORS

- Receptors are cellular macromolecular proteins located either in the cell membrane or 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)

Non Drug-Molecular Target Model

- Few drugs act through non-receptor (non-target)-mediated mechanisms
- Mannitol is a sugar that acts as a diuretic
- ✓ It has NO molecular target in the nephron
- ✓ Mannitol acts by creating an increased intraluminal osmotic pressure
- ❑ Antacids act nonspecifically by absorbing or chemically neutralizing gastric acid

Receptor Classification

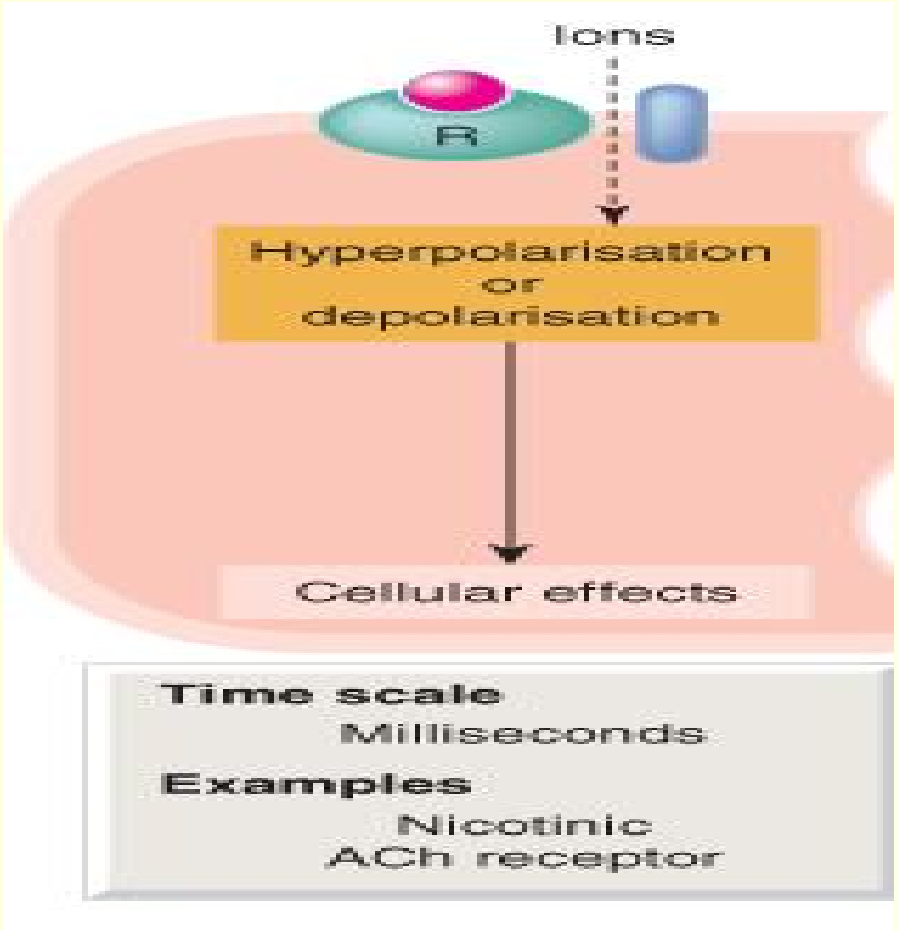
- ***Receptor classification*** **relies upon both molecular structure and pharmacological functional aspects**
- **The *operational (functional)* aspects of receptors involve both recognition as well as transduction characteristics**

RECEPTOR STRUCTURE

- **Membrane receptors are usually composed of three parts:**
  - **one or more than one hydrophobic *membrane-spanning α-helical segment***
  - **the *extracellular ligand-binding* *domain***
  - **the intracellular *transduction domain***

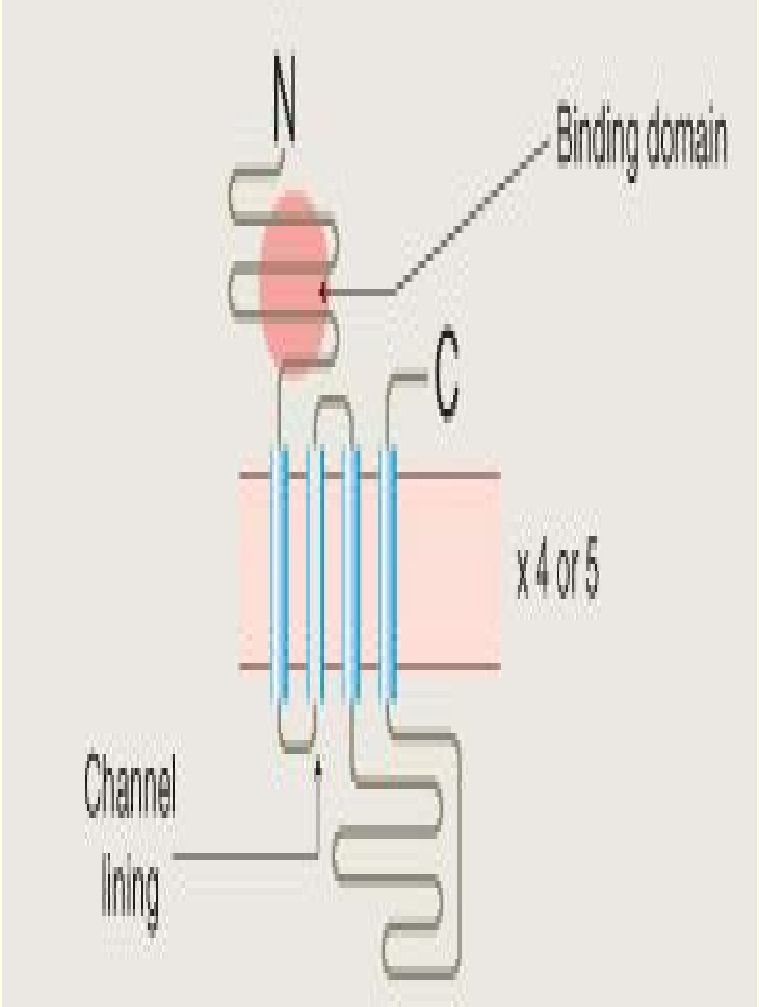
CLASS 1: TRANSMITTER-GATED ION CHANNELS (IONOTROPIC RECEPTORS)

- The receptor is an integral part of an ion channel
- Opening and closing of the ion channel is controlled by agonist binding, mostly fast neurotransmitters
- Examples: nicotinic ACh (nACh) receptors, 5-HT_3 & the $GABA_A$ receptors



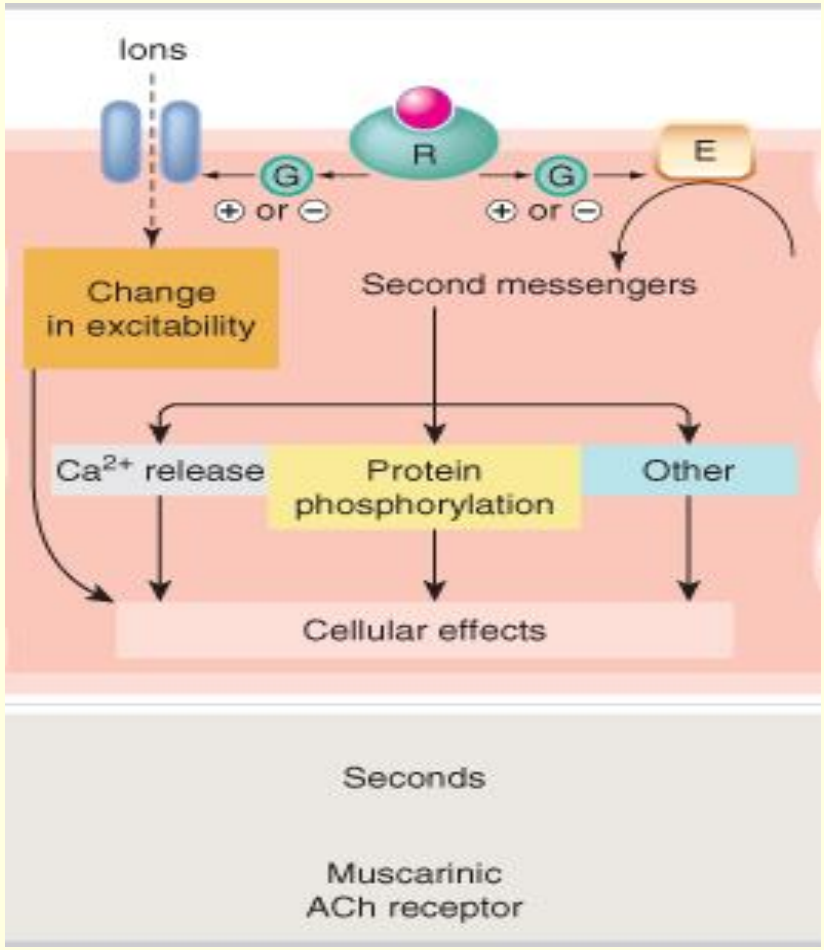
Class 1: Ionotropic Receptors Structure

- 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



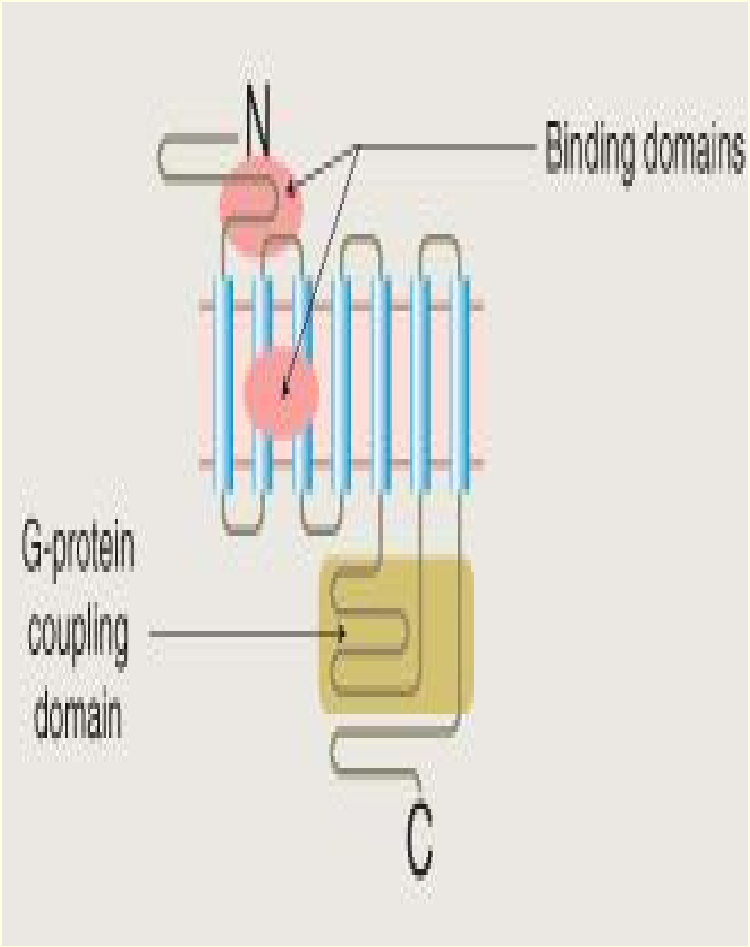
Class 2: G-protein-Coupled (Metabotropic) Receptors

- 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 IP_3



Class 2: G-Protein-Coupled Receptors Structure

- A single 400-500-amino acid polypeptide chain as seven transmembrane α-hydrophobic helices
- Three regions exist the extracellular amino terminus, the intracellular carboxy terminus & a 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



Major Types of G-Proteins

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-proteins

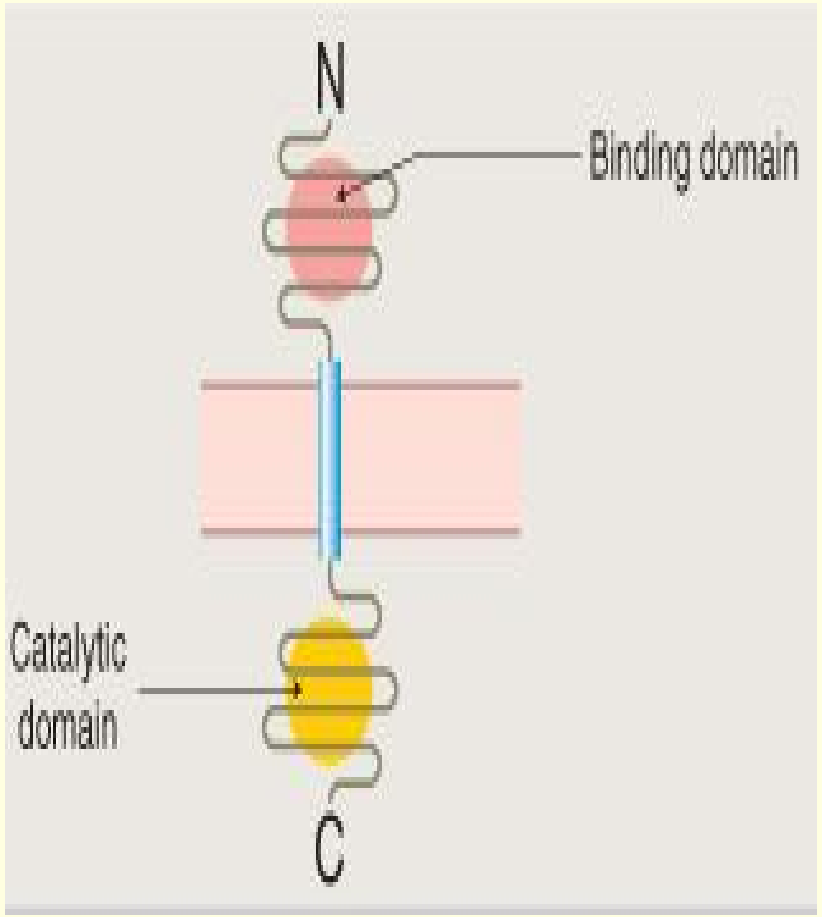
- The adenylate cyclase/c-AMP system/PKA cascade
- The phospholipase C (PLC)/ inositol triphosphate (IP_3)-Ca^{2+} release/DAG-PKC system
- G-protein direct regulation of ion channel, e.g., muscarinic ACh receptors stimulate cardiac potassium channels

Class 3: Enzyme-associated Receptors

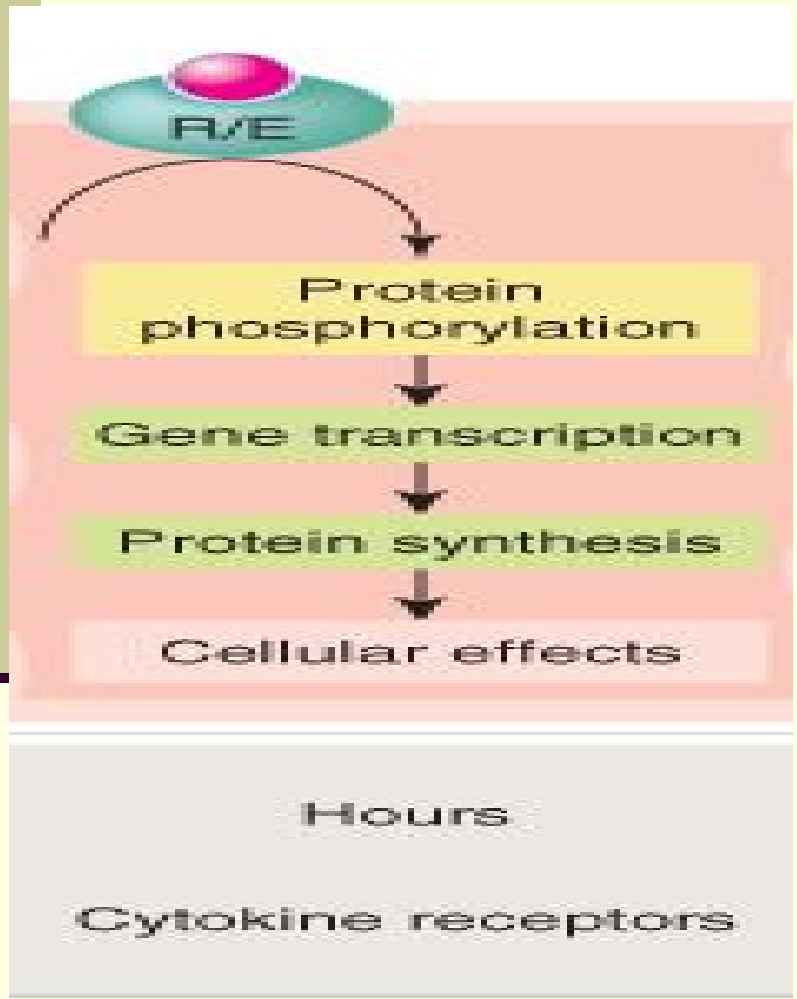
- **The receptors functions both as recognition site (receptor) as well as an enzyme usually on the intracellular side, activated upon agonist binding**
- **They are two main groups**
  - **(1) *tyrosine-kinase-linked receptors* such as receptors for insulin, growth factors and many cytokines,**
  - **(2) *guanylate cyclase-coupled receptors* for atrial natriuretic peptide (ANP)**

Class 3: Enzyme-associated Receptors

- **Receptors consist of a single polypeptide chain of 3 parts**
- **One hydrophobic *membrane-inserted segment***
- **Extracellular agonist-binding domain**
- **Intracellular catalytic (enzyme) domain**



Class 3: Enzyme-associated Receptors



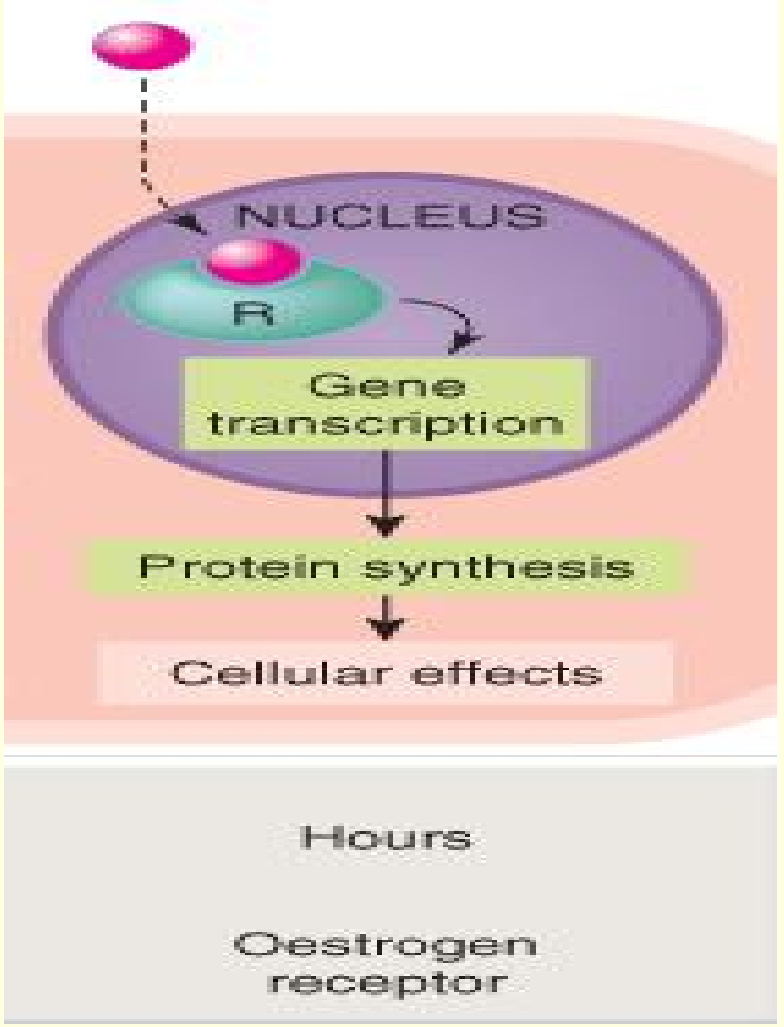
- ***tyrosine-kinase receptors*** **for insulin and cytokines**
- **Guanylate cyclase receptors for ANP**

Class 4: Gene Transcription-Regulating Receptor

- **This is the only intracellular cytoplasmic protein receptors, NO membrane segments**
- **Ligands are lipophilic molecules that can readily cross cell membrane like slow acting hormones including steroid and thyroid hormones**

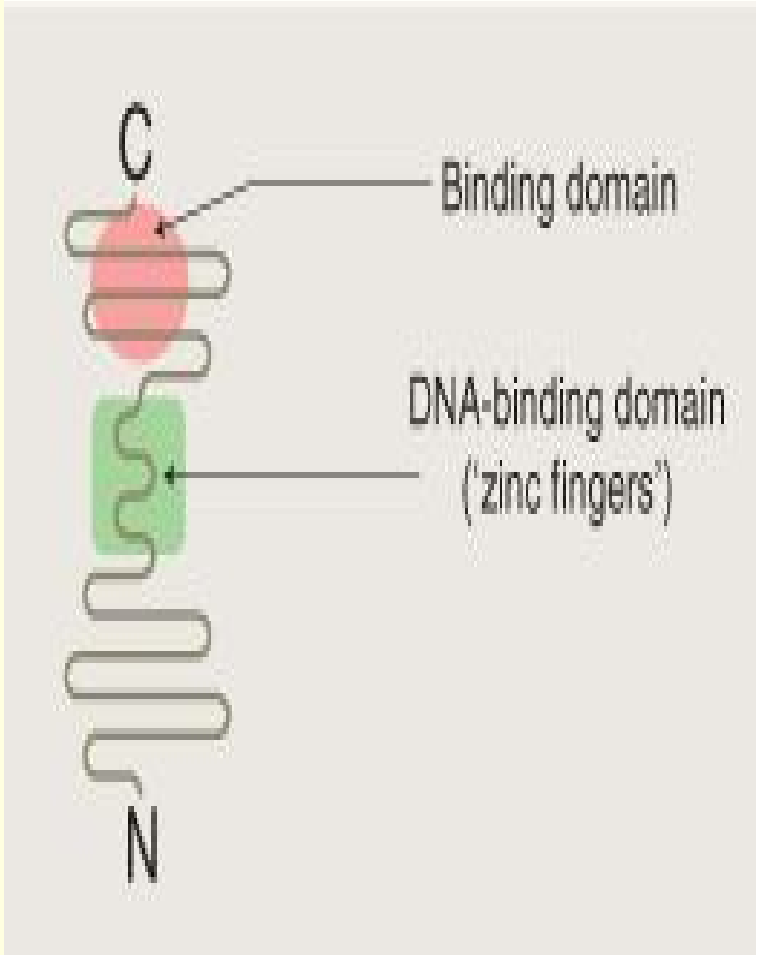
Class 4: Gene Transcription-Regulating Receptor

- 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



Class 4: Gene Transcription-Regulating Receptor

- 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
- Glucocorticoids inhibit the transcription of the gene responsible for the synthesis of cyclo-oxygenase-2 (COX-2)



The Four Main Classes of Receptors