INTRODUCTION TO PHARMACODYNAMICS AND MECHANISM OF DRUG ACTION

Sources:

Bertram G. katzung Basic & Clinical Pharmacology 15th Edition

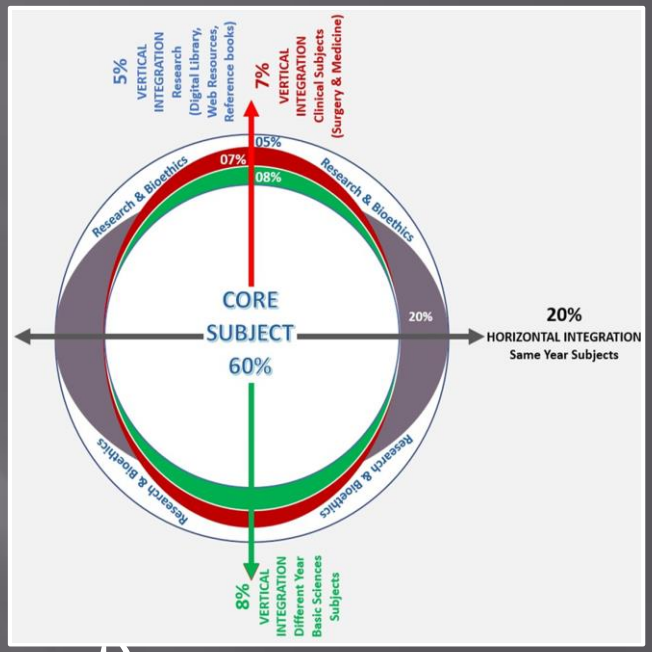
Goodman and Gilman's The Pharmacological Basis of Therapeutics 13th edition.

LEARNING OBJECTIVES

- At the end of session, student should be able to
  - Discuss different ways of drug interaction
  - Define receptors, its types and distribution
  - Define ligand
  - Discuss different receptor ligand interaction
  - Describe different receptor signal transduction mechanism

SEQUENCE OF LECTURE

- Core Subject
- Spiral Integration
- Horizontal Integration
- Vertical integration
- Digital Library References (Research & Bioethics)
- EOLA(End of lecture assessment)



PHARMACODYNAMICS

- DEFINITION

  "Study of biochemical and physiological effects of drugs and their mechanisms of action."

- INCLUDES
  - **Mechanism of action**
  - **Effects**
  - **Adverse effects**
  - **Contraindications**
  - **Drug interactions**

Core subject

- DRUG ACTION
- DRUG EFFECT

Core subject

- Drug undergo 3 phases to reach site of action
  - Pharmaceutical- dissociation, disintegeration
  - Pharmacodynamic
  - Pharmacokinetic

Core Subject

TYPES OF DRUG ACTION

- NON-RECEPTOR MEDIATED (Physiochemical, non cellular)
- RECEPTOR MEDIATED, (Pharmacodynamic, cellular)

Core subject

NON RECEPTOR DRUG INTERACTIONS

- Physical Mechanisms
- Chemical Mechanisms

Core subject

PHYSICAL MECHANISMS

- Mass Action-
- Adsorptive Action-
- Osmotic Action-
- Radio activity-
- Radio opacity-
- Soothing action-
- Mucoprotective-
- Paste, ointment, counter irritants

Core subject

CHEMICAL MECHANISMS

- Chelating Agents-
- Antacids-
- Acidifying Agents-
- Alkalizing Agents-
- Oxidizing Agents-
- Charge-

RECEPTORS

- DEFINITION

"A macromolecule or binding site located on the surface or inside the efferent cell that serves to recognize the signal molecule/drug and initiate response to it."

OR

"A macromolecule or the component of the cell or organism that interacts with a drug and initiates the chain of biochemical events leading to the drug's observed effects."

RECEPTORS

- Recognition of the specific ligand molecule
- Transduction of the signal into a response

Receptor molecule has

- Ligand binding domain
  - Orthosteric site
  - Allosteric site (allotropic site)
    - +ive allosteric modulation, facilitation
    - -ive allosteric modulation, allosteric antagonist
- Effector domain

TYPES OF RECEPTORS

- Protein in nature
- Regulatory in nature
- Enzymes
- ion channels
- Transport proteins

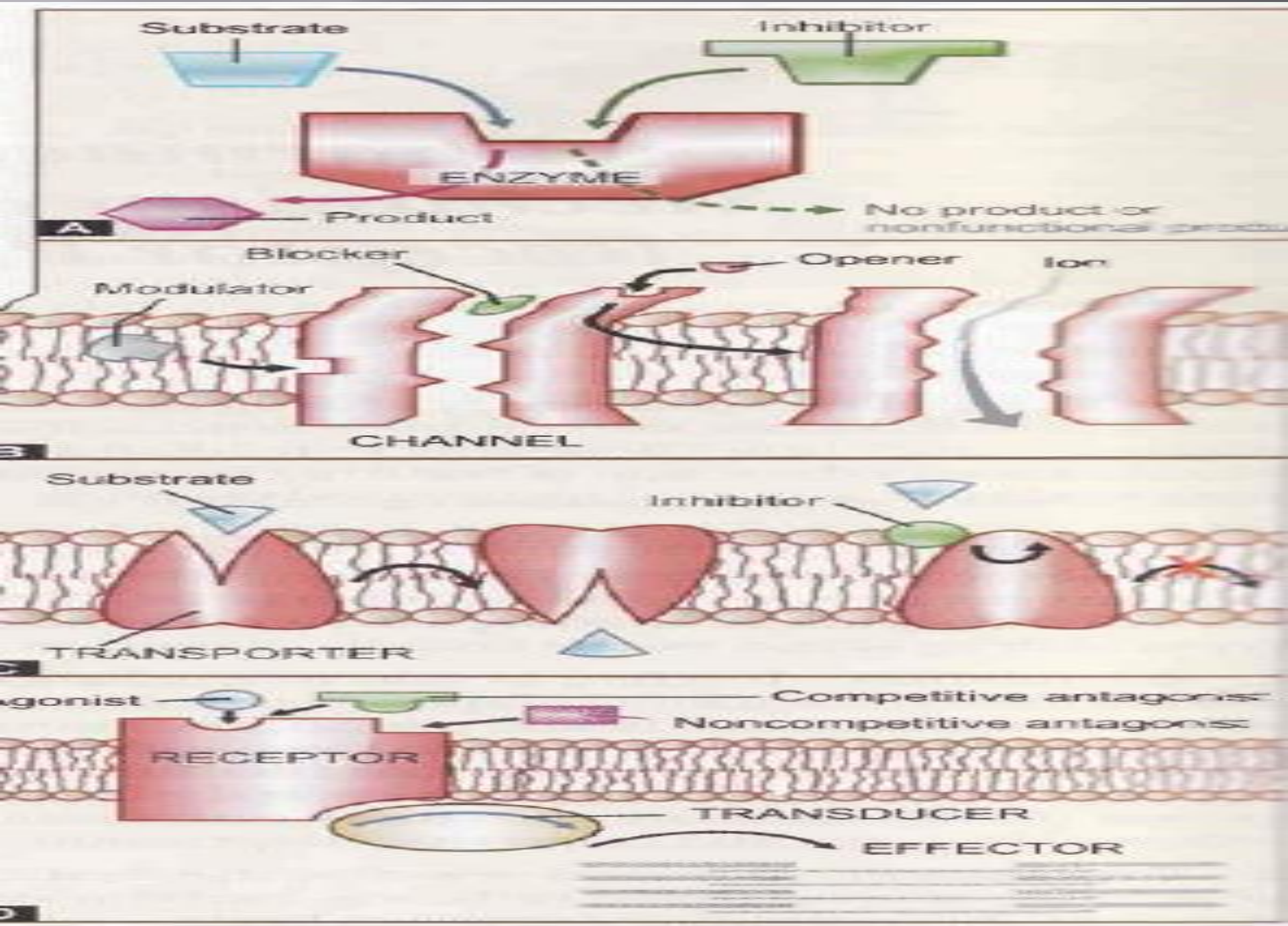


Fig. 4.1: Four major types of biomacromolecular targets of drug action

DRUG RECEPTOR BINDING- RECEPTOR OCCUPANCY THEORY

D +R → **DR Complex** ⟷ Effect

- ✓ Affinity
- ✓ Efficacy

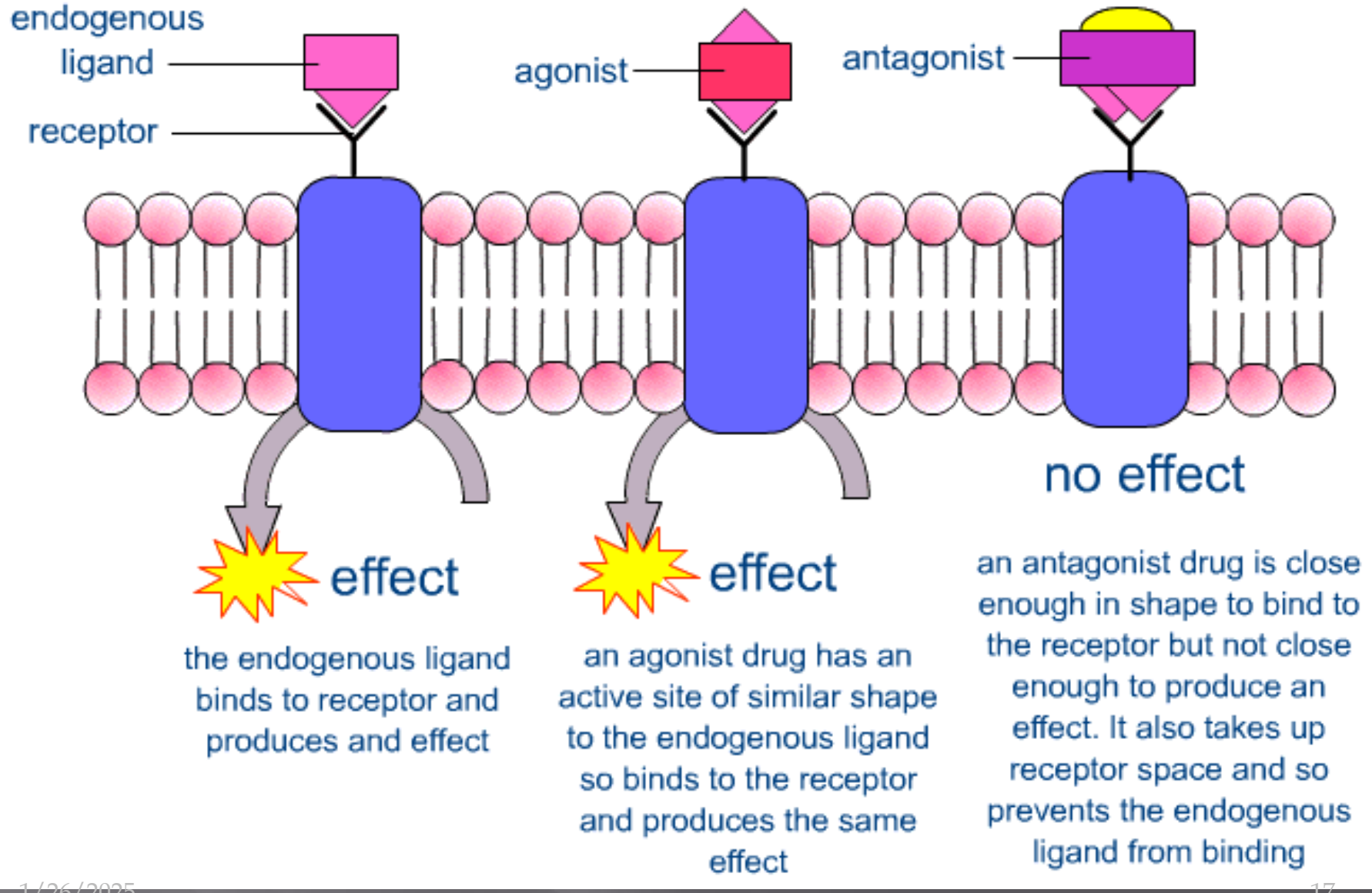
Core subject

DRUG-RECEPTOR INTERACTION

- Binding of drug to receptor can be as
- ✓ Ligand
- ✓ Agonist
- ✓ Antagonist (Neutral antagonist)
- ✓ Partial agonist
- ✓ Inverse agonist
- ✓ Mixed agonist-antagonist

Core subject

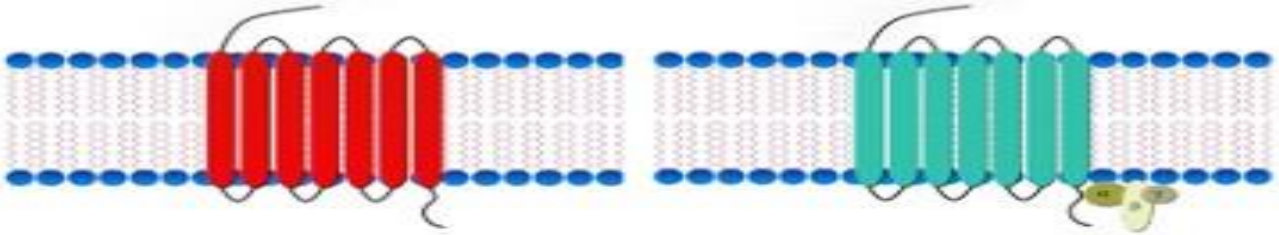
DRUG RECEPTOR INTERACTION



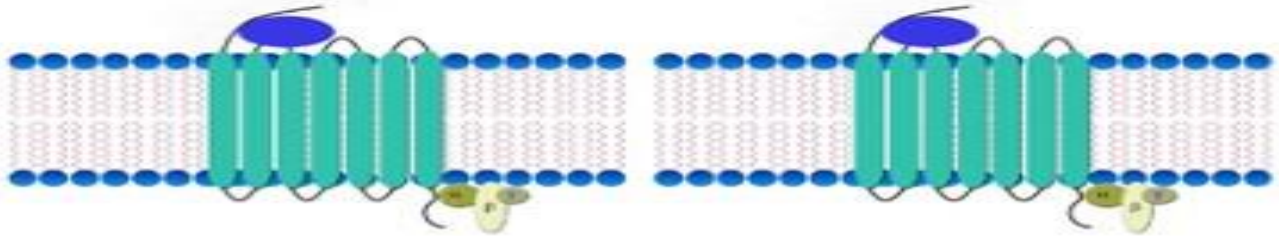
RECEPTOR MODELS

- Traditional receptor model
- 2 receptors model state

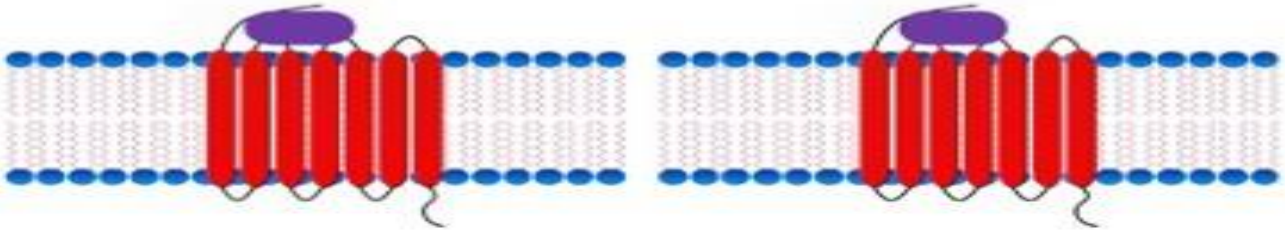
a Constitutively active receptor



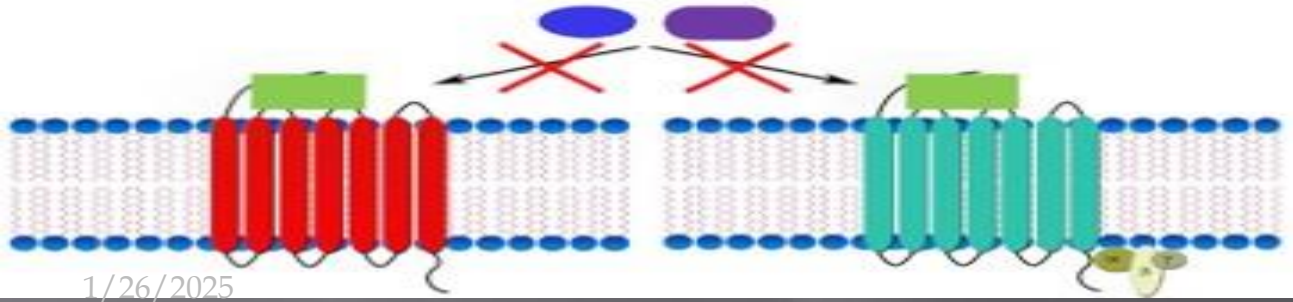
b Agonist-induced activation

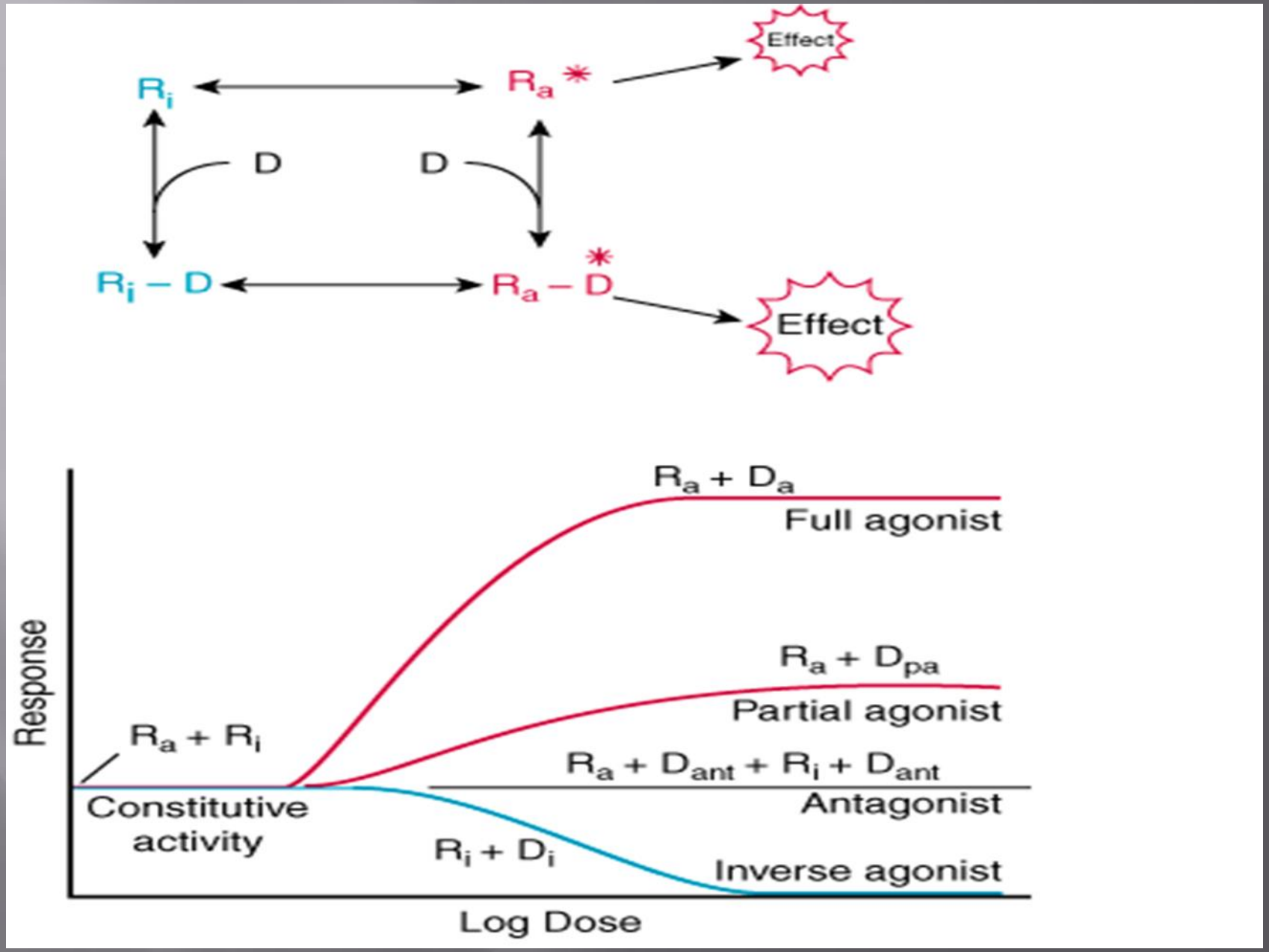


c Inverse agonist suppresses constitutive activity



d Neutral antagonist maintains constitutive activity
....but prevents (endogenous) ligand binding




Effect
R_i
R_a *
D
D
R_i – D
R_a – D *
Effect
$R_a + D_a$
Full agonist
$R_a + D_{pa}$
Partial agonist
$R_a + R_i$
$R_a + D_{ant} + R_i + D_{ant}$
Antagonist
Constitutive activity
$R_i + D_i$
Inverse agonist
Response
Log Dose

DRUG ANTAGONISM

- Competitive
- Non competitive
- Pseudo irreversible
- Irreversible

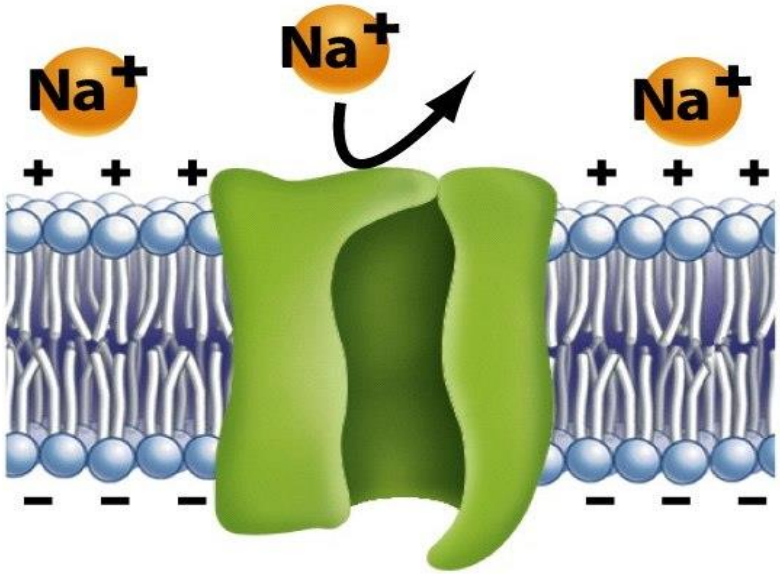
Core subject

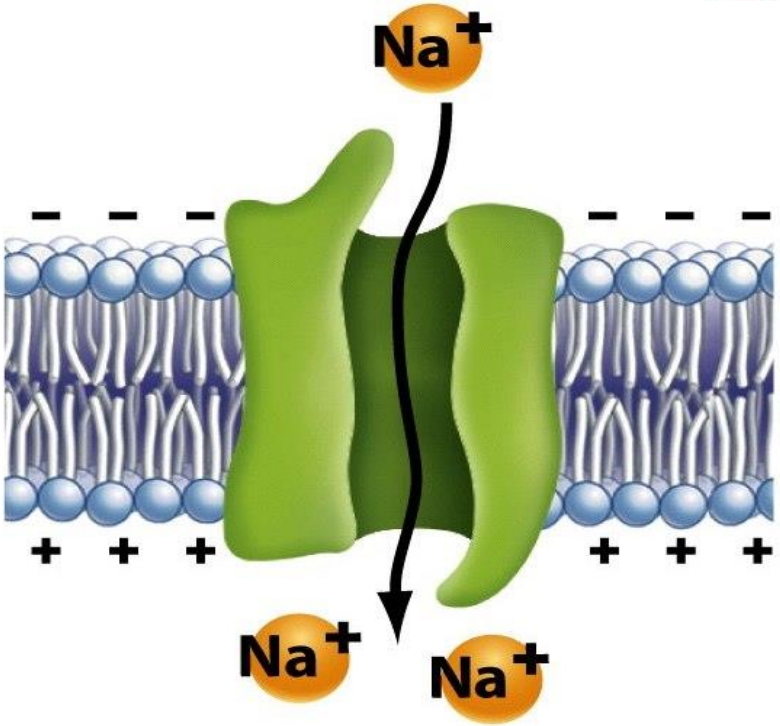
TRANSDUCER MECHANISMS

1) Receptors with intrinsic ion channels
2) Intracellular receptors (Regulating gene expression)
3) Ligand regulated transmembrane enzymes
4) Cytokine receptors
5) Receptors linked to G proteins (Metabotropic receptors)

ION CHANNEL LINKED RECEPTOR

Voltage gated ion channel





At the resting potential, voltage-gated Na^+ channels are closed.

When the membrane is depolarized, conformational changes open the voltage-gated channel.

Ligand gated ion channel

- Ionotropic receptors
- GABA gated Cl- Ion channel - eg. Barbiturates
- Glutamate gated cation Ch. (NMDA r)

  e.g. Ketamine

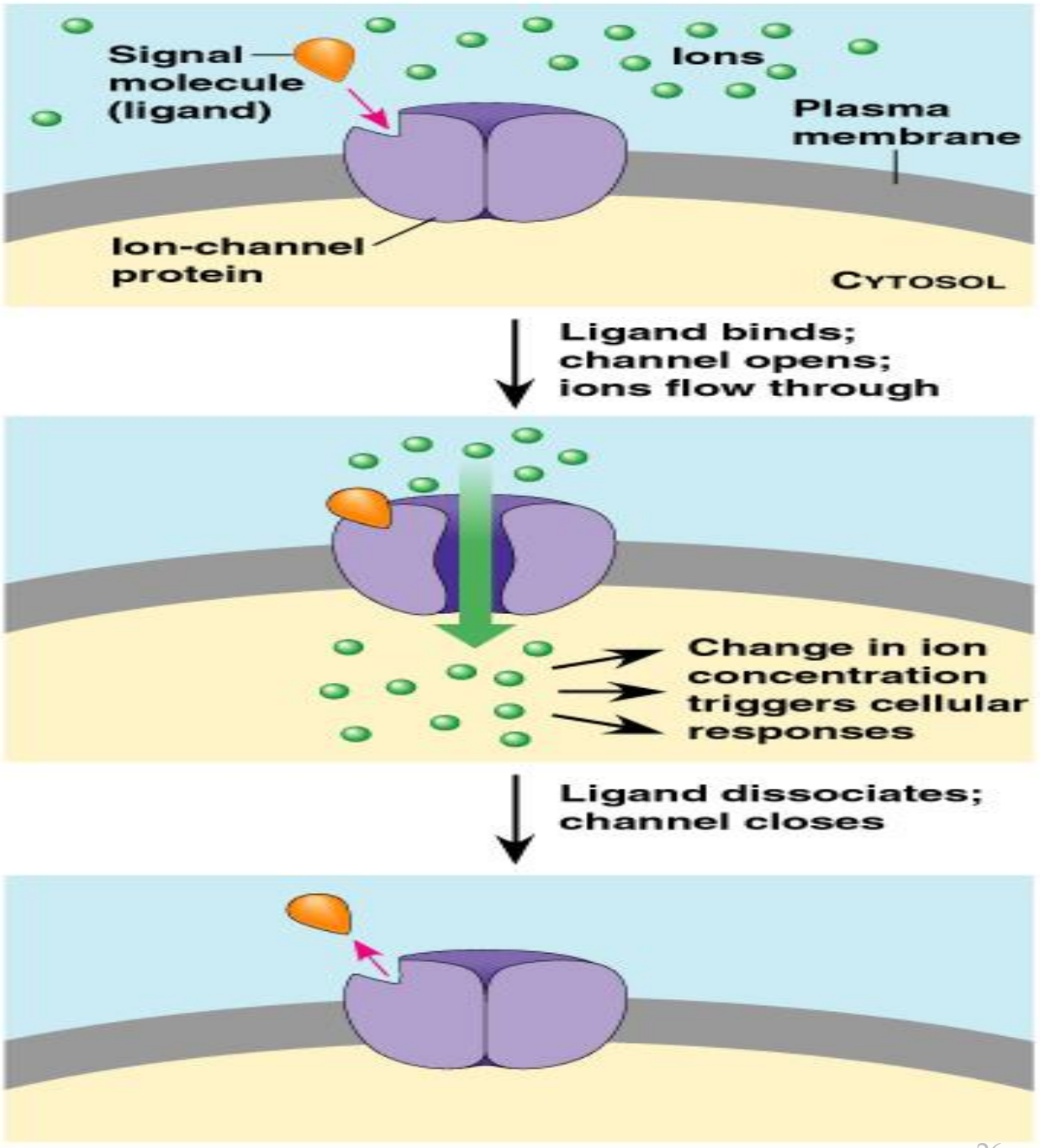
- Action occurs very fast in millisecond

Core subject, spiral integration with physiology

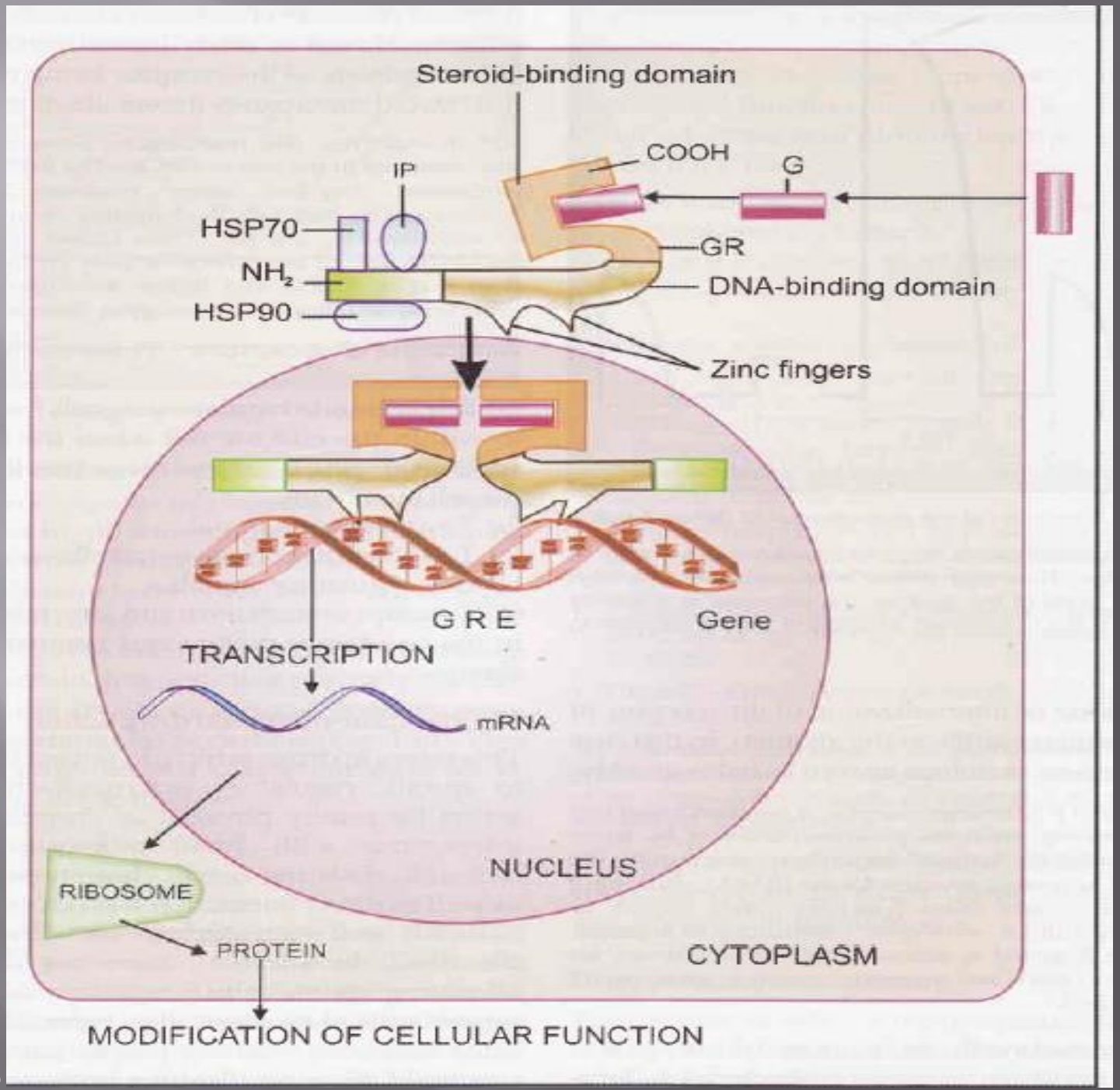
Signal molecule binds as a ligand at a specific site on the receptor

Conformational changes open the channel allowing ions to flow into the cell

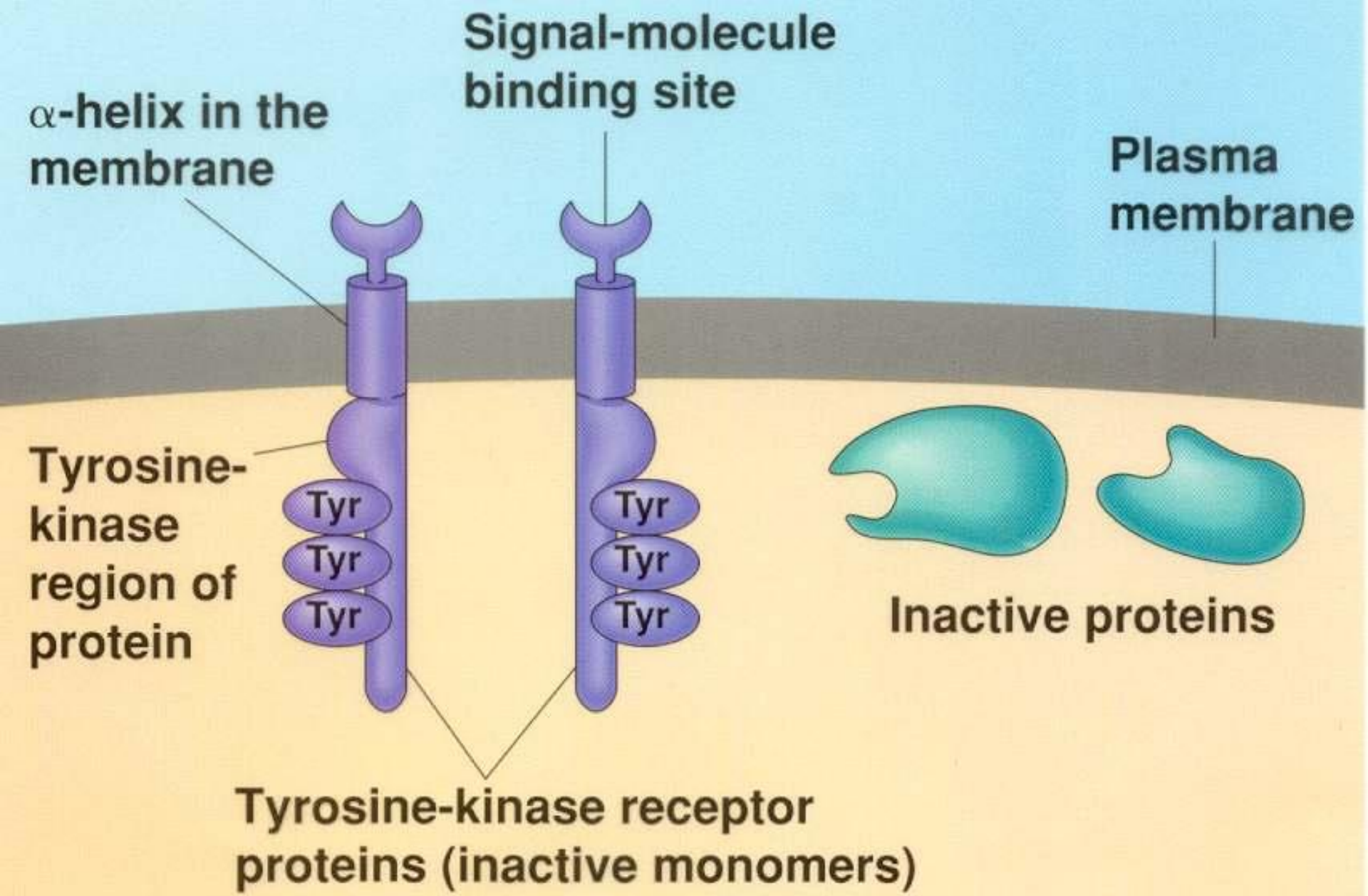
The change in ion concentration within the cell triggers cellular responses



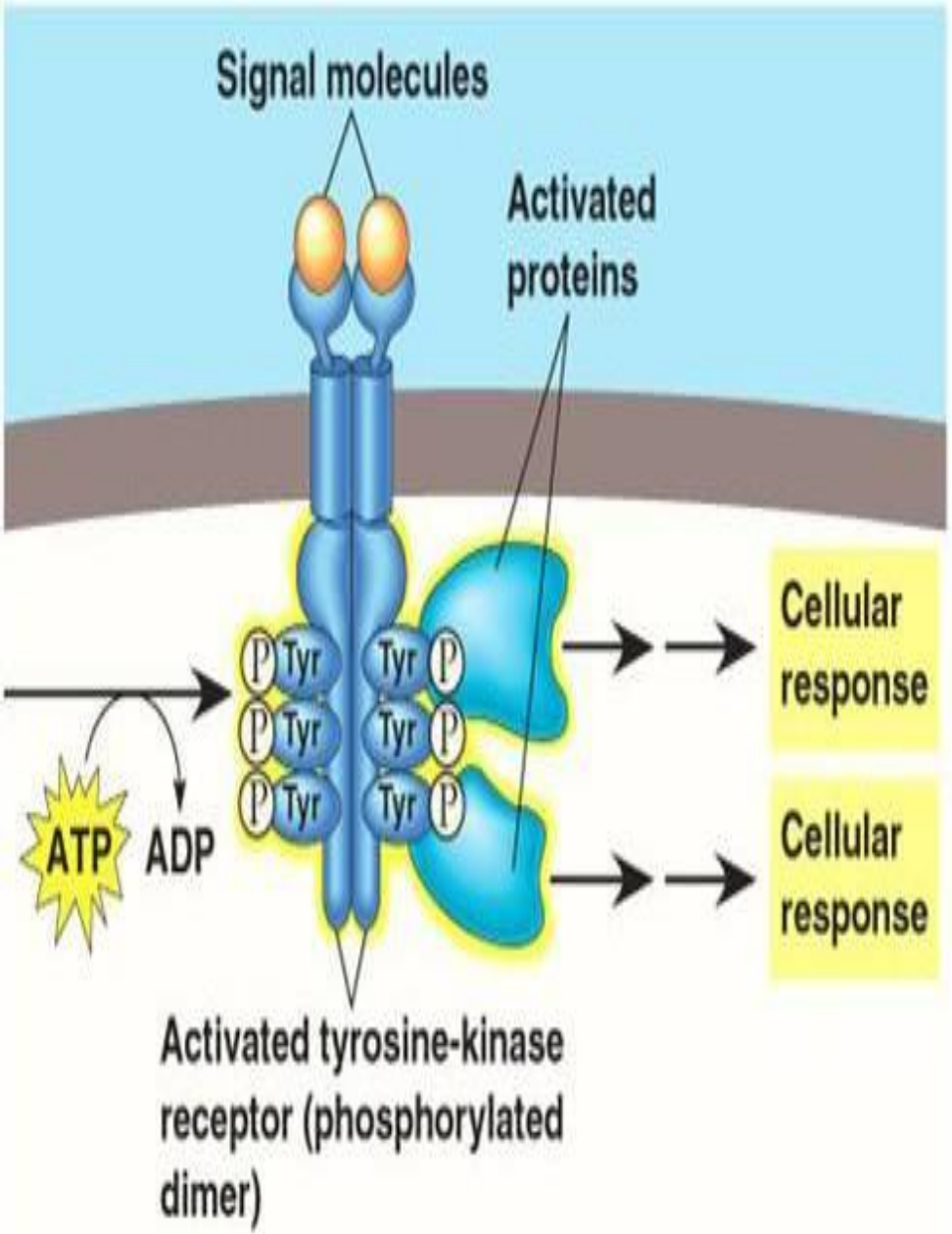
INTRACELLULAR RECEPTORS


Steroid-binding domain
COOH
G
IP
HSP70
GR
NH_2
DNA-binding domain
HSP90
Zinc fingers
G R E
Gene
TRANSCRIPTION
mRNA
NUCLEUS
RIBOSOME
PROTEIN
CYTOPLASM
MODIFICATION OF CELLULAR FUNCTION

LIGAND REGULATED TRANSMEMBREANE ENZYMES



(a) Inactive tyrosine-kinase receptor system



Ligands bind to both receptors

The two receptor polypeptides aggregate forming a dimer

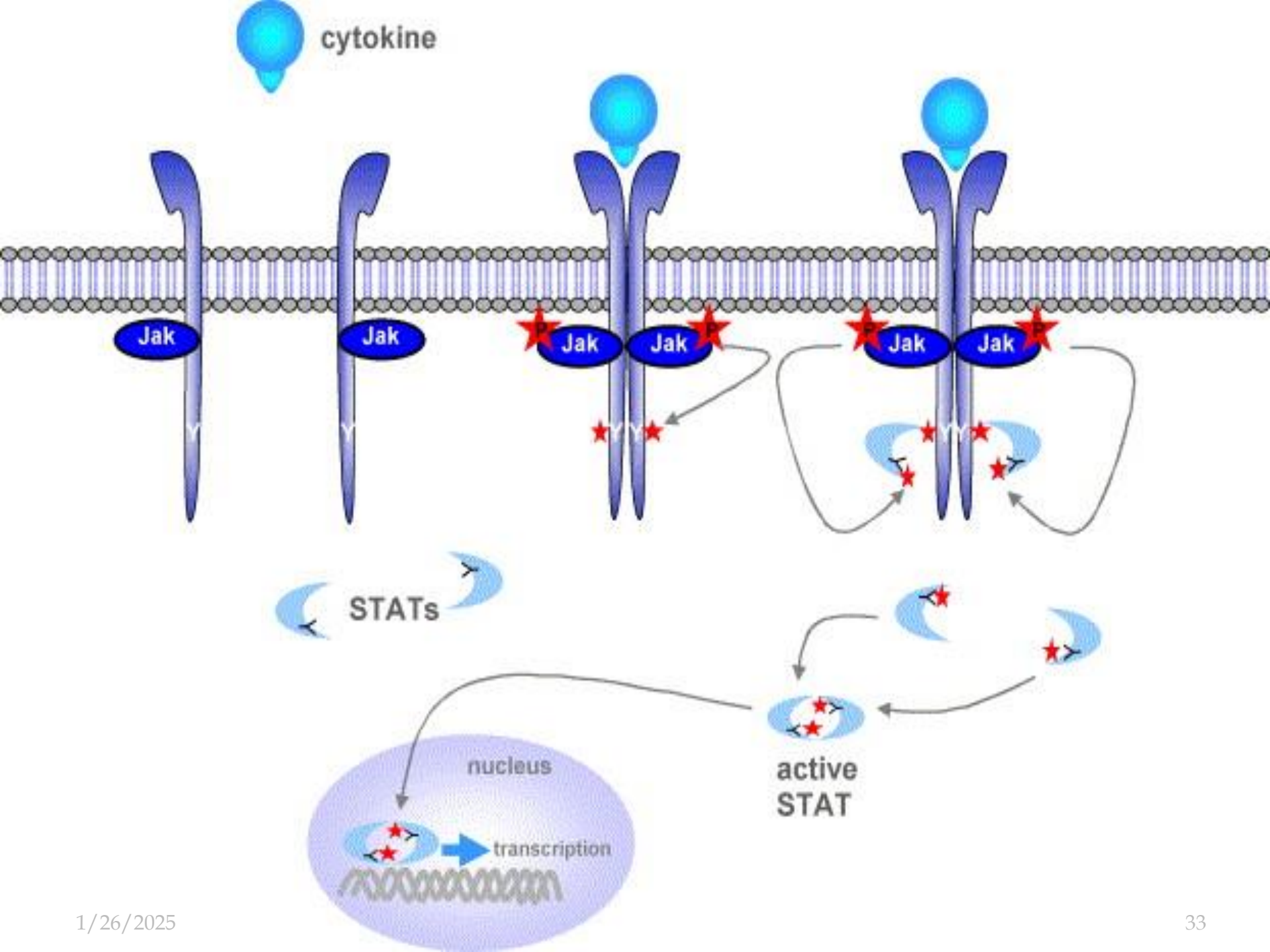
Activates the tyrosine-kinase parts of the dimer

Each phosphorylates (using ATP) the tyrosines on the tail of the other polypeptide

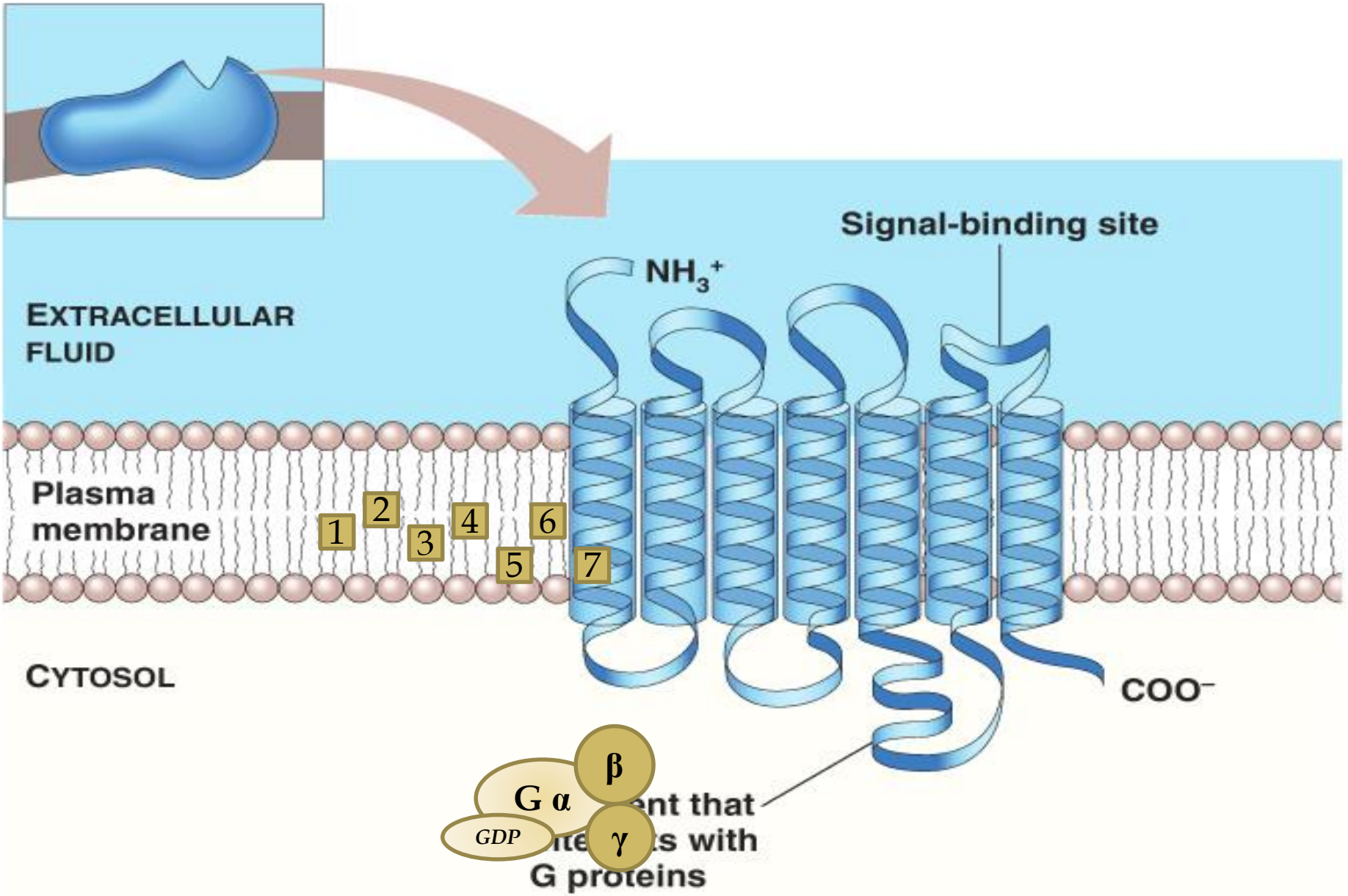
Receptor proteins are now recognized by relay proteins inside the cell

Relay proteins bind to the phosphorylated tyrosines (may activate 10 or more different transduction pathways)

CYTOKINE RECEPTORS


cytokine
Jak
Jak
Jak
Jak
P
P
Jak
Jak
P
P
STATs
active
STAT
nucleus
transcription

RECEPTORS LINKED TO G-PROTEINS



CLASSES OF G- PROTEINS

- 3 major classes
  - Gs
  - Gi
  - Gq
- Gs stimulate adenyl cylase(ATP into cAMP)
- Gi inhibits adenyl cylase
- Gq stimulates phospholipase C(converts PIP2 into IP3 and DAG)

Spiral integration with biochemistry

cAMP AS A SECOND MESSANGER

- cAMP stimulate cAMP dependant protein kinases.
- cAMP regulates many aspects of cell function like
  - ❖Different enzymes-increased glycogenolysis

Spiral integration with biochemistry

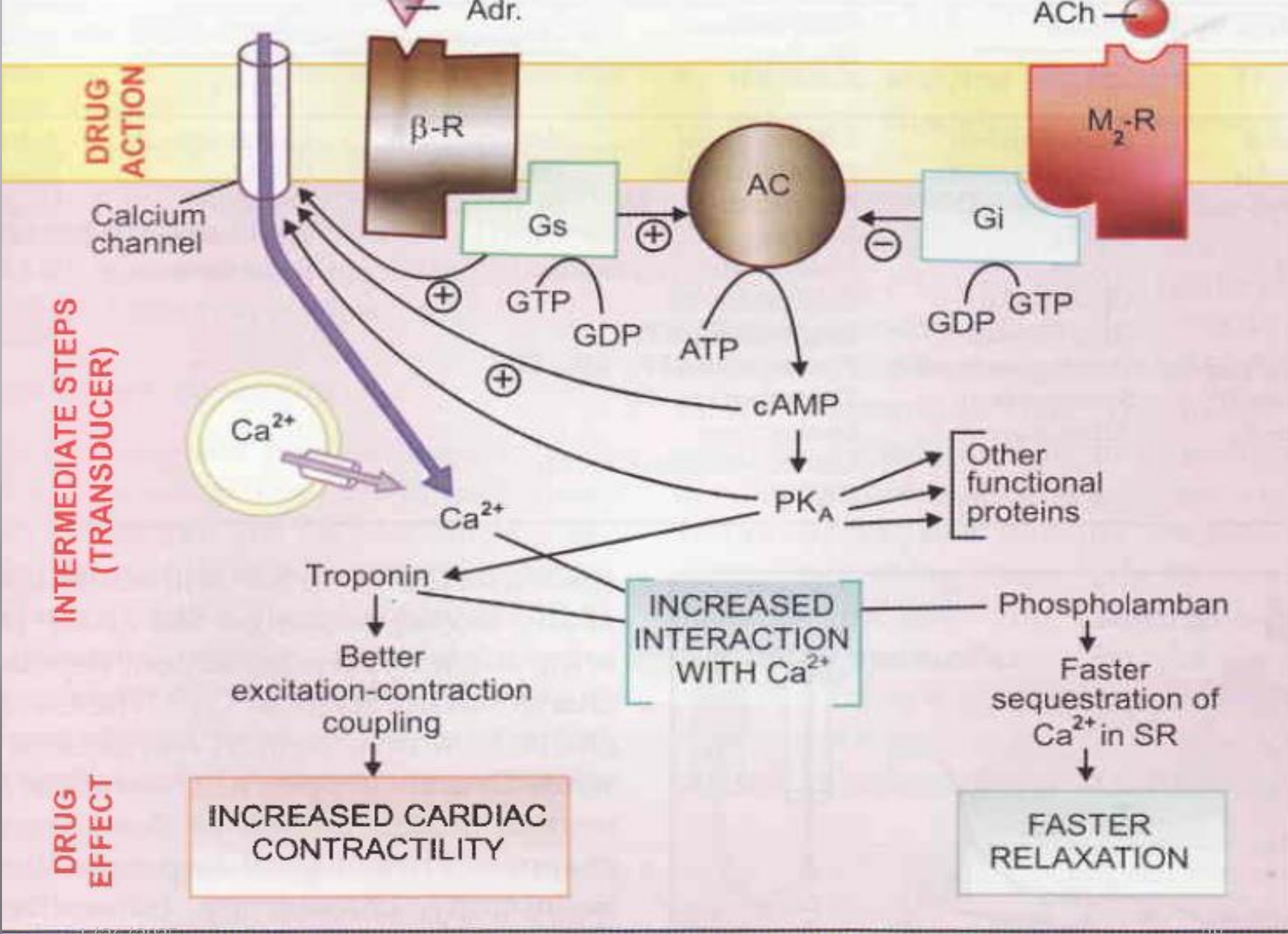


Fig. 4.6: The action-effect sequence of two G-protein coupled (β adrenergic and muscarinic M_2)

DAG AND IP3 AS SECOND MESSENGERS

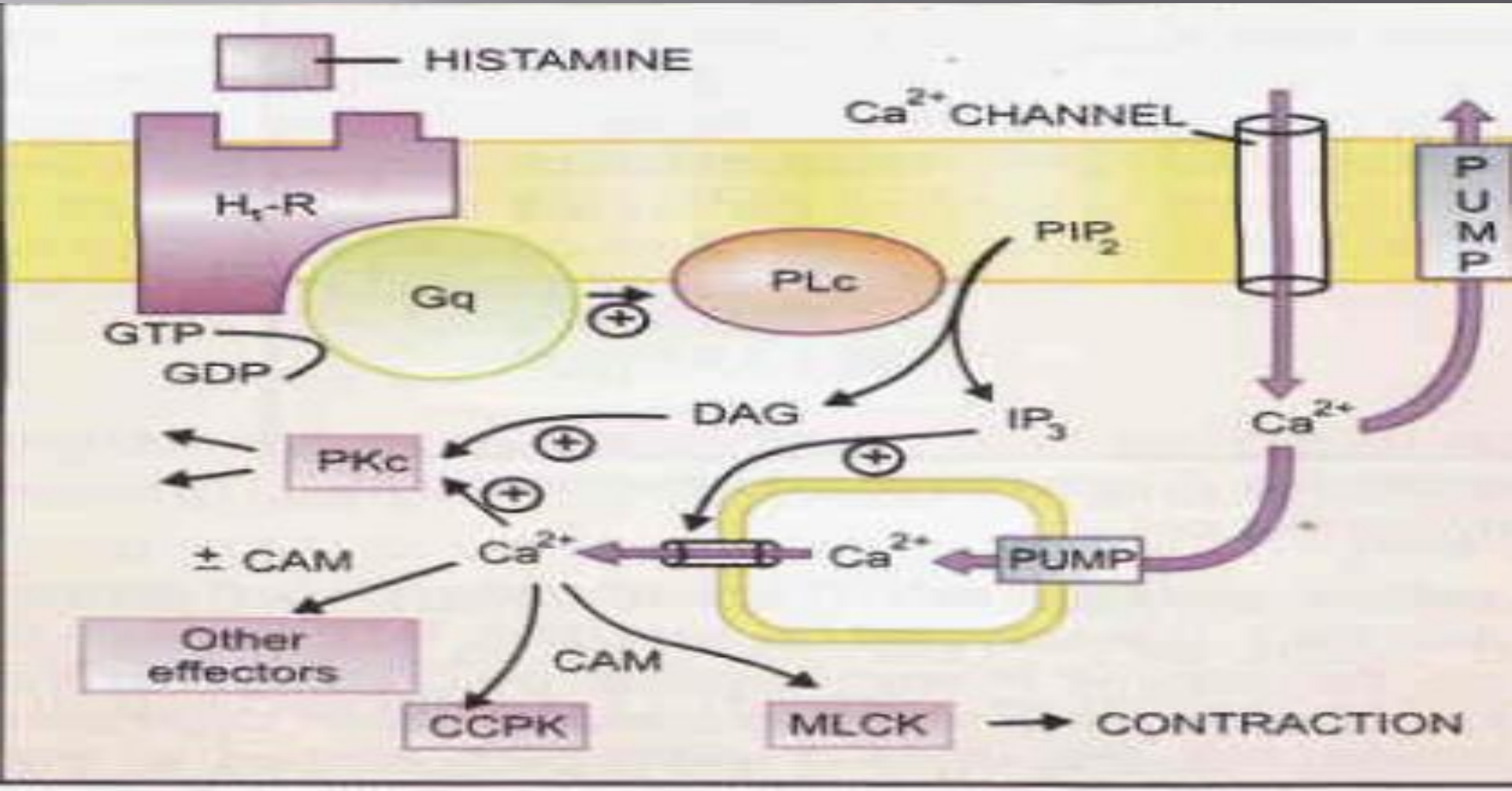


Fig. 4.7: The important steps of phospholipase C(PLc) pathway of response effectuation (in smooth muscle)

cGMP AS A SECOND MESSENGER

- Less common than cAMP
- Causes relaxation of vascular smooth muscle by kinase mediated mechanism that results in dephosphorylation of myosin light chains.
- Examples include
  - ANP
  - NO

Spiral integration with biochemistry, physiology

EXAMPLES OF RECEPTORS THAT ARE COUPLED BY G-PROTEINS

Receptor Types	Coupling Protein	Effector	Effector Substrate	Second Messenger Response	Result
M_1, M_3, α	G_q	Phospholipase C	Membrane lipids	↑ IP_3 ↑ DAG	↑ Ca^{2+} ↑ Protein kinase
β, D_1	G_s	Adenylyl cyclase	ATP	↑ cAMP	↑ Ca^{2+} influx ↑ Enzyme activity
α_2, M_2	G_i	Adenylyl cyclase	ATP	↓ cAMP	↓ in Ca^{2+} influx and enzyme activity

- Emergence of diseases due to distruption of signal transduction pathways

Horizontalintegration with pathology/vertical integeration with medicine

BIOETHICS

- Loss of selectivity of receptors at high doses

RESEARCH

- Wu L, Cheng Y, Geng D, Fan Z, Lin B, Zhu Q, Li J, Qin W, Yi W. O-GlcNAcylation regulates epidermal growth factor receptor intracellular trafficking and signaling. Proceedings of the National Academy of Sciences. 2022 Mar 8;119(10):e2107453119.

- Muromoto R, Oritani K, Matsuda T. Current understanding of the role of tyrosine kinase 2 signaling in immune responses. World Journal of Biological Chemistry. 2022 Jan 1;13(1):1.

END OF LECTURE ASSESMENT (EOLA)

- A 16 years old girl suffering from seasonal rhinitis started a therapy with loratidine an anti-histamine. Which of the following term best describes the intrinsic ability of a drug to bind with receptors?

A. Intrinsic activity
B. Potency
C. Efficacy
D. **Affinity**
E. Receptor activities

Q02. Which of the following onset of actions of various signaling mechanisms is correctly matched?

a) Cytokine receptor-Milliseconds
b) G-Coupled linked receptor - Days
c) Insulin receptor – Minutes *
d) Ion channel linked receptor - Hours
e) Steroid receptor - Seconds

Q03. Drugs liked corticosteroids are capable of targeting intracellular receptors secondary to their ability to:

a) Diffuse through lipid membranes *
b) Dimerise upon ligand binding
c) Induce conformational change in the receptor
d) Interact with adenyl cyclase
e) Undergo autophosphorylation

Q04. Clonidine is an agonist that may produce hypertensive crisis upon sudden withdrawal. This is due to a decrease in a number of its receptors that mediate a decrease in BP. Such a phenomenon is called.

a) Desensitization
b) Down regulation *
c) Tolerance
d) Tachyphylaxis
e) Up-regulation