M.Sc. 4th Semester

Subject: Human Physiology

Paper: PHY-401

Unit:33

Module: 01

Topics: General concepts of endocrinology and hormonal actions, Neuroendocrinology

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GENERAL CONCEPTS OF ENDOCRINOLOGY

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Introduction to Endocrinology

Endocrine System

•Complex System

•Coordinates and maintain a steady state

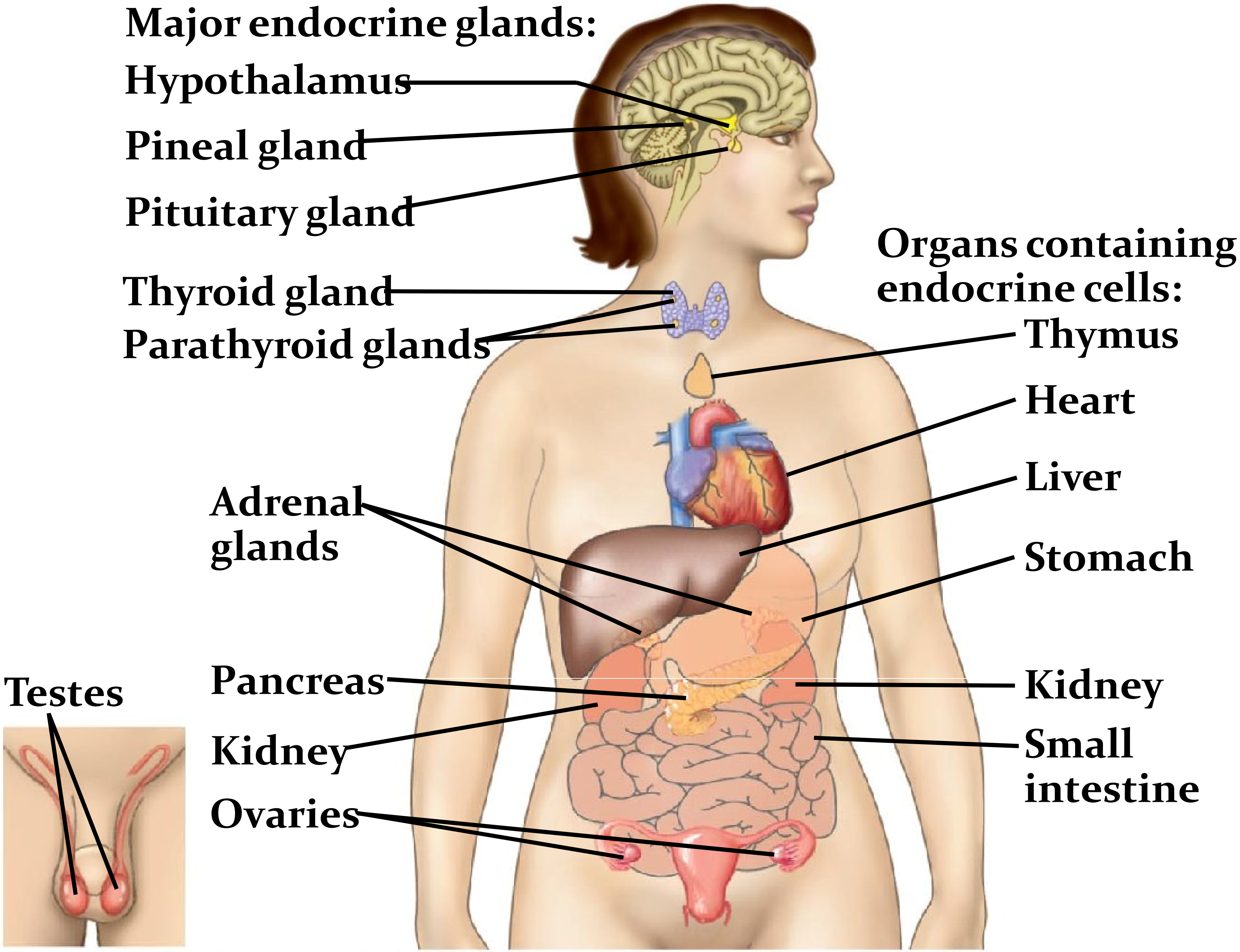
•Hormones activated by other hormones or neural impulses

•Regulated feedback system

Chemical messengers: Compounds that serves to transmit a message. Interplay of several types of chemical messenger systems coordinate the multiple activities of the cells, tissues and organs of the body.

Introduction to Endocrinology

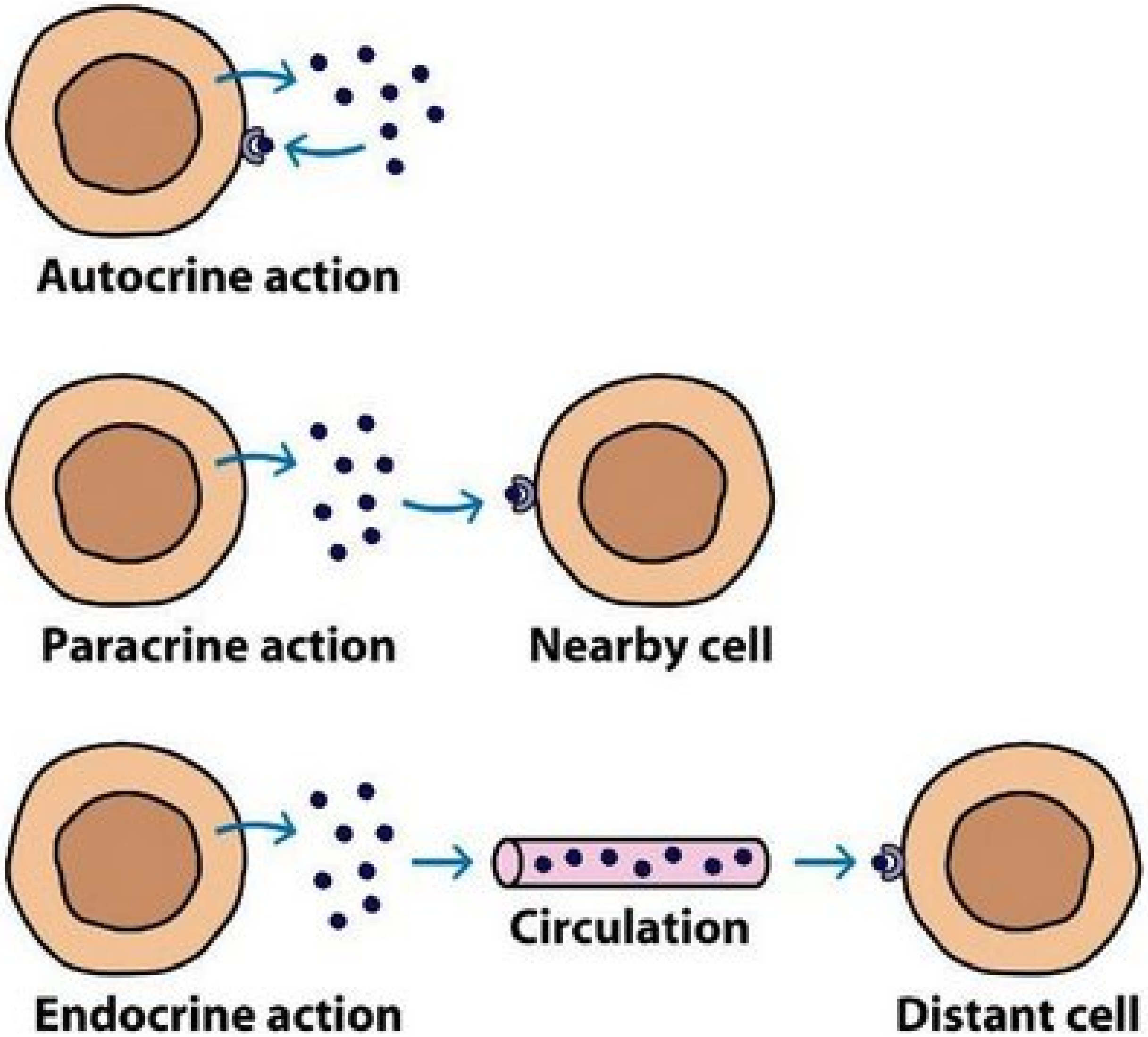
- Endocrine cells are glandular secretory cells that release hormones directly into the interstitial fluids, lymphoid system or blood.
- Hormones alter the metabolic activities of many different tissues and organs.


Major endocrine glands:
Hypothalamus
Pineal gland
Pituitary gland
Thyroid gland
Parathyroid glands
Adrenal glands
Pancreas
Kidney
Ovaries
Testes
Organs containing endocrine cells:
Thymus
Heart
Liver
Stomach
Kidney
Small intestine

Coordination of Body Functions by Chemical Messengers

The type of intercellular communication in the ECF include the following:

1. Neural: Neurotransmitters are released from glands reach blood and influence function of target cells.
2. Endocrine: Hormones released from glands reach blood and influence function of target cells.
3. Neuroendocrine: Secretion from neurons reach blood and influence target cell some distance away.
4. Paracrine: Cell secretion products diffuse into ECF and affect neighbouring target cells.
5. Autocrine: Cell secretion products affect the function of the same cell by binding to the surface receptors.
6. Cytokine: Secreted cell proteins act as autocrine, paracrine or endocrine (broad range).



Autocrine action
Paracrine action
Nearby cell
Endocrine action
Circulation
Distant cell

Maintenance of Homeostasis and Regulation of Processes

Body's chemical messenger systems interact with one another to maintain homeostasis.

Example: Adrenal medulla and pituitary gland secrete their hormones in response to neuroendocrine cells located in the hypothalamus that secrete neuro hormones such as ADH, oxytocin, hypophysiotropic hormones.

Chemical Structure/ Types

The general classes of hormones:

1. Proteins and polypeptides including hormones secreted by the anterior and posterior pituitary gland, the pancreas, the parathyroid and others.
2. Steroids secreted by the adrenal cortex, ovaries, testes and placenta.
3. Derivatives of the amino acid tyrosine secreted by the thyroid and adrenal medullae.

Synthesis and Storage

Protein/peptide-hormone synthesized in endocrine cell RER as preprohormone then prohormone then transferred to Golgi apparatus for packaging in secretory vesicles. Prohormones cleaved into small active proteins diffused to ECF by exocytosis.

Steroid Hormone

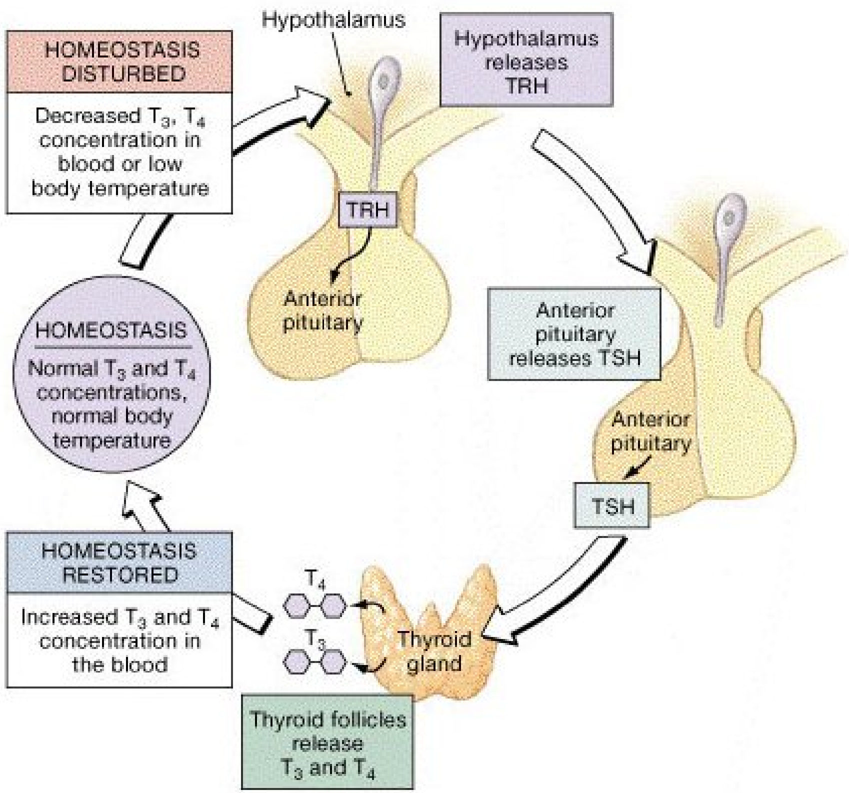
- Similar and synthesized from cholesterol
- Little hormone storage in cell
- Large stores of cholesterol esters in cytoplasm vacuoles can be rapidly mobilized for steroid synthesis after a stimulus

Amine Hormone Derived from Tyrosin

- Thyroid hormones are synthesized and stored in the thyroid gland and incorporated into macromolecules of the protein thyroglobulin.
- Catecholamine from adrenal medullary cells are taken up into performed vesicles stored in secretory vesicles until secreted by exocytosis.

Feedback Control of Hormones

- Negative Feedback prevents over activity of hormone systems
- Surge of Hormones can occur with positive feedback.
- Cyclical variations occur in hormone release



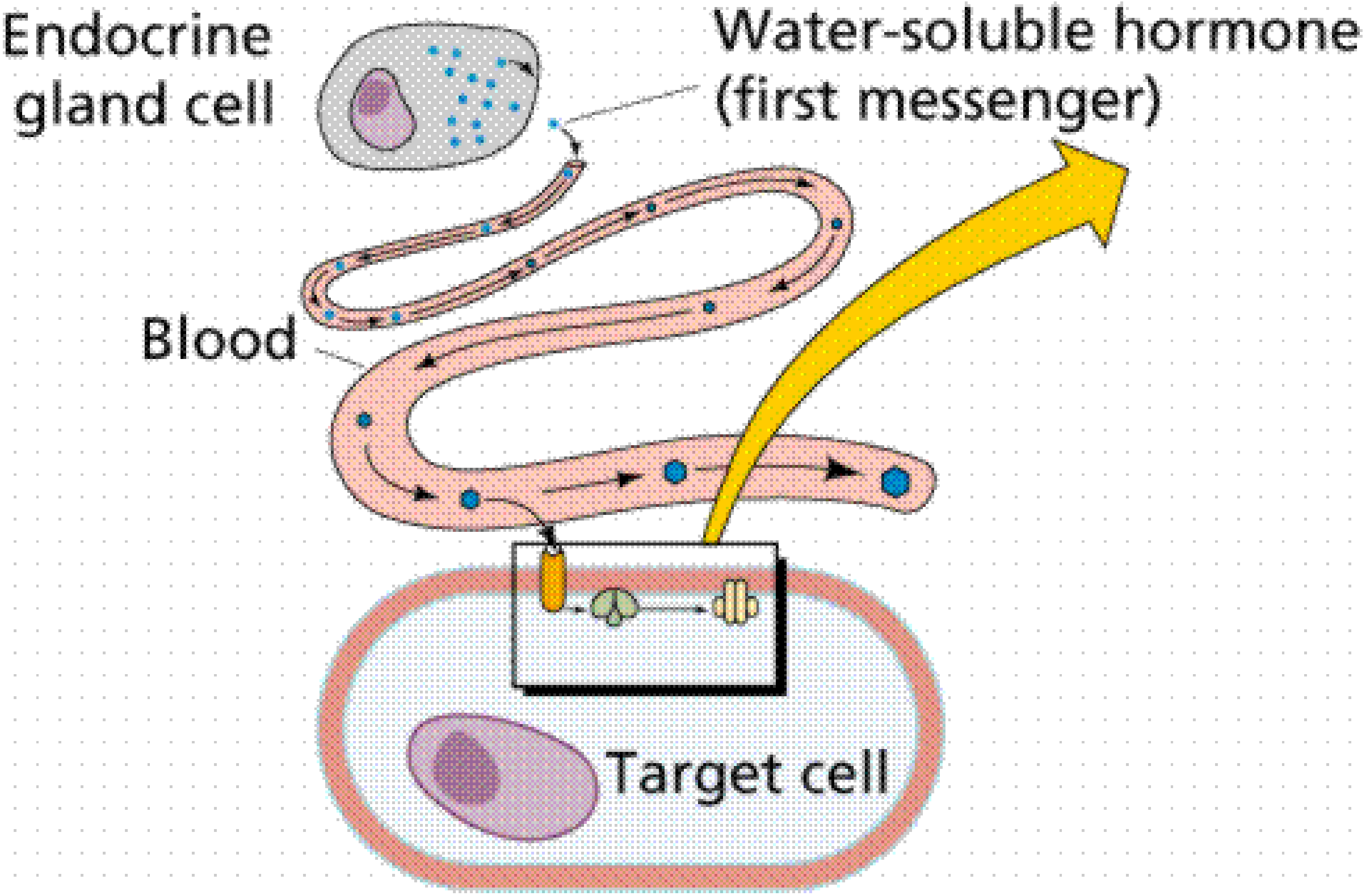
Transport of Hormones

Hydrophilic Hormones

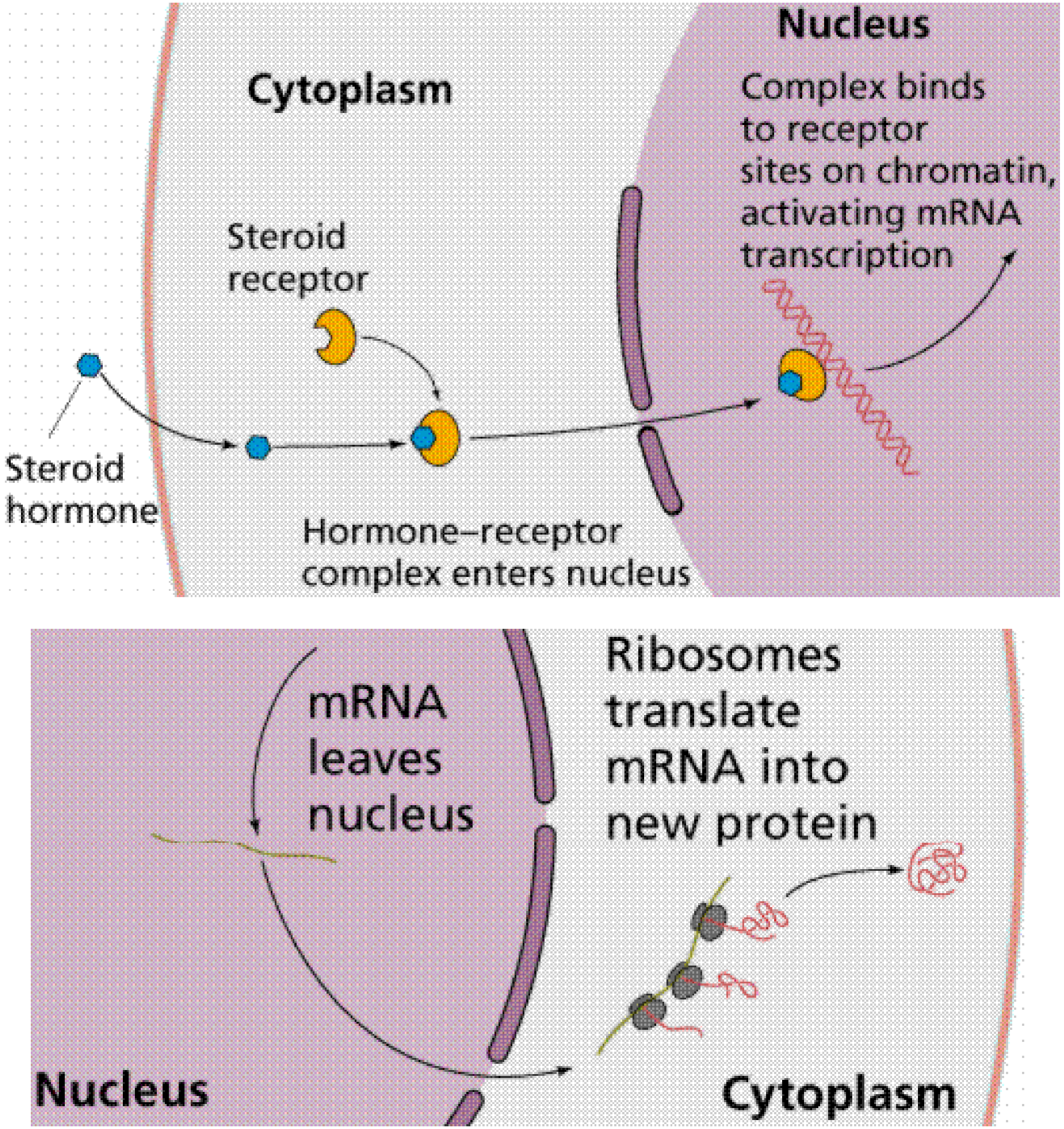
- Peptides, catecholamines
- Dissolved in plasma

Hydrophobic Hormones

- Steroids, thyroid hormones
- Bound to carrier proteins
- Only free hormone can bind to receptor
- Only free hormone can be metabolized
- Longer half-life



Hydrophilic Hormones/ Non-steroid hormones



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Hydrophobic Hormones

Hormone Clearance

➢Hormone signals must be turned off when they have served their purpose.

➢Taken up and degraded by liver or kidney

➢Metabolic Clearance Rate (MCR)

- Rate of hormone removal from blood
- Half life, time required to clear 50% of hormone from blood
- Faster the MCF shorter the half life

Mechanism of Hormonal Action

Hormone receptor location

1. In or on the same surface of the cell membrane (peptide, catecholamine)
2. In the cell cytoplasm (steroid)
3. In the nucleus (thyroid)

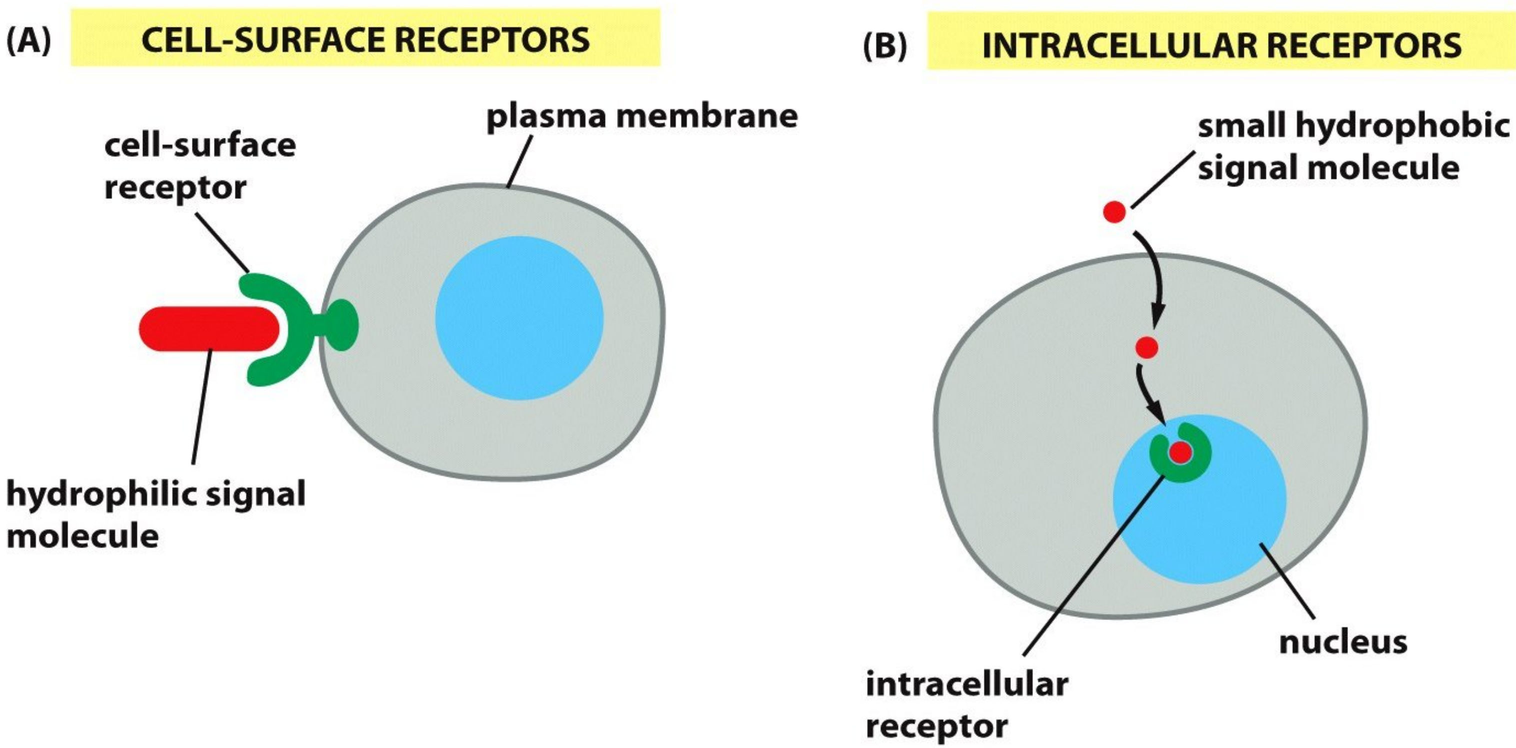


Figure 16-8 Essential Cell Biology 3/e (© Garland Science 2010)

Regulation of receptors

Down Regulation

A mechanism in which a hormone decreases the number or affinity of its receptors in a target tissue. Down- regulation may occur by decreasing the synthesis of new receptors, by increasing the degradation of existing receptors, or by inactivating receptors.

Up regulation

A mechanism in which a hormone increase the number or affinity of its receptors. Up-regulation may occur by increasing synthesis of new receptors, decreasing degradation of the existing receptors or activating receptors.

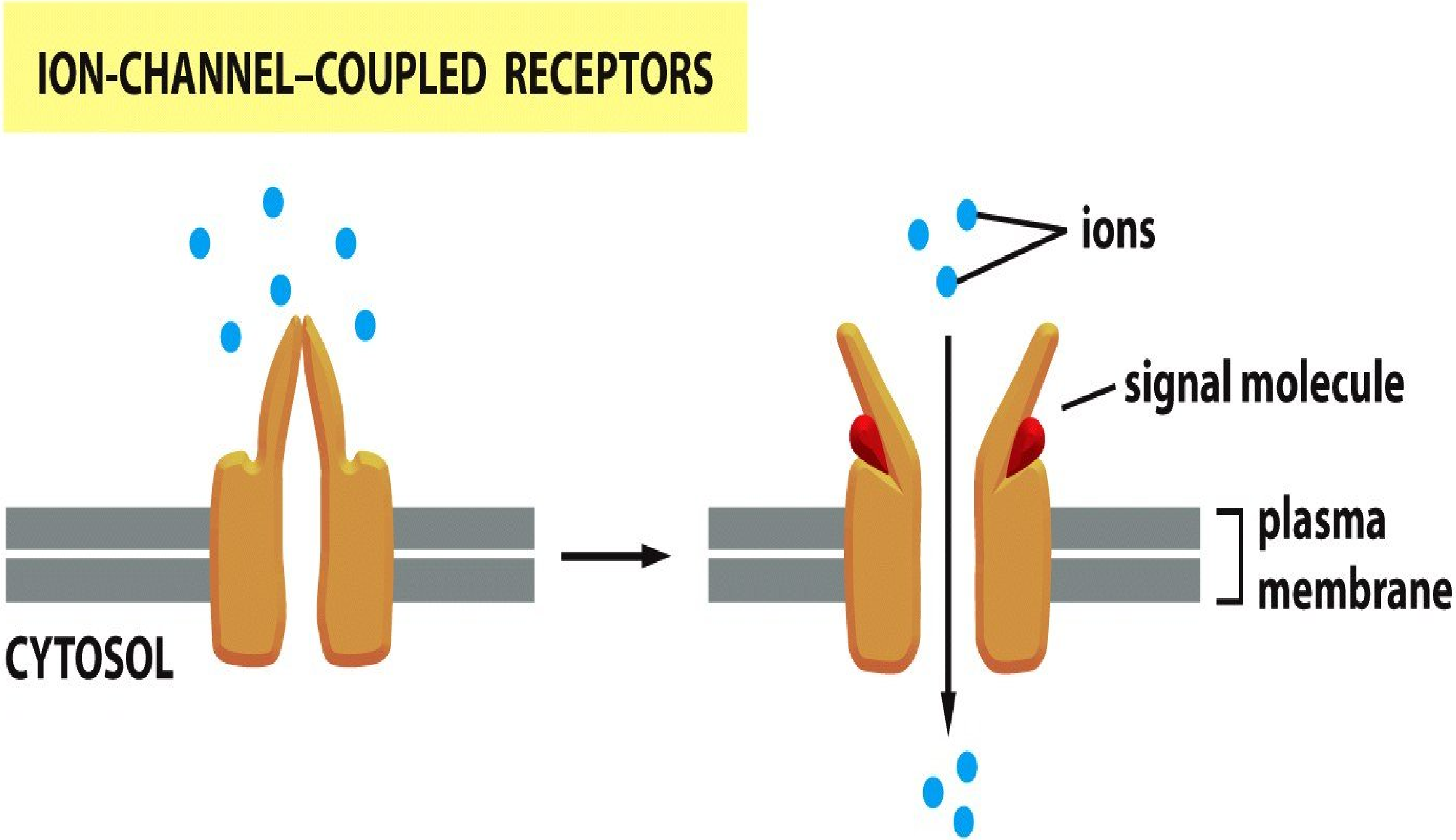


Figure 16-15a Essential Cell Biology 3/e (© Garland Science 2010)

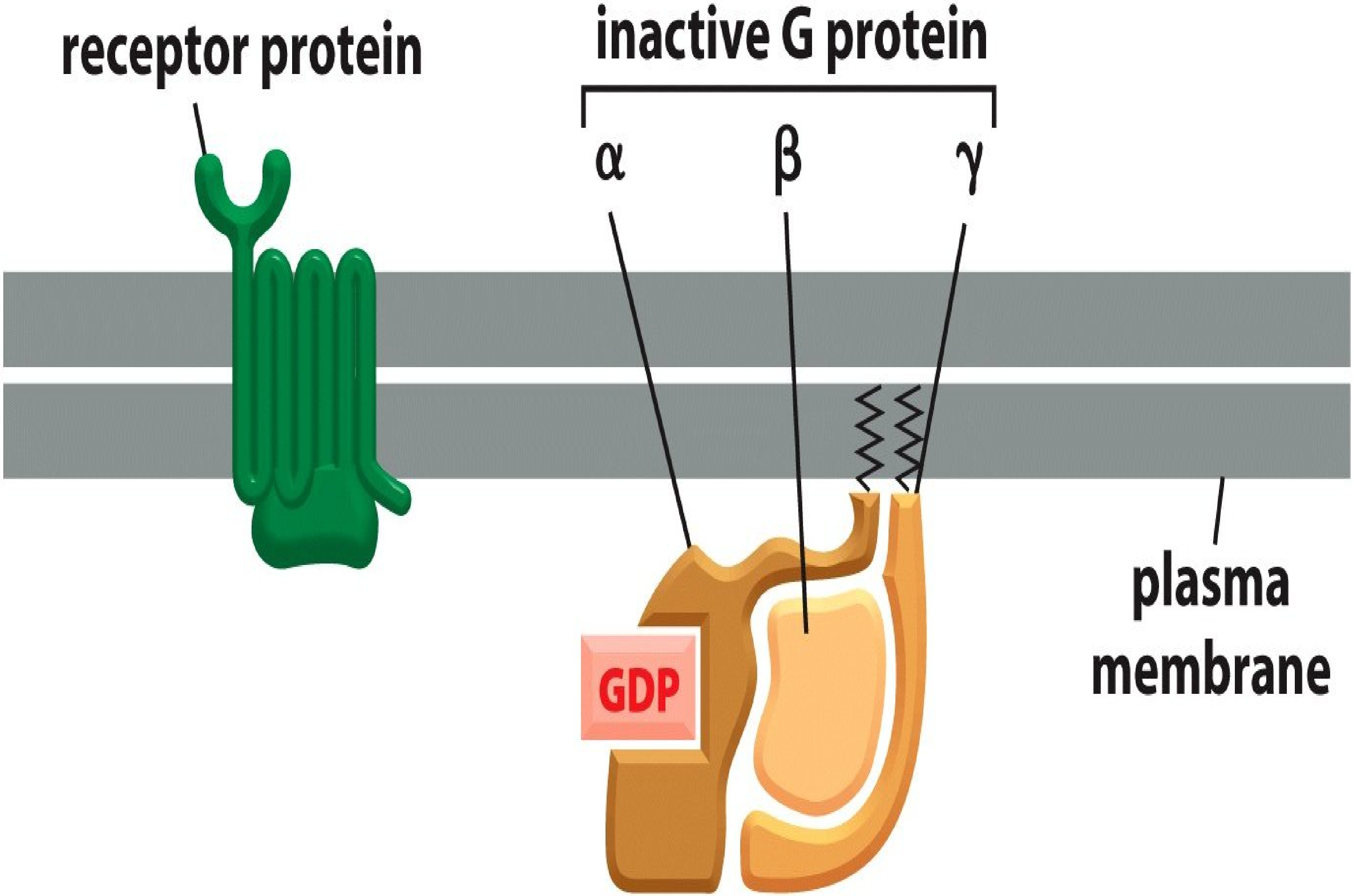


Figure 16-17a Essential Cell Biology 3/e (© Garland Science 2010)

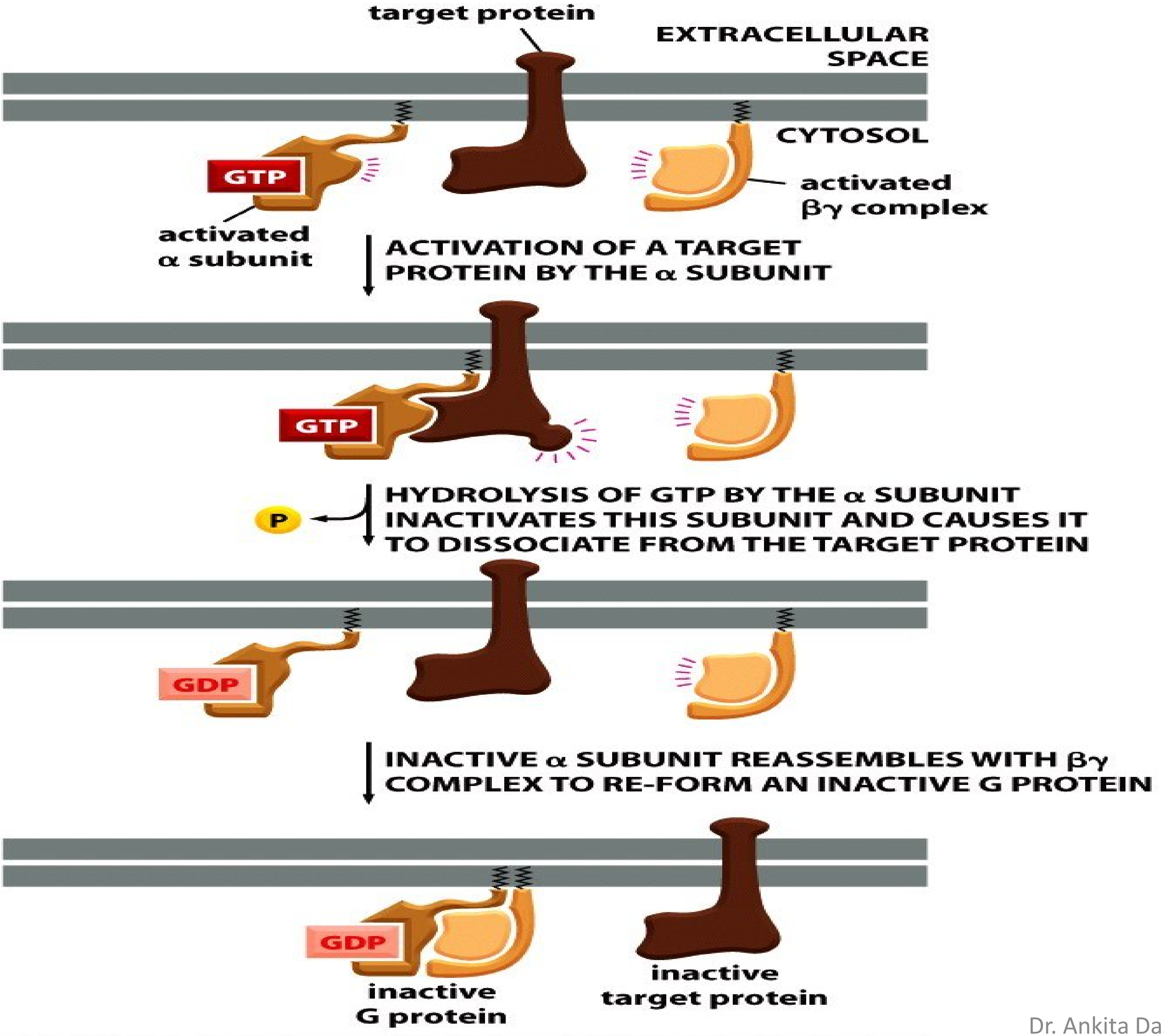


Figure 16-18 Essential Cell Biology 3/e (© Garland Science 2010)

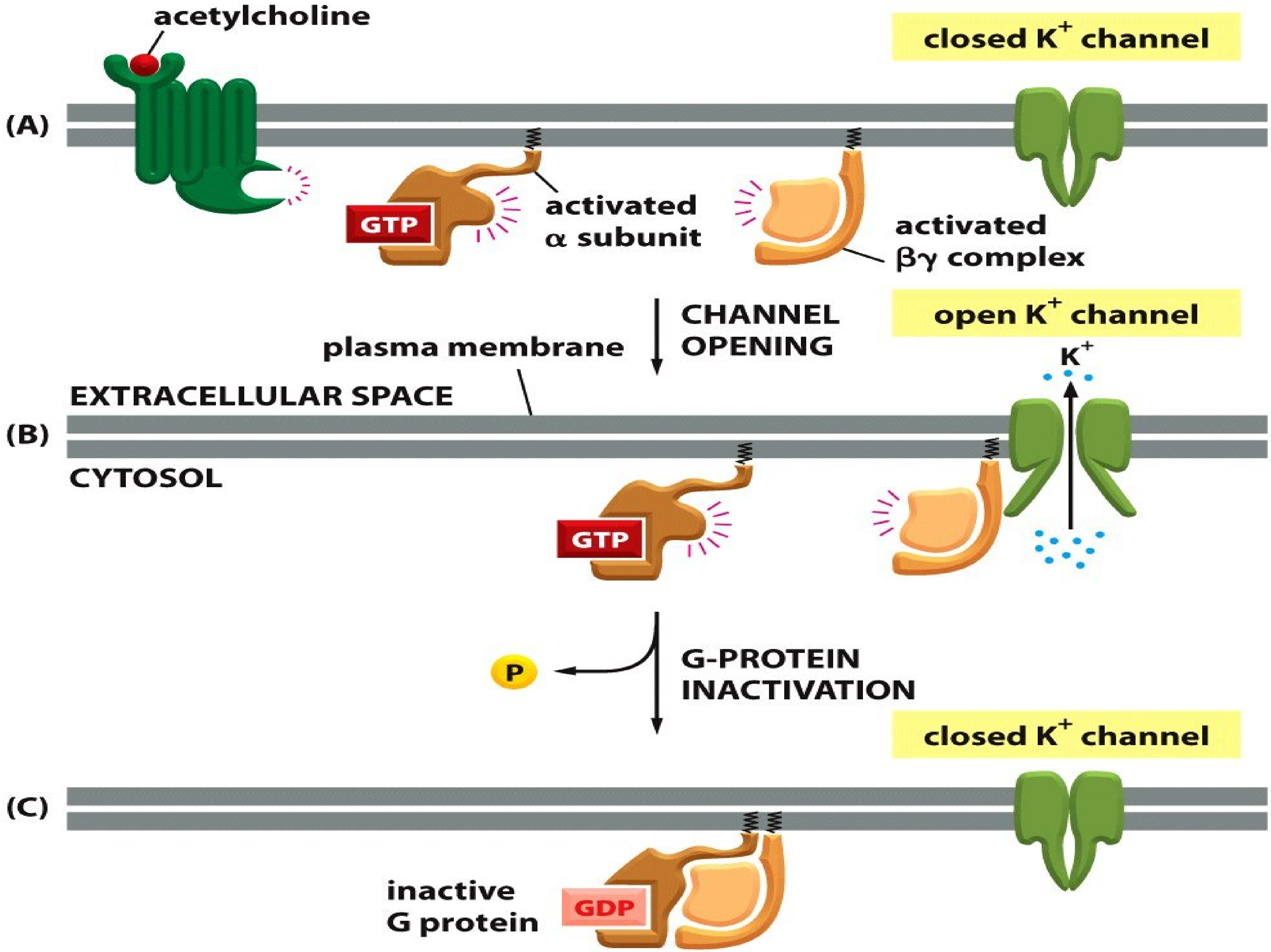


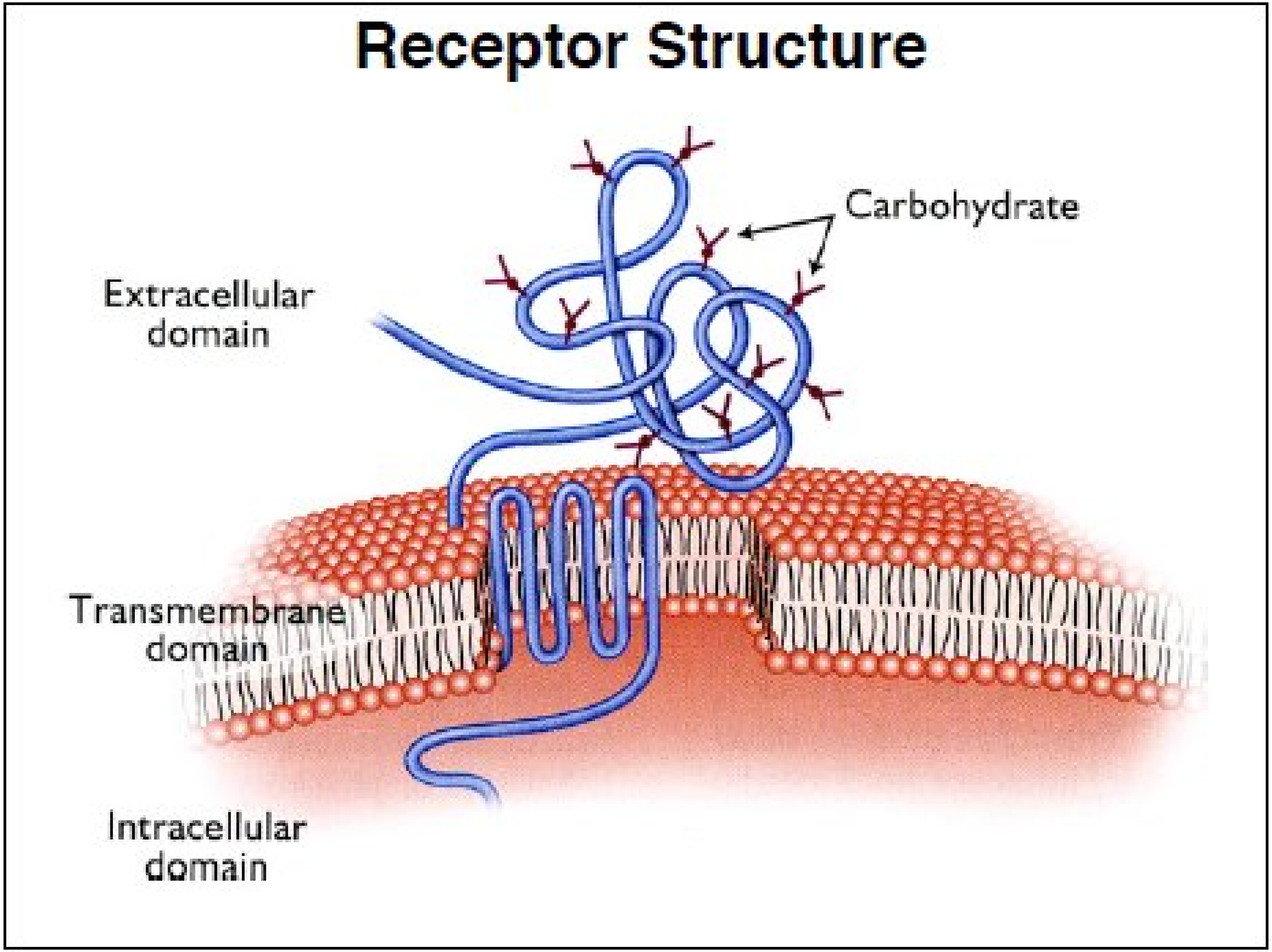
Figure 16-19 Essential Cell Biology 3/e (© Garland Science 2010)

- The first step of a hormone's action is to bind to specific receptors at the target cell.

- Receptors for some hormones are located on the target cell membrane, whereas, other hormone receptors are located in the cytoplasm or the nucleus.

- Hormonal receptors are large proteins, and each cell that is to be stimulated, usually has some2000 to 100000 receptors. Each receptor is highly specific for a single hormone.

- The locations for the different types of hormone receptors are generally the following:



Receptor Structure
Carbohydrate
Extracellular domain
Transmembrane domain
Intracellular domain

Nuclear receptors
Estrogens and thyroid hormone

Cytoplasmic receptors
Most steroids

Cell surface membrane receptors
Polypeptide hormones and catecholamines

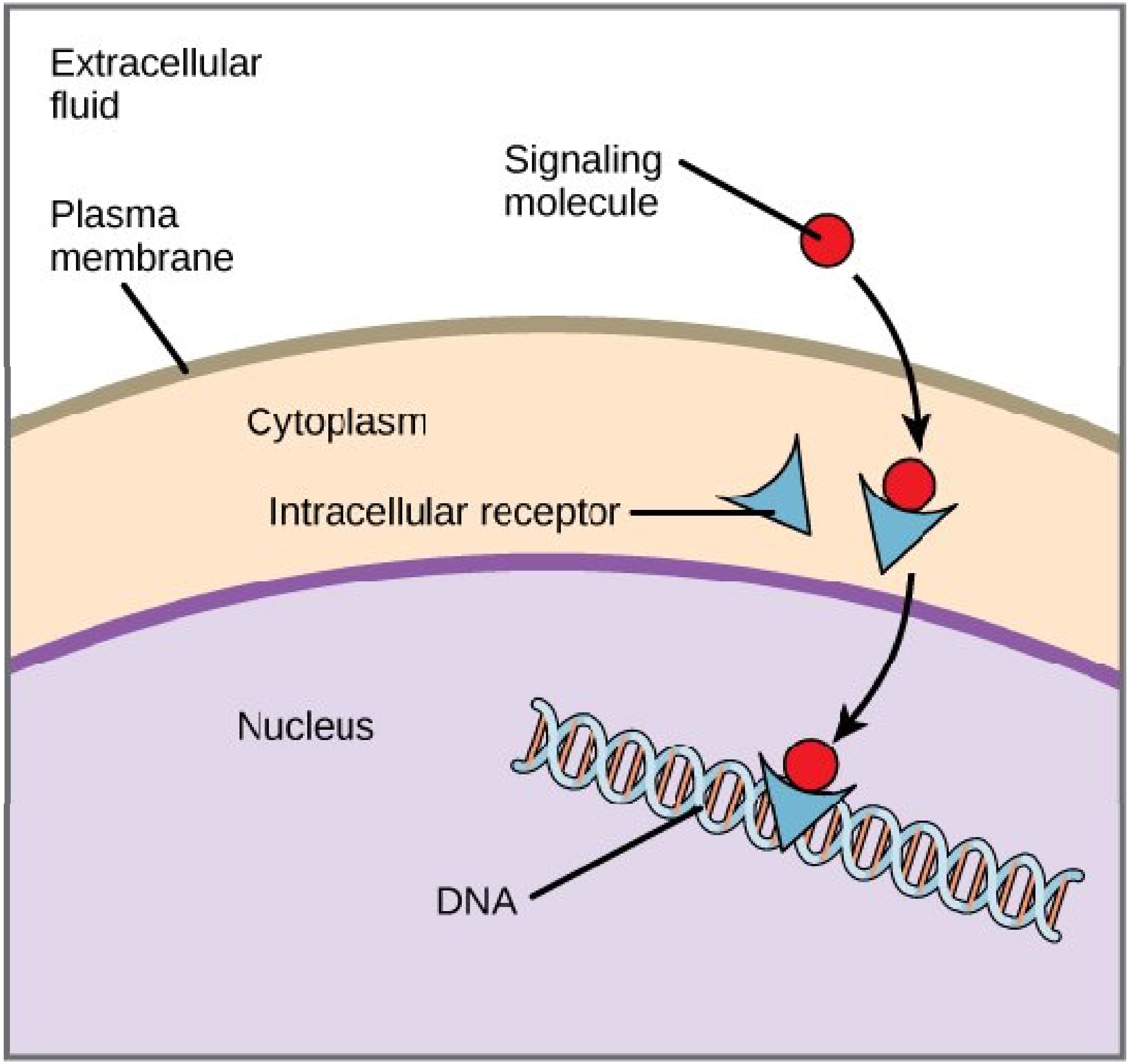
Receptors are protein molecules inside the target cell or on its surface that receive a chemical signal. Chemical signals are released by signaling cells in the form of small, usually volatile or soluble molecules called **ligands.**

A ligand is a molecule that binds another specific molecule, in some cases, delivering a signal in the process. Ligands can thus be thought of as signaling molecules. Ligands and receptors exist in several varieties; however, a specific ligand will have a specific receptor that typically binds only that ligand.

INTERNAL RECEPTORS

Internal receptors, also known as intracellular or cytoplasmic receptors, are found in the cytoplasm of the cell and respond to hydrophobic ligand molecules that are able to travel across the plasma membrane. Once inside the cell, many of these molecules bind to proteins that act as regulators of mRNA synthesis. mRNA carries genetic information from the DNA in a cell's nucleus out to the ribosome, where the protein is assembled. When the ligand binds to the internal receptor, a change in shape is triggered that exposes a DNA-binding site on the receptor protein.

The ligand-receptor complex moves into the nucleus, then binds to specific regions of the DNA and promotes the production of mRNA from specific genes . Internal receptors can directly influence gene expression (how much of a specific protein is produced from a gene) without having to pass the signal on to other receptors or messengers.



INTERNAL RECEPTORS

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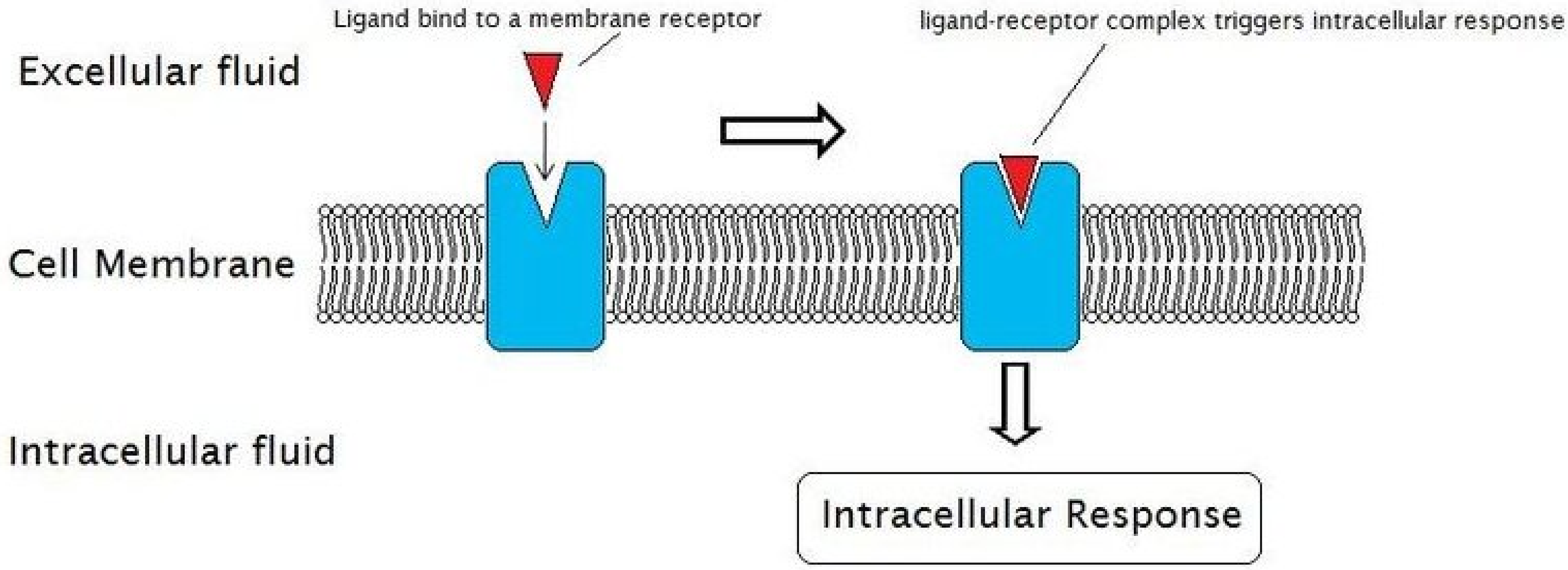
CELL-SURFACE RECEPTORS

Cell-surface receptors, also known as **transmembrane receptors**, are proteins that are found attached to the cell membrane. These receptors bind to external ligand molecules (ligands that do not travel across the cell membrane). This type of receptor spans the plasma membrane and performs **signal transduction**, in which an extracellular signal is converted into an intercellular signal. Ligands that interact with cell-surface receptors do not have to enter the cell that they affect. Cell-surface receptors are also called cell-specific proteins or markers because they are specific to individual cell types.

Each cell-surface receptor has three main components: an external ligand-binding domain, a hydrophobic membrane-spanning region, and an intracellular domain inside the cell. The size and extent of each of these domains vary widely, depending on the type of receptor.

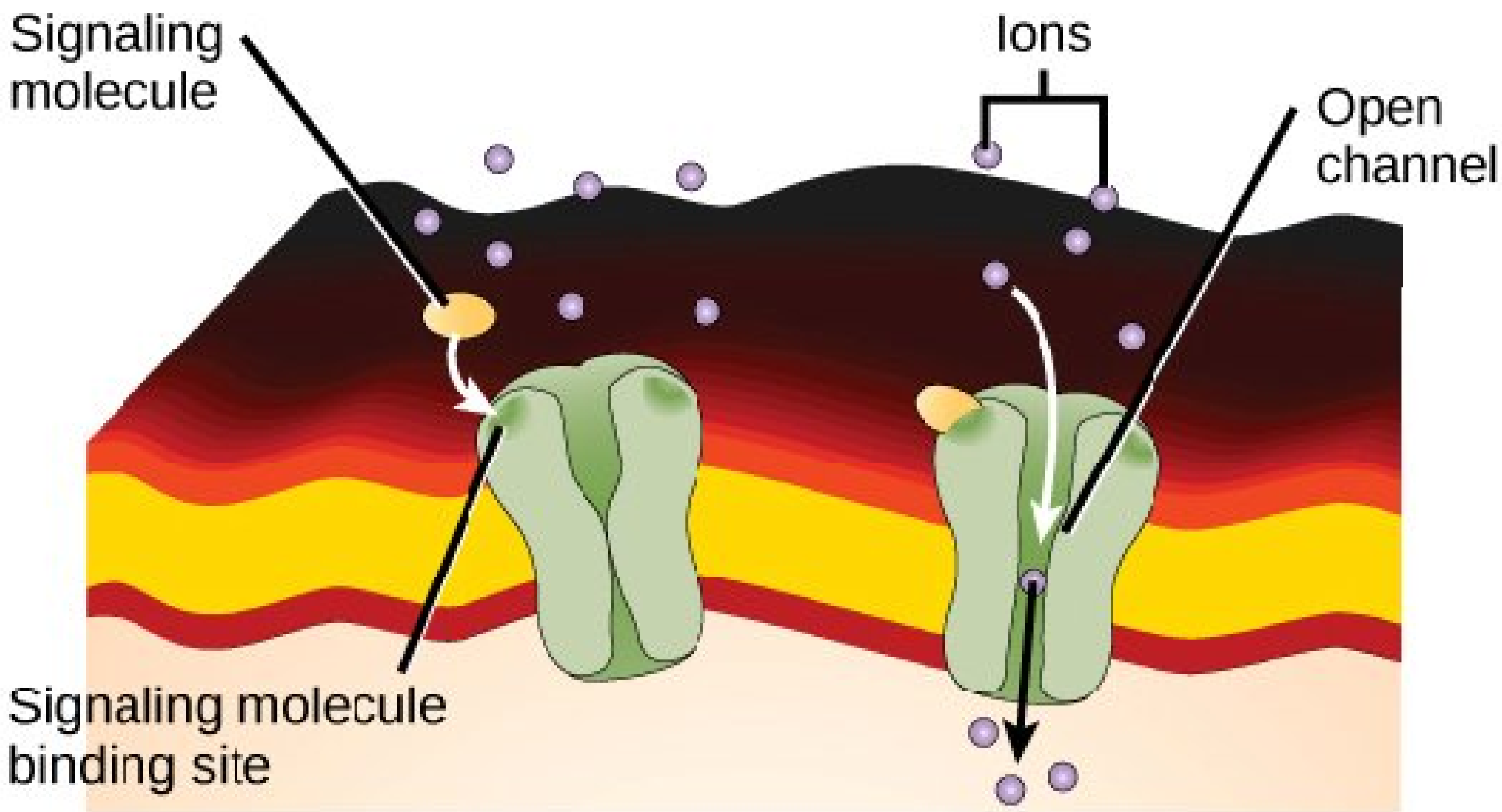


CELL-SURFACE RECEPTORS

Cell-surface receptors are involved in most of the signaling in multicellular organisms. There are three general categories of cell-surface receptors: ion channel-linked receptors, G-protein-linked receptors, and enzyme-linked receptors.

Ion channel-linked receptors

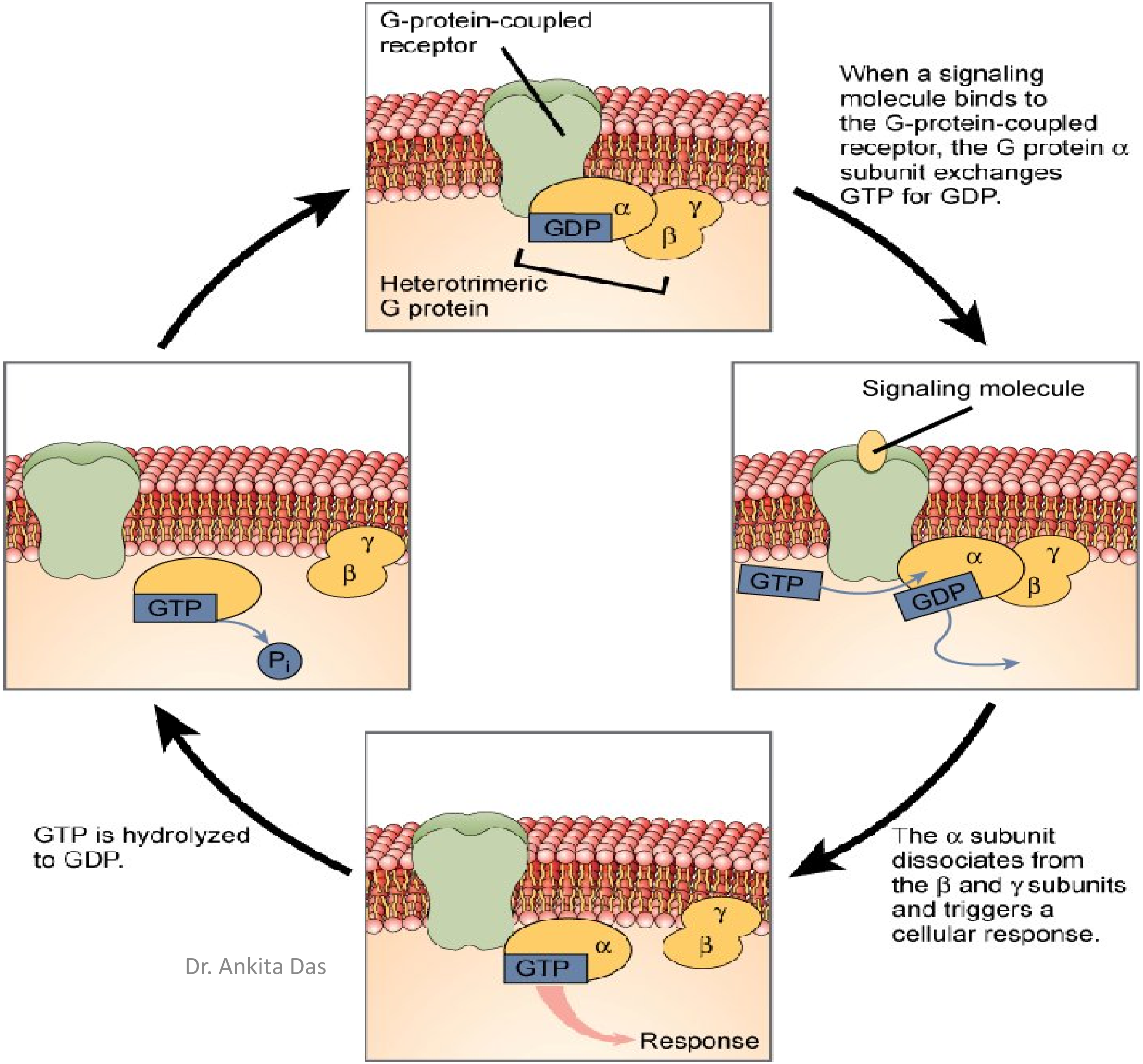
Ion channel-linked receptors bind a ligand and open a channel through the membrane that allows specific ions to pass through. To form a channel, this type of cell-surface receptor has an extensive membrane-spanning region. When a ligand binds to the extracellular region of the channel, there is a conformational change in the proteins structure that allows ions such as sodium, calcium, magnesium, and hydrogen to pass through



Ion channel-linked receptors

G-protein-coupled receptors

G-protein-coupled receptors (GPCRs) bind a ligand and activate a membrane protein called a G-protein. The activated G-protein then interacts with either an ion channel or an enzyme in the membrane. Before the ligand binds, the inactive G-protein can bind to a site on a specific receptor. Once the G-protein binds to the receptor, the G-protein changes shape, becomes active, and splits into two different subunits. One or both of these subunits may be able to activate other proteins as a result.



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Enzyme-linked receptors

Enzyme-linked receptors are cell-surface receptors with intracellular domains that are associated with an enzyme. In some cases, the intracellular domain of the receptor itself is an enzyme. Other enzyme-linked receptors have a small intracellular domain that interacts directly with an enzyme. When a ligand binds to the extracellular domain, a signal is transferred through the membrane, activating the enzyme. Activation of the enzyme sets off a chain of events within the cell that eventually leads to a response.

A hormonal stimulus typically produces one or more of the following changes:

- Alters plasma membrane permeability or membrane potential, or both, by opening or closing ion channels.
- Stimulates synthesis of proteins or regulates molecules such as enzymes within the cell.
- Activates or deactivates enzymes.
- Induces secretory activity.
- Stimulates mitosis.

An **agonist** is a chemical that binds to a receptor and activates the receptor to produce a biological response. Whereas an agonist causes an action, an antagonist blocks the action of the agonist, and an inverse agonist causes an action opposite to that of the agonist.

A **hormone antagonist** is a specific type of receptor antagonist which acts upon hormone receptors.

Protagonist: The main affector.

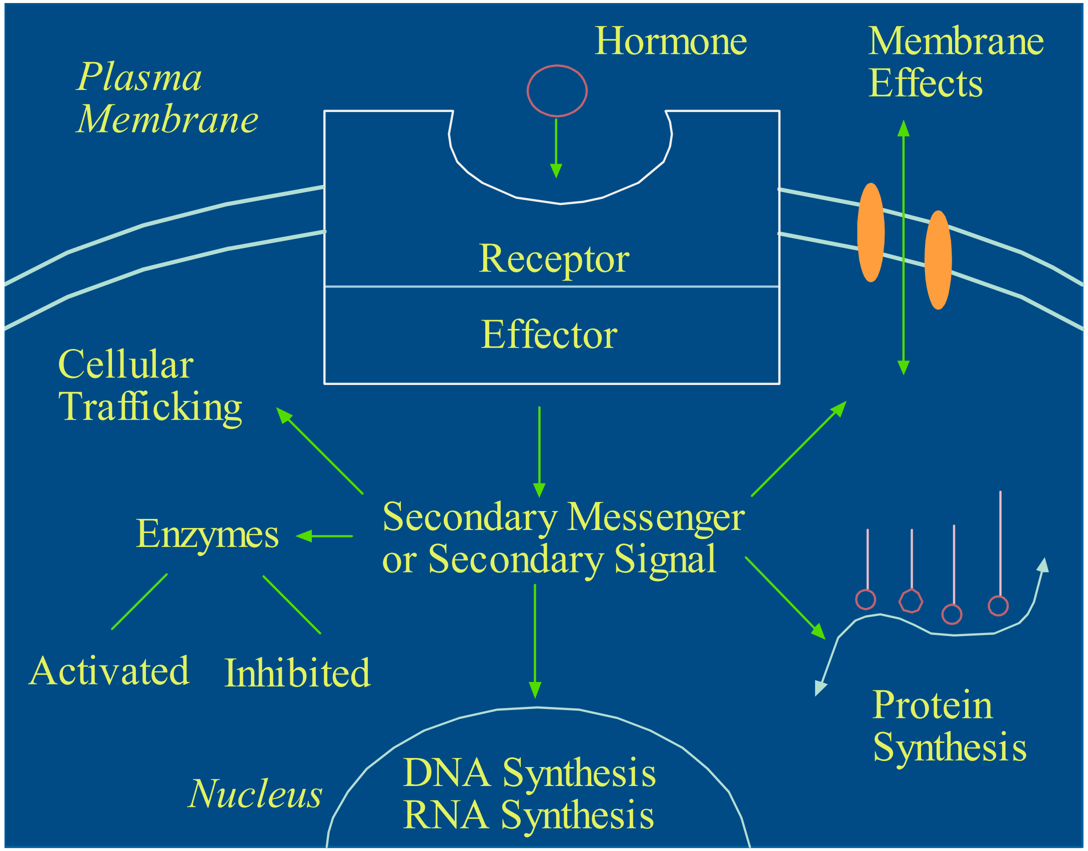
The main mechanisms of hormone actions are:

- Action through change in membrane permeability

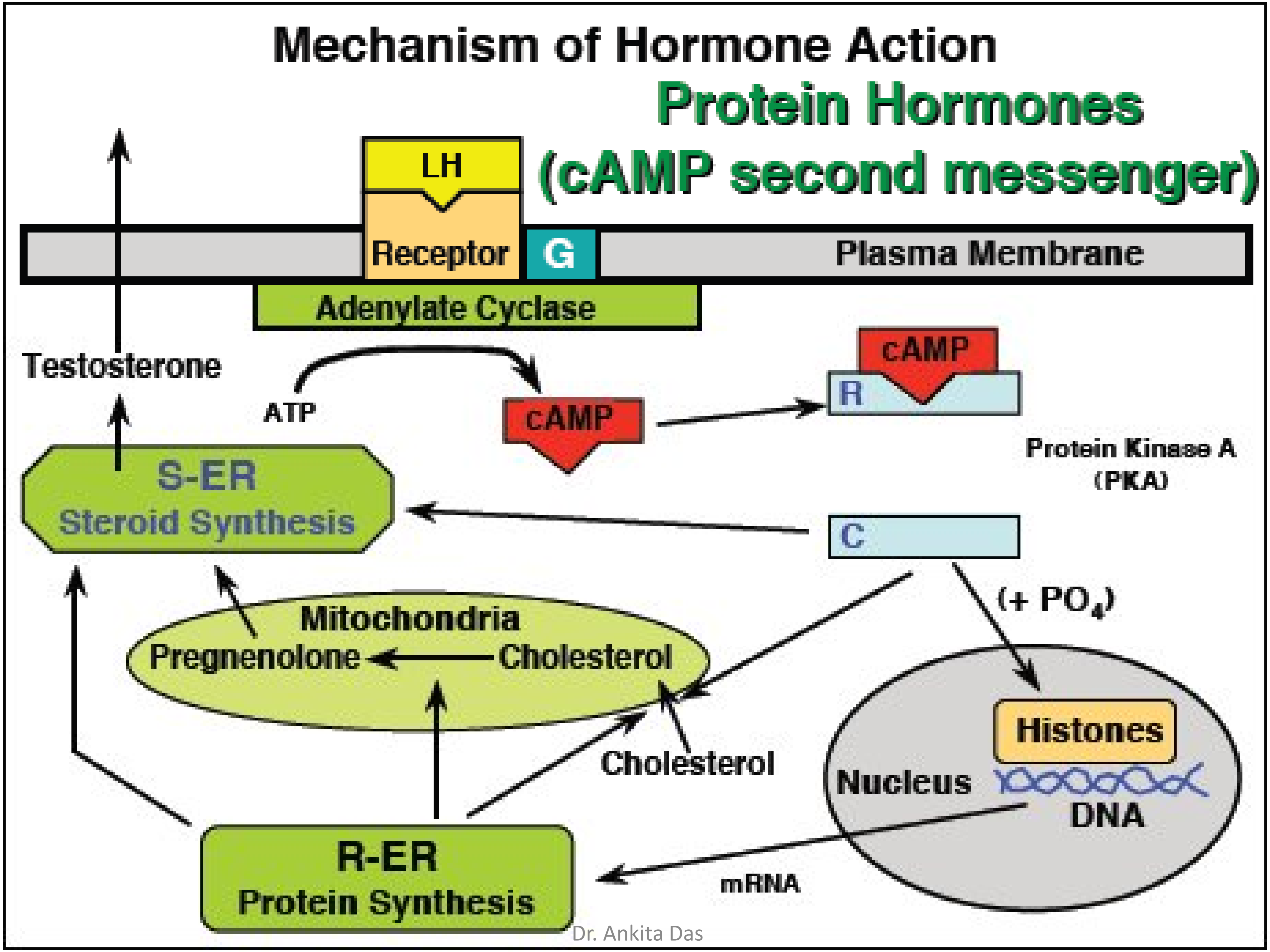
- Action through secondary/second messengers which activates intracellular enzymes when hormone combines with membrane receptors.

- Action through effect on gene expression by binding of hormones with intracellular receptors.

- Action through tyrosine kinase activation.

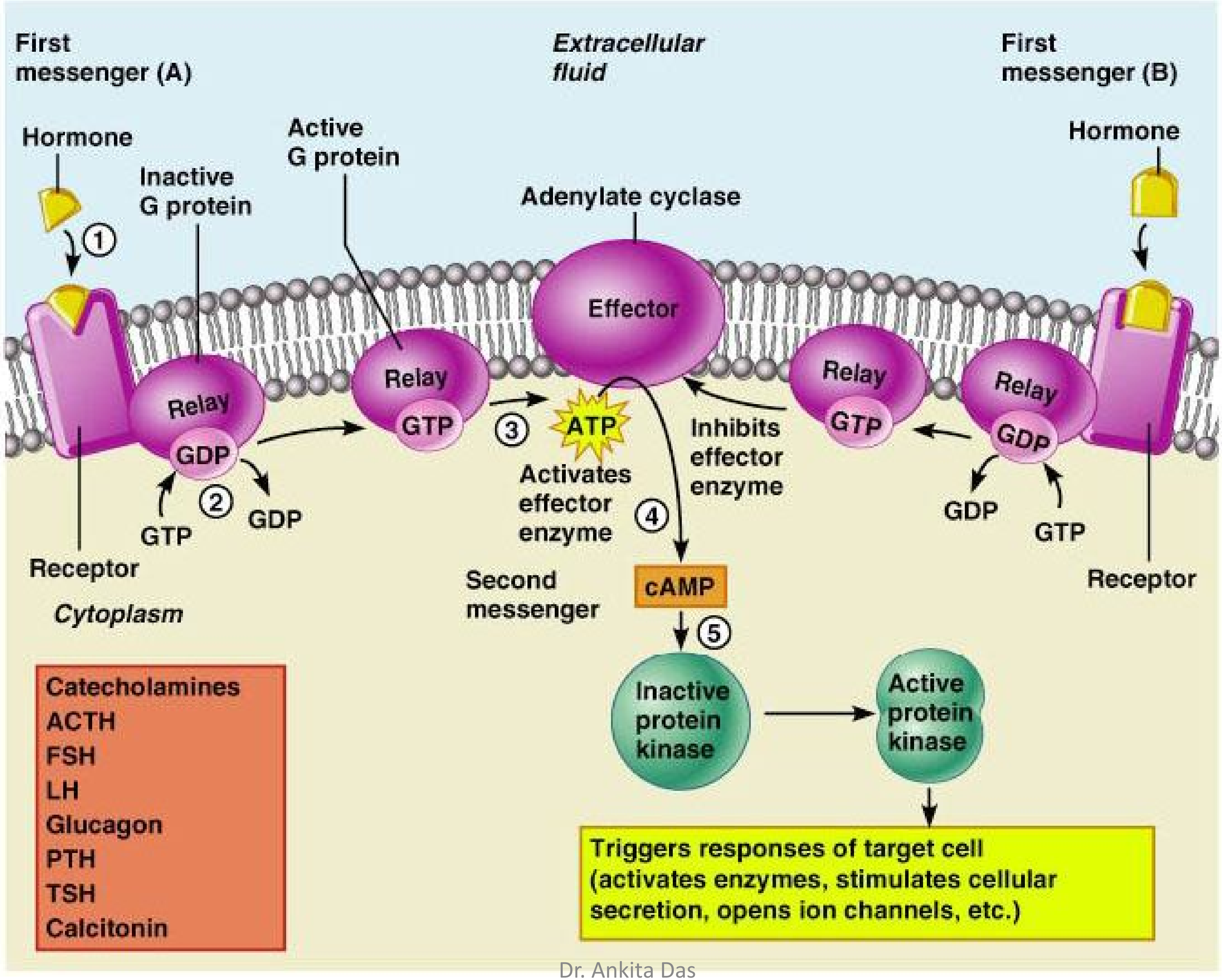


A general model for the action of peptide hormones, catecholamines, and other membrane-active hormones. The hormone in the extra cellular fluid binds to the receptor and activates associated effector(s) systems, that may or may not be in the same molecule. This activation results in generation of an intracellular signal or second messenger that, through a variety of common and branched pathways, produces the final effects of the hormone on metabolic enzyme activity, protein synthesis, or cellular growth and differentiation.


Mechanism of Hormone Action
Protein Hormones
(cAMP second messenger)
LH
Receptor
G
Plasma Membrane
Adenylate Cyclase
Testosterone
ATP
cAMP
cAMP
R
Protein Kinase A
(PKA)
S-ER
Steroid Synthesis
C
(+ PO4)
Mitochondria
Pregnenolone
Cholesterol
Cholesterol
Histones
Nucleus
DNA
R-ER
Protein Synthesis
mRNA

cAMP Second Messenger Hormones

- Anterior Pituitary Hormones
  - » LH, FSH, Prolactin
  - » STH, *ACTH*, TSH
- Placental Hormones
  - » *HCG*, *eCG*


First messenger (A)
Extracellular fluid
First messenger (B)
Hormone
Inactive G protein
Active G protein
Adenylate cyclase
Hormone
1
Effector
Relay
Relay
Relay
Relay
GDP
GTP
ATP
GTP
GDP
3
Inhibits effector enzyme
2
Activates effector enzyme
GDP
GTP
GTP
GDP
4
Receptor
Receptor
Second messenger
cAMP
Cytoplasm
5
Inactive protein kinase
Active protein kinase
Catecholamines
ACTH
FSH
LH
Glucagon
PTH
TSH
Calcitonin
Triggers responses of target cell (activates enzymes, stimulates cellular secretion, opens ion channels, etc.)

Books to refer:

1. Medical Physiology, Guyton and Hall
2. Medical Physiology, Ganong
3. General Physiology, A.K. Jain

Practice Questions:

1. What do you mean by autocrine and paracrine communication of hormones?
2. What is homeostasis? How is it maintained in the body?
3. What do you mean by feedback control of hormone secretion? Give one example.
4. What is upregulation and downregulation of hormone receptors?
5. What are GPCRs?
6. Briefly describe the mechanism of hormone action through second messengers.
7. Differentiate between internal and cell surface receptors.
8. How IP3 and DAG performs the hormonal action?