SAWA UNIVERSITY

Clinical Endocrinology

Mechanism Of Action Of Hormones

Sawa University

College of health and medical techniques

Department of Medical Laboratories

.Third . Stage

جامعـــــــة ســـــــاوة الاهلية

كليـــــة التقنيـــات الصحيـة والطبيـة

قسم تقنيات المختبرات الطبية

المرحلـــــــــــــة الثالـثة

تدريسي المادة : م.م عقيل محمد رسول

الجانب النظري

محاضرة رقم 2,3

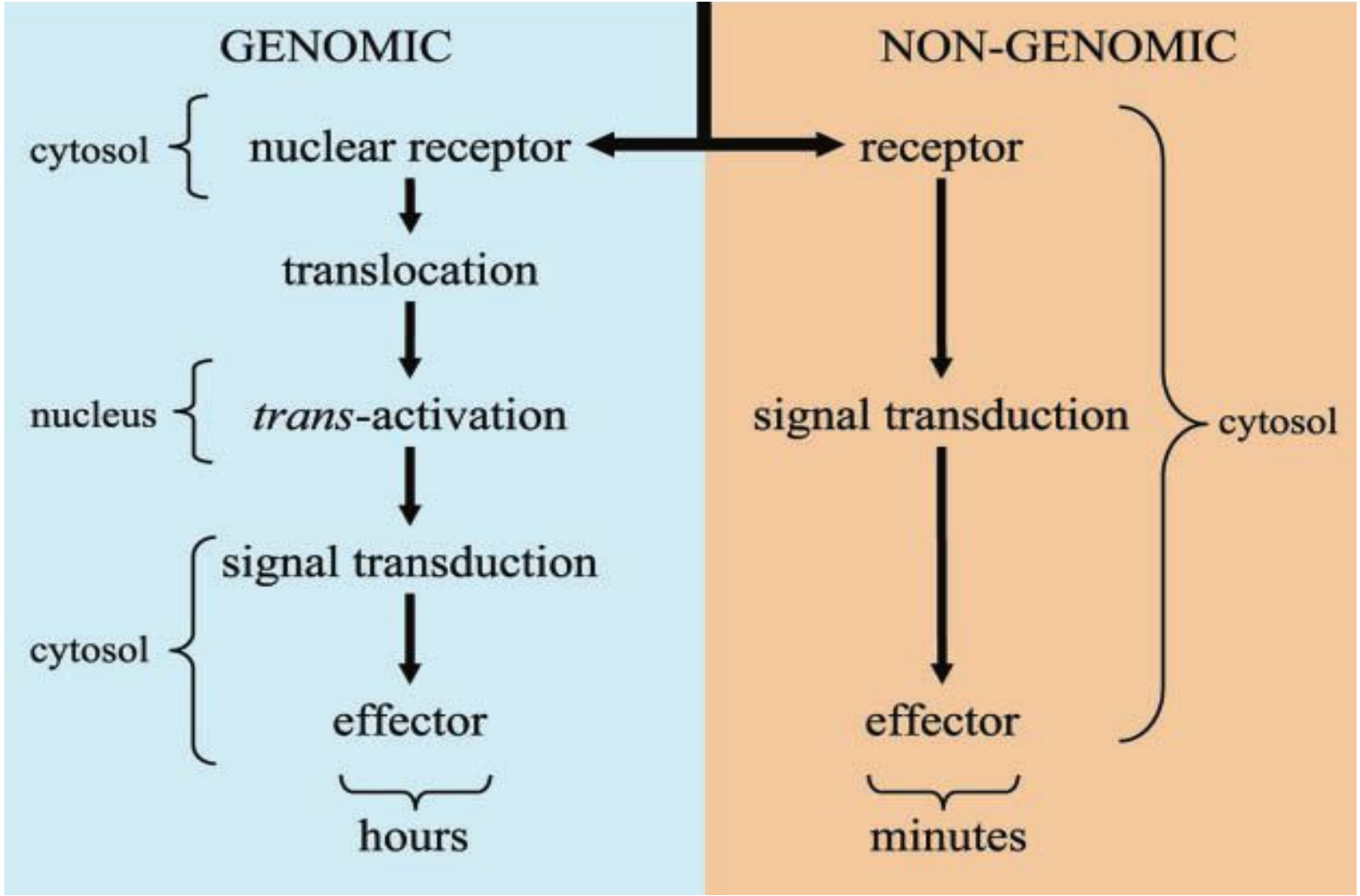
Theoretical

Lecture No. 2,3

Although the physiological apparently secondary effects of most of the hormones have been rather completely known for a number of years, their primary biochemical mechanisms of actions at a cellular/molecular level are also known in much details now. ***Many hormones serve as inducers or repressors in the genetically controlled synthesis of certain key cellular enzymes***.

Protein (Enzymes or Channels) Synthesis	Protein (Enzymes or Channels) Activation
Genomic action. Lipid soluble hormones i.e., steroid, T3, T4.	Non-genomic action. Lipid insoluble hormones i.e., protein, peptide hormone, catecholamines, serotonin & melatonin.

.A table the two main mechanisms of hormone action: *genomic and non-genomic*


GENOMIC
NON-GENOMIC
cytosol
nuclear receptor
receptor
translocation
nucleus
trans-activation
signal transduction
cytosol
signal transduction
cytosol
effector
effector
hours
minutes

1- Interaction with nuclear chromatin *(nuclear action or genomic action)*:

- Steroid hormones act mostly by changing the transcription rate of specific genes in the nuclear DNA.
- The steroid hormone has a **specific soluble**, **oligomeric receptor protein** (**mobile receptor**) either in the **cytosol and/or inside the nucleus**.
- This brings about **conformational changes** and also **changes in the surface charge of the receptor protein** to **favors its binding** to the **nuclear chromatin** attached to nuclear matrix.

- The receptor-steroid complex (R-H complex) is **trans located** to the **nuclear chromatin** and binds to a steroid recognizing acceptor site called **the hormone-responsive element (HRE) of a DNA strand** on the **upstream side** of the promoter site for a specific steroid responsive gene.
- The consequent **change in the intracellular concentration of m-RNA** alters the **rate of synthesis of a structural, enzymatic, carrier or receptor protein coded by it**.
- This **results** in ultimate cellular effects. The receptor-steroid complex subsequently **leaves** the acceptor site **as the free receptor and the steroid**. In addition to regulating the transcription, some **steroid hormones may also act as regulatory agents.**

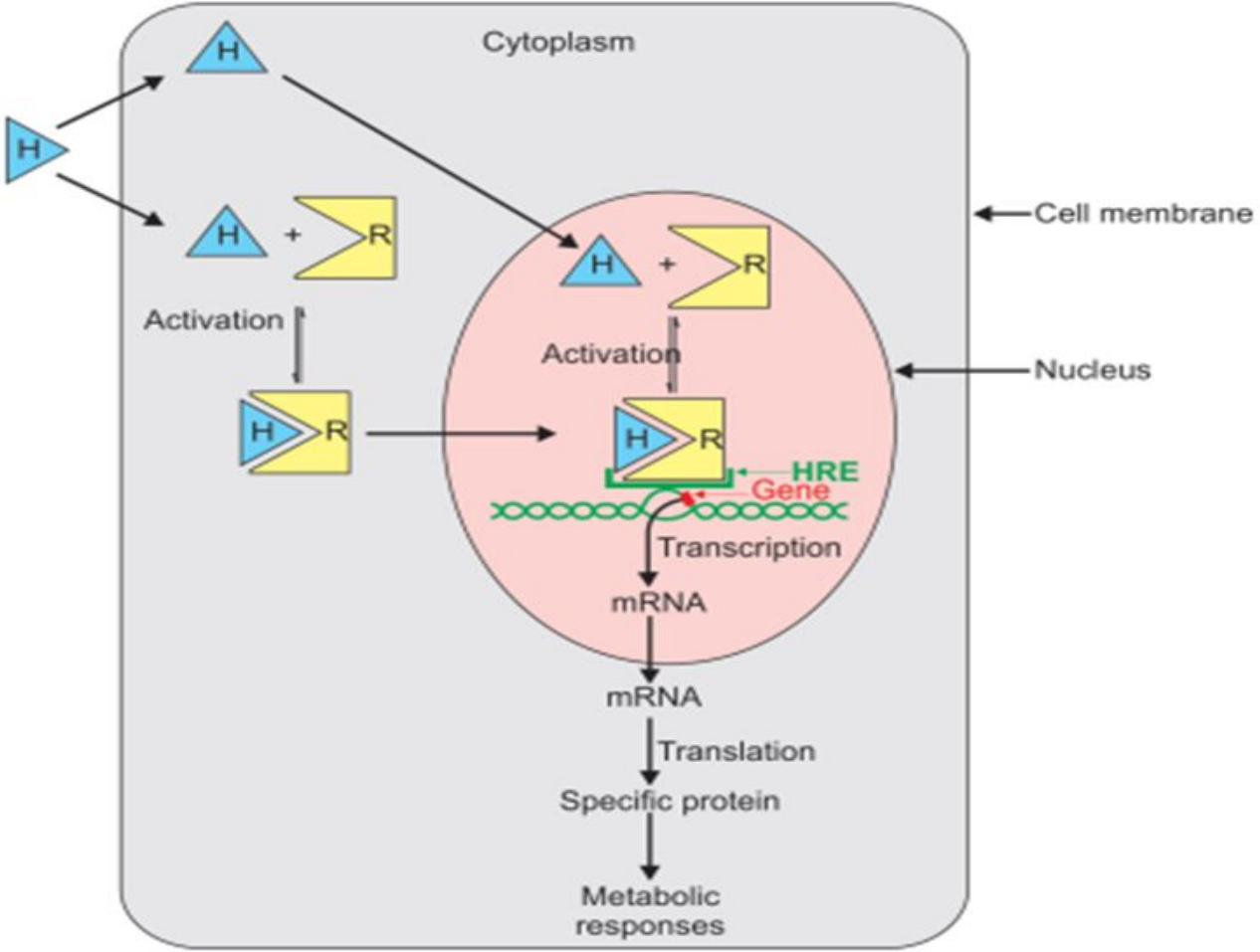
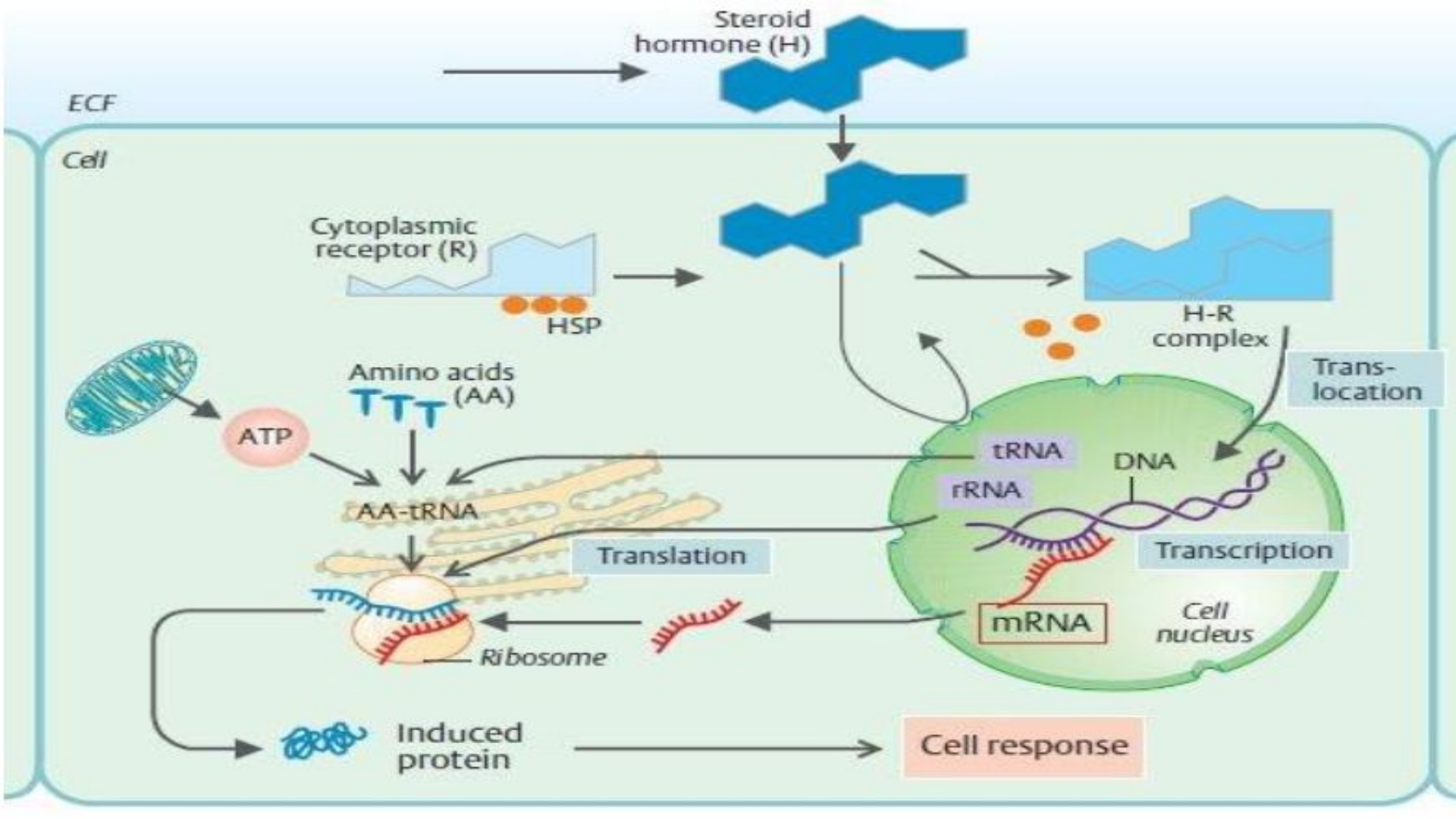


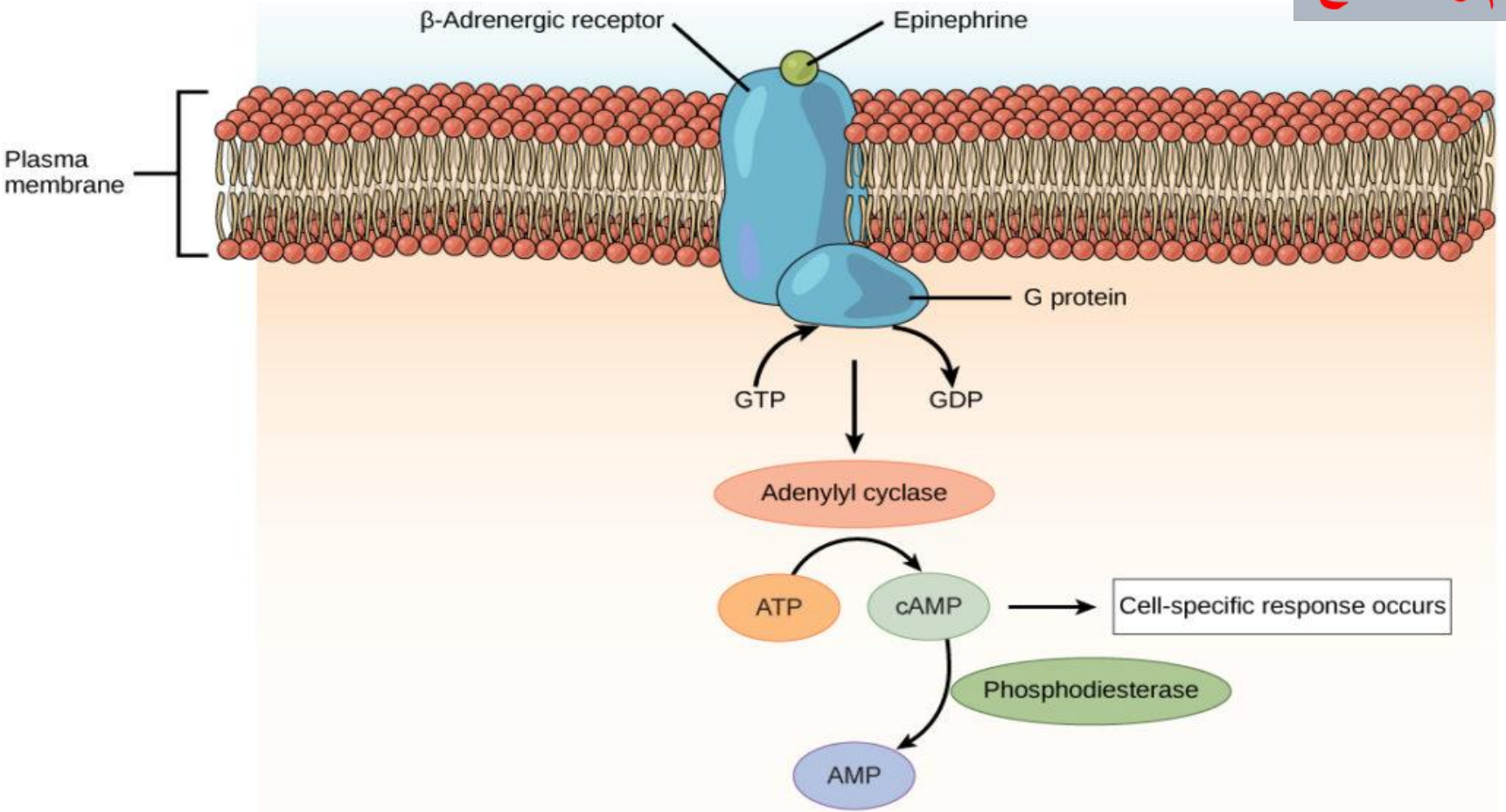
Fig. 23.2: Schematic representation of mechanism of hormone action at cytosolic or nuclear level. (H: Hormone; R: Receptor; R-H: Hormone receptor complex; HRE: Hormone response element)


Steroid hormone (H)
ECF
Cell
Cytoplasmic receptor (R)
HSP
H-R complex
Trans-location
Amino acids (AA)
ATP
tRNA
DNA
rRNA
AA-tRNA
Translation
Transcription
mRNA
Cell nucleus
Ribosome
Induced protein
Cell response

-2Membrane receptors (non-genomic action):

- certain molecules cannot enter target cells **through** the **membrane lipid bilayer**. This is **achieved by** the **specific receptor** molecules **present on the surface of the plasma membrane.**
- **Many hormones** seen specifically involved in the **transport of a variety of substances across cell membrane**.
- In general, these **hormones specifically bind to** the **receptors** on cell membrane. They **cause rapid secondary metabolic changes in the tissue** but have **little effect** on **metabolic activity** of membrane-free preparations.
- Most protein **hormones and catecholamine's activate** transport of **membrane enzyme systems by direct binding** to specific receptors on the membrane

للفهم والاطلاع



3- c-AMP and hormone action:

- ***3'-5' c-AMP plays a unique role*** *in* *the action of many protein hormones*. Its level may be **decreased or increased** **by hormonal action** as **the effect varies depending on the tissue**.
- The hormones such as **glucagon, catecholamines, PTH, etc**. **act by** influencing a change in intracellular c-AMP concentration through **the adenylate cyclase c-AMP system**. The hormone binds to **a specific membrane receptor**.
- *Different types of these receptors* remain **associated with either Gs or Gi type of GTP dependent** trimeric nucleotide regulatory complexes of the membrane. Both Gs and Gi are made up of 3 subunits: **Gs contains αs β γ while Gi contains αi β γ.**

- Formation of the receptor-hormone complex **promotes the binding of GTP to the α subunit** of **either Gs or Gi**. When **αs-GTP is released**, it binds to adenylate cyclase located on the cytoplasmic surface of the membrane and **changes its conformation to activate it**.
- **Adenylate cyclase catalyses** the **conversion of ATP to c-AMP** thus **increasing the intracellular c-AMP concentration.**
- **On the other hand**, **αi-GTP inhibits** adenylate cyclase by **binding with it**. This lowers the intracellular concentration of c-AMP.
- **Note**: Insulin can **decrease** **hepatic c-AMP** in opposition to the increase caused by glucagon

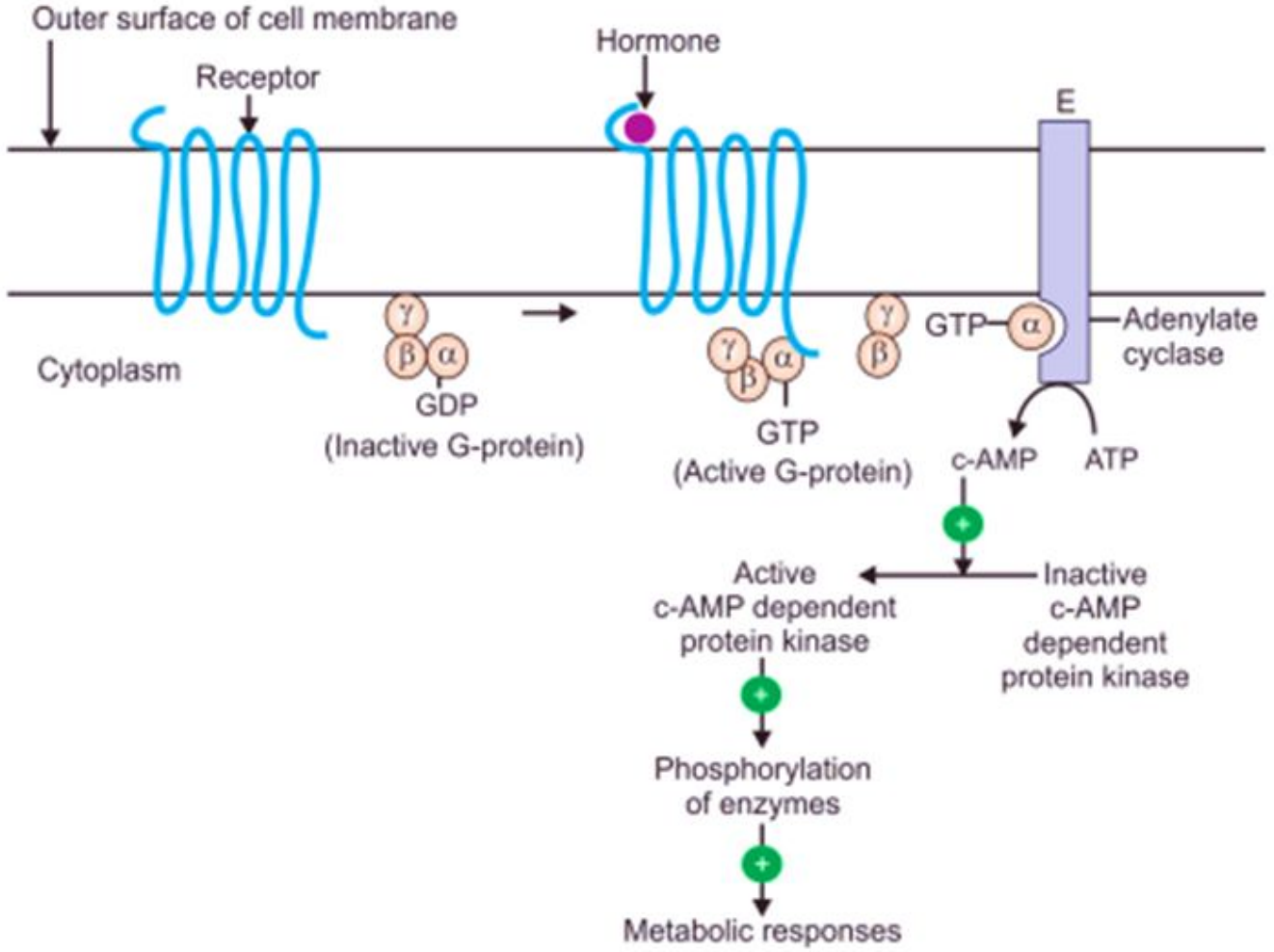
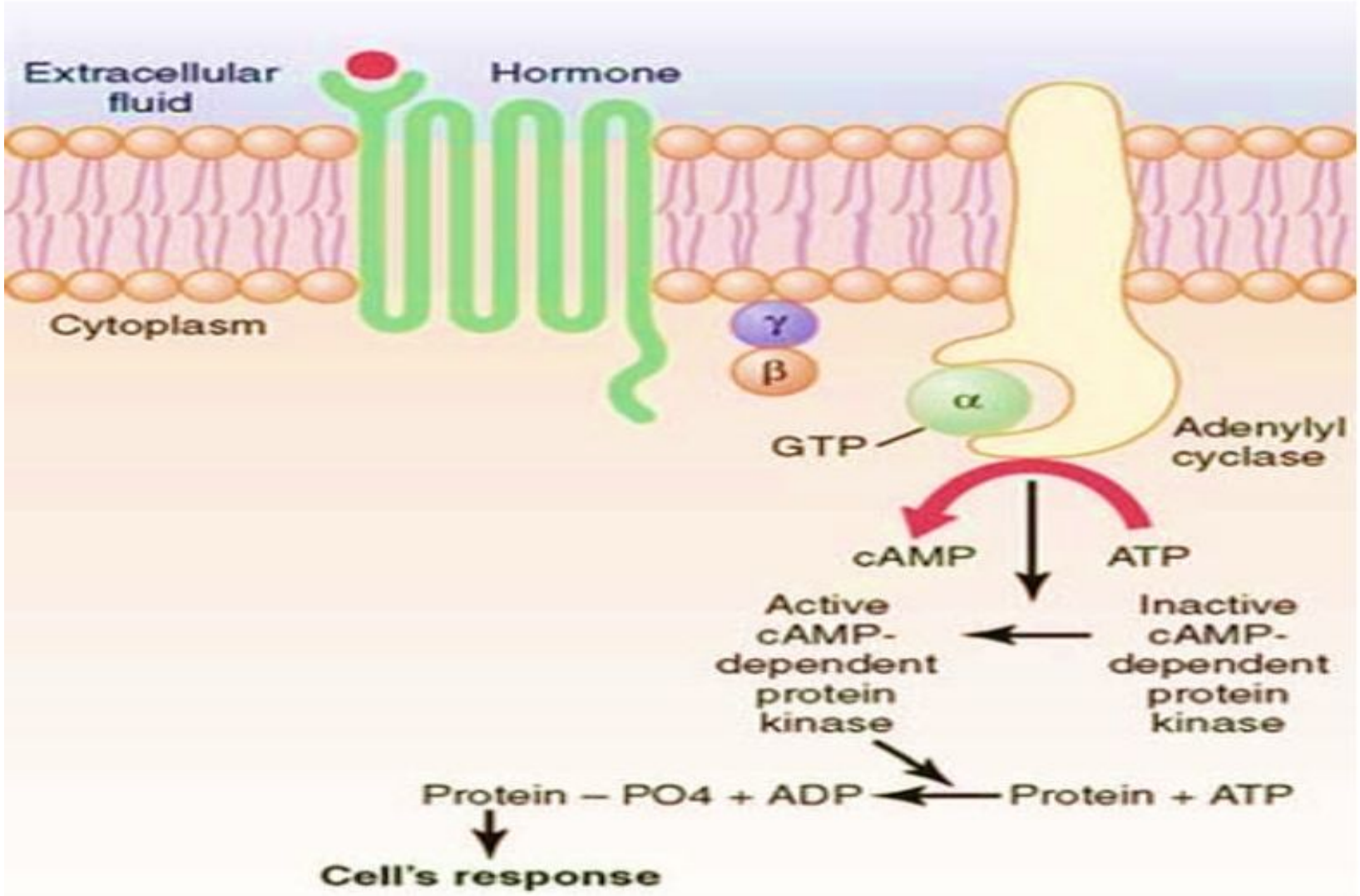
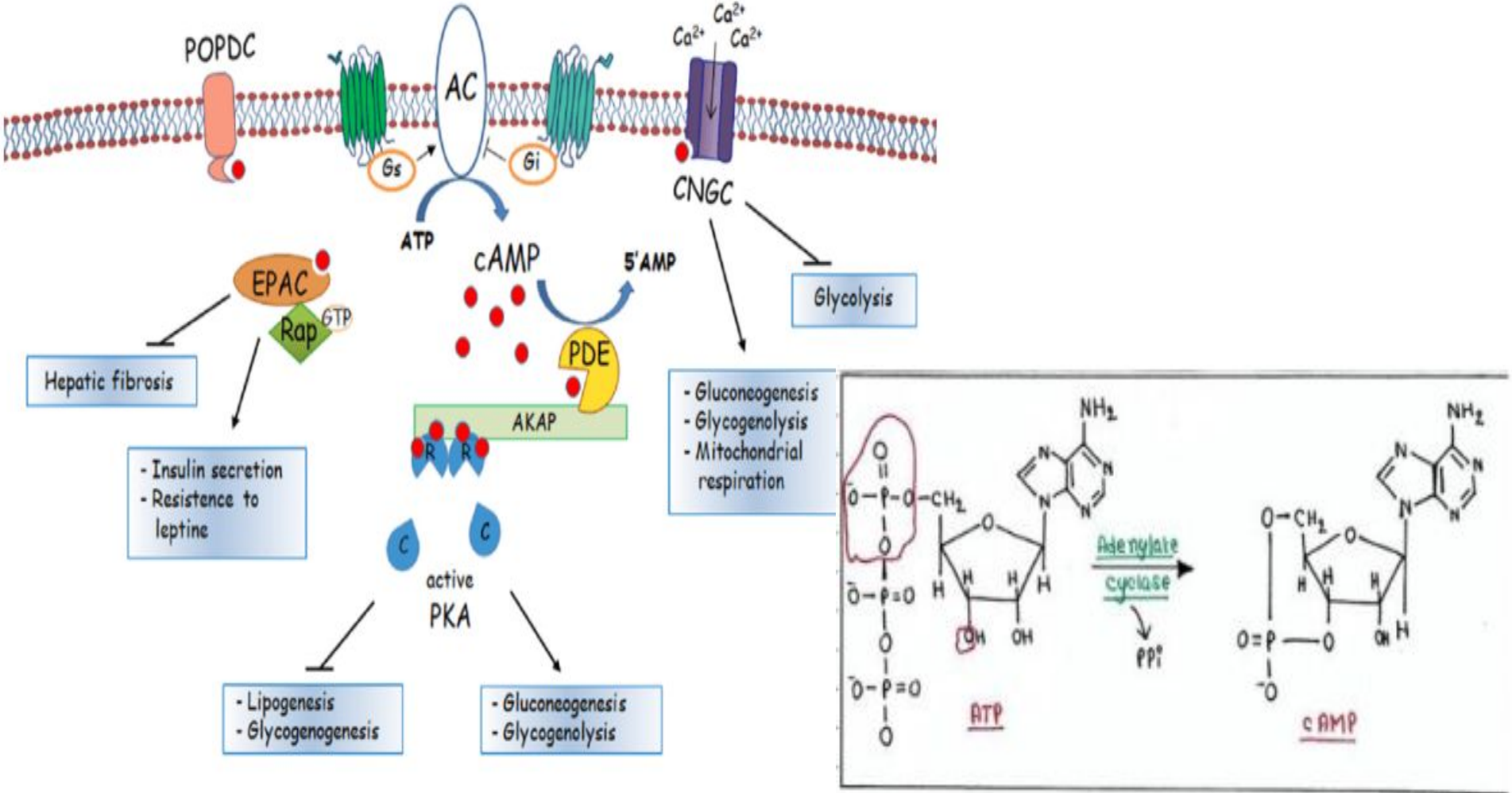


Fig. 23.3: Cell membrane receptor mechanism of hormone action through c-AMP as a second messenger.


Extracellular fluid
Hormone
Cytoplasm
γ
β
α
GTP
Adenylyl cyclase
cAMP
ATP
Active cAMP-dependent protein kinase
Inactive cAMP-dependent protein kinase
Protein – PO4 + ADP
Protein + ATP
Cell's response

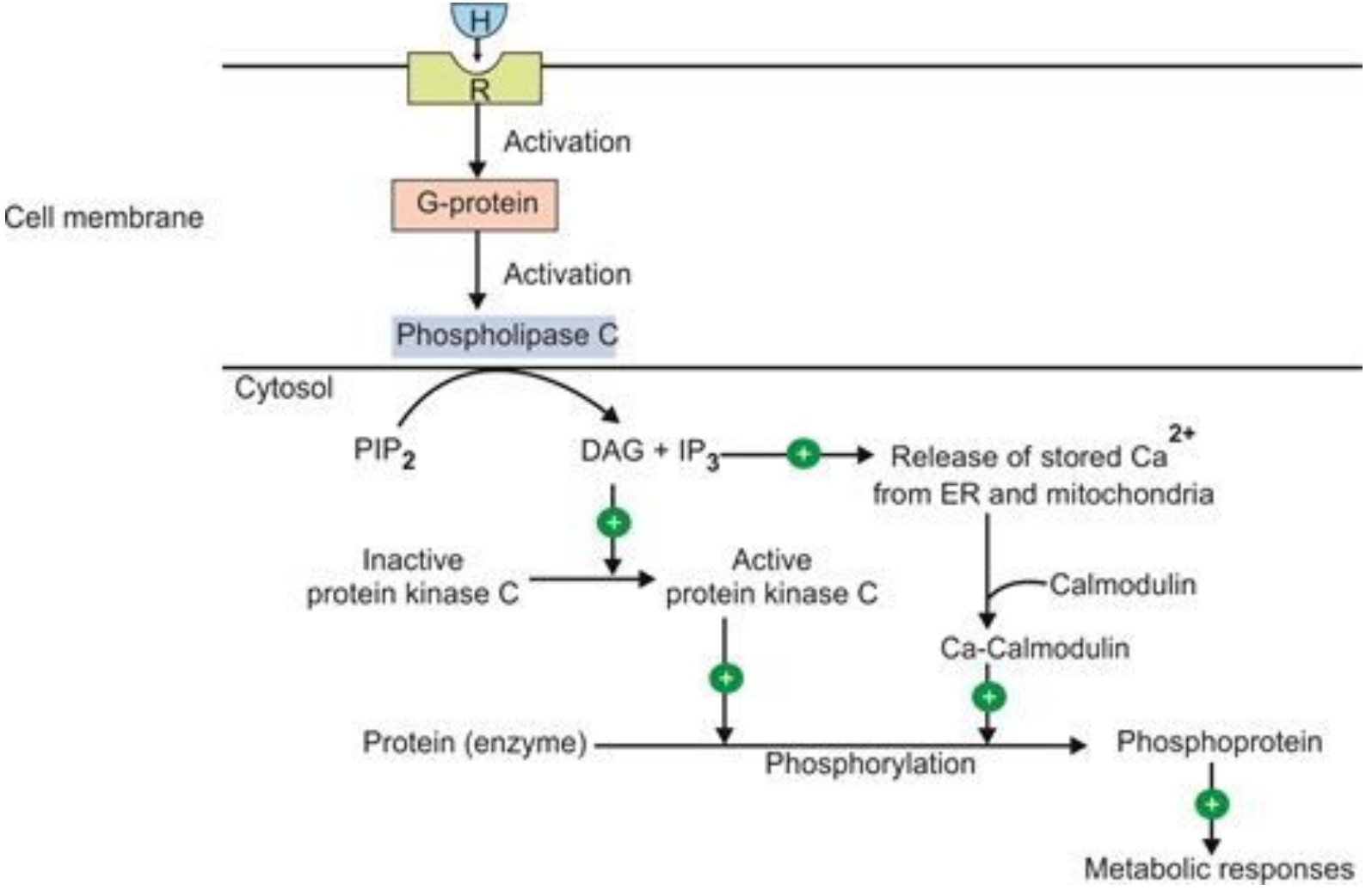

POPDC
AC
Gs
Gi
Ca^{2+}
Ca^{2+}
Ca^{2+}
CNGC
ATP
cAMP
5'AMP
PDE
EPAC
Rap
GTP
Hepatic fibrosis
- Insulin secretion
- Resistence to leptine
AKAP
R
R
C
C
active PKA
- Lipogenesis
- Glycogenogenesis
- Gluconeogenesis
- Glycogenolysis
Glycolysis
- Gluconeogenesis
- Glycogenolysis
- Mitochondrial respiration
Adenylate cyclase
PPi
ATP
c AMP

4. Role of polyphosphoinositol and diacylglycerol in hormone action:

- Just like c-AMP other compounds such as **1, 4, 5 inositol triphosphate (ITP) and diacylglycerol (DAG**) **act as second messengers**.
- This is specially found in case of **vasopressin, TRH, GnRH, etc**. These ***hormones activate*** the phospholipase C-polyphosphoinositol (PIP2) system to produce ITP **(IP3)** and DAG. **By binding** with the specific receptor protein on cell membrane, the **hormone activates a trimeric nucleotide regulatory complex**.
- The complex in turn **activates** phospholipase C on the inner surface of the membrane.

a) **Inositol triphosphate enhances** the **mobilization of Ca++ into the cytosol** from intracellular Ca++ pool from mitochondria, **calcium ions** then ***act as tertiary messenger.***

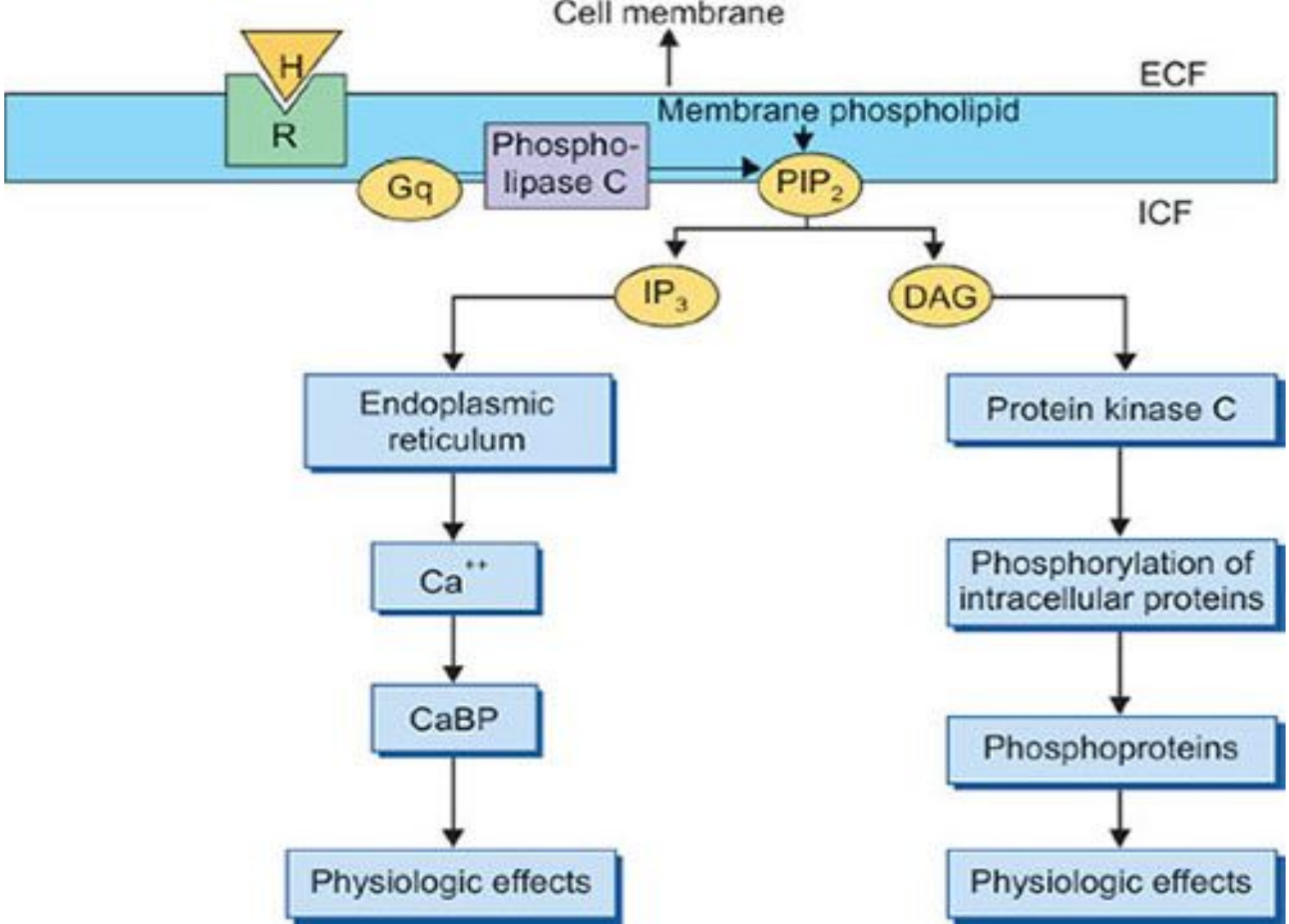
b) While **DAG activates** the **Ca++ phosphatidyl-serine-dependent protein kinase C located** on the inner surface of the membrane, **by lowering its Km for Ca++.** This **enzyme** then ***phosphorylates*** **specific enzymes and other proteins** in the cytosol to **modulate their activities.**


H
R
Activation
G-protein
Cell membrane
Activation
Phospholipase C
Cytosol
PIP2
DAG + IP3
Release of stored Ca2+
from ER and mitochondria
Inactive
protein kinase C
Active
protein kinase C
Calmodulin
Ca-Calmodulin
Protein (enzyme)
Phosphorylation
Phosphoprotein
Metabolic responses

5. Role of calcium in hormone action:

- **The action of most protein hormones is inhibited in absence of calcium** even though ability to increase or decrease c-AMP is comparatively unimpaired. Thus, **calcium may be more terminal signal for hormone action than c-AMP**. It is suggested that **ionized calcium** of the cytosol is the **important signal**.
- **The source of this calcium may be extracellular fluid or** it **may arise from mobilization of intracellular tissue bound calcium**.
- As mentioned, **membrane-receptor binding may be responsible for this**.
- The hormone receptor binding **may directly inhibit the Ca++–ATPase**.

- It **may also directly open up voltage-independent Ca++ channels** in the membrane to **increase the diffusion of Ca++** into the cell down its inward concentration gradient resulting in **increased cytosolic Ca++ concentration** which then acts **as a second messenger** *to affect cellular activities.*
- The **receptor-hormone complex may produce ITP** which in turn ***can increase cytosolic Ca++ concentration*** **by enhancing the mobilization of Ca++ from mitochondrial and endoplasmic reticular pools**. All these enzymes have special biochemical metabolic roles.
- **Ca++ also changes membrane permeability**.
- ***Many of its effects are mediated*** through its **binding to Ca++–dependent regulatory proteins *like calmodulin and troponin***.

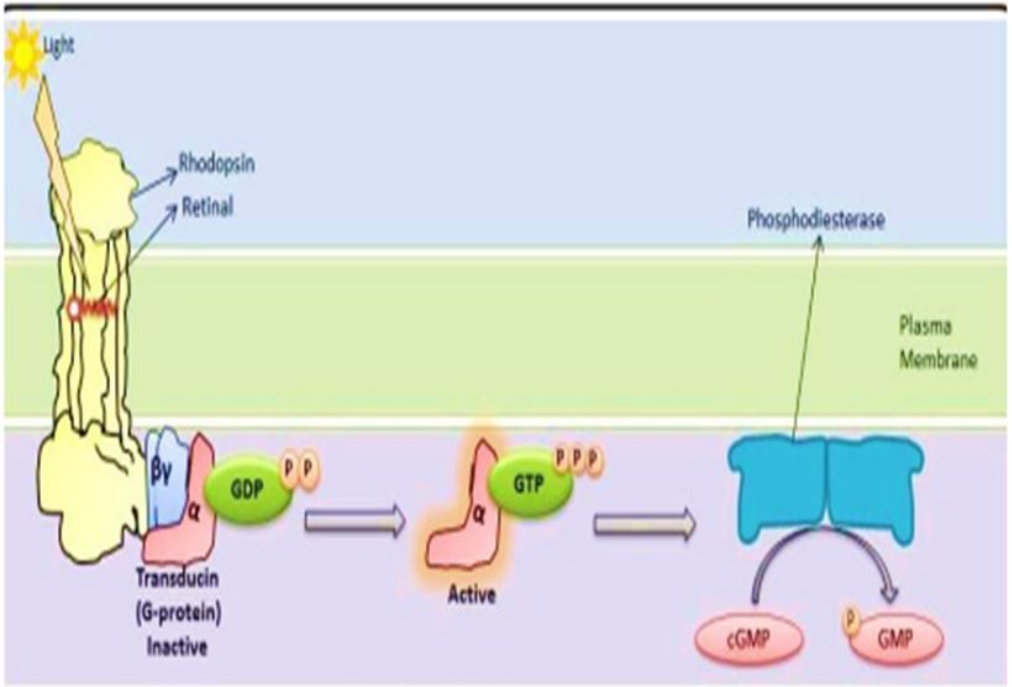

Cell membrane
H
R
ECF
Membrane phospholipid
Phospho-
lipase C
Gq
PIP2
ICF
IP3
DAG
Endoplasmic
reticulum
Protein kinase C
Ca++
Phosphorylation of
intracellular proteins
CaBP
Phosphoproteins
Physiologic effects
Physiologic effects

6. Role of c-GMP in hormone action:

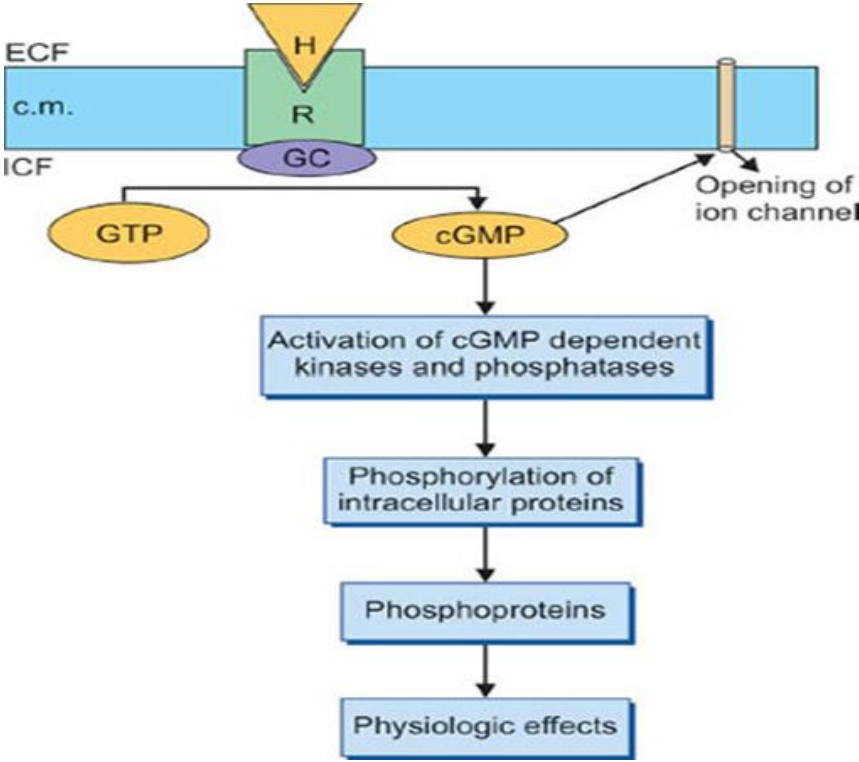
Hormones such as **insulin and growth hormone affect** the **guanylate cyclase c-GMP system**. This will **increase the intracellular conc. of c-GMP and activate cGMP-dependent protein kinases.**

The ***active c-GMP-protein kinase*** would in turn bring about **phosphorylation of specific cellular proteins to change their activities**, **leading to *relaxation of smooth muscles*, *vasodilatation and other effects***.

It is likely that **Ca++ may act as a *second messenger* to activate guanylate cyclase** and thereby **increasing the conc. of c-GMP inside the cell**.

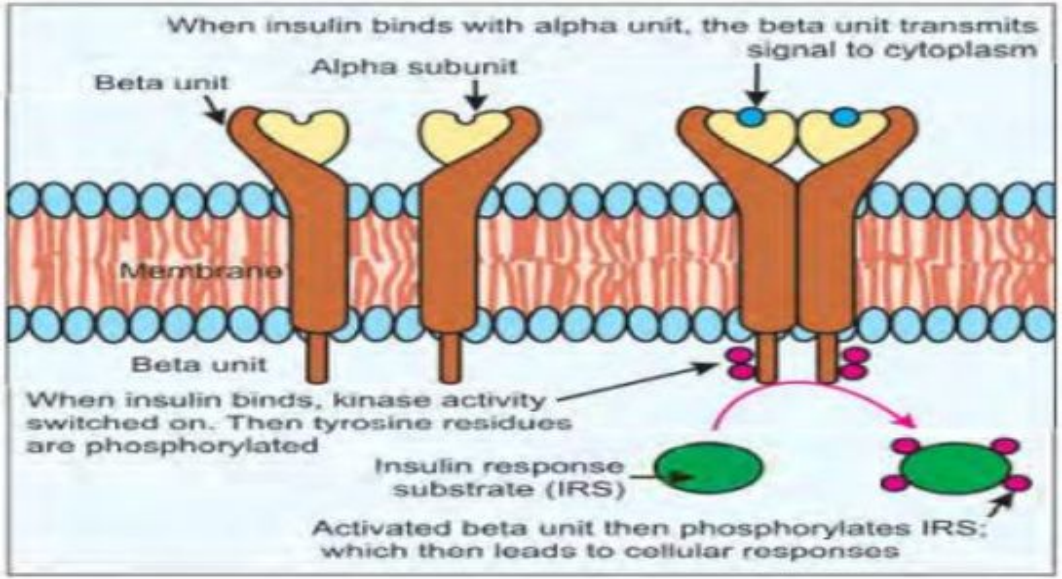


Role of cGMP in Photoreception



7. Role of phosphorylation of tyrosine kinase:

- In fact, **a second messenger** ***for insulin, growth hormone, prolactin, oxytocin, etc***. **has not been identified so far.**
- However, binding of them to their respective membrane receptors **activates** ***a specific protein kinase called*** **tyrosine kinase** which **phosphorylates tyrosine residue** of specific proteins.
- This may bring about some metabolic changes



Hormone(s)	Origin	Major Function(s)
Group I. HORMONES THAT BIND TO INTRACELLULAR RECEPTORS		
Estrogens	Ovaries and adrenal cortex	Female sexual characteristics, menstrual cycle.
Progestins	Ovaries and placenta	Involved in menstrual cycle and maintenance of pregnancy.
Androgens	Testes and adrenal cortex	Male sexual characteristics, spermatogenesis.
Glucocorticoids	Adrenal cortex	Affect metabolisms, suppress immune system.
Mineralocorticoids	Adrenal cortex	Maintenance of salt and water balance.
Calcitriol (1, 25–DHCC)	Kidney (final form)	Promotes absorption of Ca^{2+} from intestine, kidney and bone.
Thyroid hormones (T_3, T_4)	Thyroid	Promote general metabolic rate.
Group II. HORMONES THAT BIND TO CELL SURFACE RECEPTORS		
A. The second messenger is cAMP		
Adrenocorticotropic hormone (ACTH)	Anterior pituitary	Stimulates the release of adrenocorticosteroids.
Follicle stimulating hormone (FSH)	Anterior pituitary	In females, stimulates ovulation and estrogen synthesis. In males, promotes spermatogenesis.
Luteinizing hormone (LH)	Anterior pituitary	Stimulates synthesis of estrogens and progesterone and causes ovulation. Promotes androgen synthesis by testes.
Chorionic gonadotropin (hCG)	Anterior pituitary	Stimulates progesterone release from placenta.
Thyroid stimulating hormone (TSH)	Anterior pituitary	Promotes the release of thyroid hormones (T_3, T_4).
β-Endorphins and enkephalins	Anterior pituitary	Natural endogenous analgesics (pain relievers).
Antidiuretic hormone (ADH)	Posterior pituitary (stored)	Promotes water reabsorption by kidneys.
Glucagon	Pancreas	Increases blood glucose level, stimulates glycogenolysis and lipolysis.
Parathyroid hormone (PTH)	Parathyroid	Increases serum calcium, promotes Ca^{2+} release from bone.
Calcitonin	Thyroid	Lowers serum calcium. Decreases Ca^{2+} uptake by bone and kidney.
Epinephrine	Adrenal medulla	Increases heart rate and blood pressure. Promotes glycogenolysis in liver and muscle and lipolysis in adipose tissue.
Norepinephrine	Adrenal medulla	Stimulates lipolysis in adipose tissue.

B. The second messenger is phosphatidyl inositol/calcium		
Thyrotropin-releasing hormone (TRH)	Hypothalamus	Promotes TSH release.
Gonadotropin-releasing hormone (GnRH)	Hypothalamus	Stimulates release of FSH and LH.
Gastrin	Stomach	Stimulates gastric HCl and pepsinogen secretion.
Cholecystokinin (CCK)	Intestine	Stimulates contraction of gall bladder and secretion of pancreatic enzymes.
C. The second messenger is unknown/unsettled		
Growth hormone (GH)	Anterior pituitary	Promotes growth of the body (bones and organs).
Prolactin (PRL)	Anterior pituitary	Growth of mammary glands and lactation.
Oxytocin	Posterior pituitary (stored)	Stimulates uterine contraction and milk ejection.
Insulin	Pancreas	Lowers blood glucose (hypoglycemic effect), promotes protein synthesis and lipogenesis.
Somatomedins (insulin-like growth factors, IGF-I, IGF-II)	Liver	Growth related functions of GH are mediated. Stimulates growth of cartilage.

Questions & Explanations

1. Binding of the following hormones to receptor activate adenylate cyclase, except:
2. The following are the intracellular second messenger for hormone action, except:
3. Water soluble hormones have cell surface receptors, except:
4. Hormone that have intracellular receptor:
5. Second messenger that mobilizes intracellular calcium is:

Learning Resources for Hormone Mechanisms

Here are excellent sources to deepen your understanding of this topic:

Medical Textbooks:

"Harper's Illustrated Biochemistry" (Chapter on Hormones & Signal Transduction): Provides a detailed, yet clear, biochemical perspective on second messenger systems.

"Guyton and Hall Textbook of Medical Physiology" (Chapter 74: Introduction to Endocrinology): Excellent for understanding the physiological principles of hormone-receptor interactions and signaling.

"Greenspan's Basic & Clinical Endocrinology": A comprehensive resource that links basic mechanisms to clinical practice.

YouTube Channels:

Armando Hasudungan: His detailed drawings are fantastic for visualizing signal transduction pathways.

Dr. Najeeb Lectures: Provides extremely detailed lectures on the entire process.