Hormone Receptors

by

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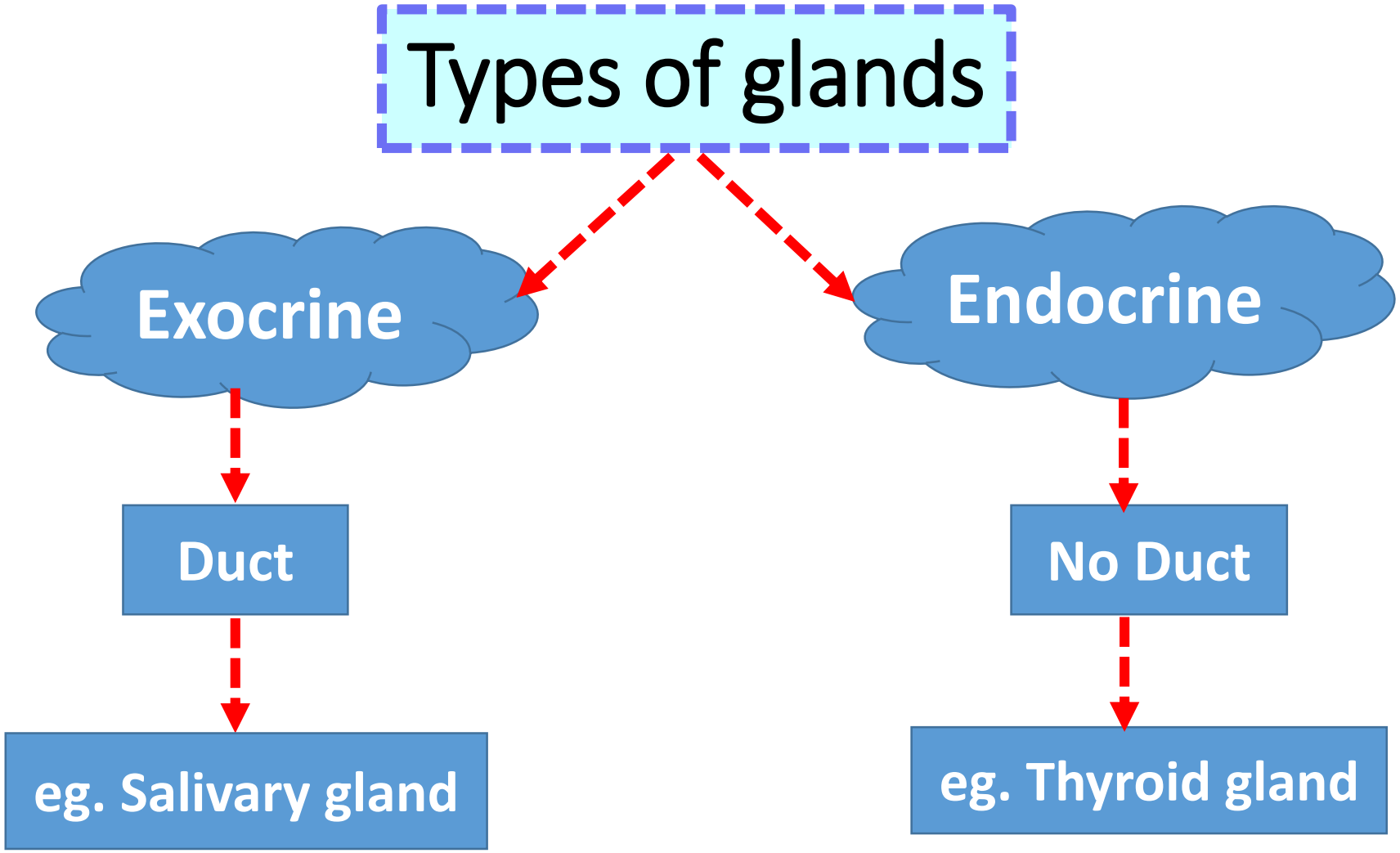


N.B. The pancreas is a gland that has both endocrine & exocrine parts.

Mechanism of hormone signal transduction

Signal transduction: transport of the signal into the cell. This signal modulate the activity of the cell. So there are 2 types of cells (sender and receiver cells).

Types of signal transduction:

1. Autocrine: the same cell is the sender & recipient as in immunity & inflammation

(e.g. IL1 cytokine from monocytes)

3. Juxtacrine : the sender and recipient cells are **adjacent** to each other

(cell-cell interaction e.g. though gap junction)

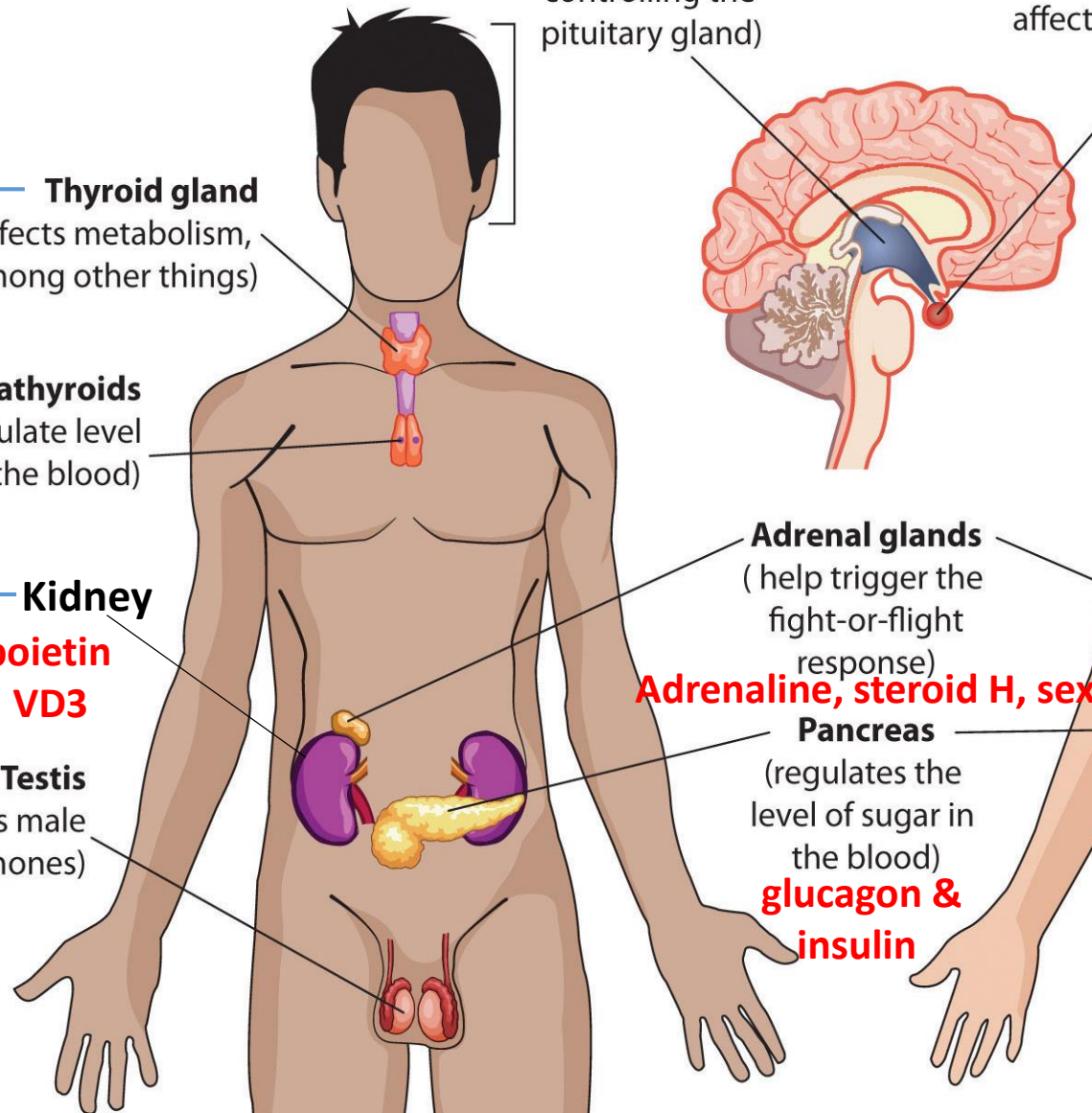
2. Paracrine: from sender cells to the **neighbouring** recipient cells

(the hormone does not enters the circulation, short distance, local action)

4. Endocrine: the hormone or chemical messenger enters the circulation

(long distance, remote action)

Overview of the endocrine system



Hypothalamic hormones
CRH, TRH, ……

Hypothalamus
(brain region controlling the pituitary gland)

Pituitary gland
(secretes many different hormones, some of which affect other glands)

Ant. Pit.: ACTH, TSH, FSH, LH, growth hormone, prolactin, somatotropin
Post. Pit.: ADH & oxytocin

T3, T4 & calcitonin

Thyroid gland
(affects metabolism, among other things)

PTH

Parathyroids
(help regulate level of calcium in the blood)

Kidney

Erythropoietin
Renin & VD3

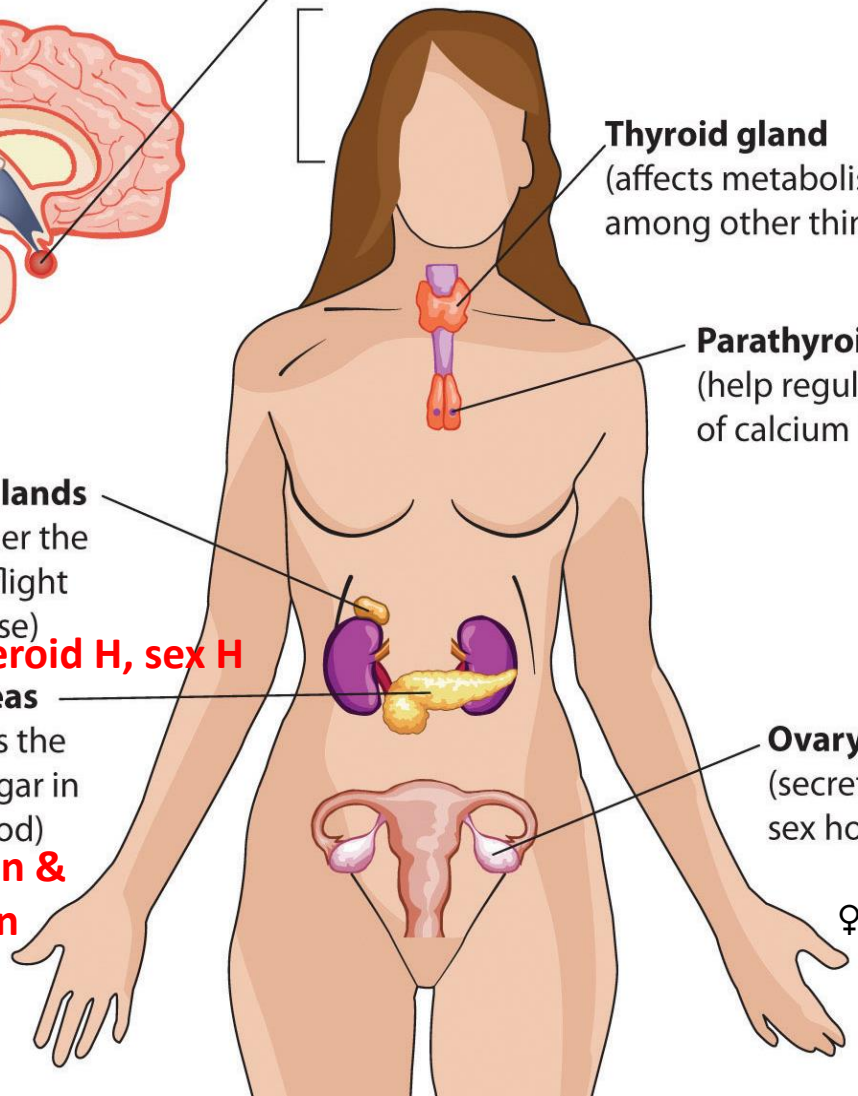
Adrenal glands
(help trigger the fight-or-flight response)

Adrenaline, steroid H, sex H

Pancreas
(regulates the level of sugar in the blood)

glucagon & insulin

Testis
(secretes male sex hormones)



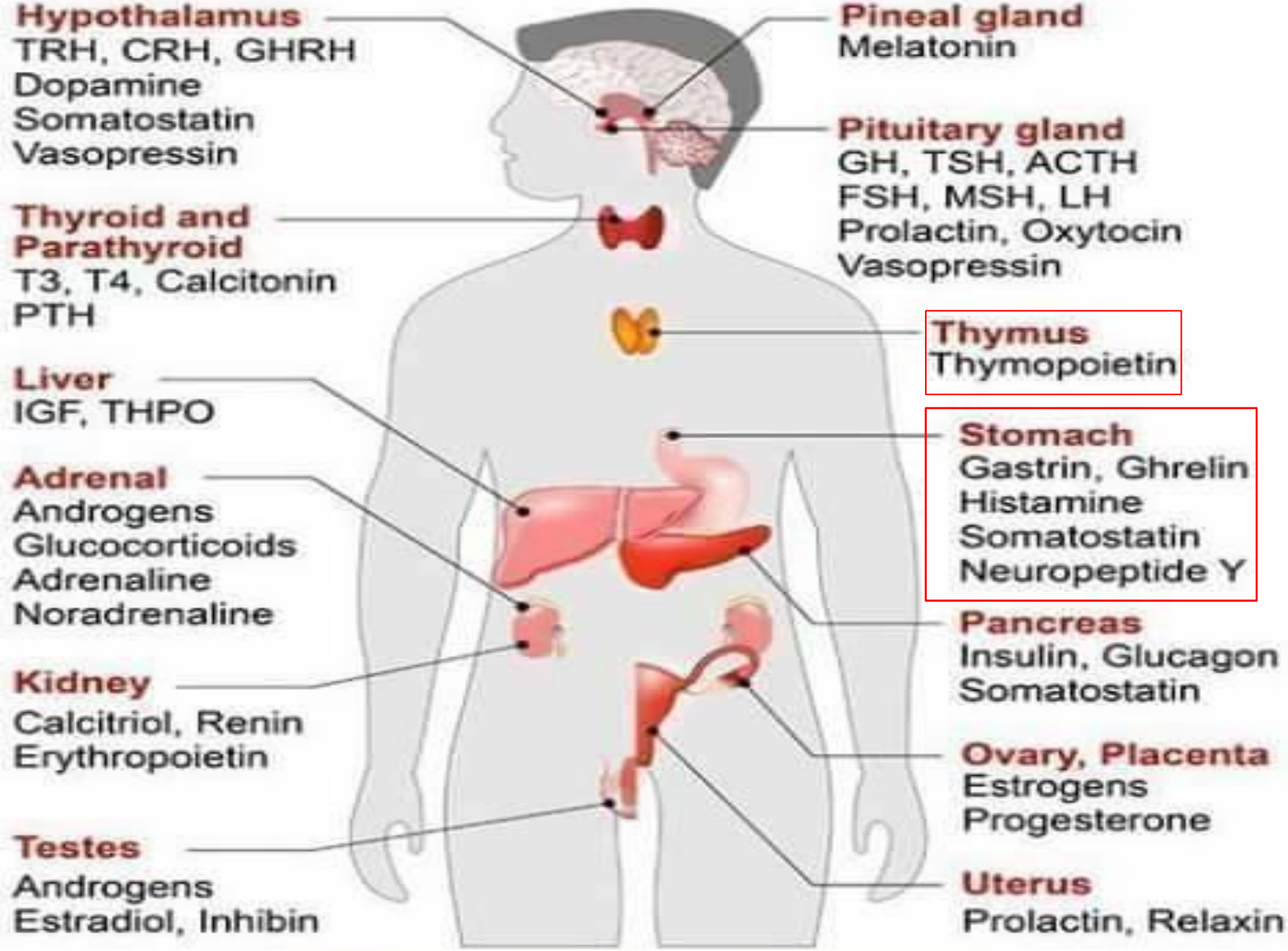
Thyroid gland
(affects metabolism, among other things)

Parathyroids
(help regulate level of calcium in the blood)

Ovary
(secretes female sex hormones)

Placenta
♀ sex h, HCG,

HORMONES


Hypothalamus
TRH, CRH, GHRH
Dopamine
Somatostatin
Vasopressin
Thyroid and Parathyroid
T3, T4, Calcitonin
PTH
Liver
IGF, THPO
Adrenal
Androgens
Glucocorticoids
Adrenaline
Noradrenaline
Kidney
Calcitriol, Renin
Erythropoietin
Testes
Androgens
Estradiol, Inhibin
Pineal gland
Melatonin
Pituitary gland
GH, TSH, ACTH
FSH, MSH, LH
Prolactin, Oxytocin
Vasopressin
Thymus
Thymopoietin
Stomach
Gastrin, Ghrelin
Histamine
Somatostatin
Neuropeptide Y
Pancreas
Insulin, Glucagon
Somatostatin
Ovary, Placenta
Estrogens
Progesterone
Uterus
Prolactin, Relaxin

Hormones

Chemical mediators secreted by the endocrine glands in a trace amount directly into blood stream to be carried to the target organ to produce specific biochemical and physiological effects.

CNS

stimulation or inhibition

Hypothalamus

stimulation or inhibition

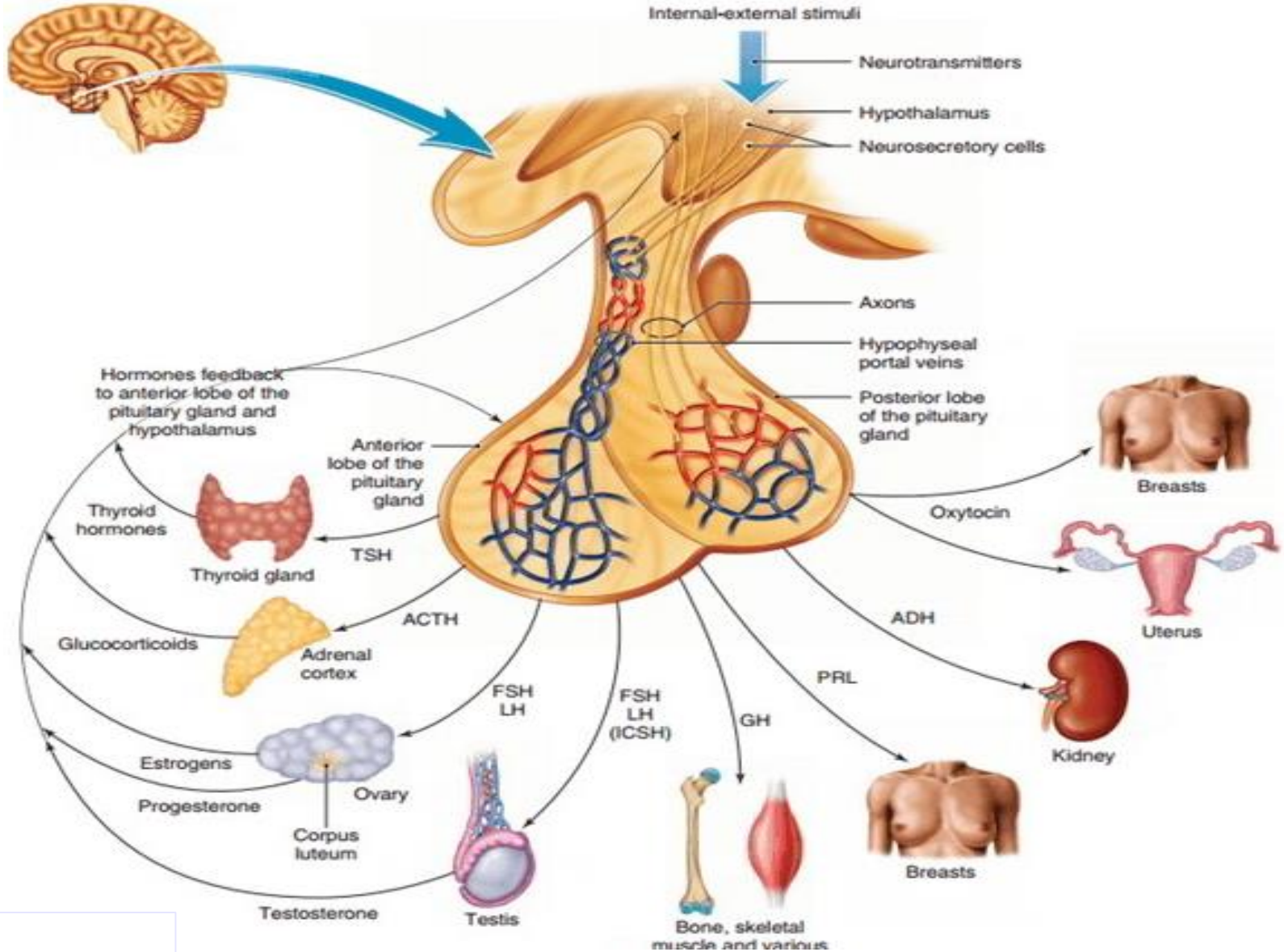
Pituitary gland

stimulation or inhibition

Target endocrine gland

stimulation or inhibition

Target tissue cells



Classification of Hormones

According to

Structure

Derivatives of

Cholesterol

Steroid H:
Sex H, vit D3
Mineralo-&
Gluco-
corticoids

Fatty acids

Ecosanoids:
from
arachidonic
acid (20 C)

peptide

Few aa-100aa
TSH (small)
insulin (large)
Prolactin
GH
Vasopressin
ANP

Amino acids

Tyrosine:
Thyroid &
catechol-
amines
Tryptophan:
serotonin &
melatonin

Solubility

Water-soluble

Hormones derived from amino acids and peptides
*indirectly act on target cells

Lipid-soluble

Steroid H:
* able to pass the cell membrane,
*acting directly on target cells

Action

Trophic

* act on target endocrine **glands**
* ACTH, TSH, FSH, LH

Non-trophic

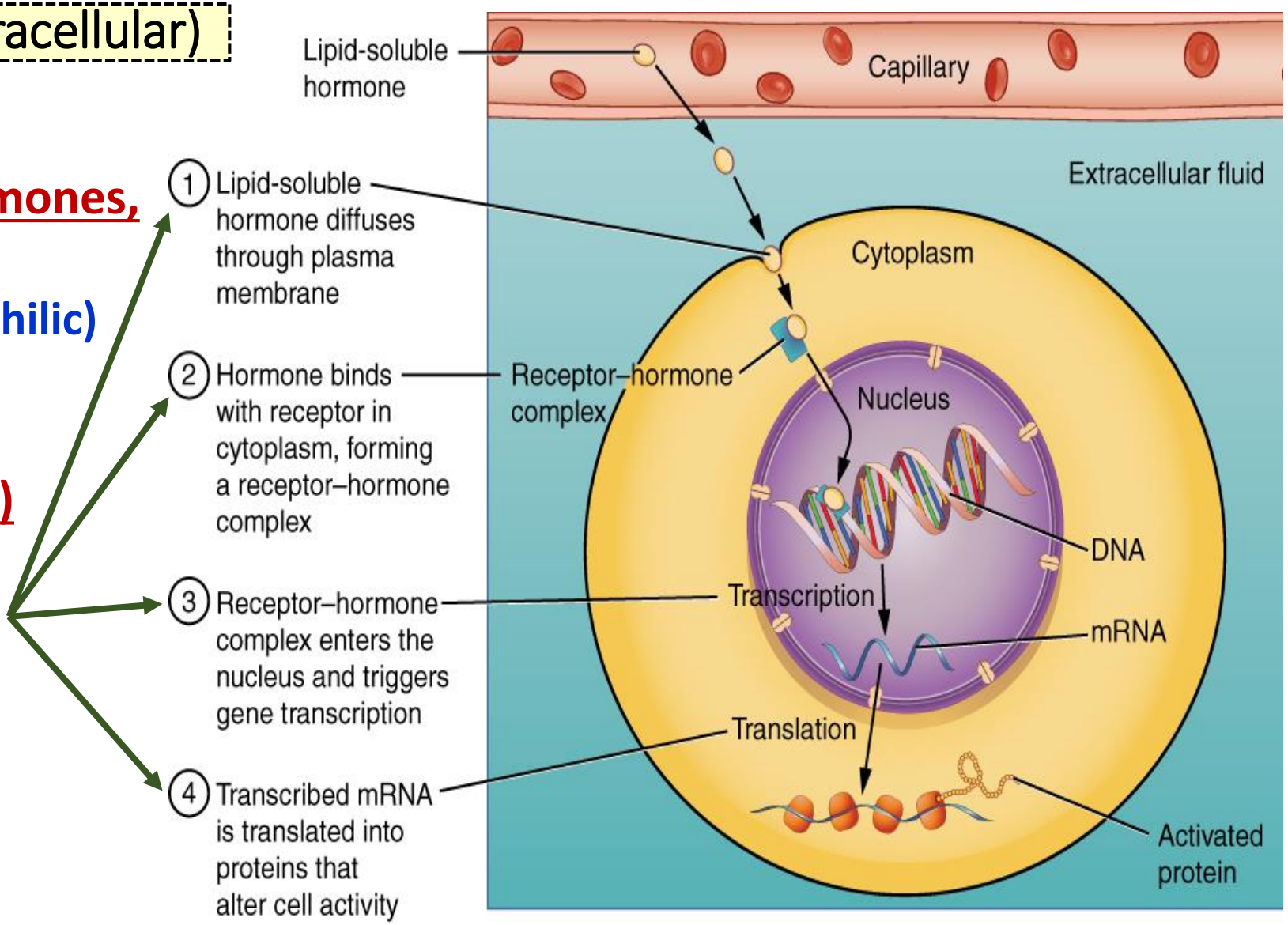
*act on target **tissue** cells

Mechanism of Hormone Action (mobile & fixed receptor mechanisms)

I. Mobile receptor (intracellular)

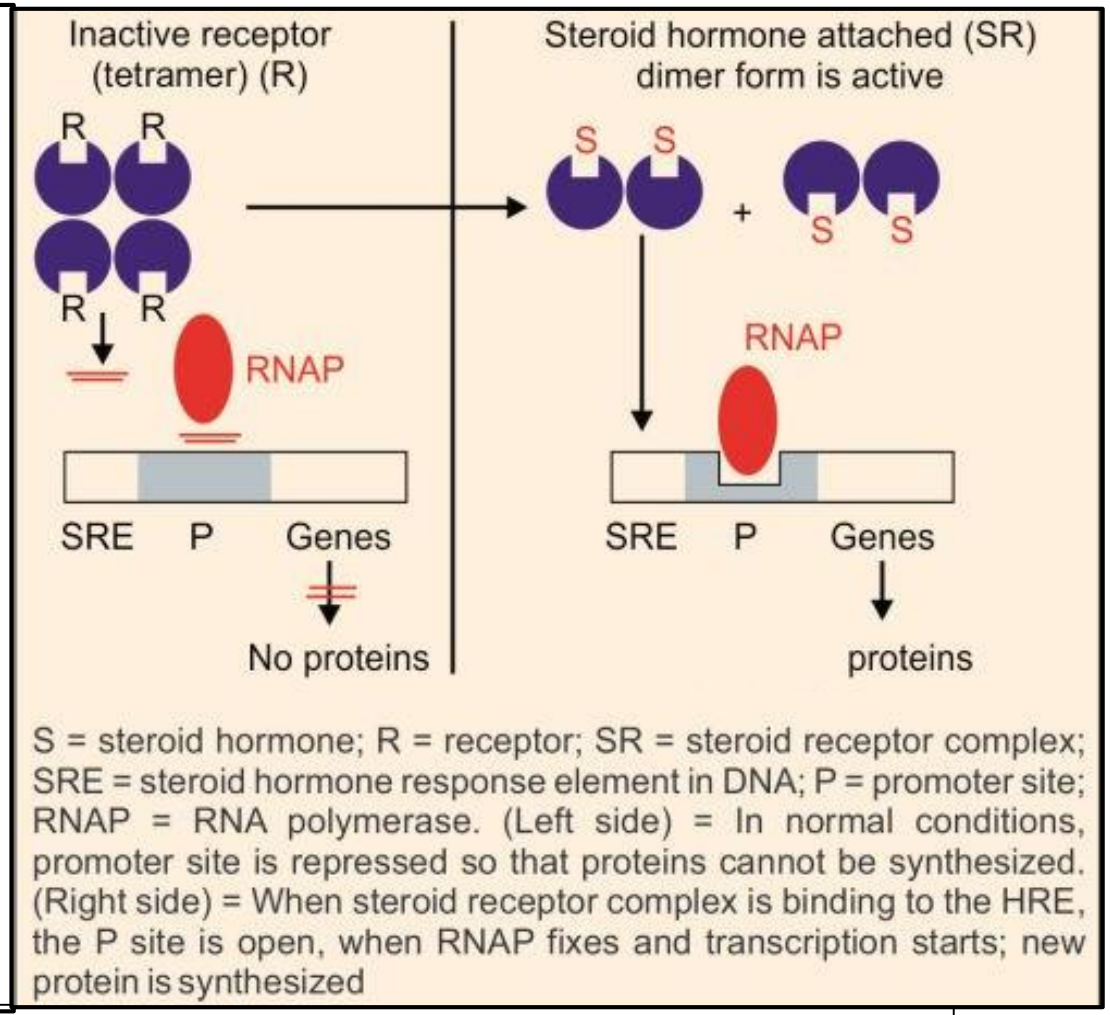
- **Steroid hormones, sex hormones, thyroid hormones, & Vitamin D**
- **Insoluble in water (lipophilic) (pass the cell membrane)**
- **Intracellular receptors (cytoplasmic or nuclear)**

Mechanism:



I. Mobile receptor (intracellular)

- Steroid hormone receptor protein is **tetramer** (inactive) & is 80-100 KDa
- Each monomer binds a single steroid molecule at a hydrophobic site
- On binding to the genes, they **dimerize**
- In the nucleus, the hormone receptor complex (HR) binds the hormone response element **(HRE)** or steroid response element **(SRE)** →→ enhance binding of **RNA polymerase** to the **promotor** →→ enhance initiation of transcription →→ proteins perform the metabolic functions of hormones



S = steroid hormone; R = receptor; SR = steroid receptor complex; SRE = steroid hormone response element in DNA; P = promoter site; RNAP = RNA polymerase. (Left side) = In normal conditions, promoter site is repressed so that proteins cannot be synthesized. (Right side) = When steroid receptor complex is binding to the HRE, the P site is open, when RNAP fixes and transcription starts; new protein is synthesized

- Examples of hormone effect on genes:

1. The induction of synthesis of **aminotransferases by glucocorticoids**
2. The induction of synthesis of **calcium binding protein by calcitriol**

Mechanism of Hormone Action (fixed or mobile receptor mechanisms)

II. Fixed receptor (extracellular)

- **Peptide & some amino acid-derived** hormones; insulin, ADH, TSH, FSH, LH & adrenaline
- **Water-soluble (cannot pass the cell membrane)**
- **Extracellular receptors (cell surface receptors or plasma membrane receptors)**
- **Mechanism:**

1. **1st messenger: the hormone itself (hormone-receptor complex activates G-protein)**
2. **Activation of G-protein (activates certain enzyme to produce 2nd messenger)**
3. **2nd messenger (cAMP, cGMP, DAG, IP3, calcium- calmodulin)**
4. **Phosphorylation of protein kinases that modulate the hormone action**

G protein

- About 30 proteins; each one is used for a specific signal transduction.

The G protein is **heterotrimeric**; α, β and γ subunits

G-protein families and their functions	
Gα class	*Downstream signal*
Gs	Stimulates adenylate cyclase
Gi	Inhibits adenylate cyclase
Gq	Increases IP3 and intracellular calcium
Gt (Transducin)	Stimulates cGMP phosphodiesterase

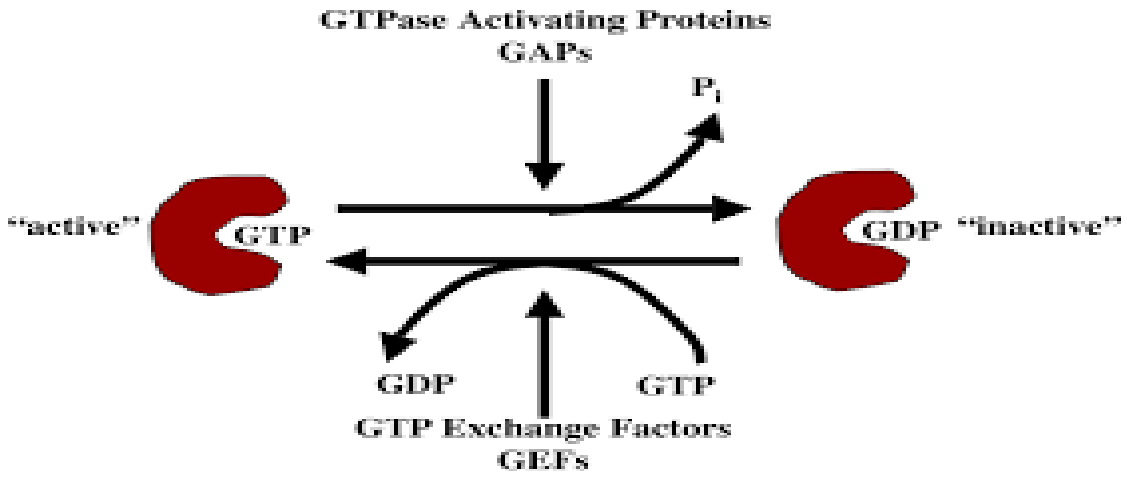
G protein

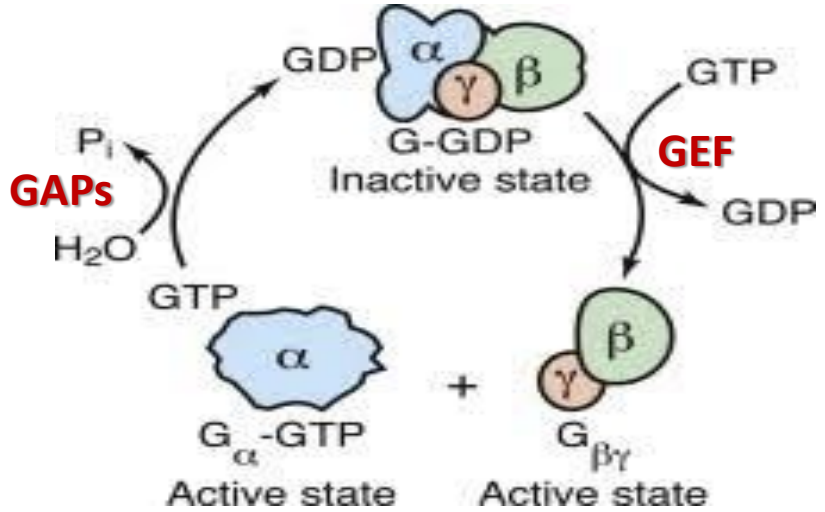
- <u>The 2 types of G protein that work on adenylate cyclase are:</u>

1. Stimulatory G protein (Gs) with αs subunit: stimulate adenylate cyclase
2. Inhibitory G protein (Gi) with αi subunit: inhibits adenylate cyclase

N.B. the stimulator and inhibitory α subunits are different but the β and γ subunits are the same.

- **The G proteins are named so, because they allow binding of GTP & GDP**
- **The GTP-GDP exchange is mediated by GEF (guanine nucleotide exchange factor)**





G protein

G protein

1. Binding of the hormone to the receptor

→→ conformational change of G protein

→→ release of GDP & binding of GTP

2. Then the βγ subunits dissociates from the α subunit

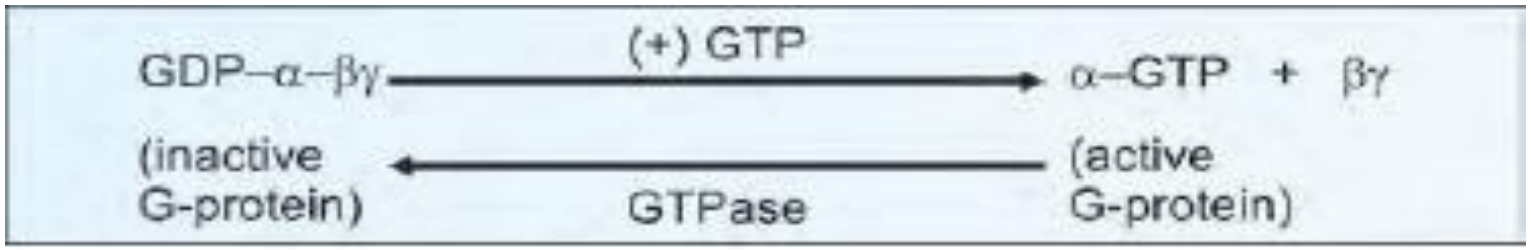
→→ activation of adenylate cyclase by GTP-Gα

3. Immediate inactivation of GTP-Gα by intrinsic GTPase activity of α subunit

GTP-Gα →(hydrolysis)→→→→→ GDP-Gα **(so activation is switched off)**

4. The α subunit re-associate with βγ subunits

N.B. The activity of adenylate cyclase is decided by the GTP-GDP exchange



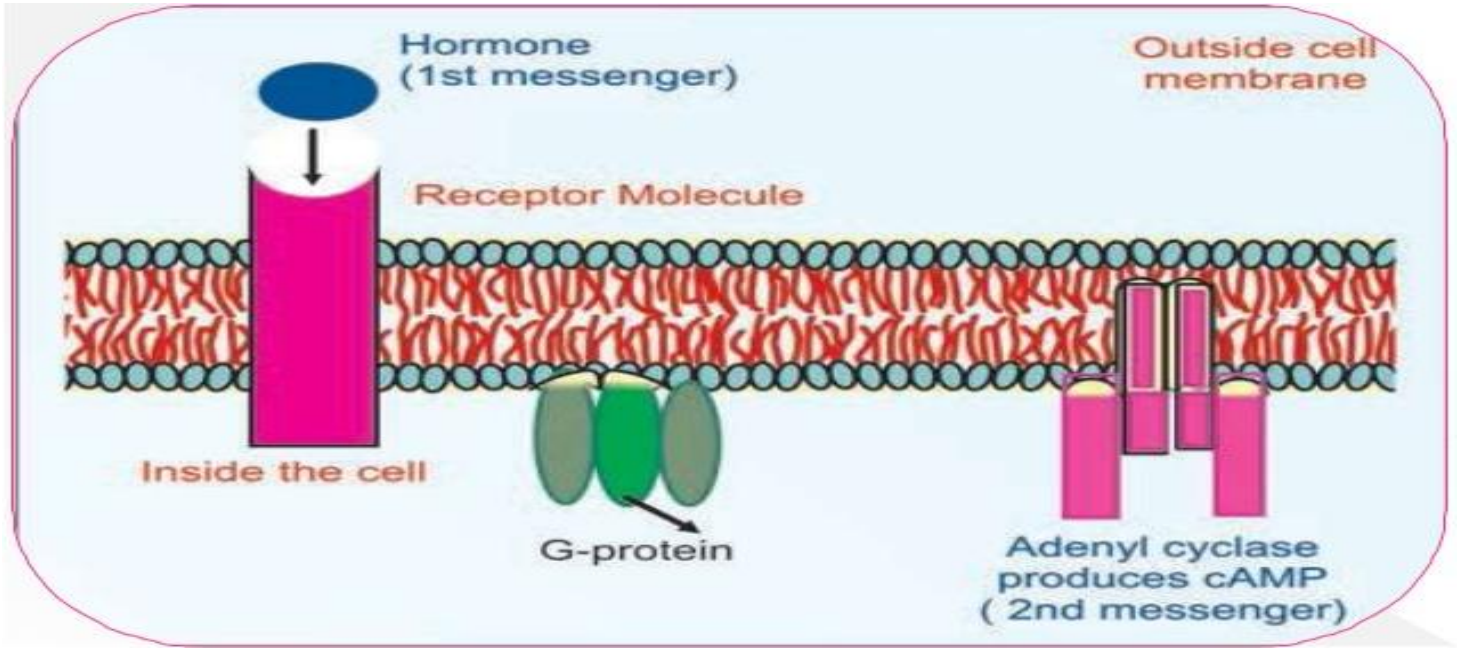
cAMP (2nd messenger)

1. Binding of hormone with the receptor →→ →
2. Hormone receptor complex →→→
3. Activates Gs-protein →→→
4. Activation of adenylate cyclase→→→
5. Release of cAMP→→→ actions

a. Activation of PKA

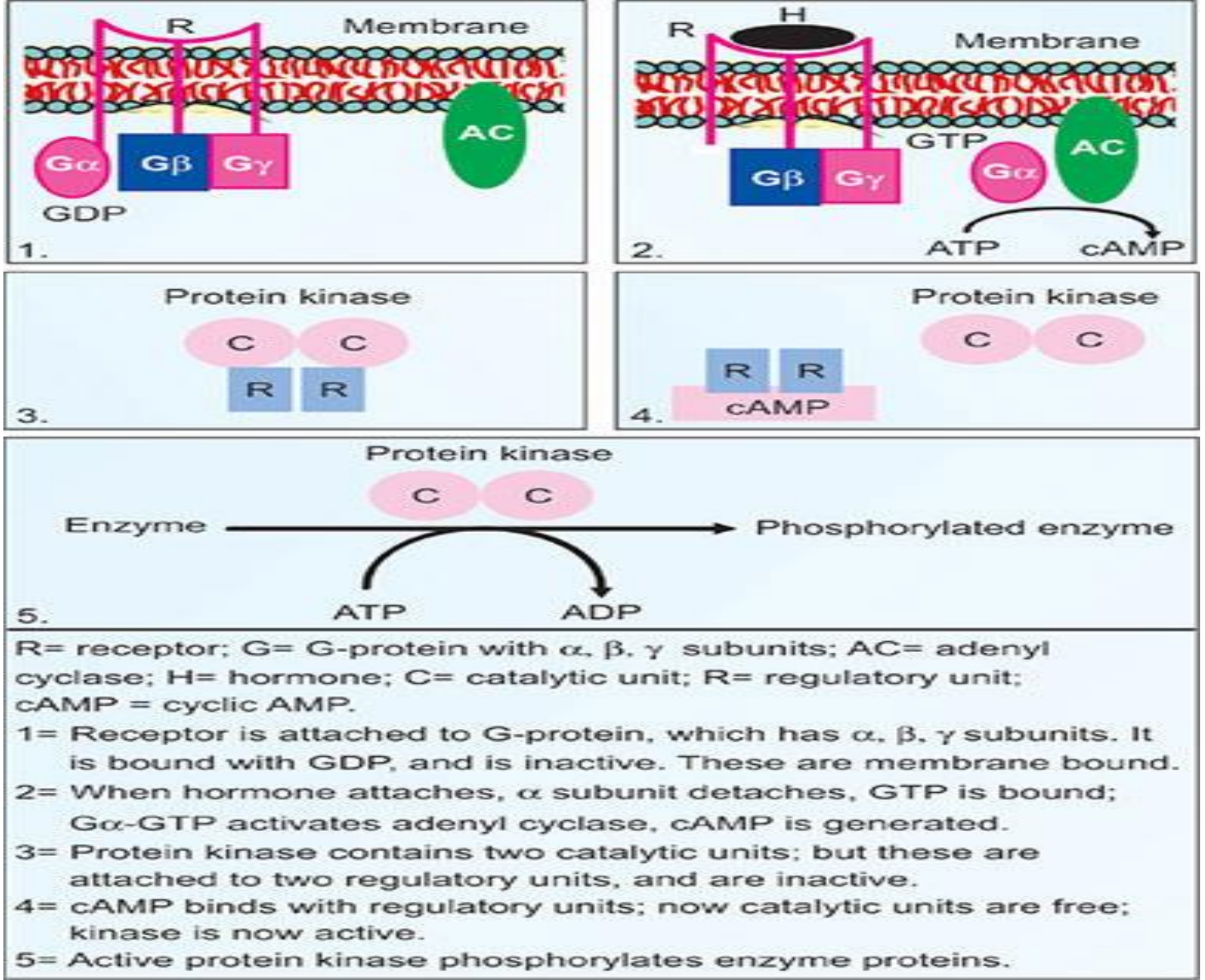
B. Phosphorylation of CREB

c. Signalling cascade via SH2 or PTB domain containing proteins




Some G proteins
activate
adenylate cyclase

cAMP (2nd messenger)



R= receptor; G= G-protein with α, β, γ subunits; AC= adenyl cyclase; H= hormone; C= catalytic unit; R= regulatory unit; cAMP = cyclic AMP.

1= Receptor is attached to G-protein, which has α, β, γ subunits. It is bound with GDP, and is inactive. These are membrane bound.

2= When hormone attaches, α subunit detaches, GTP is bound; Gα-GTP activates adenyl cyclase, cAMP is generated.

3= Protein kinase contains two catalytic units; but these are attached to two regulatory units, and are inactive.

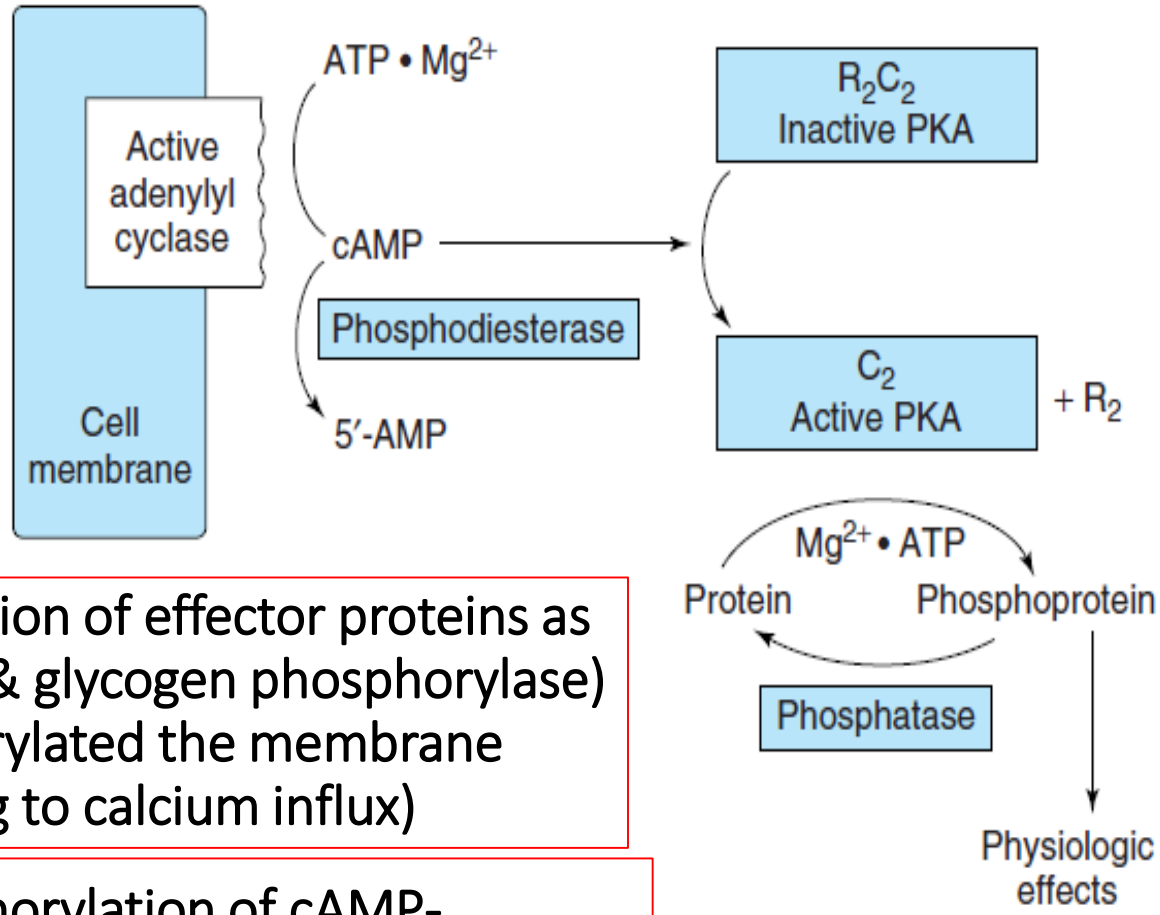
4= cAMP binds with regulatory units; now catalytic units are free; kinase is now active.

5= Active protein kinase phosphorylates enzyme proteins.

3. Release of cAMP

The cellular level of cAMP is:

- ↑ by caffeine & thyeophylline (inhibitors of PDE)
- ↓ by Insulin (activator of PDE)



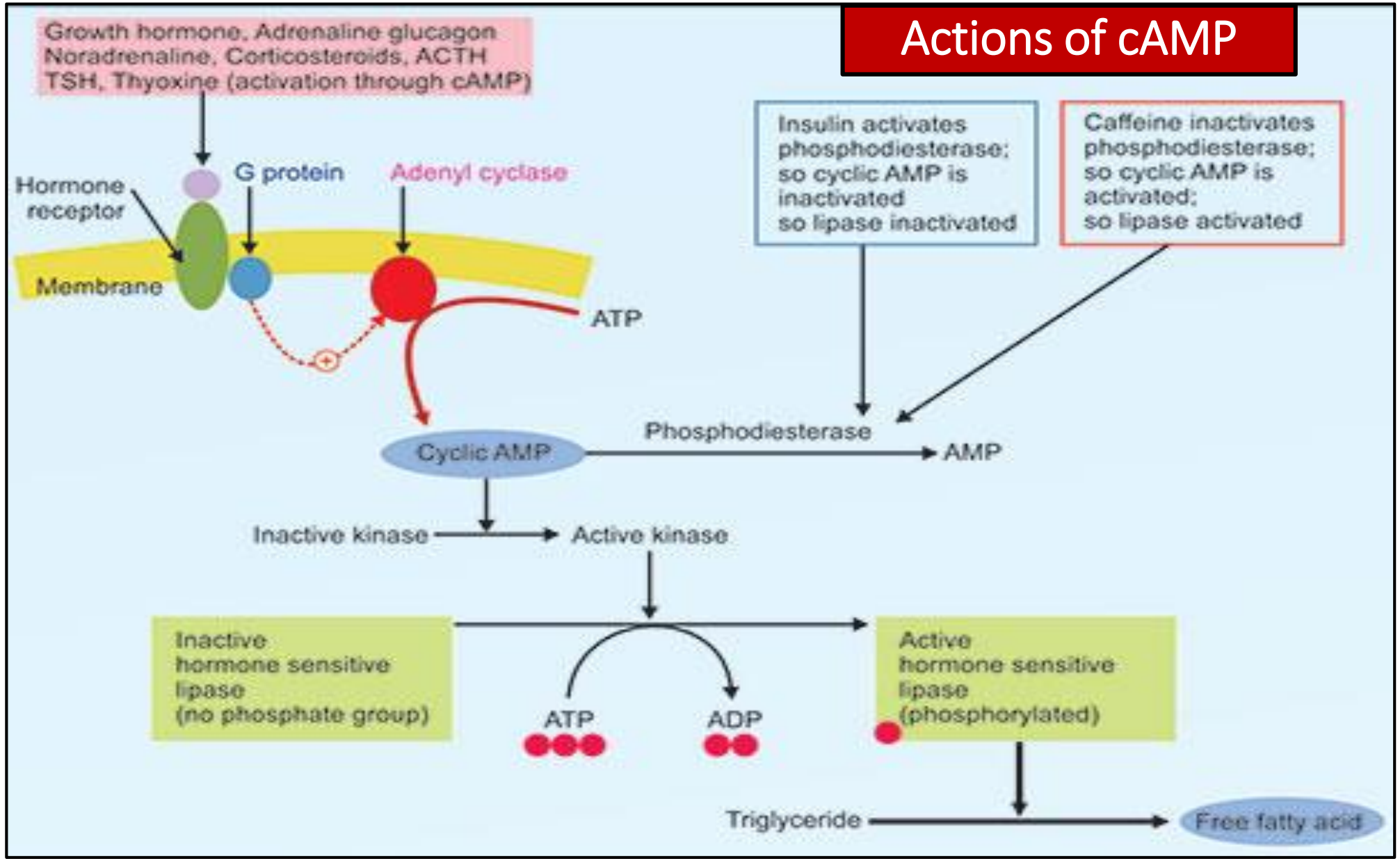
Actions of cAMP

a. Activation of PKA & phosphorylation of effector proteins as enzymes (hormone sensitive lipase & glycogen phosphorylase) & ion channels (when phosphorylated the membrane potential is modified leading to calcium influx)

b. Effect on gene expression (phosphorylation of cAMP-response element binding protein (CREB) →→ ↑ transcription

c. Role in signalling cascade mediated by adaptor or anchoring proteins as proteins with SH2 (src homology type 2) or PTB (phosphotyrosine binding) domains which localise & concentrate signalling proteins to their site of action

Actions of cAMP



Actions of cAMP

Sutherland
NP 1971
1915–1974

Epinephrine/Glucagon attaches to receptor

Cell membrane

Adenyl cyclase

ATP → Cyclic AMP + PPi

Inactive protein kinase A → Active protein kinase A

Glycogen synthase (Active) (Dephosphorylated) → (ATP / ADP) → Glycogen synthase (inactive) (Phosphorylated) **(Glycogen synthesis inhibited)**

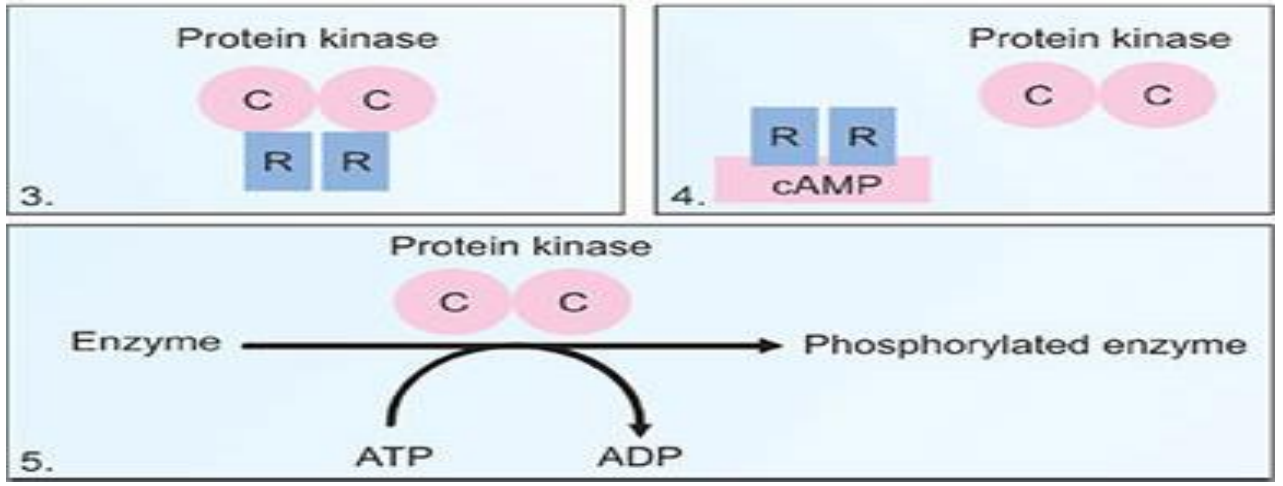
Phosphorylase kinase (inactive) (dephosphorylated) → (ATP / ADP) → **Phosphorylase kinase (active) (phosphorylated)**

Glycogen phosphorylase-b (inactive) (dephosphorylated) → (ATP / ADP) → Glycogen phosphorylase-a (active)(phosphorylated)

Glycogen (n residues) → Glycogen (n-1 units) + **Glucose -1- phosphate**

(Glycogen breakdown is favored)

Protein kinase A



Protein kinase A is a tetramer (4 subunits); 2 regulatory + 2 catalytic

- cAMP dissociates the tetramer; the catalytic subunit is now free (active)
- More than 1000 protein kinases are known

Examples of hormone sensitive protein kinases:

1. cAMP-dependent protein kinases
2. Epidermal growth factor-dependent tyrosine kinase
3. Insulin–dependent tyrosine kinase
4. Serine/thereonine kinases

Protein kinase
Protein kinase A
Protein kinase G
Cam kinase
Protein kinase C
Protein kinase B
Tyrosine kinase
Janus kinase (JAK)

cGMP (2nd messenger)

- cGMP is formed by **guanyl cyclase** & degraded by membrane-bound **PDE**
- cGMP is the **2nd hormone messenger** for:

1. **Visual signal transduction**
2. **Contractile function of smooth muscles**
3. **Maintenance of blood volume**
4. **Vasodilatation**

- The G protein for cGMP is called **transducin (Gt)**
- cGMP activates cGMP-dependent **protein kinase G** which phosphorylates effector proteins that regulate Ca- dependent contraction by modulating Ca influx.
- **The activity of guanyl cyclase is increased** by nitroprusside, nitroglycerine, sodium nitrite, atriopeptides (from the atria) & sildenafil (Viagra). All these compounds are potent vasodilators, triggers rapid & sustained smooth muscle relaxation.

Calcium 2nd hormone messenger

- **Calcium is an important regulator of cell function like:**

1. Muscle contraction
2. Secretion of hormones & neurotransmitters
3. Cell division
4. Gene regulation

- **There 3 types of calcium transport systems:**

1. Voltage gated calcium channels
2. Sodium/calcium antiporter
3. **Calcium transporting ATPase**

When intracellular Ca increases, it binds and activates several regulatory proteins

Calmodulin mediates the regulatory action of calcium

Release of calcium

- The **calcium transporting ATPase** accumulate calcium within the lumen of sarcoplasmic reticulum of muscle.
- The accumulated calcium ions can be released into the cytoplasm by **IP3-gated calcium channels or ligand-gated calcium release channels (ryanodine receptors)**.
- When cytosolic calcium increases, it binds & activates several regulatory proteins
- Calmodulin present in various tissues, modulates the action of calcium: calcium binding →→→ **conformational changes in calmodulin** →→→ interaction with **CAM kinases**, phosphatases, nitric oxide synthase (NOS),…
- These kinases **phosphorylate** many proteins that alter the cell function

N.B. Calmodulin kinase II autophosphorylates, so that its activity is maintained.

Release of calcium

- Intracellular Ca acts as 2nd messenger (either independent or in conjunction with cAMP)
- **<u>Hormones increase the intracellular calcium by:</u>**

1. Increased cell membrane permeability
2. Ca^{2+} – H^{+} ATPase
3. Release from intracellular stores
4. Calmodulin

Calmodulin

- Calmodulin is 17 kDa protein with structural & functional similarity with troponin C of muscle.
- It is a calcium-dependent regulatory protein
- It has 4 calcium binding sites

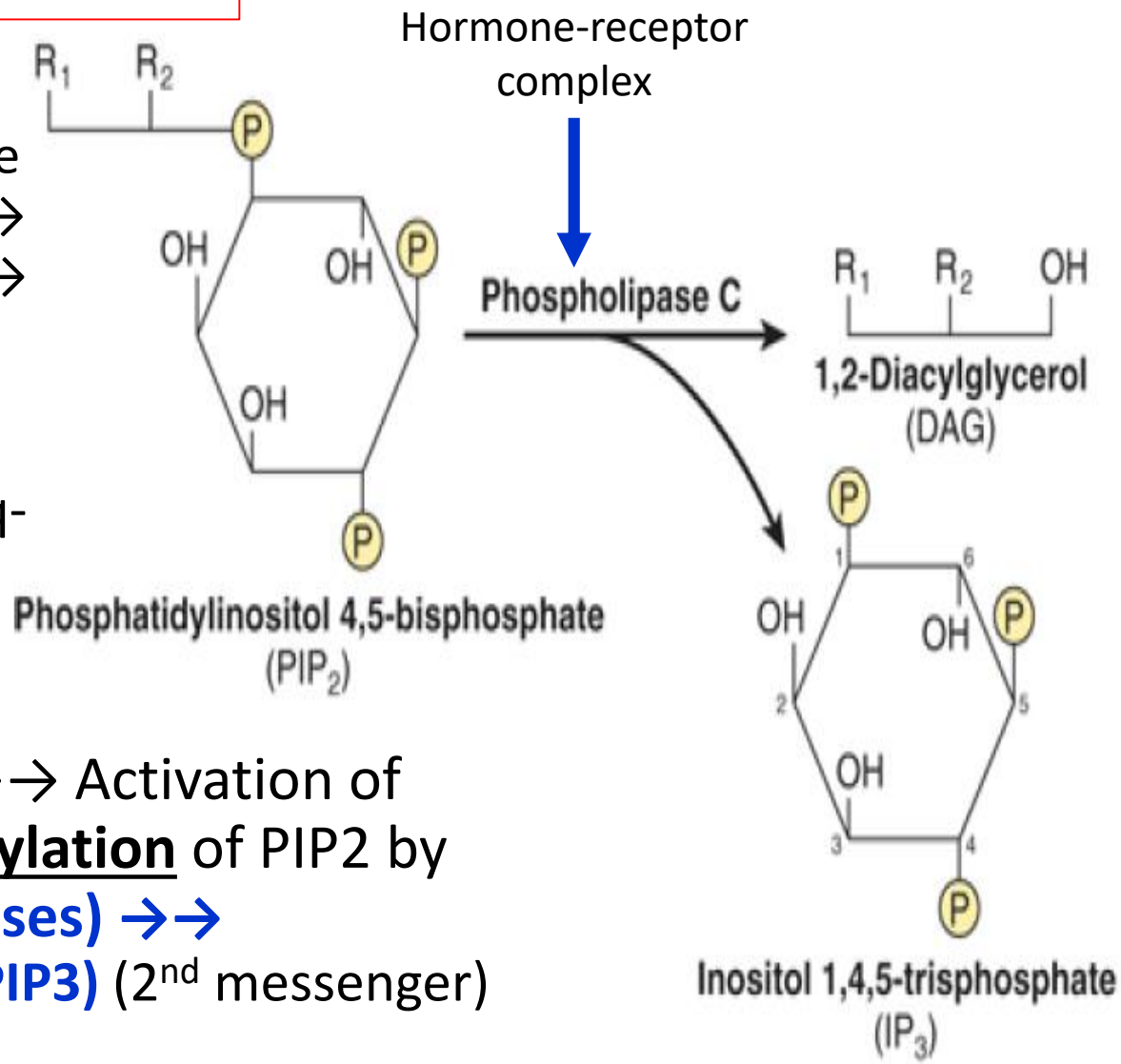
Enzymes regulated by calmodulin:

1. **Calcium-dependent protein kinases**
2. **Adenylate cyclase**
3. **Ca^{+2} - Mg^{+2} ATPase**
4. **Nitric oxide synthase (NOS)**
5. **Phosphodiestrase**
6. **Phosphorylase kinase**

Phospholipase C → DAG and IP3 (2nd hormone messengers)

DAG and IP3 (2nd hormone messengers)

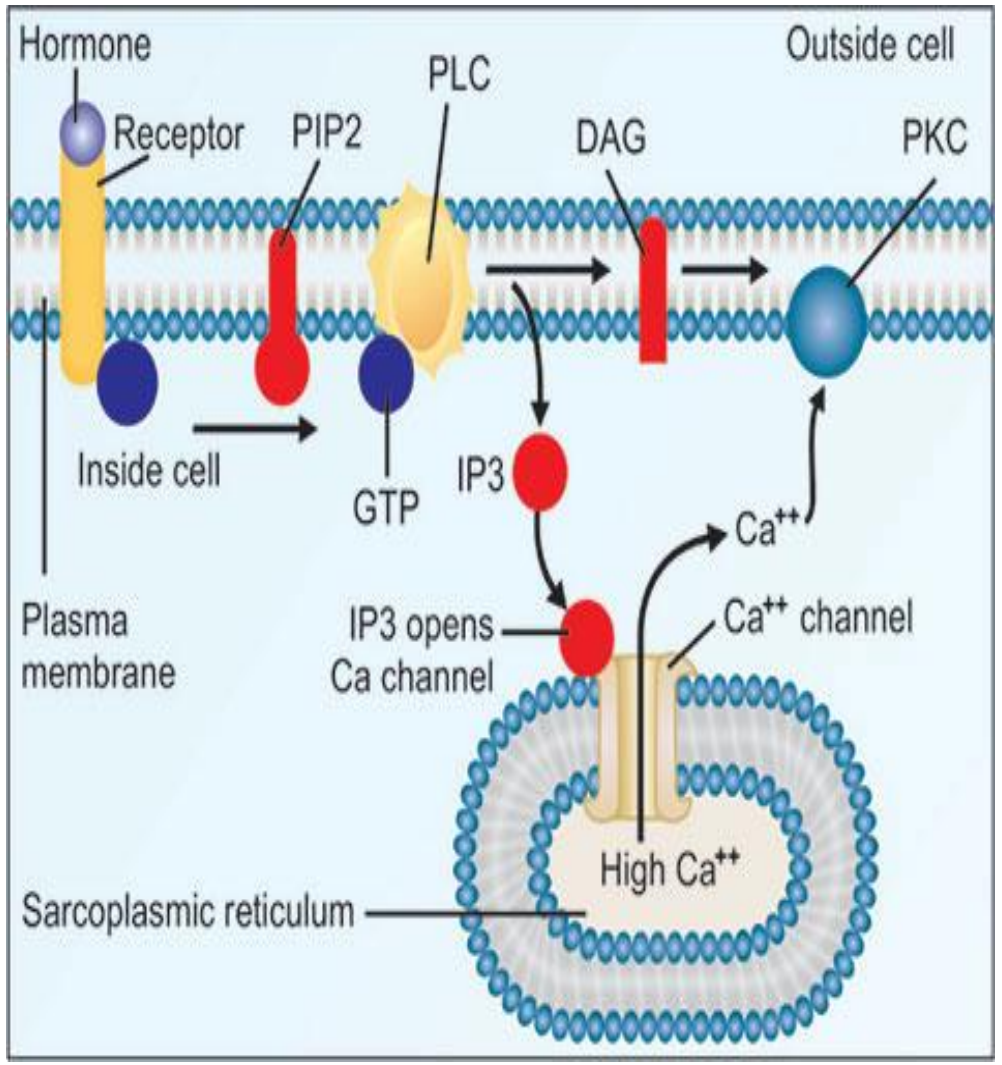
- Hormone as serotonin bind cell membrane receptor →→ activation of Gq-protein →→ **hydrolysis** of PIP2 by **Phospholipase C** →→ DAG & IP3 (both act as 2nd messengers)
- DAG activates **protein kinase C (PKC)**
- Phospholipase C may be activated by Gq-protein or Ca^{2+} ions



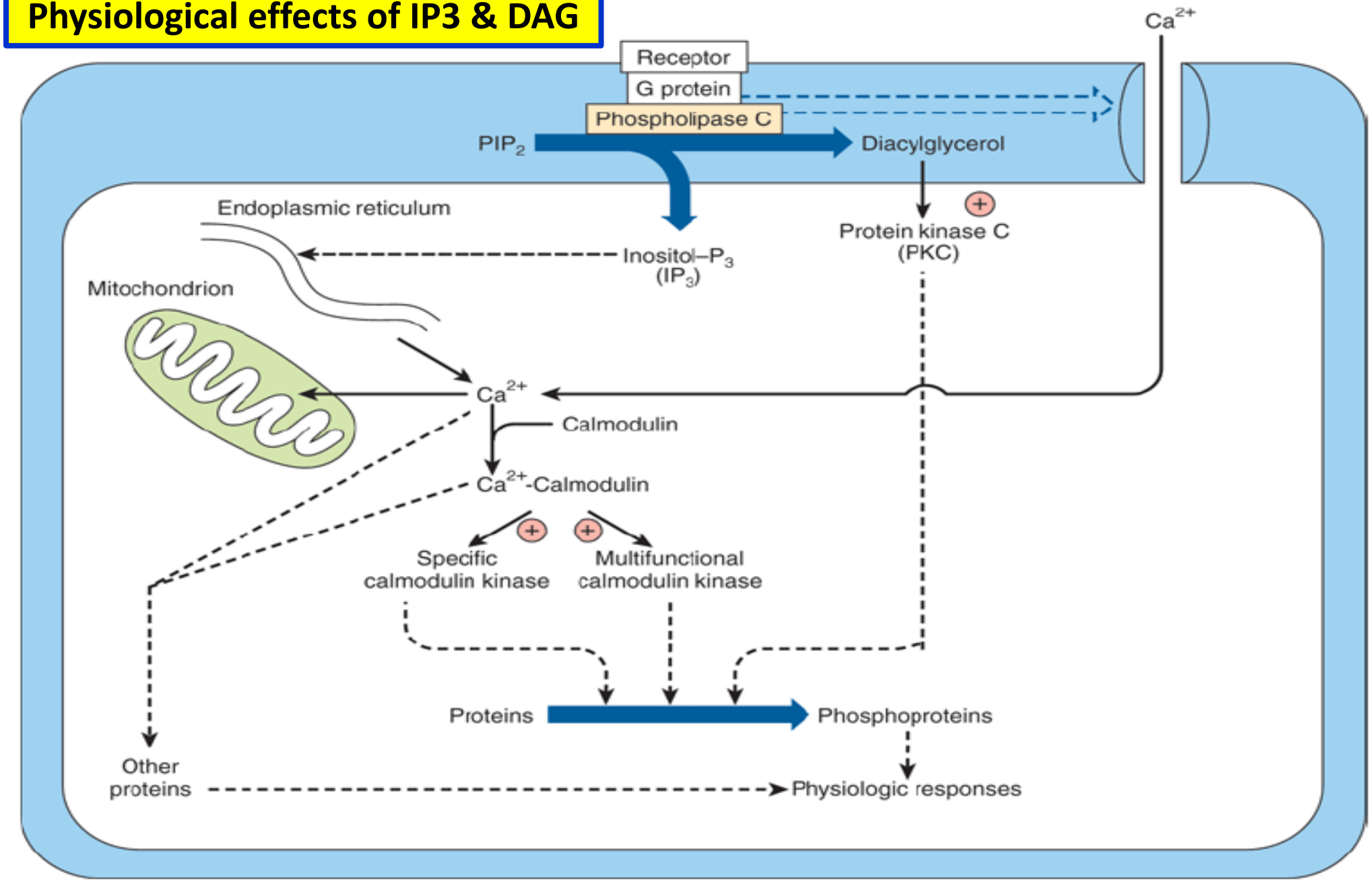
N.B. Cytokines bind cell membrane →→ Activation of protein kinase B (PKB) →→ **Phosphorylation** of PIP2 by **phosphoinositide 3-kinases (PI3-kinases) →→ phosphoinositide 3, 4, 5 triphosphate (PIP3)** (2nd messenger)

DAG and IP3 (2nd hormone messengers)

- DAG activates **protein kinase C** & increases its affinity for Ca^{2+} ions. **PKC** phosphorylates certain target serine / threonine kinases including transcription factors, transporters & ion channels.
- IP3 help calcium release from its intracellular stores as ER.
- Increases intracellular calcium triggers certain processes as smooth muscle contraction, exocytosis and glycogen breakdown
- The actions of DAG & IP3 are **synergistic**



Physiological effects of IP3 & DAG



Protein kinases

Signal molecule	*Second messenger*	*Protein kinase*	*Type*
Hormones (glucagon, epinephrine, HSL, ADH, glycogen, ACTH, PTH, etc.	cAMP	Protein kinase A	Ser/Thr
Nitric oxide, ANP	cGMP	Protein kinase G	Ser.Thr
Serotonin, TRH	Calcium, IP3	Cam kinase	Ser/Thr
Oxytocin, PDGF	DAG	Protein kinase C	Ser/Thr
Growth factors, cytokines	PIP3	Protein kinase B	Ser/Thr
Insulin and insulin like growth factors	RTK in receptor	Tyrosine kinase	Tyr
GH, prolactin, cytokines	RTK in receptor	Janus kinase (JAK)	Tyr

Any Questions

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