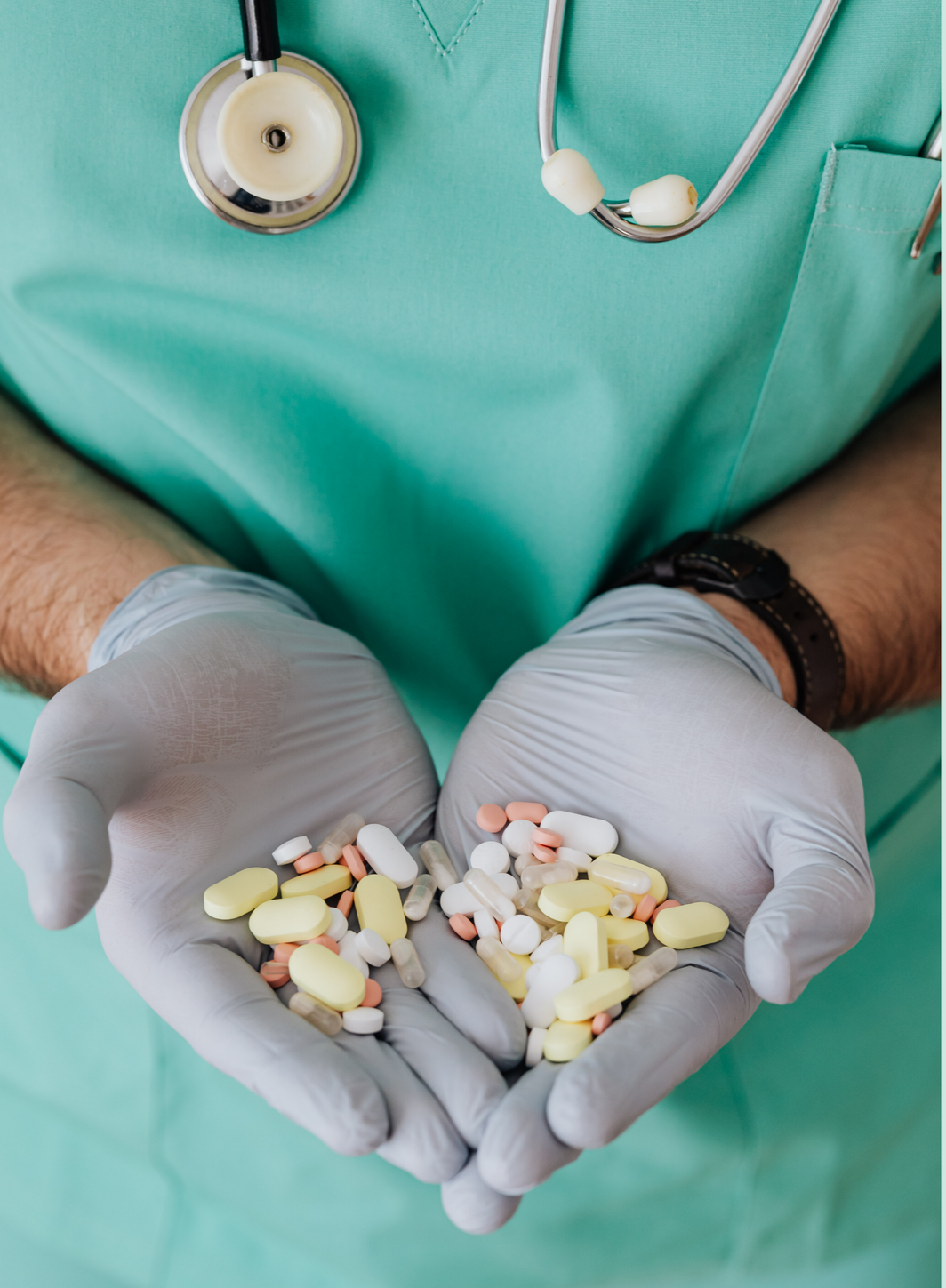

Sheet# 5

PASSION ACADEMIC TEAM YU – MEDICINE

Endocrine system

Lec. Title : Hormone Action & Signal Transduction (Part 1)

Written By : Ahmad Haider

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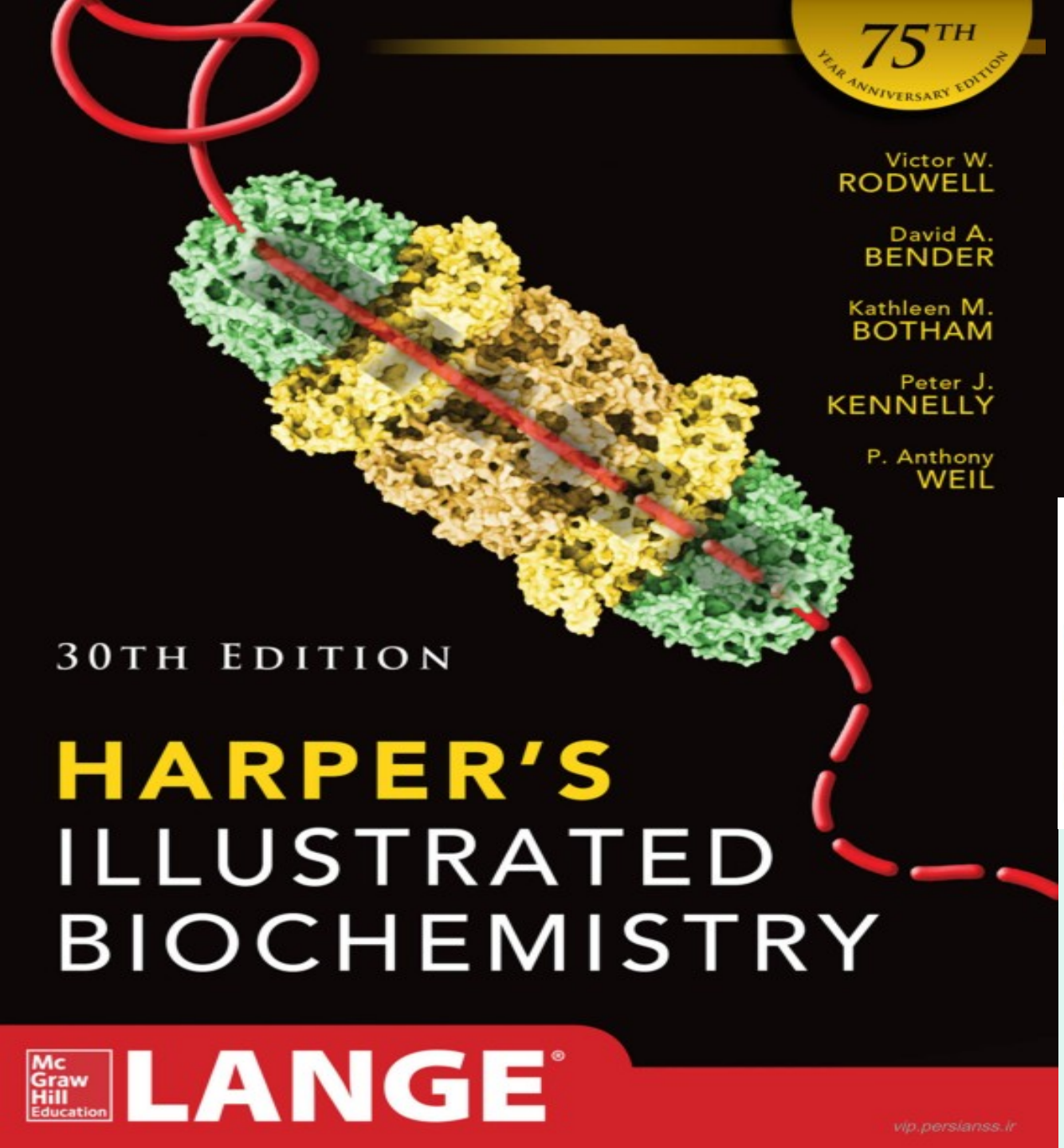


CHAPTER

Hormone Action & Signal Transduction

42

CHAPTER

Hormone Action & Signal Transduction

42

HORMONES TRANSDUCE SIGNALS TO AFFECT HOMEOSTATIC MECHANISMS

The stimulus can be a challenge or a threat to:

1. Organism.
2. Organ.
3. Integrity of a single cell within that organism.
 as in unicellular organisms that depend on responsiveness for stimulus like light or heat to survive

Signal transduction: This means how we transfer the signal from the effector molecules to inside the cells.

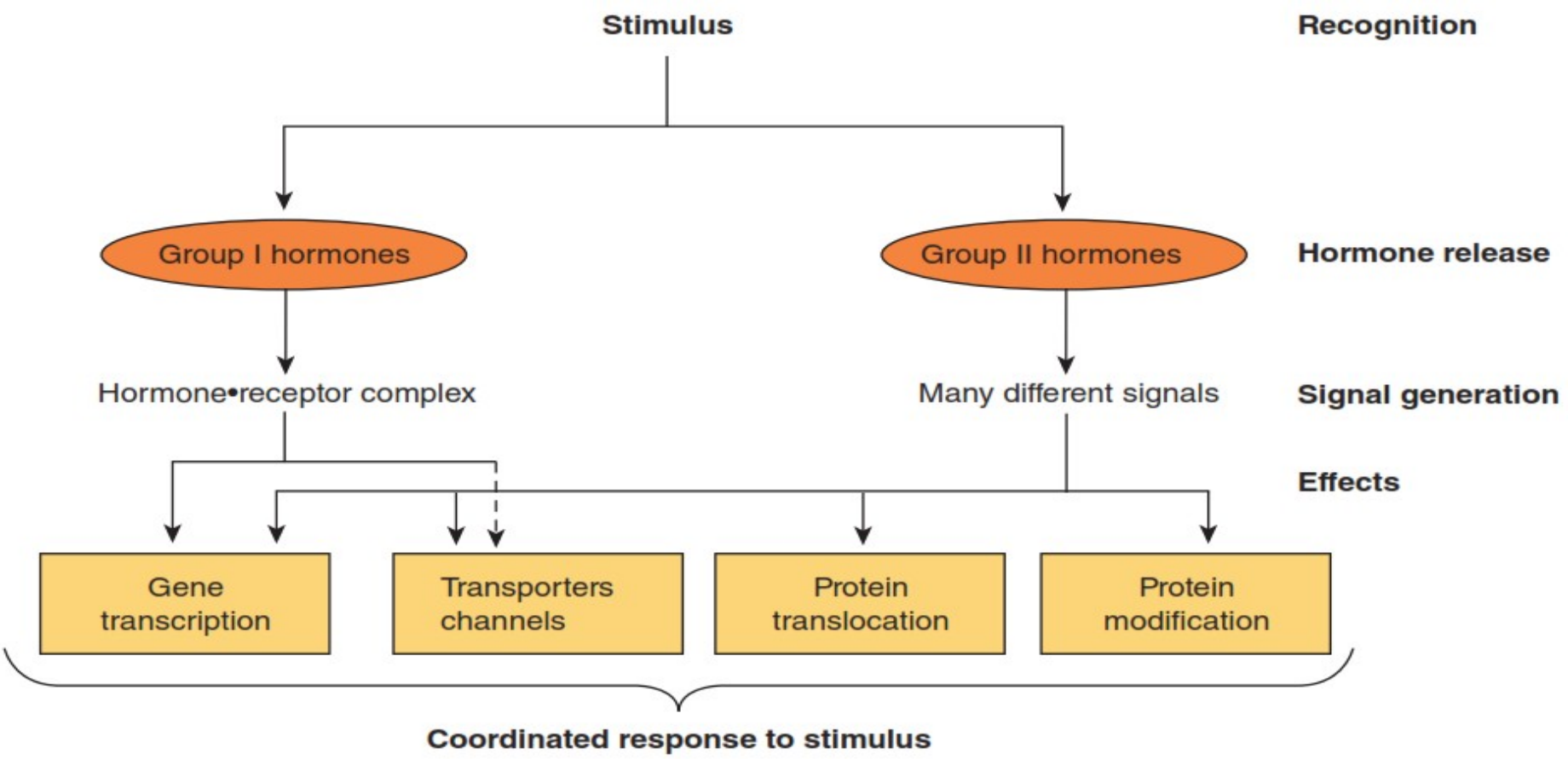


FIGURE 42–1 Hormonal involvement in responses to a stimulus. A challenge to the integrity of the organism elicits a response that includes the release of one or more hormones. These hormones generate signals at or within target cells, and these signals regulate a variety of biologic processes that provide for a coordinated response to the stimulus or challenge. See Figure 42–8 for a specific example.

group 1 hormones: lipophilic hormones that have a role in gene regulation (activating or inhibiting).

Or may bind to the internal receptor and affect transporter channels of ions, minerals or other molecules.

group 2 hormones: hydrophilic hormones that bind a membrane receptor that transfer the signal to inside the cell to be translated as gene regulation (activating or inhibiting) or protein production, translocation ...etc; to give the cellular response depending on the organ, organism, and the tissue affected.

SIGNAL GENERATION

The Ligand-receptor Complex Is the Signal for Group I hormones

Lipophilic group I hormones diffuse through the plasma membrane of all cells but only encounter their specific, high affinity **intracellular receptors** in target cells.

A given hormone directly affects <1% of the genes, mRNA, or proteins in a target cell.

microRNAs: are small fragments of RNA in average 20 polypeptides that have been implicated in mediating some of the diverse actions of hormones and regulating genes mostly inhibition like crispers.

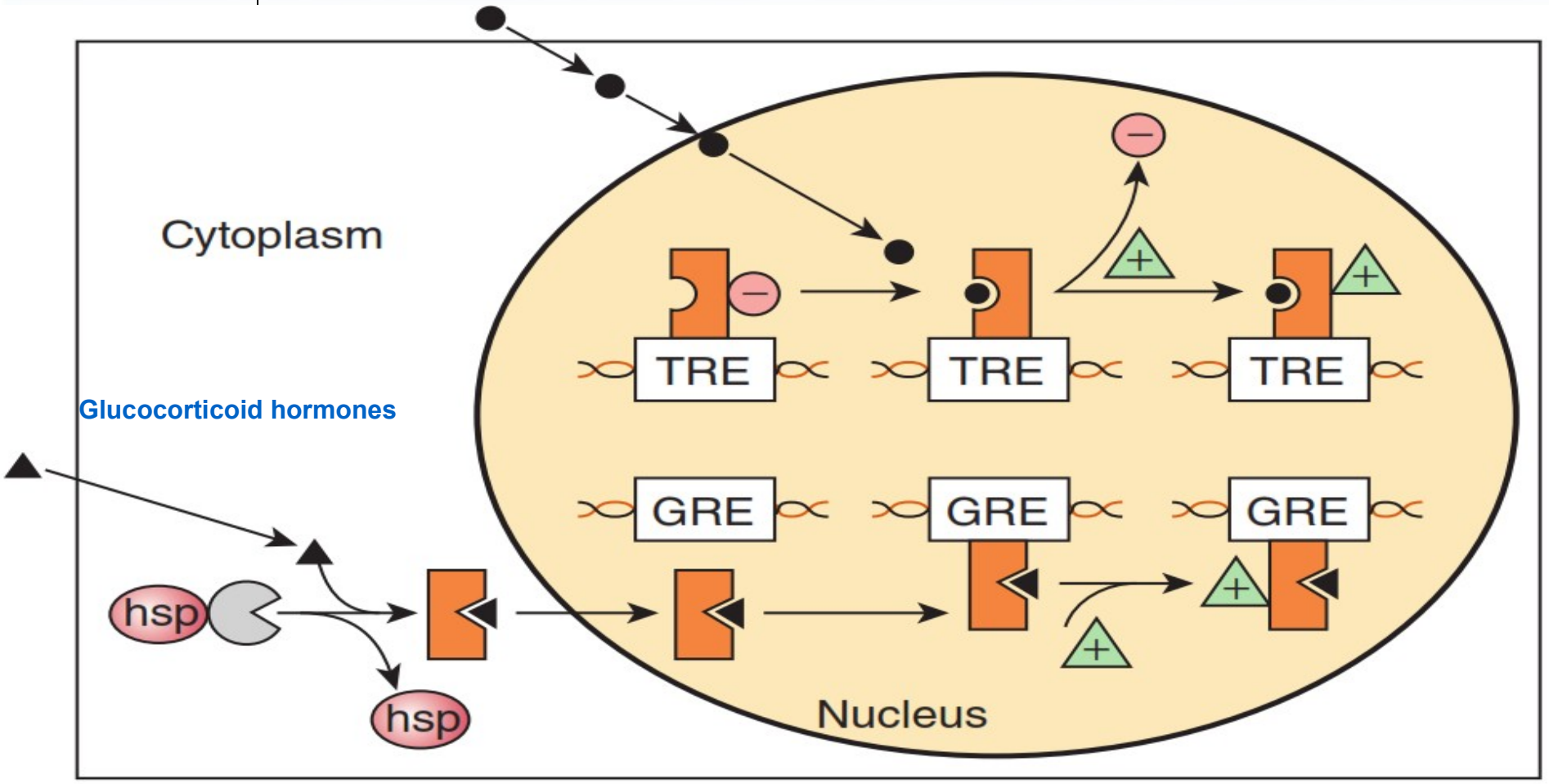


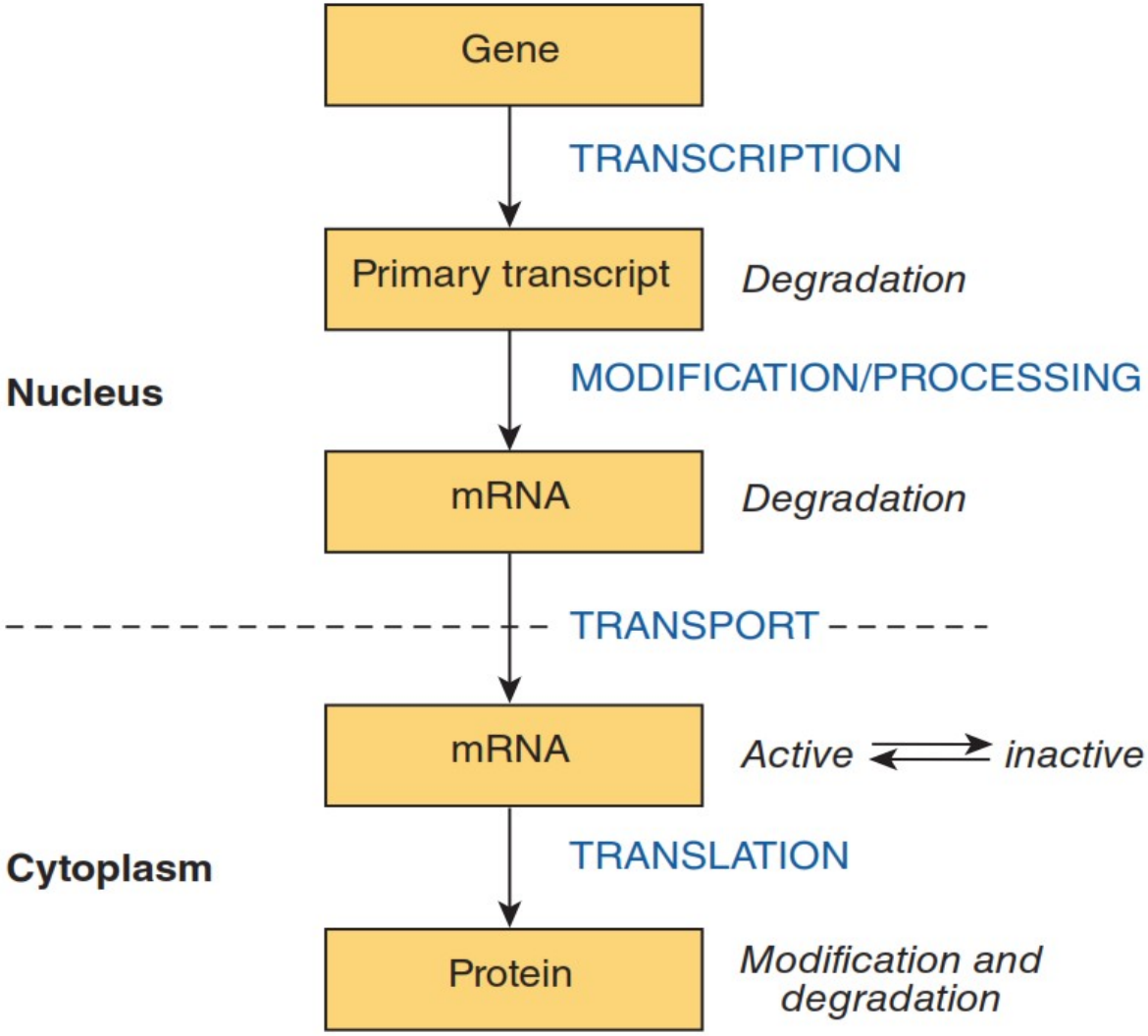
FIGURE 42–2 Regulation of gene expression by two different group I hormones, thyroid hormone and glucocorticoids.

- group 1 hormones need two parts to act, the ligand and the receptor (ligand-receptor complex) unlike group 2 hormone in which binding of ligand to the surface receptor starts a series of signal transducers and whatever happens to the ligand it's no more important.

- group 1 hormones have two types of receptors:
- 1. in the nucleus: binding of the ligand cause dissociation of the inhibitory molecule and forming of the ligand-receptor complex that binds to the gene-regulating element(RE) to regulate gene transcription mainly. ex. thyroid and retinoid hormones.

- 2. in the cytoplasm: binding of the ligand cause dissociation of the inhibitory molecule (HSP) and forming of the ligand-receptor complex that's transferred to the nucleus and binds to the gene-regulating element(RE) to regulate gene transcription mainly. ex. glucocorticoids

Hormones can affect any of the steps involved and can affect the rates of processing, degradation or modification of the various products.



IGURE 42–3 The "information pathway". Information flows om the gene to the primary transcript to mRNA to protein. Hormones

- Hormones apply their effect by degradation or inactivation of the products in the process of gene transcription or by affecting the processes of forming these products.

GROUP II
(PEPTIDE & CATECHOLAMINE) HORMONES HAVE MEMBRANE RECEPTORS & USE INTRACELLULAR MESSENGERS

have a short plasma half-life

G protein–Coupled receptors

These receptors typically have seven hydrophobic plasma membrane-spanning domains.

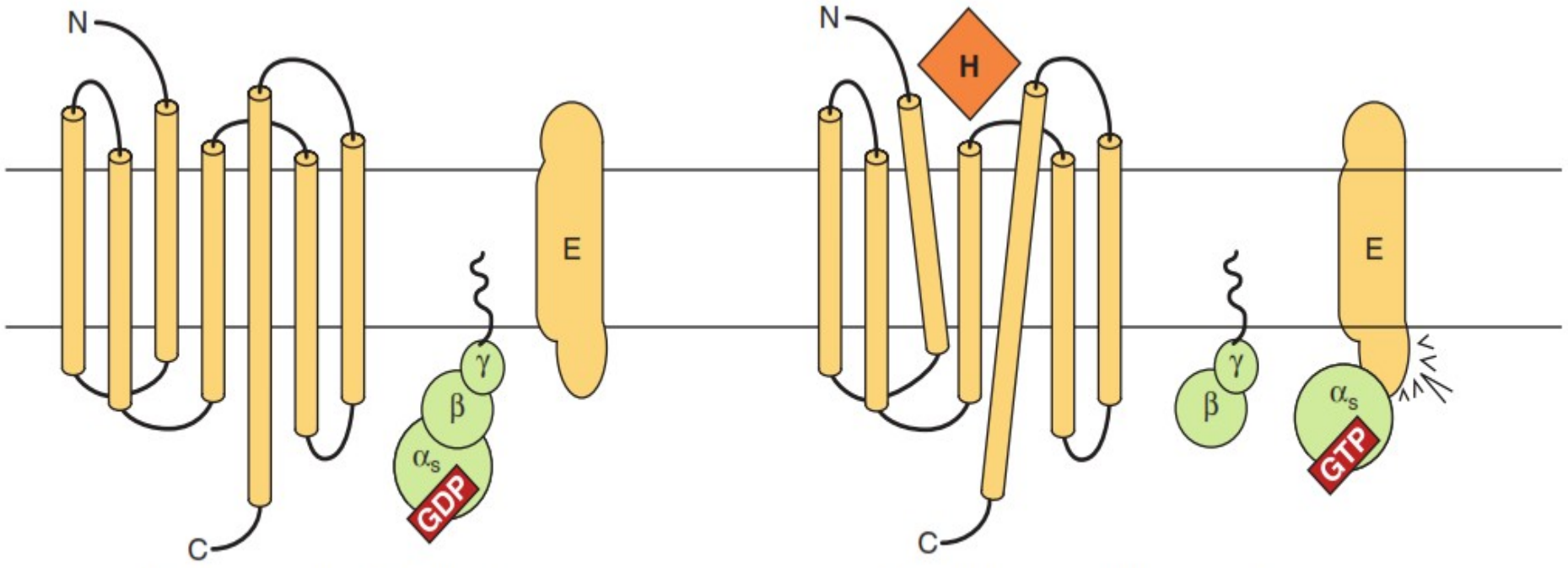


FIGURE 42–4 Components of the hormone receptor–G protein effector system. Receptors that

cAMP Is the Intracellular Signal for Many Responses

Adenylyl Cyclase

Protein Kinase

Phosphoproteins

Phosphodiesterases

Phosphoprotein Phosphatases

TABLE 42–2 Subclassification of Group II.A Hormones

Hormones That Stimulate Adenylyl Cyclase (H_s)	Hormones That Inhibit Adenylyl Cyclase (H_i)
ACTH	Acetylcholine
ADH	α_2-Adrenergics
β-Adrenergics	Angiotensin II
Calcitonin	Somatostatin
CRH	
FSH	
Glucagon	
hCG	
LH	
LPH	
MSH	
PTH	
TSH	

TABLE 42–3 Classes and Functions of Selected G Proteins[a]

Class or Type	Stimulus	Effector	Effect
G_s			
α_s	Glucagon, β-adrenergics	↑Adenylyl cyclase	Glyconeogenesis, lipolysis, glycogenolysis
		↑Cardiac Ca^{2+}, Cl^-, and Na^+ channels	Olfaction
α_{olf}	Odorant	↑Adenylyl cyclase	
G_i			
$\alpha_{i\text{-}1,2,3}$	Acetylcholine, α_2-adrenergics	↓Adenylyl cyclase	Slowed heart rate
		↑Potassium channels	
	M_2 cholinergics	↓Calcium channels	
α_o	Opioids, endorphins	↑Potassium channels	Neuronal electrical activity
α_t	Light	↑cGMP phosphodiesterase	Vision
G_q			
α_q	M_1 cholinergics		
	α_1-Adrenergics	↑Phospholipase C-β1	↓Muscle contraction and
α_{11}	α_1-Adrenergics	↑Phospholipase C-β2	↓Blood pressure
G_{12}			
α_{12}	Thrombin	Rho	Cell shape changes

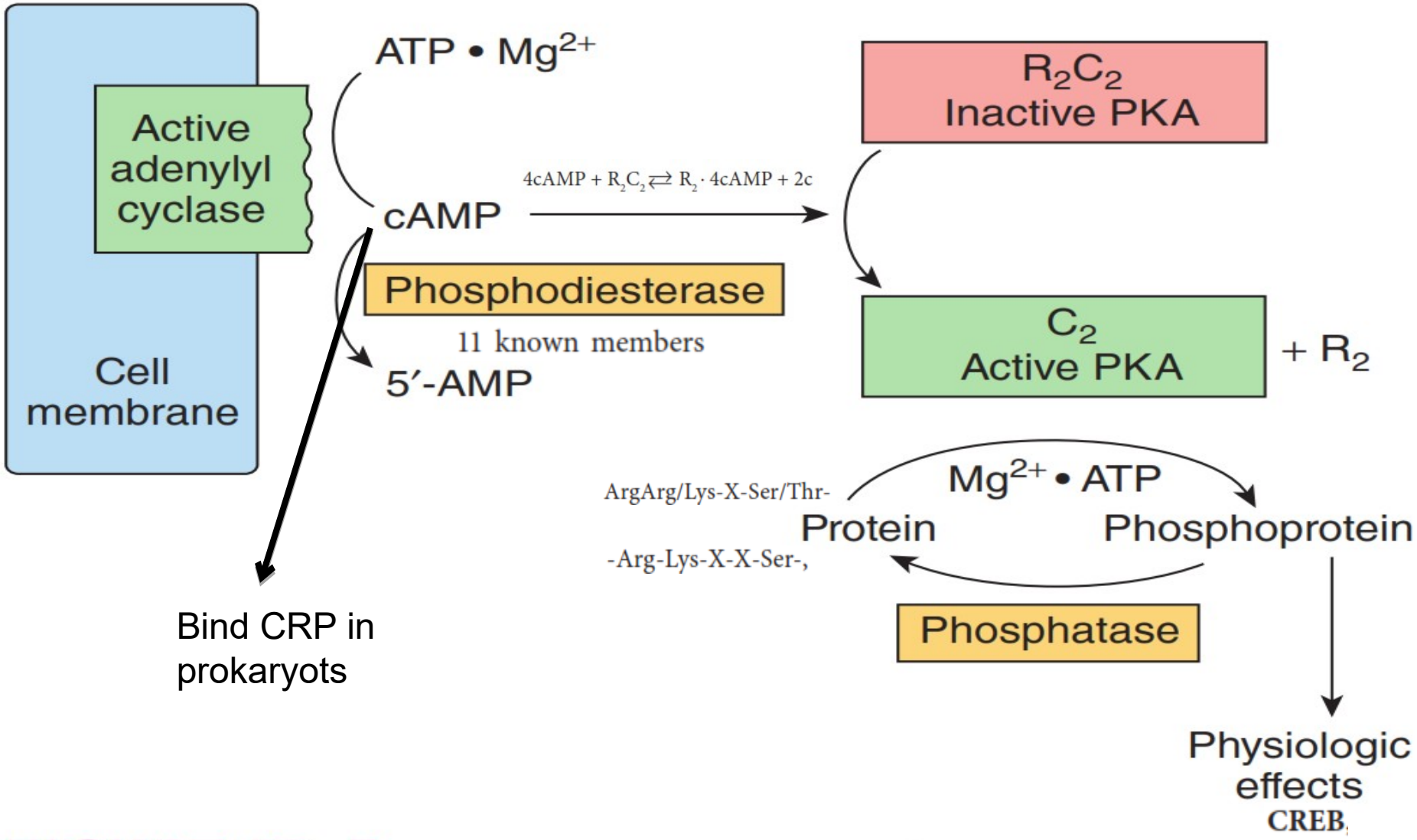


FIGURE 42–5 Hormonal regulation of cellular processes

- After activation of adenylyl cyclase CAMP is formed from ATP that converts PKA into the active form by dissociation of regulatory R2 and activation of catalytic C2 domains then activated PKA will phosphorylate special proteins using Mg+2 and ATP to give the cellular response.
- CAMP is degraded by phosphodiesterase.
- Adenylyl Cyclase, Protein Kinase, Phosphoproteins, Phosphodiesterases, Phosphoprotein Phosphatases are the steps occurring after activation of the Gs receptor _adenylyl Cyclase pathway.

cGMP Is also an Intracellular Signal

Cyclic GMP is made from GTP by the enzyme guanylyl cyclase, which exists in soluble and membrane-bound forms.

Formed by:

The atriopeptins, a family of peptides produced in cardiac atrial tissues, cause natriuresis, diuresis, vasodilation, and inhibition of aldosterone secretion.

Other stimulators: nitroprusside, nitroglycerin, nitric oxide, sodium nitrite, and sodium azide, all cause smooth muscle relaxation and are potent vasodilators.

Inhibitors: phosphodiesterase (the drug sildenafil [Viagra])

Several hormones act Through Calcium or phosphatidylinositols

Calcium Metabolism

Intracellular = 0.05 to 10 µmol/L.

There are three ways of changing cytosolic Ca^{2+} levels:

(1) Certain hormones by binding to receptors that are themselves Ca^{2+} channels, enhance membrane permeability to Ca^{2+}, and thereby increase Ca^{2+} influx.

(2) Hormones also indirectly promote Ca^{2+} influx by modulating the membrane potential at the plasma membrane. Membrane depolarization opens voltage-gated Ca^{2+} channels and allows for Ca^{2+} influx.

(3) Ca^{2+} can be mobilized from the endoplasmic reticulum, and possibly from mitochondrial pools.

The first two mechanisms depend on extracellular Ca+2 but the third one on intracellular Ca+2.

Calmodulin

Is homologous to the muscle protein troponin C in structure and function.

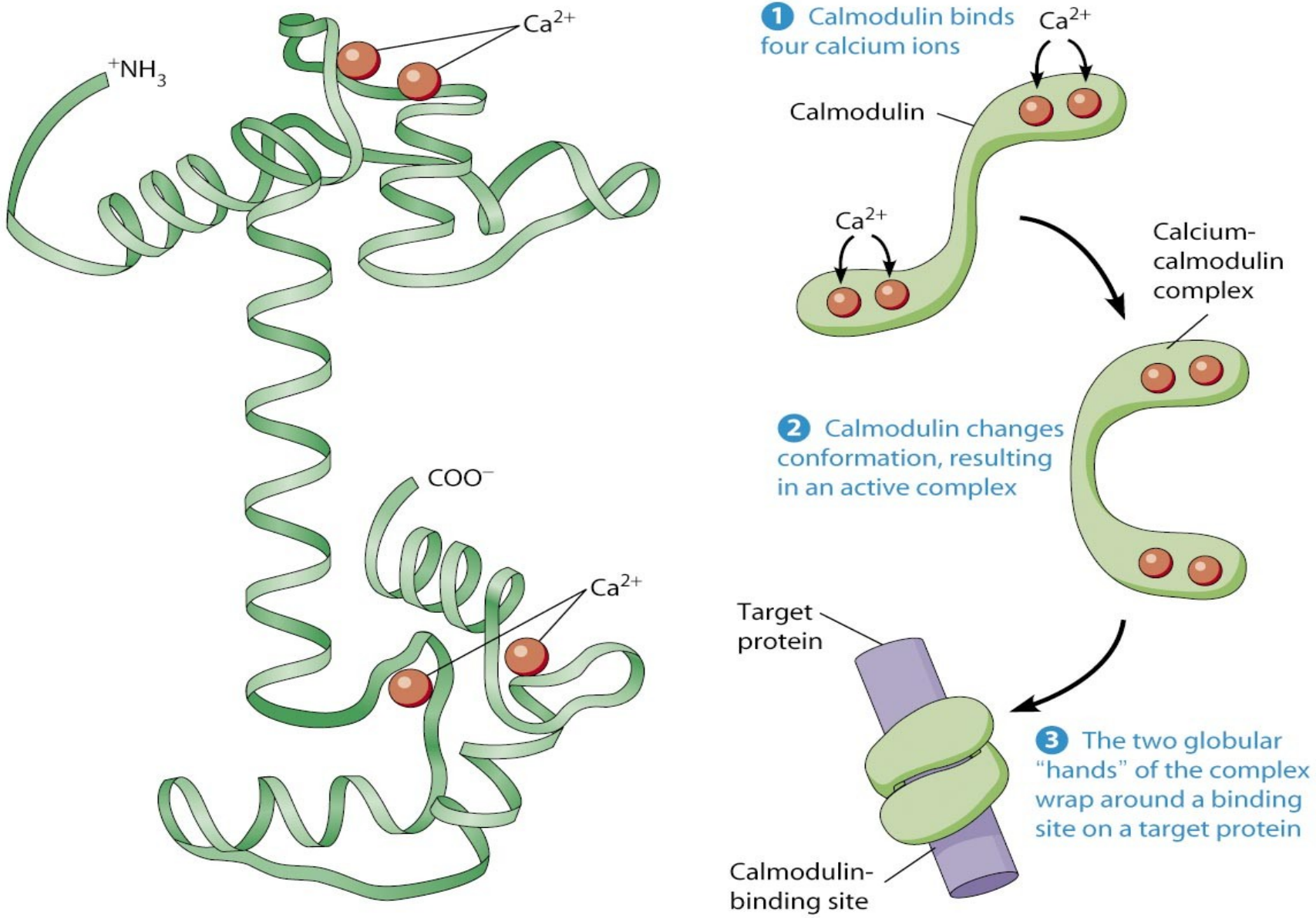
Binding of 4 Ca will lead to activate enzymes and ion channels.

Regulates the activity of many structural elements in cells:

Actin-myosin complex of smooth muscle.

Various microfilament-mediated processes in noncontractile Cells.

Cell motility, cell conformation changes, mitosis, granule release, and endocytosis.



(a) Structure of Ca^{2+}-calmodulin complex

(b) Function of Ca^{2+}-calmodulin complex

Calcium Is a Mediator of Hormone Action

How they found this:

(1) Blunted by Ca^{2+}-free media or when intracellular calcium is depleted.

(2) Can be mimicked by agents that increase cytosolic Ca^{2+}

(3) Influences cellular calcium flux.

Number of critical metabolic enzymes are regulated by Ca, phosphorylation, or both.

These include glycogen synthase, pyruvate kinase, pyruvate carboxylase, glycerol3-phosphate dehydrogenase, and pyruvate dehydrogenase.

Phosphatidylinositide Metabolism Affects Ca^{2+}-Dependent Hormone Action

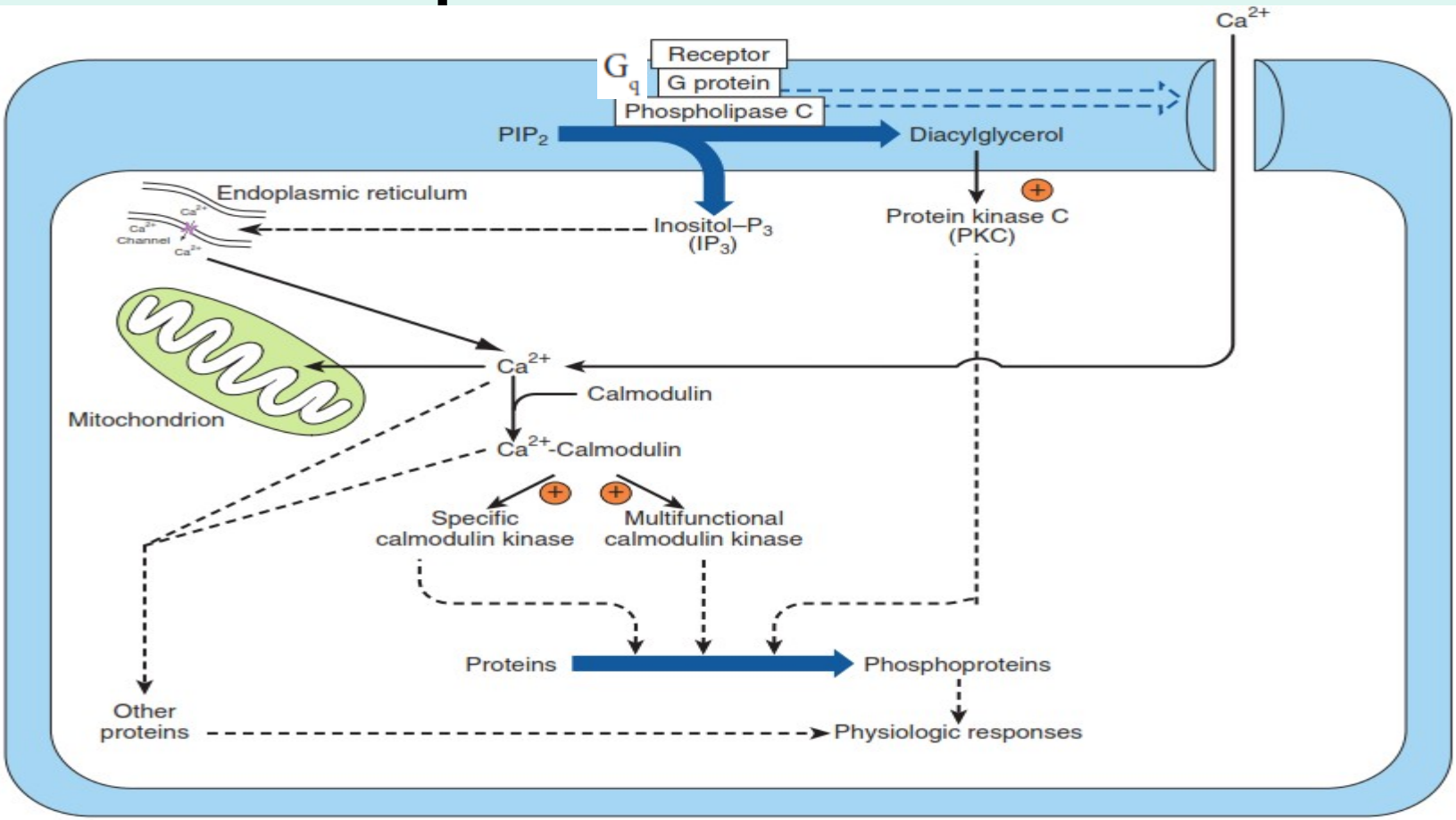


FIGURE 42–6 **Certain hormone-receptor interactions result in the activation of phospholipase C (PLC).** PLC activation appears to involve a specific G protein, which also may activate a calcium channel. Phospholipase C generates inositol trisphosphate (IP_3), which liberates stored intracellular Ca^{2+}, and diacylglycerol (DAG), a potent activator of protein kinase C (PKC). In this scheme, the activated PKC phosphorylates specific substrates, which then alter physiologic processes. Likewise, the Ca^{2+}–calmodulin complex can activate specific kinases, two of which are shown here. These actions result in phosphorylation of substrates, and this leads to altered physiologic responses. This figure also shows that Ca^{2+} can enter cells through voltage- or ligand-gated Ca^{2+} channels. The intracellular Ca^{2+} is also regulated through storage and release by the mitochondria and endoplasmic reticulum. (Courtesy of JH Exton.)