General Principles of Endocrine Physiology

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The major human endocrine glands

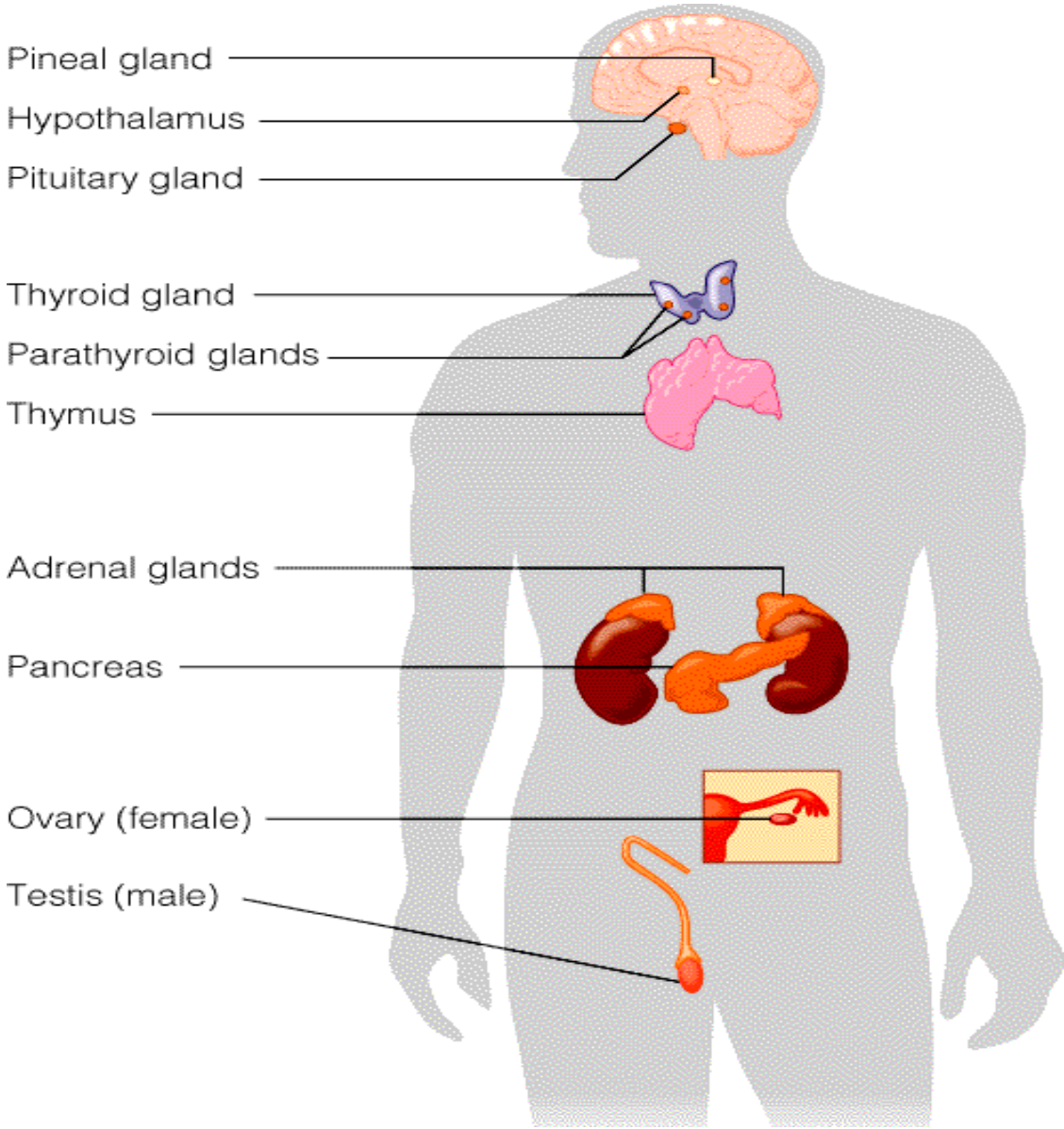

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TABLE 11–1 *Summary of the Hormones*

SITE PRODUCED (ENDOCRINE GLAND)	HORMONE	MAJOR FUNCTION* IS CONTROL OF:
Adipose tissue cells	Leptin	Appetite; metabolic rate; reproduction
Adrenal:		
Adrenal cortex	Cortisol	Organic metabolism; response to stress; immune system; development
	Androgens	Sex drive in women; adrenarche
	Aldosterone	Sodium and potassium excretion by kidneys
Adrenal medulla	Epinephrine Norepinephrine	Organic metabolism; cardiovascular function; response to stress
Gastrointestinal tract	Gastrin	Gastrointestinal tract motility and secretions; exocrine and endocrine secretions from pancreas; Secretion of bile from gallbladder
	Secretin	
	Cholecystokinin (CCK)†	
	Glucose-dependent insulinotropic peptide (GIP)	
	Motilin	
Gonads:		
Ovaries: female	Estrogen (Estradiol in humans)	Reproductive system; breasts; growth and development; development of ovarian follicles
	Progesterone	
	Inhibin	Follicle-stimulating hormone (FSH) secretion
	Relaxin	? Relaxation of cervix and pubic ligaments
Testes: male	Androgen (Testosterone and Dihydrotestosterone)	Reproductive system; secondary sex characteristics; growth and development; sex drive; gamete development
	Inhibin	FSH secretion
	Müllerian-inhibiting substance (MIS)	Regression of Müllerian ducts

Heart	Atrial natriuretic peptide (ANP, atriopeptin)	Sodium excretion by kidneys; blood pressure
Hypothalamus	Hypophysiotropic hormones: Corticotropin-releasing hormone (CRH) Thyrotropin-releasing hormone (TSH) Growth hormone-releasing hormone (GHRH) Somatostatin (SS) Gonadotropin-releasing hormone (GnRH) Dopamine (DA)	Secretion of hormones by the anterior pituitary Secretion of adrenocorticotropic hormone (ACTH) Secretion of thyroid-stimulating hormone (TSH) Secretion of growth hormone (GH) Secretion of growth hormone Secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) Secretion of prolactin (PRL)
Kidneys	Erythropoietin (EPO) 1,25-dihydroxyvitamin D	Erythrocyte production in bone marrow Calcium absorption in GI tract
Leukocytes, macrophages, endothelial cells, and fibroblasts	Cytokines‡ (these include the interleukins, colony-stimulating factors, interferons, tumor necrosis factors)	Immune defenses; immune cell growth and secretory processes
Liver and other cells	Insulin-like growth factor-I (IGF-I)	Cell division and growth of bone and other tissues
Pancreas	Insulin Glucagon Somatostatin (SS)	Organic metabolism; plasma glucose, amino acids and fatty acids
Parathyroids	Parathyroid hormone (PTH, parathormone)	Plasma calcium and phosphate; synthesis of 1,25-dihydroxyvitamin D
Pineal	Melatonin	? Sexual maturity; body rhythms

SITE PRODUCED (ENDOCRINE GLAND)	HORMONE	MAJOR FUNCTION* IS CONTROL OF:
Pituitary glands:		
Anterior pituitary	Growth hormone (somatotropin)	Growth, mainly via local production of IGF-I; protein, carbohydrate, and lipid metabolism
	Thyroid-stimulating hormone (thyrotropin)	Thyroid gland
	Adrenocorticotropic hormone (corticotropin)	Adrenal cortex
	Prolactin	
	Gonadotropic hormones:	
	Follicle-stimulating hormone	
	Males	Gamete production
	Females	Ovarian follicle growth
	Luteinizing hormone:	
	Males	Testicular production of testosterone
	Females	Ovarian production of estradiol; ovulation
	β-lipotropin and β-endorphin	? Fat mobilization and analgesic during stress
Posterior pituitary§	Oxytocin	Milk let-down; uterine motility
	Vasopressin (antidiuretic hormone, ADH)	Blood pressure; water excretion by the kidneys
Placenta	Human chorionic gonadotropin (hCG)	Secretion by corpus luteum
	Estrogens	See Gonads: ovaries
	Progesterone	See Gonads: ovaries
	Human placental lactogen (hPL)	Breast development; organic metabolism
Thymus	Thymopoietin	T-lymphocyte function
Thyroid	Thyroxine (T_4)	Metabolic rate; growth; brain development and function
	Triiodothyronine (T_3)	
	Calcitonin	? Plasma calcium
Multiple cell types	Growth factors‡ (e.g., epidermal growth factor)	Growth and proliferation of specific cell types
Other (blood)	Angiotensin II	Blood pressure; production of aldosterone from adrenal cortex

Endocrine glands and hormones

- **Help regulate metabolic processes**

Endocrine system

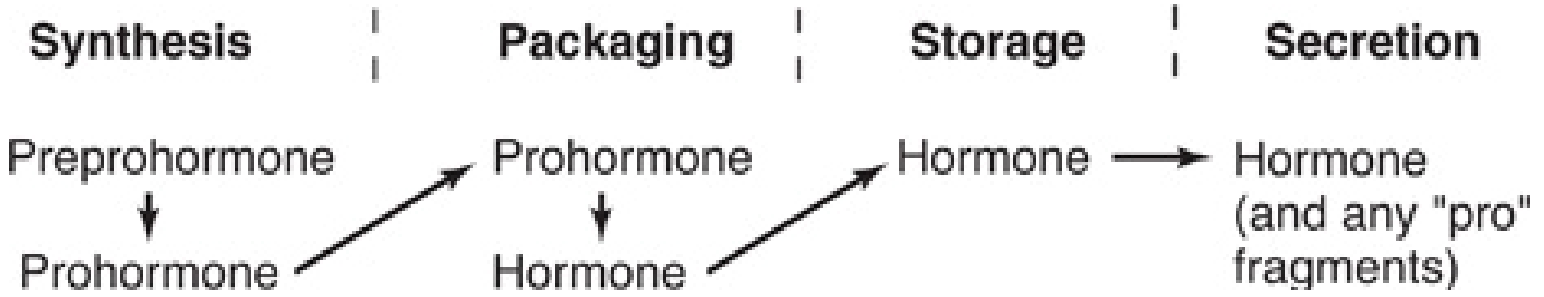
1. Structure/synthesis.
2. Physiological effects.
3. Regulation of synthesis & secretion.
4. Disorders.
    - Causes, etiology
    - Signs & symptoms
    - Diagnoses
    - Treatment

What is a hormone?

- Chemical ***messenger*** synthesized by specific endocrine cells in response to certain stimuli and secreted into the blood, which carries it to the ***target cells.***
- Signal target cells to perform specific chemical reactions

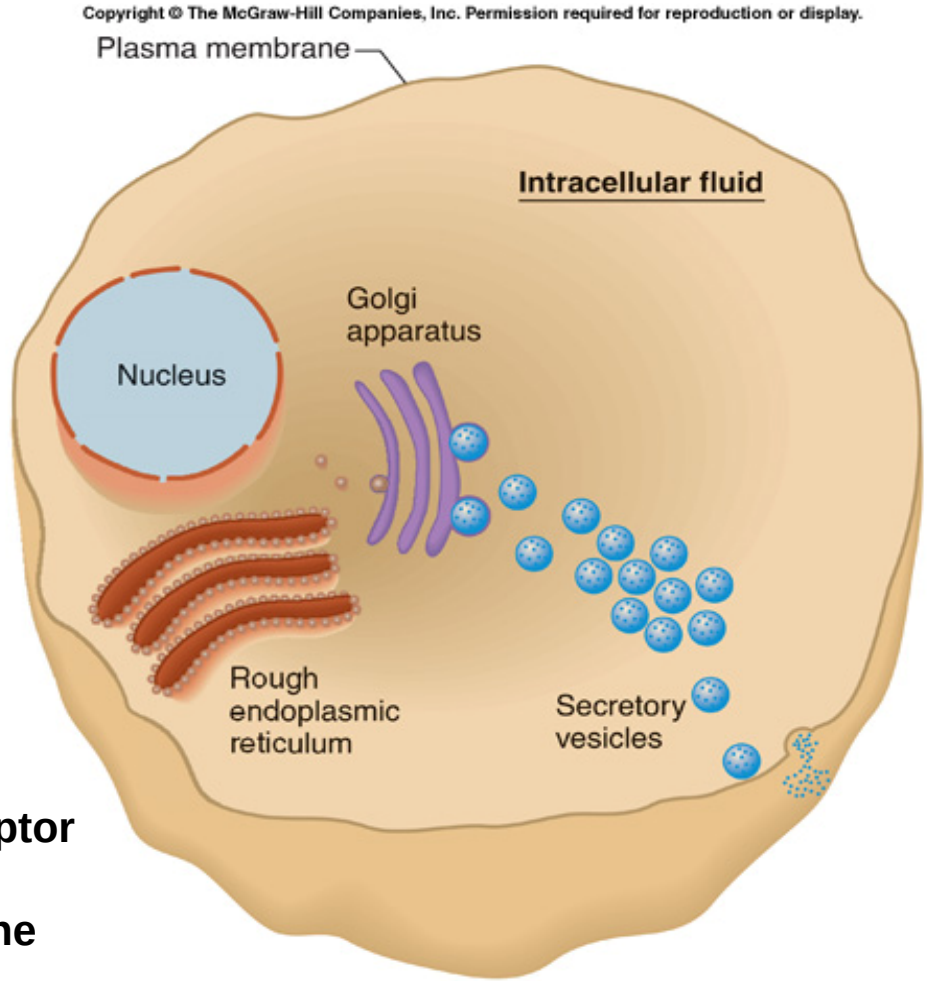
Typical synthesis of peptide hormones

- **Preprohormones- larger hormones produced on the ribosomes of the endocrine cells**
- **Prohormones- cleavage of preprohormones by proteolytic enzymes in rER**
- **Prohormones- packaged into secretory vesicles by the Golgi apparatus**
- **Prohormones- cleaved to give active hormone and pro-fragments**



Many protein hormones undergo modifications during packaging and after they have been secreted, e.g.,

pre-pro-insulin → pro-insulin → insulin.



rER- contains the receptor for the signal receptor particle and binds ribosomes engaged in translating mRNA for secreted proteins and the majority of transmembrane proteins

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Figure 3-16

NUCLEUS

The DNA code is "transcribed" into mRNA.

RIBOSOMES

The mRNA is "translated" to give instructions for proteins synthesis.

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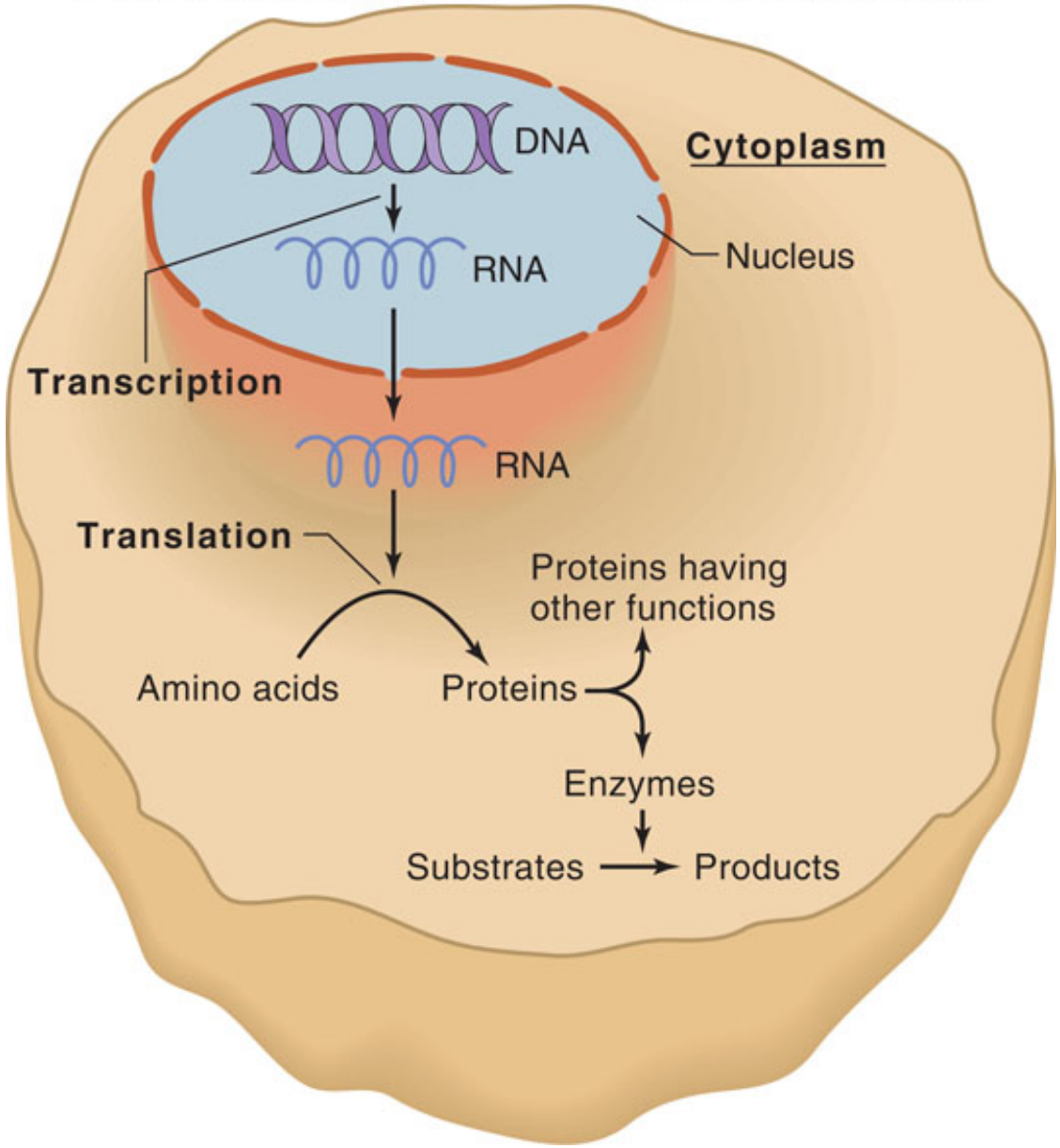


A hormone,

- Regulates ***rate of reaction***
- Do not initiate
- Very specific
- Present in very small quantity

The “metabolic fate” of a given hormone molecule in the blood is not always fully characterized, but some of the main possibilities are:

- **Excretion**
- **Inactivation by metabolism**
- **Activation by metabolism**
  Binding to receptor and produces a cellular response

Modes of Action.

- **Can be categorized by the site of action relative to the site of secretion.**

- **Endocrine**
- **Paracrine**
- **Autocrine**
- **Neurocrine**

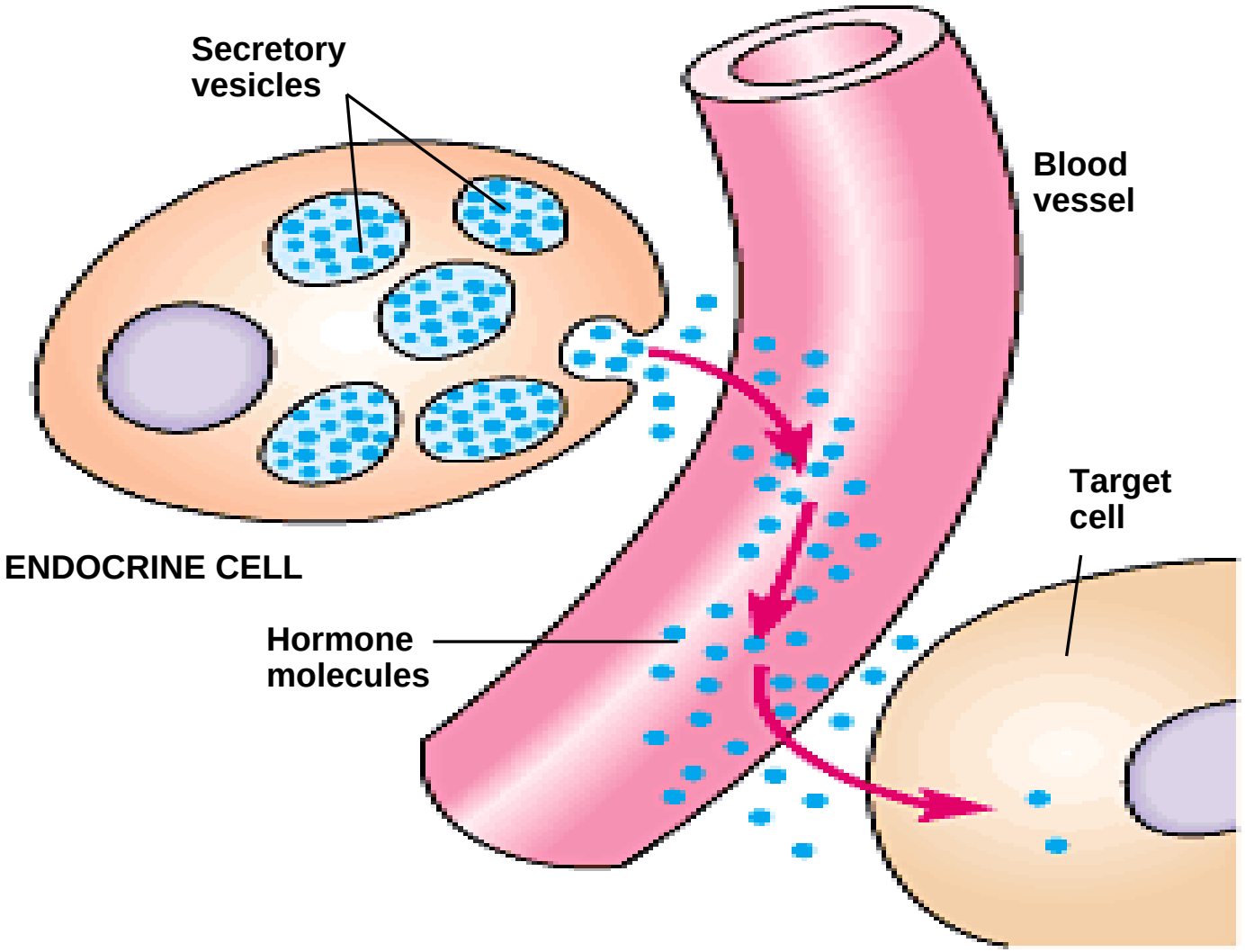
  - secreted by nerve endings, via axonal transport and then via blood

Endocrine secretion

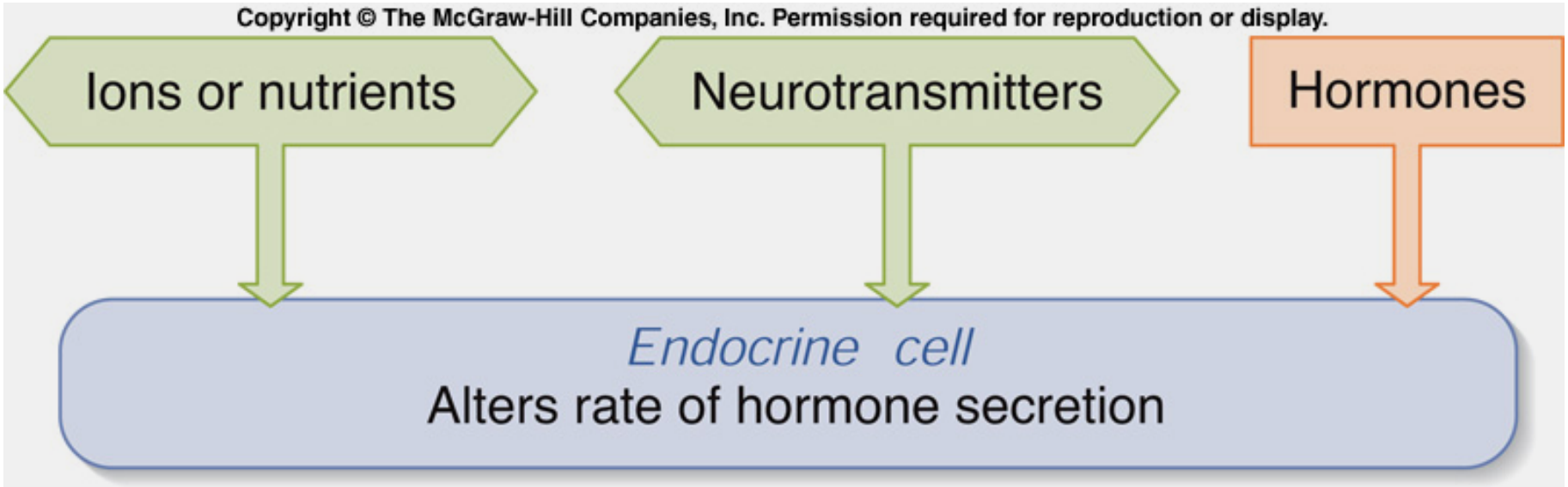
- **From gland via blood into a distance**
- **Substance released by cell into bloodstream that affects distant cells.**

  e.g. testosterone is secreted by Leydig cells in testis.

Hormone from an endocrine cell



Three types of inputs to endocrine cells that stimulate or inhibit hormone secretion.



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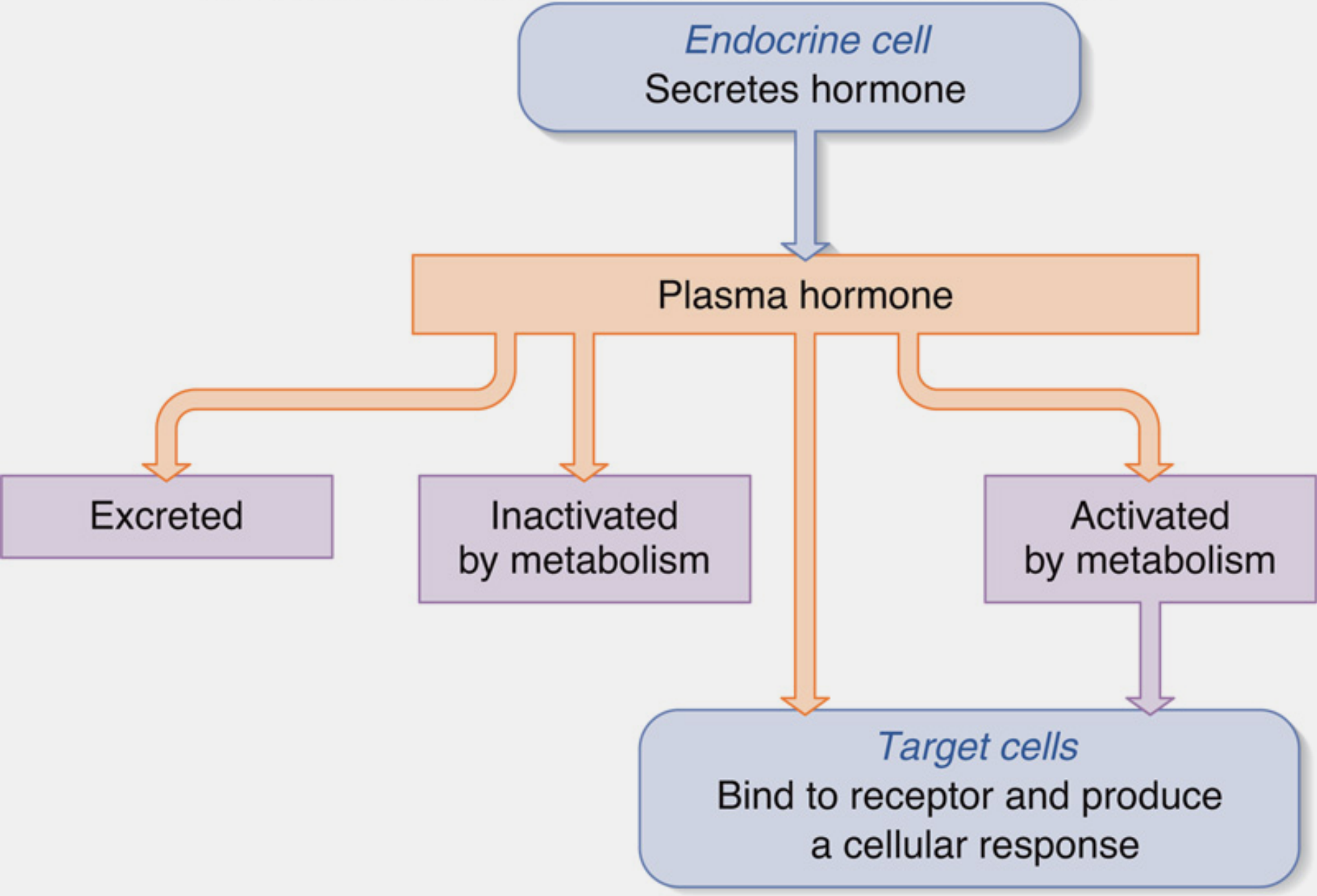
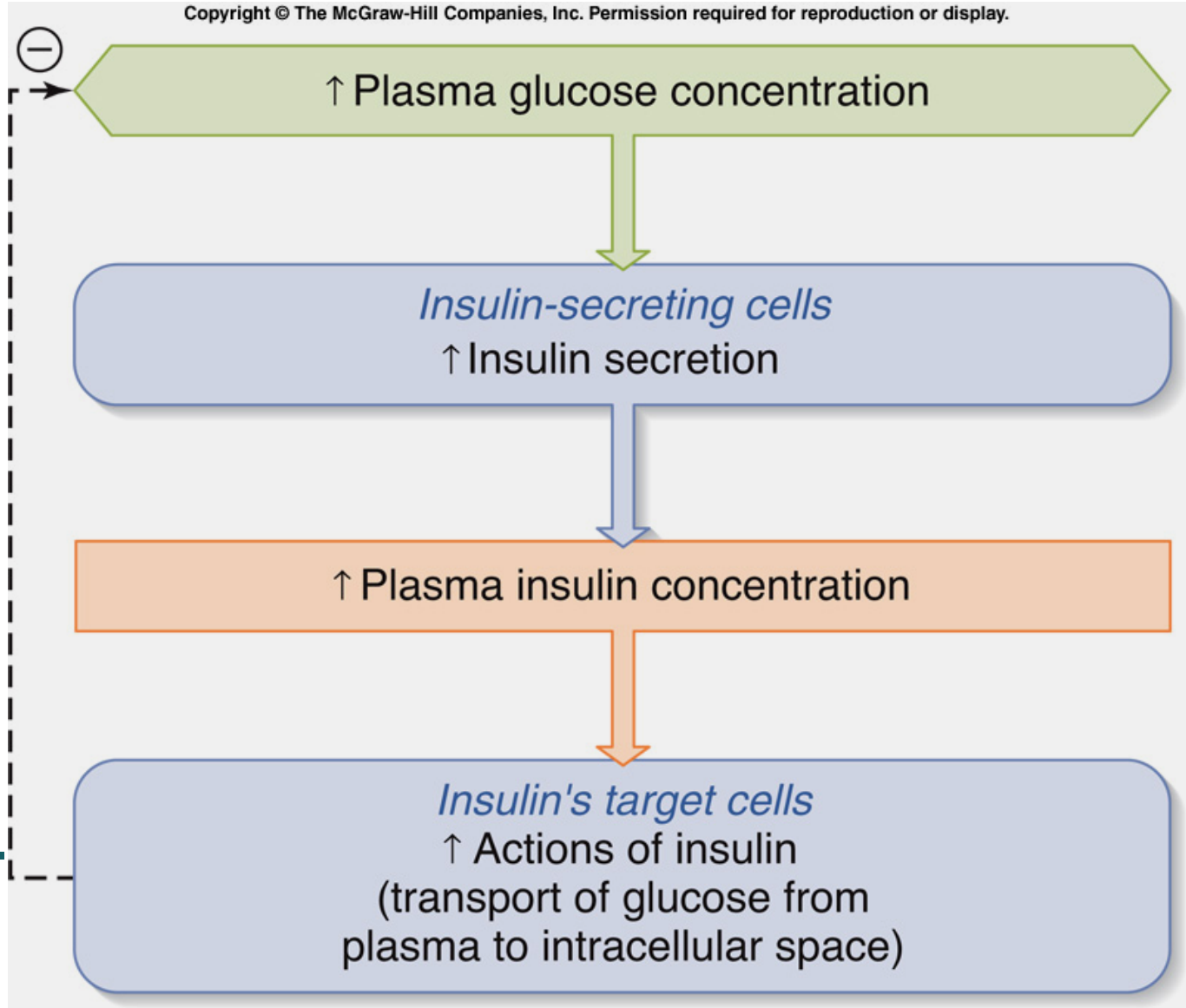


Increased glucose levels in the pancreas directly stimulate secretion of insulin.

“Insulin targets” are cells that have insulin-receptors.



Paracrine secretion

- **Neighboring cells of different types**
- **Substance released by cell that affects neighboring cells.**
- **Not released into bloodstream**
- **e.g. histamine released at site of injury to constrict blood vessel walls and stop bleeding)**

Autocrine secretion

- **Neighboring cells of the same type or the secreting cell itself**
- **substance released by cell that affects the secreting cell itself**
- **(e.g. norepinephrine is released by a secretory cell in the adrenal medulla, and**
- **norepinephrine itself inhibits further release by that cell - this is also an example of direct negative feedback)**

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Figure 1-7

A given signal can fit into all 3 categories:

e.g., the steroid hormone cortisol affects the very cells in which it is made, the nearby cells that produce other hormones, and many distant targets, including muscles and liver.

Multi-factorial control of signal release adds more complexity.

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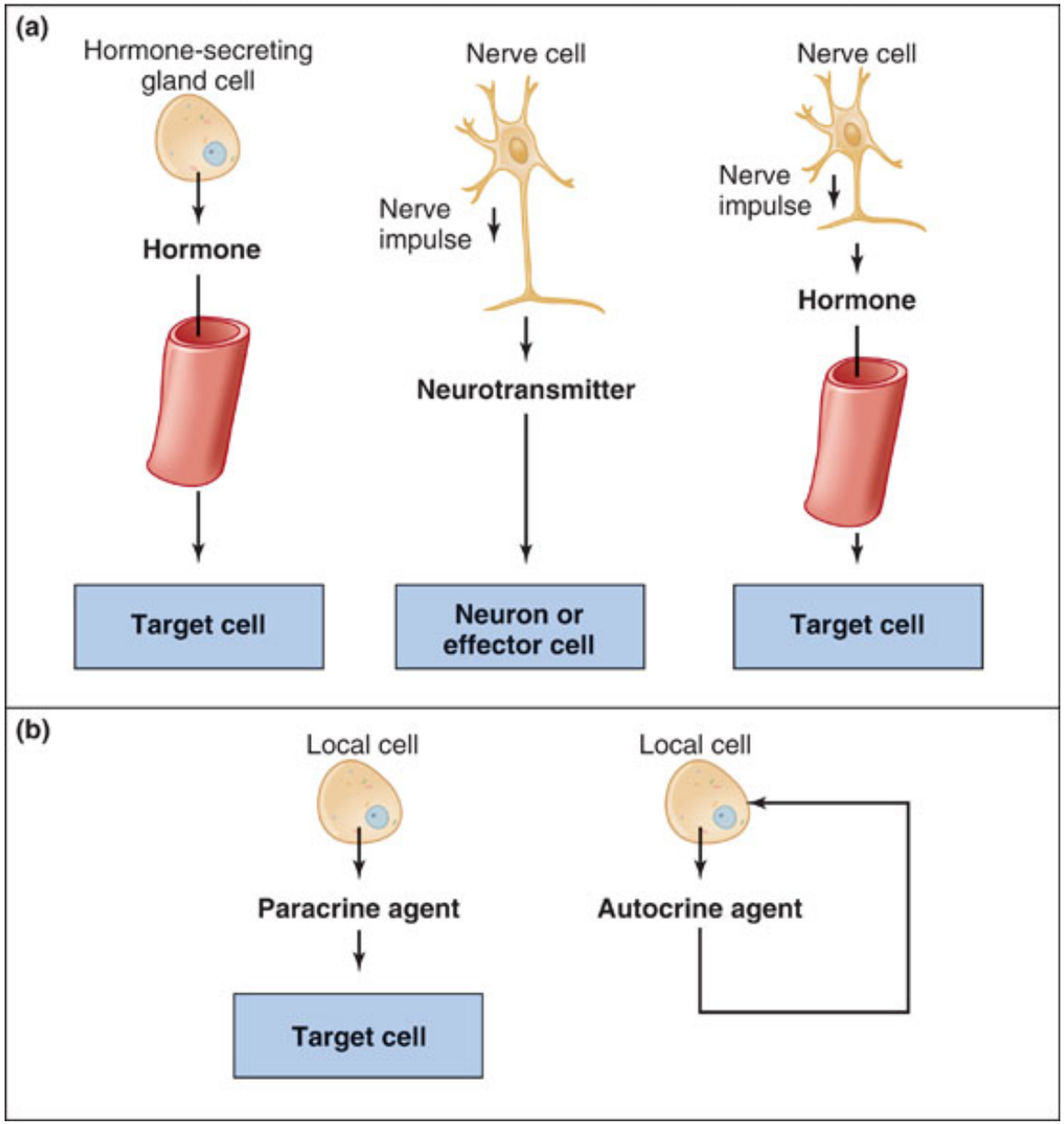


A secretion may have several sites of action simultaneously.

Example:

- **Norepinephrine**

  - *Autocrine* action causes negative feedback on secretion.

  - Simultaneously, *endocrine* action causes respiration rate to ↑ , peripheral blood vessels to constrict, etc.

Hormone Structures & Synthesis

Hormones fall into 3 chemical classes:

1. **Amines- derivatives of the amino acid tyrosine, e.g., adrenaline, thyroxine (T_4), *lipid insoluble***
2. **Peptides- the majority of hormones (3 to 200 amino acids), *lipid insoluble* e.g., insulin, prolactin, oxytocin, GH**
3. **Steroids- made from cholesterol, *lipid soluble*, from gonads and adrenal cortex, e.g. cortisol, androgen**

Regulation of hormone secretion

Concentration depends on

- **The rate of secretion**
- **The rate of clearance from the plasma (half-life)**

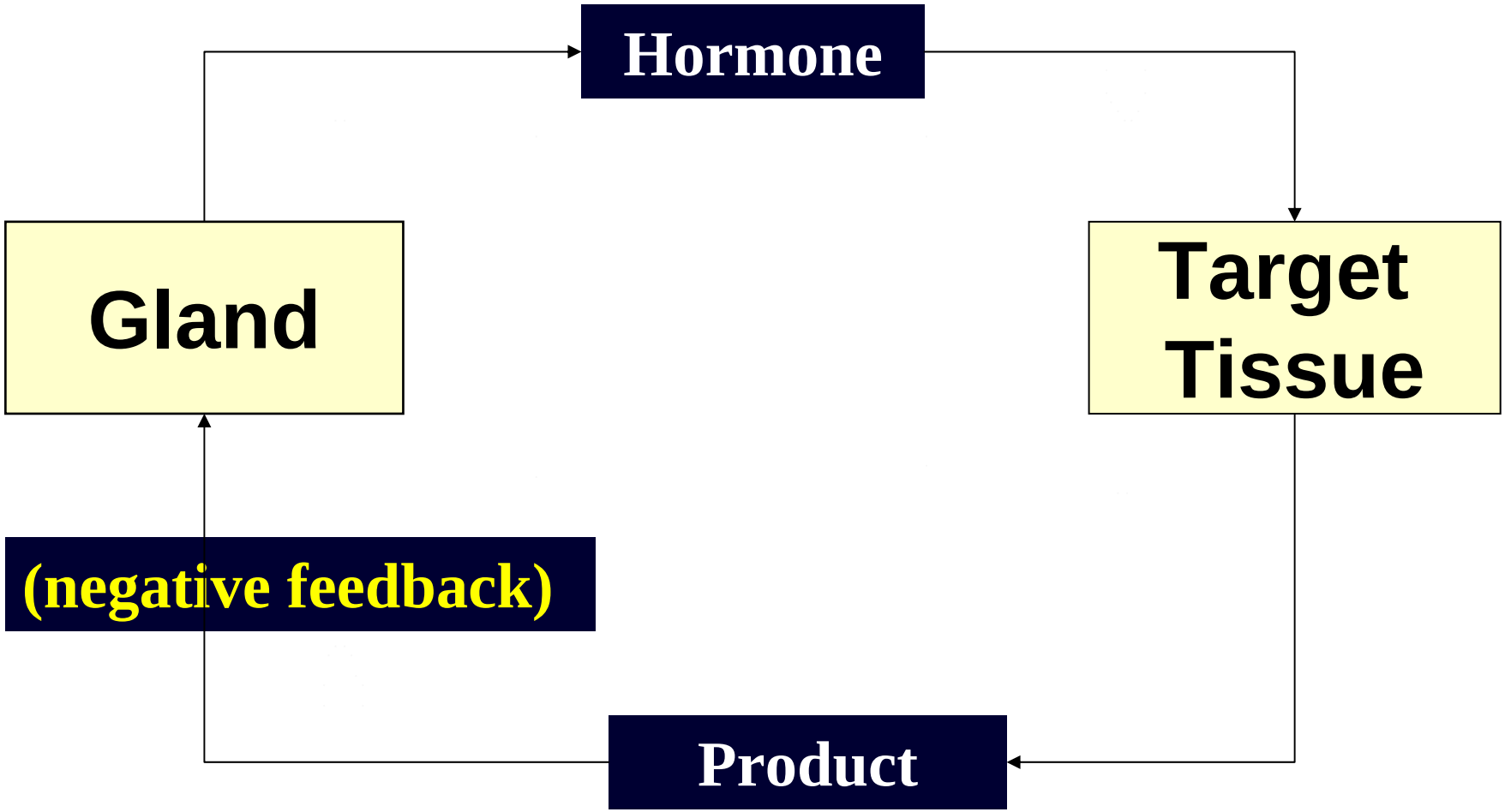
  e.g. T_4 (6 days); Insulin (0.006 days)

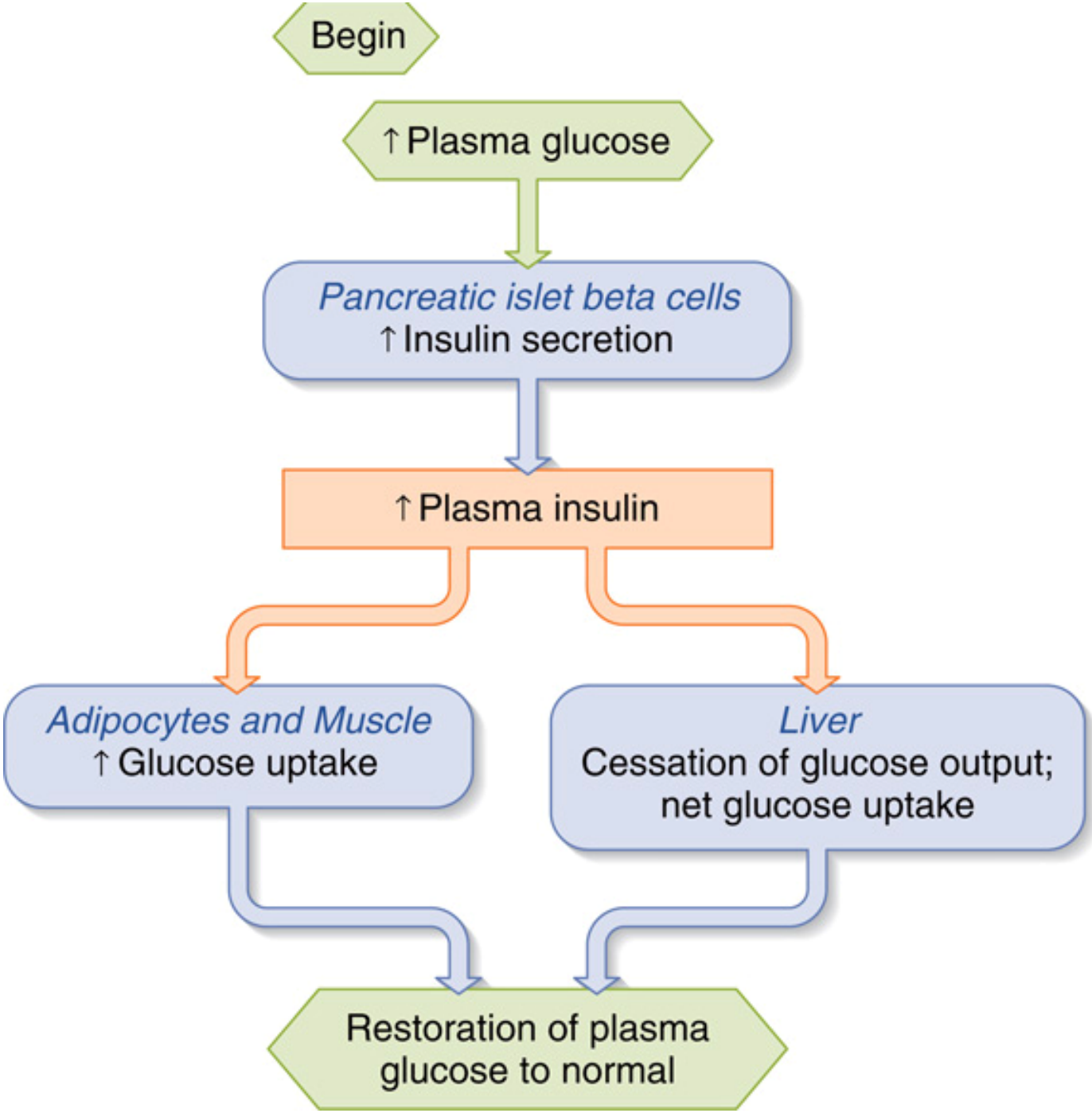
Half-life

- **Persistence of a hormone in blood**
- **A time indicating half of its activity remaining**
- **Is brief (from a fraction of a minute to 30min)**
- **But effects can last for several minutes to hours**

Negative Feedback

- **Characteristic of control systems in which system's response opposes the original change in the system.**
- **Hormone *itself* feeds back to inhibit its own synthesis.**
- **Regulated product (*metabolite)* feeds back to inhibit hormone synthesis.**
- **Important for homeostatic control.**
- **Example: Control of blood glucose by insulin**


Hormone
Gland
Target Tissue
(negative feedback)
Product


Begin
↑ Plasma glucose
Pancreatic islet beta cells
↑ Insulin secretion
↑ Plasma insulin
Adipocytes and Muscle
↑ Glucose uptake
Liver
Cessation of glucose output;
net glucose uptake
Restoration of plasma
glucose to normal

Positive Feedback

- **Characteristic of control systems in which an initial disturbance sets off train of events that *increases the disturbance even further*.**
- **Amplifies the deviation from the normal levels.**
- **Example: Oxytocin (suckling)**
- **Important for amplification of level for action.**

Rhythmic secretion (pulses)

- **Diurnal**
  - **daily, occurring in a 24-hour cycle**
  - **growth hormone, cortisol**
- **Cyclic**
  - **e.g. oestrogen, progesterone, LH.**

Mechanisms of hormone actions

- **Alter plasma permeability or electrical state**
- **Stimulate synthesis of protein within cells**
- **Activate or inactivate enzymes**
- **Induce secretory activity**
- **Stimulate mitosis/meiosis**

Mechanisms of hormone actions

1. **Amino-acid based hormone**

- **Proteins and peptides cannot freely penetrate plasma membrane (fixed receptor)**
- **Involve a second messenger**
- **Bind to a specific receptor and activate the intracellular *second messenger*, e.g., ACTH, parathyroid hormones.**

Cyclic AMP signaling-sequence of events

- The *hormone* (*1st messenger*) binds to the membrane receptor; the membrane receptor changes shape and bind to G protein (GTP-binding protein)
- G protein is activated; binds to GTP (Guanosine 5'-triphosphate) and release GDP
- Activated G protein moves to membrane and binds and activates adenylate cyclase (GTP is hydrolysed by GTPase activity of G protein)
- Activated adenylate cyclase converts *ATP to cAMP (second messenger)* (if inhibited, no catalysed reaction by AC)
- cAMP is free to circulate inside the cell; triggers activation of one to several protein kinase molecules; protein kinase phosphorylates many proteins

- The phosphorylated proteins may either be activated or inhibited by phosphorylation

Signal transduction pathway involving adenylate cyclase

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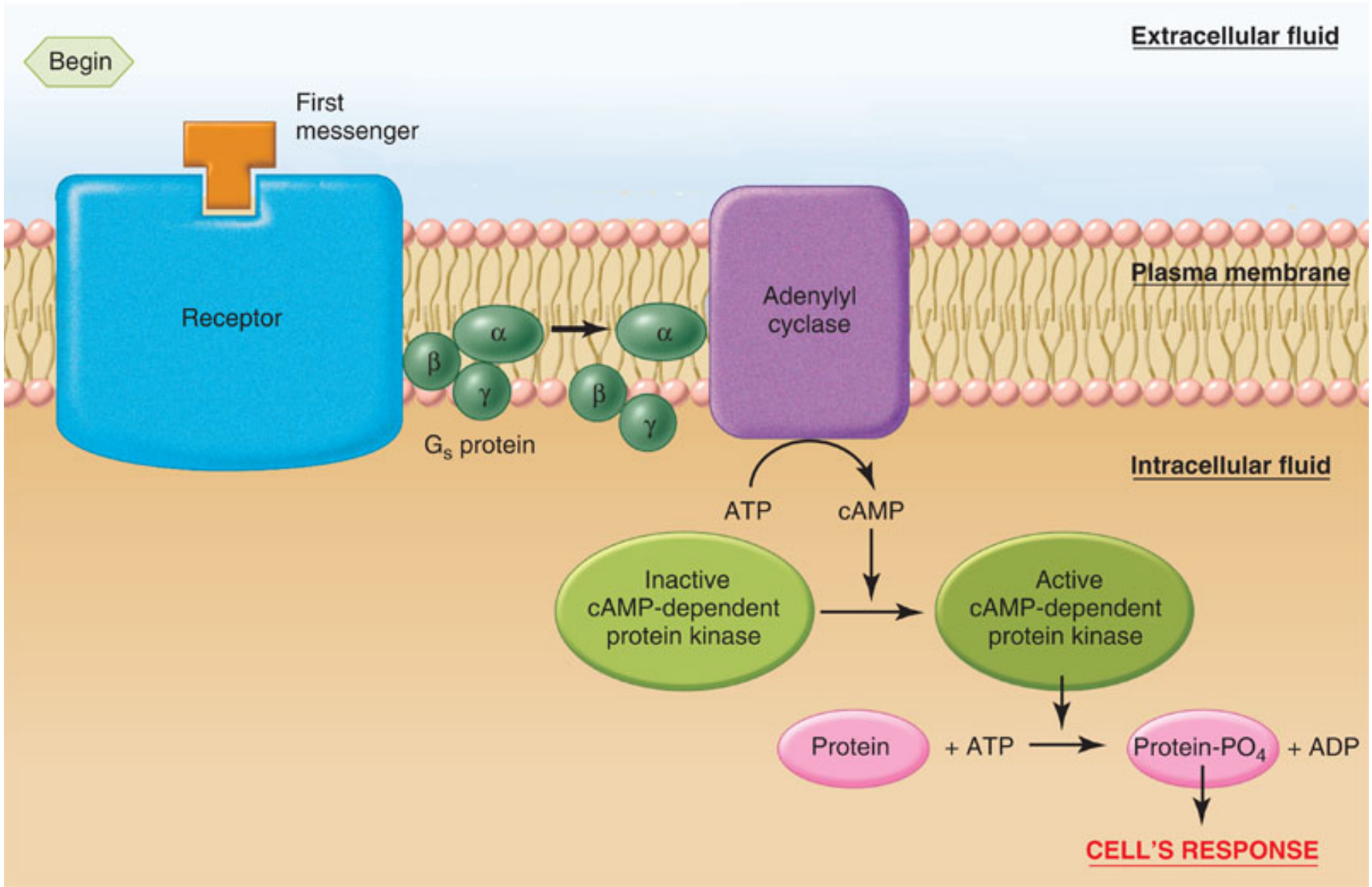

Amplication effect

- **Each activated AC can generate many cAMP molecules**
- **Each protein kinase can catalyze hundreds of reactions**
- **The end effect depends on the target cell (e.g. in thyroid cells, binding of TSH to receptor results in TH synthesis; in bone and muscle cells, binding of GH results in protein synthesis)**

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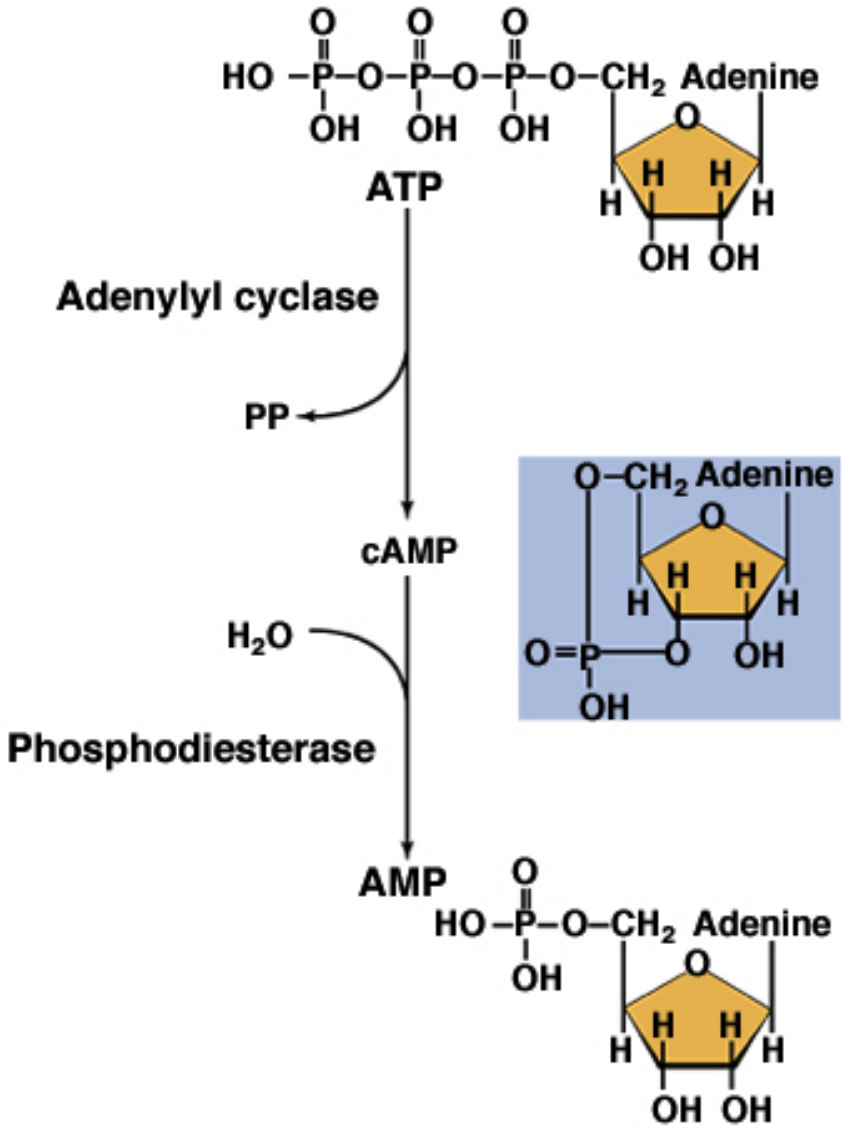
Figure 5-7

Adenylyl cyclase forms cAMP, a "second messenger" that activates enzymes used in cellular responses.

The phosphodiesterase enzymes "terminate" the second messenger cAMP.



Amplification effect

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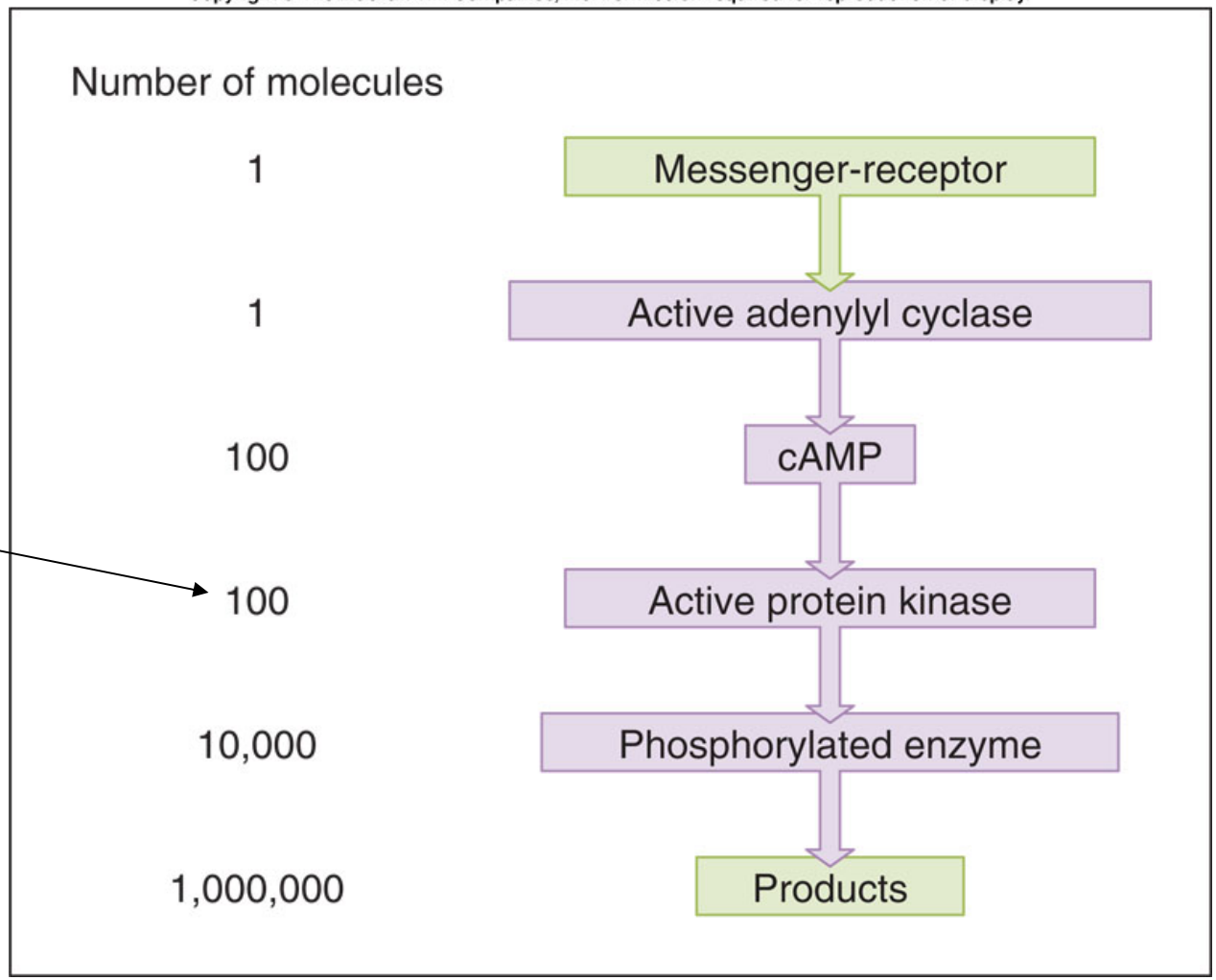

Each protein kinase can catalyse hundreds of reactions

Figure 5-8

The cAMP system rapidly amplifies the response capacity of cells: here, one “first messenger” led to the formation of one million product molecules.

Enzyme amplification

In all of the preceding mechanisms, the result is to *increase the amount of protein/enzymes* available in the cell

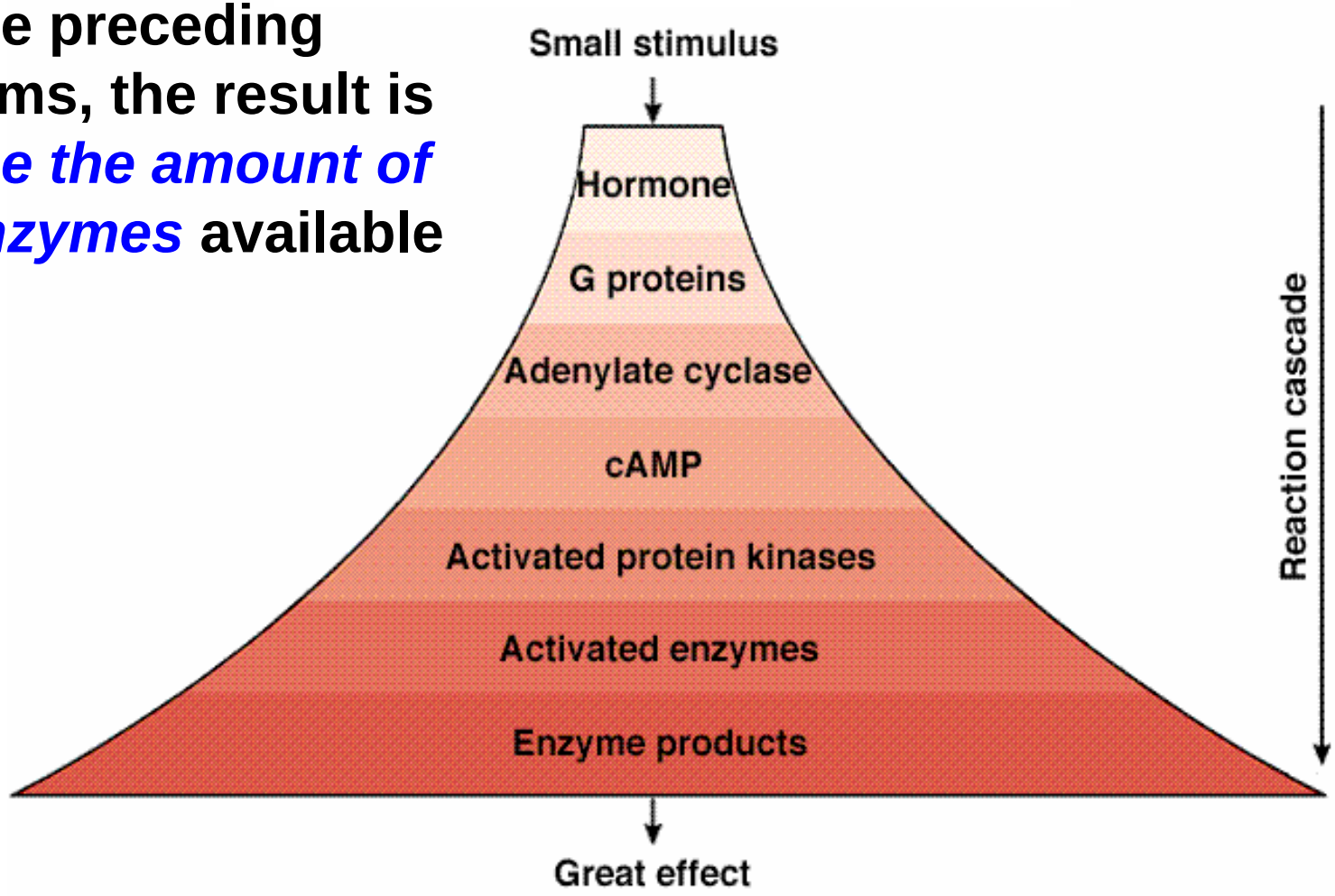

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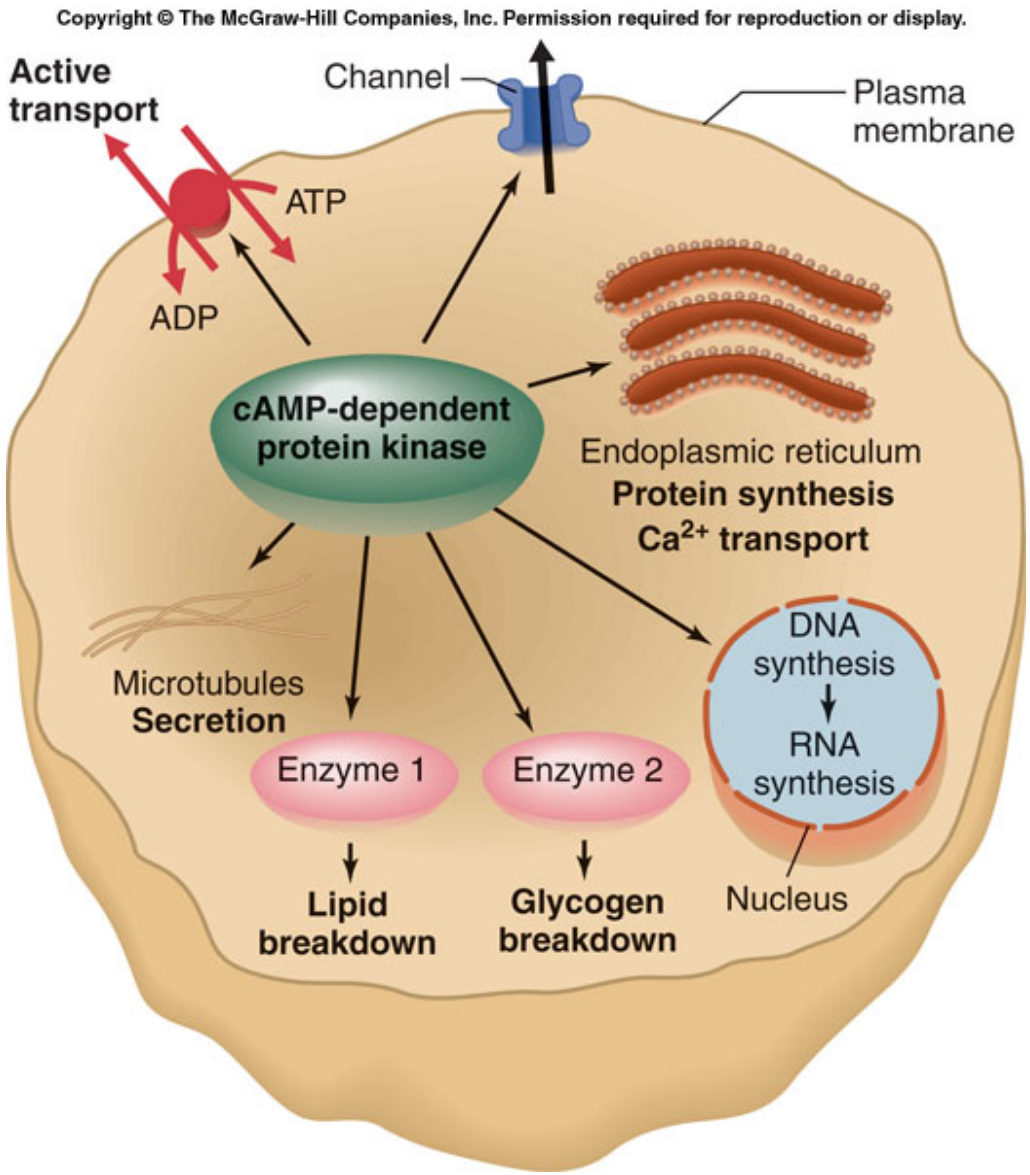
Figure 5-9

Cells can respond via the cAMP pathways using a diversity of cAMP-dependent enzymes, channels, organelles, contractile filaments, ion pumps, and changes in gene expression.



PIP-calcium signaling mechanism

- **A hormone (first messenger) binding to its receptor causes the receptor to bind inactive G protein**
- ***G protein* is activated; binds GTP & releases GDP**
- **Activated G protein binds & activates a membrane-bound phospholipase enzyme;**
- **G protein becomes inactive**
- **Phospholipase splits *phosphatidyl inositol biphosphate* (PIP2) to *diacylglycerol* (DAG) & *inositol triphosphate* (IP3);**
- ***DAG* activates protein kinases on the plasma membrane; *IP3* triggers *calcium ion* release from the ER**
- **Released *calcium ions* (second messengers) alter activity specific enzymes' activity and ion channels or bind to the regulatory protein calmodulin;**
- ***Calmodulin* also activates specific enzymes to amplify the cellular response**

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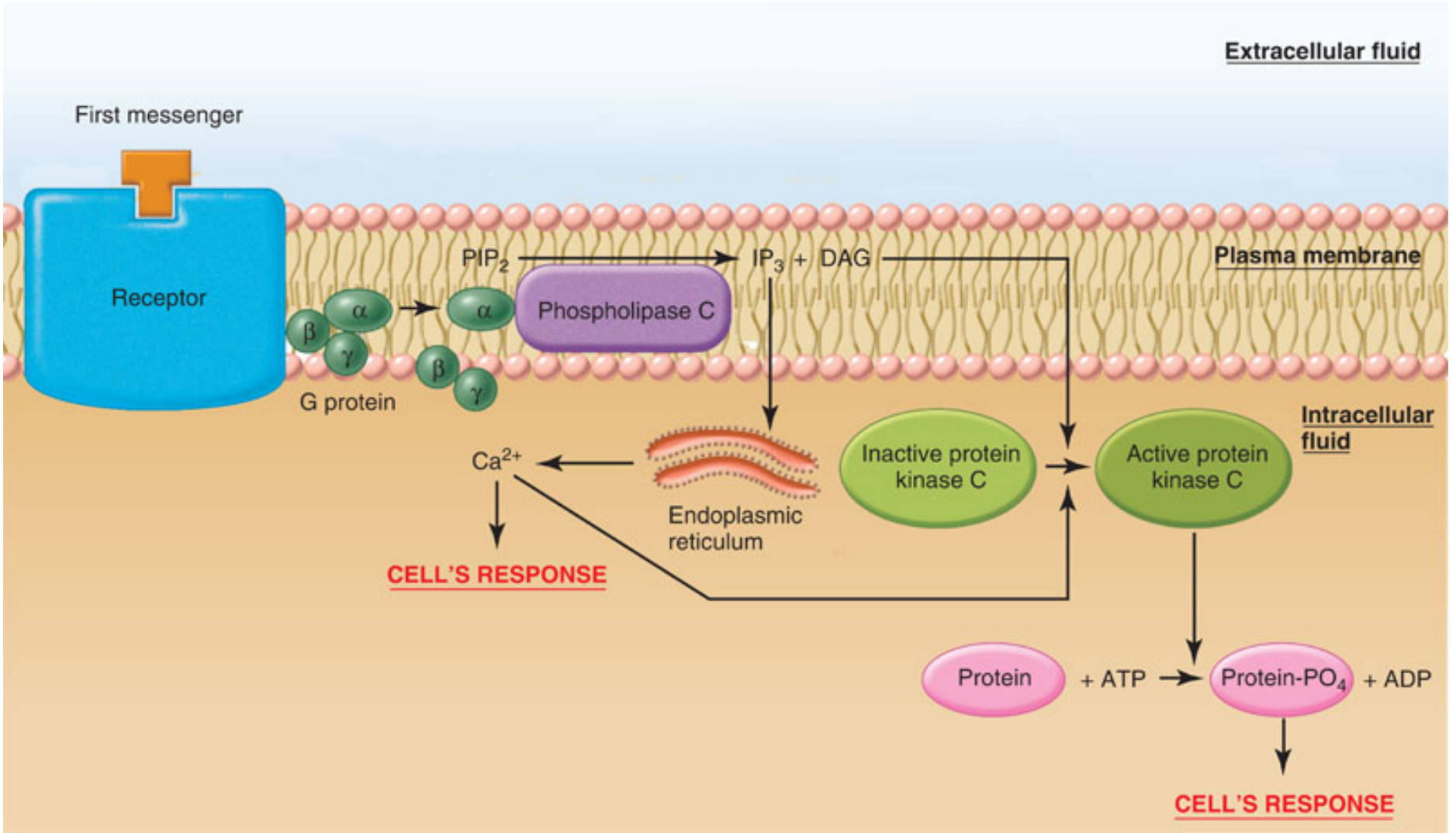


This receptor-G-protein complex is linked to and activates phospholipase C, leading to an increase in IP_3 and DAG, which work together to activate enzymes and to increase intracellular calcium levels.

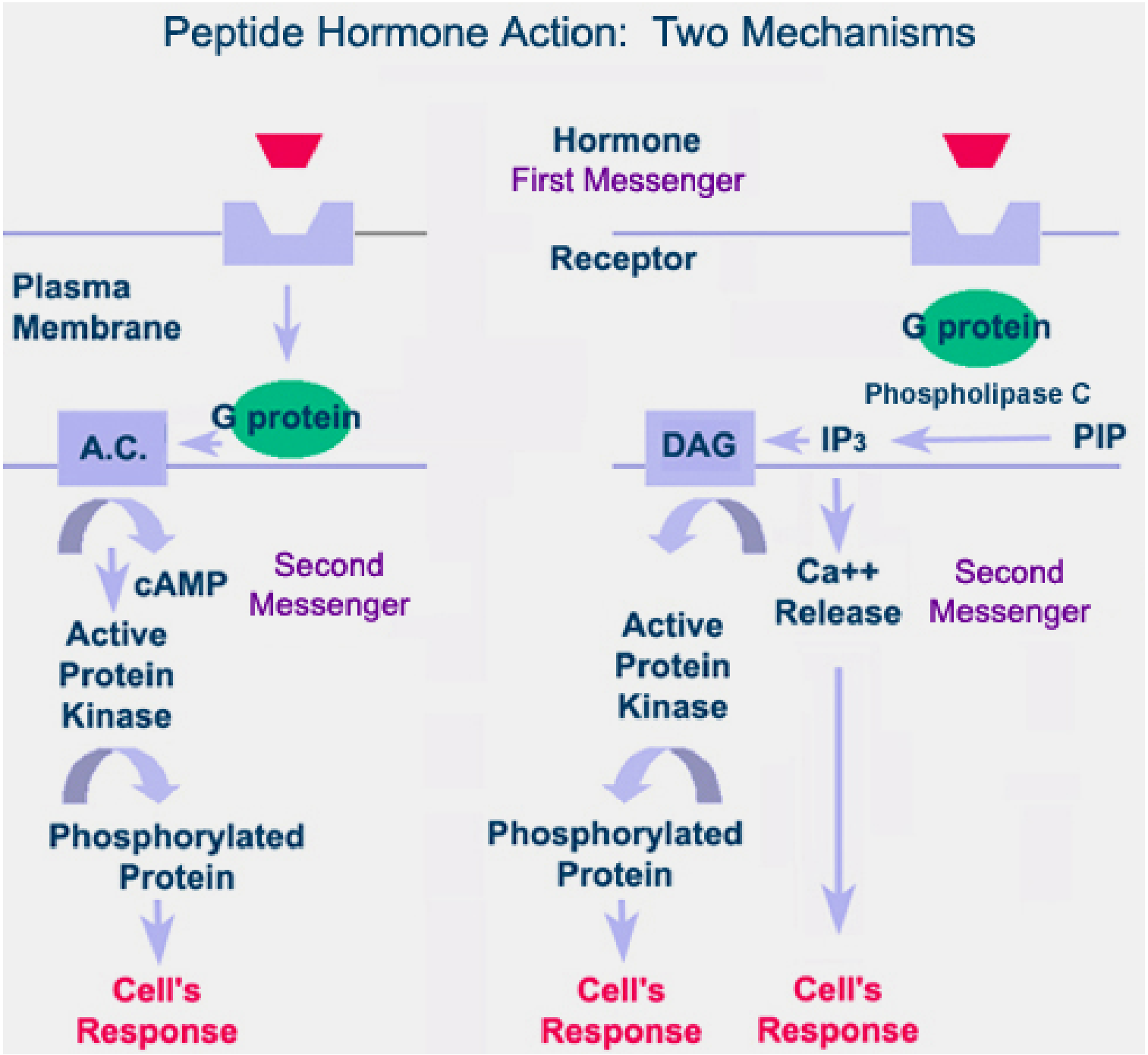
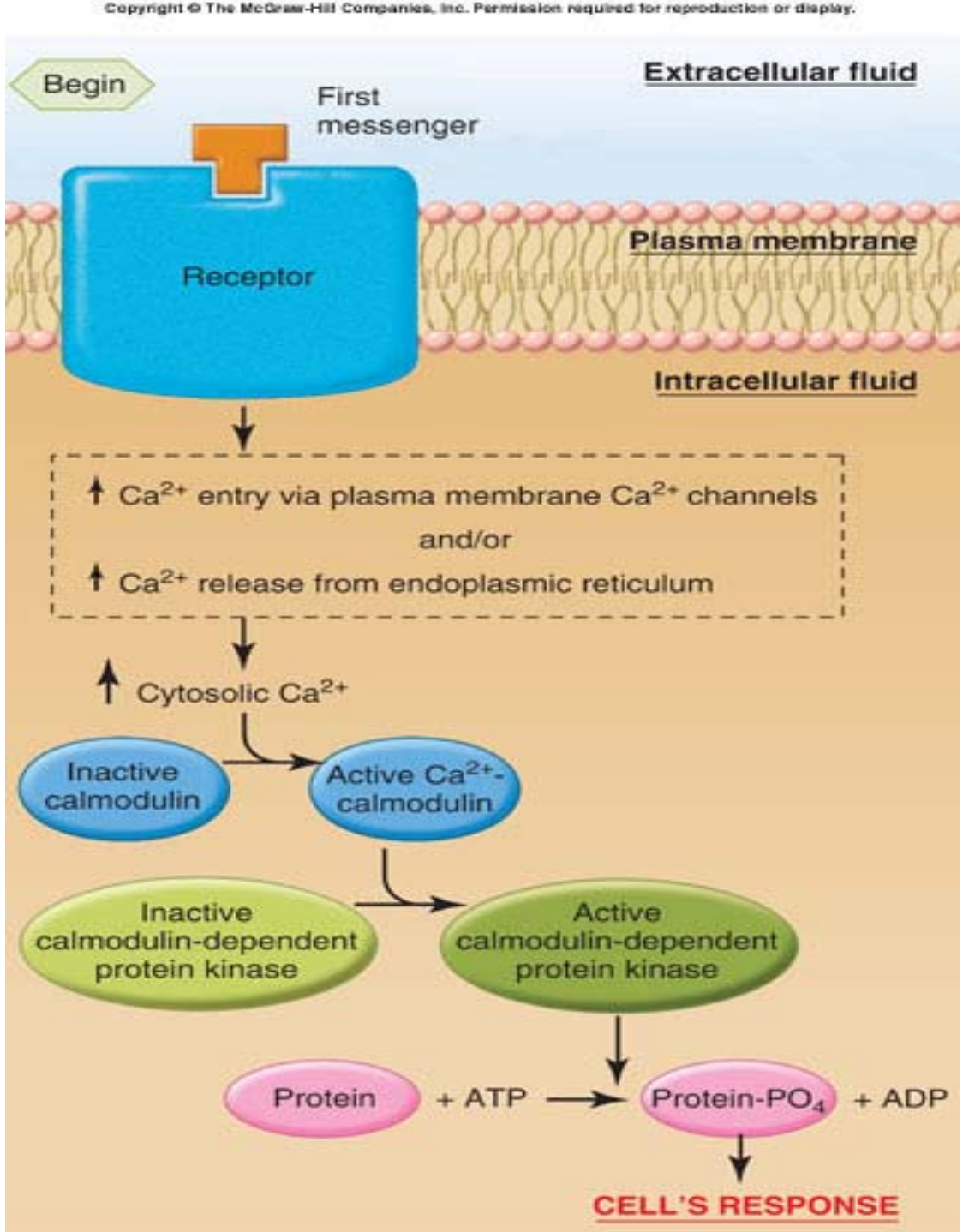

Peptide Hormone Action: Two Mechanisms
Hormone
First Messenger
Receptor
Plasma
Membrane
G protein
A.C.
cAMP
Second
Messenger
Active
Protein
Kinase
Phosphorylated
Protein
Cell's
Response
G protein
Phospholipase C
DAG
IP3
PIP
Ca++
Release
Second
Messenger
Active
Protein
Kinase
Phosphorylated
Protein
Cell's
Response
Cell's
Response

Figure 5-11

The Ca-calmodulin system is similar to some of the cAMP pathways, because it results in the activation of protein kinases that can phosphorylate key proteins required for cellular responses.

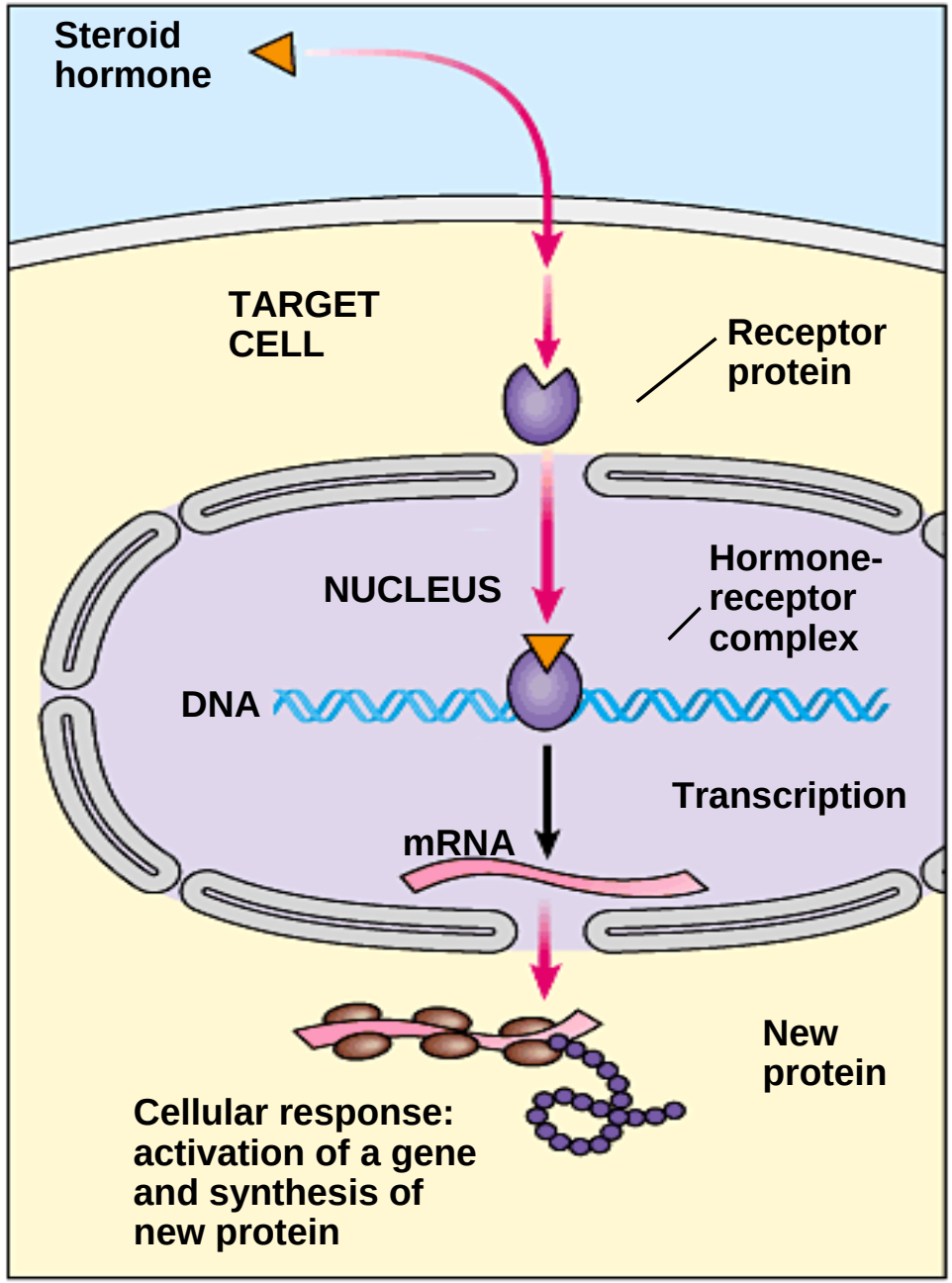


Sequence of events for steroid hormone binding

- **Steroids are lipid-based and can diffuse into cells easily**
- **No need for intracellular second messenger**
- ***Mobile receptors***
- **Some steroids bind to a cytoplasmic receptor, which then translocates to the nucleus**
- **Other receptors for steroids are located in the nucleus or are nuclear receptor proteins**
- **In both cases, the steroid-receptor complex formed can then bind to specific regions of DNA and activate specific genes**
- **Activated genes transcribe into messenger RNA and instruct the cell to synthesize specific enzyme proteins that change the metabolism of the target cell**

Steroid hormones bind to intracellular receptors

- The steroid-receptor complex binds to DNA, turning specific genes *on* or *off*

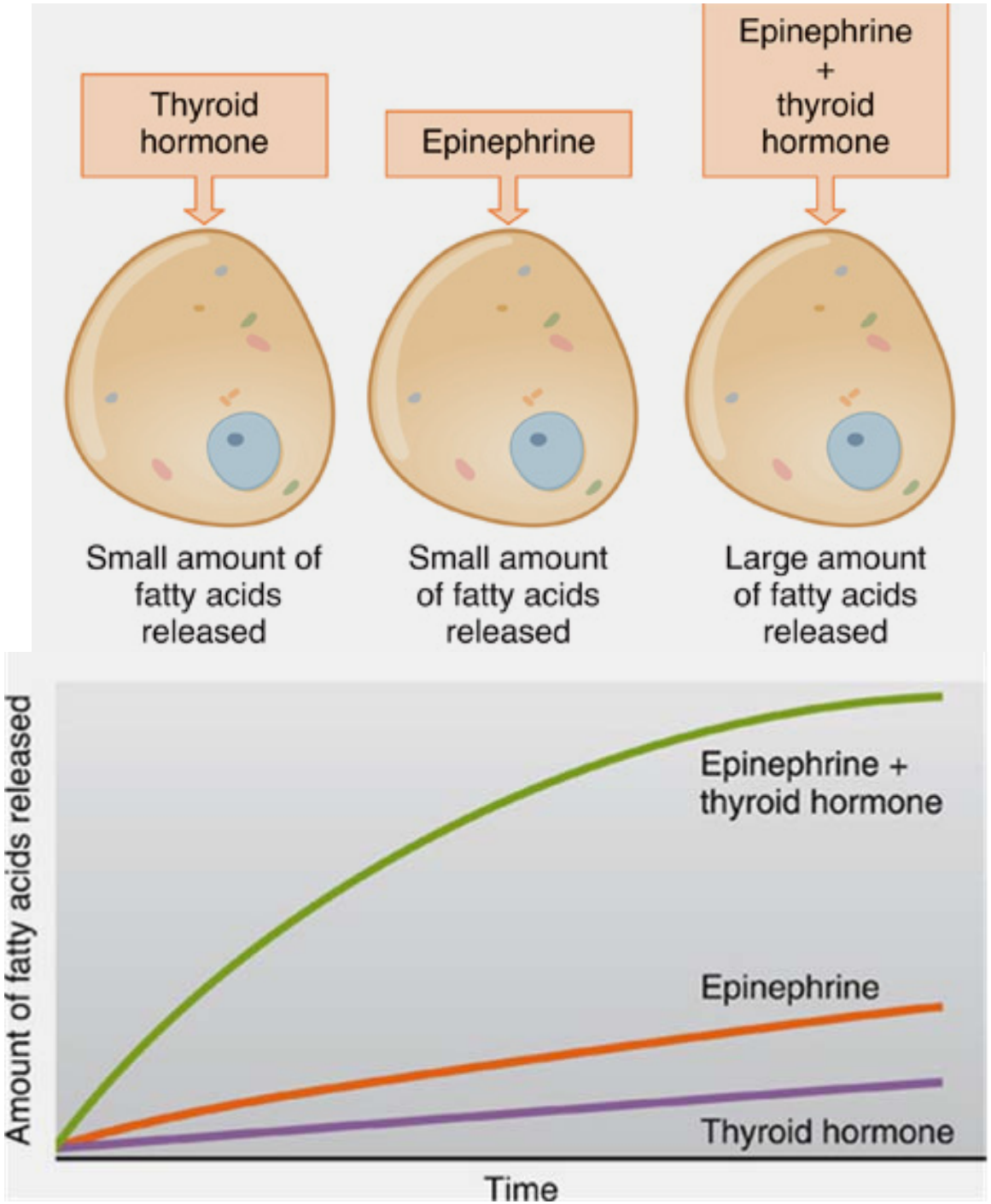


Up/down-regulation

- **Up-regulation: ↑ in number of receptors for a hormone in the target cell**
- **Down-regulation: ↓ in number of receptors for a hormone in the target cell**
- **Permissiveness: the facilitation of the action of one hormone by another**

- **Up-regulation of one hormone's receptors by another hormone leads to the phenomenon called permissiveness**

  e.g. the ability of TH to "permit" epinephrine-induced release of fatty acids from adipose tissue cells (TH causes an ↑ no of epinephrine receptors on the cell)


Thyroid hormone
Epinephrine
Epinephrine + thyroid hormone
Small amount of fatty acids released
Small amount of fatty acids released
Large amount of fatty acids released
Amount of fatty acids released
Epinephrine + thyroid hormone
Epinephrine
Thyroid hormone
Time