



Endocrine Physiology

内分泌生理学

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Endocrinology

内分泌学

■ Endocrinology

- The study of chemical communication systems that provide the means to control a huge number of physiologic processes



Endocrine system

内分泌系统

- **Endocrine glands**
内分泌腺
- Endocrine tissues
- Endocrine cells

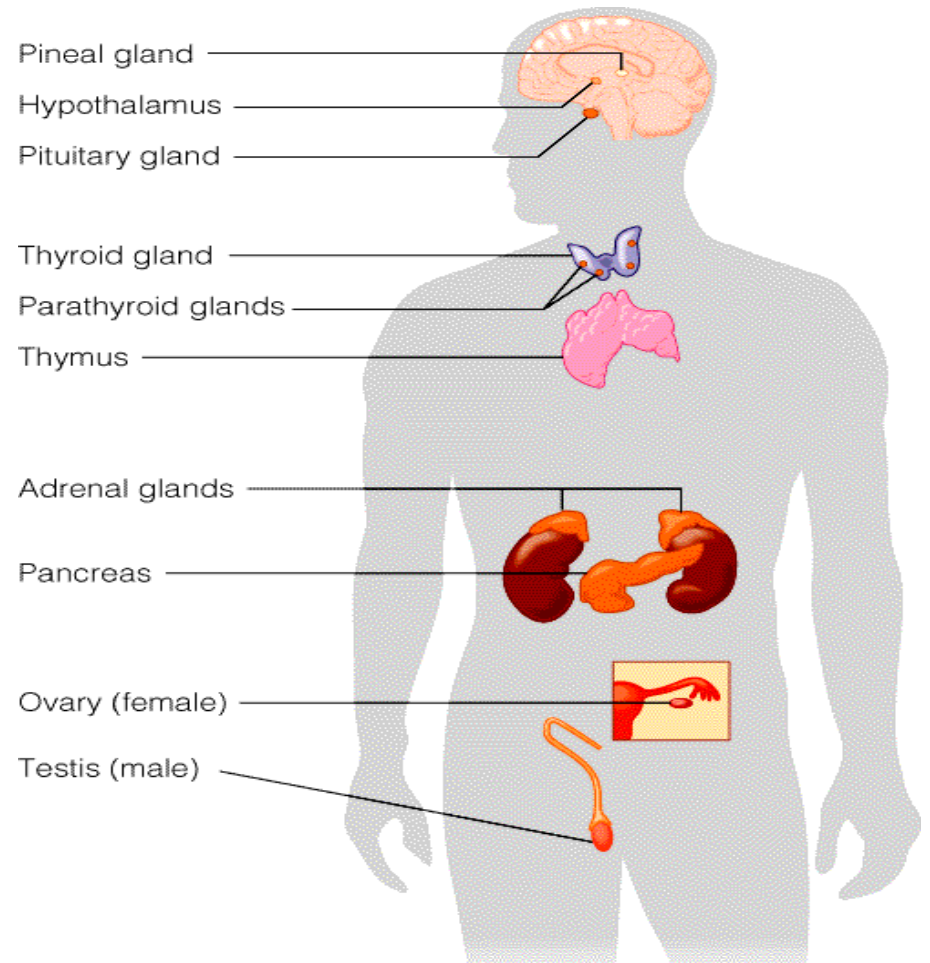


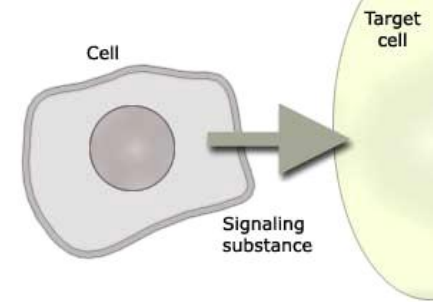
TABLE 11-1 *Summary of the Hormones*

SITE PRODUCED (ENDOCRINE GLAND)	HORMONE	MAJOR FUNCTION* IS CONTROL OF:
<i>Adipose tissue cells</i>	Leptin	Appetite; metabolic rate; reproduction
<i>Adrenal:</i>		
<i>Adrenal cortex</i>	Cortisol	Organic metabolism; response to stress; immune system; development
	Androgens	Sex drive in women; adrenarcho
	Aldosterone	Sodium and potassium excretion by kidneys
<i>Adrenal medulla</i>	Epinephrine	Organic metabolism; cardiovascular function; response to stress
	Norepinephrine	
<i>Gastrointestinal tract</i>	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	
<i>Gonads:</i>		
<i>Ovaries: female</i>	Estrogen (Estradiol in humans)	Reproductive system; breasts; growth and development; development of ovarian follicles
	Progesterone	Follicle-stimulating hormone (FSH) secretion
	Inhibin	? Relaxation of cervix and pubic ligaments
	Relaxin	Reproductive system; secondary sex characteristics; growth and development; sex drive; gamete development
<i>Testes: male</i>	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

<i>Heart</i>	Atrial natriuretic peptide (ANP, atriopeptin)	Sodium excretion by kidneys; blood pressure
<i>Hypothalamus</i>	Hypophysiotropic hormones: Corticotropin-releasing hormone (CRH) Thyrotropin-releasing hormone (TRH) 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)
<i>Kidneys</i>	Erythropoietin (EPO) 1,25-dihydroxyvitamin D	Erythrocyte production in bone marrow Calcium absorption in GI tract
<i>Leukocytes, macrophages, endothelial cells, and fibroblasts</i>	Cytokines [†] (these include the interleukins, colony-stimulating factors, interferons, tumor necrosis factors)	Immune defenses; immune cell growth and secretory processes
<i>Liver and other cells</i>	Insulin-like growth factor-I (IGF-I)	Cell division and growth of bone and other tissues
<i>Pancreas</i>	Insulin Glucagon Somatostatin (SS)	Organic metabolism; plasma glucose, amino acids and fatty acids
<i>Parathyroids</i>	Parathyroid hormone (PTH, parathormone)	Plasma calcium and phosphate; synthesis of 1,25-dihydroxyvitamin D
<i>Pineal</i>	Melatonin	? Sexual maturity; body rhythms

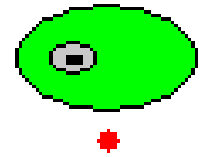
SITE PRODUCED (ENDOCRINE GLAND)	HORMONE	MAJOR FUNCTION* IS CONTROL OF:
<i>Pituitary glands:</i>		
<i>Anterior pituitary</i>	Growth hormone (somatotropin)	Growth, mainly via local production of IGF-I; protein, carbohydrate, and lipid metabolism
	Thyroid-stimulating hormone (thyrotropin)	Thyroid gland
	Adrenocorticotrophic 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	
<i>Posterior pituitary⁵</i>	Oxytocin	Milk let-down; uterine motility
	Vasopressin (antidiuretic hormone, ADH)	Blood pressure; water excretion by the kidneys
<i>Placenta</i>	Human chorionic gonadotropin (hCG)	Secretion by corpus luteum
	Estrogens	See Gonads: ovaries
	Progesterone	See Gonads: ovaries
	Human placental lactogen (hPL)	Breast development; organic metabolism
<i>Thymus</i>	Thymopoietin	T-lymphocyte function
<i>Thyroid</i>	Thyroxine (T ₄)	Metabolic rate; growth; brain development and function
	Triiodothyronine (T ₃)	? Plasma calcium
	Calcitonin	
<i>Multiple cell types</i>	Growth factors [‡] (e.g., epidermal growth factor)	Growth and proliferation of specific cell types
<i>Other (blood)</i>	Angiotensin II	Blood pressure; production of aldosterone from adrenal cortex

What is a hormone (激素) ?



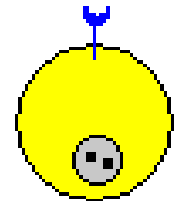
■ Definition

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



■ Functions

- Regulation of metabolism, growth and development, water and electrolyte balance, reproduction, and behavior





Hormone

- **Types of Hormones**

- **Proteins and peptides**（蛋白质和肽类）

- The majority of hormones (3 to 200 amino acids), lipid insoluble e.g., insulin, prolactin, oxytocin, GH

- **Steroids**（类固醇或甾体类）

- Made from cholesterol, lipid soluble, from gonads and adrenal cortex, e.g. cortisol, androgen

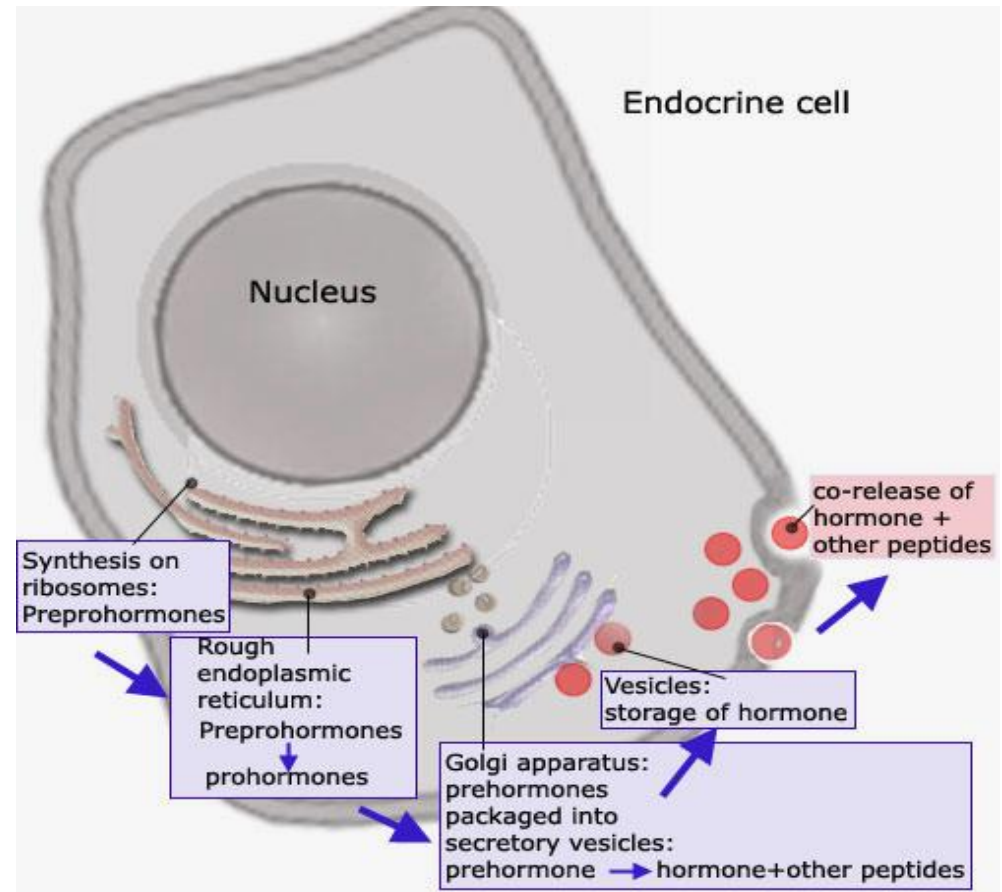
- **Amines**（胺类）

- Derivatives of the amino acid tyrosine, e.g., adrenaline, thyroxine (T4), lipid insoluble

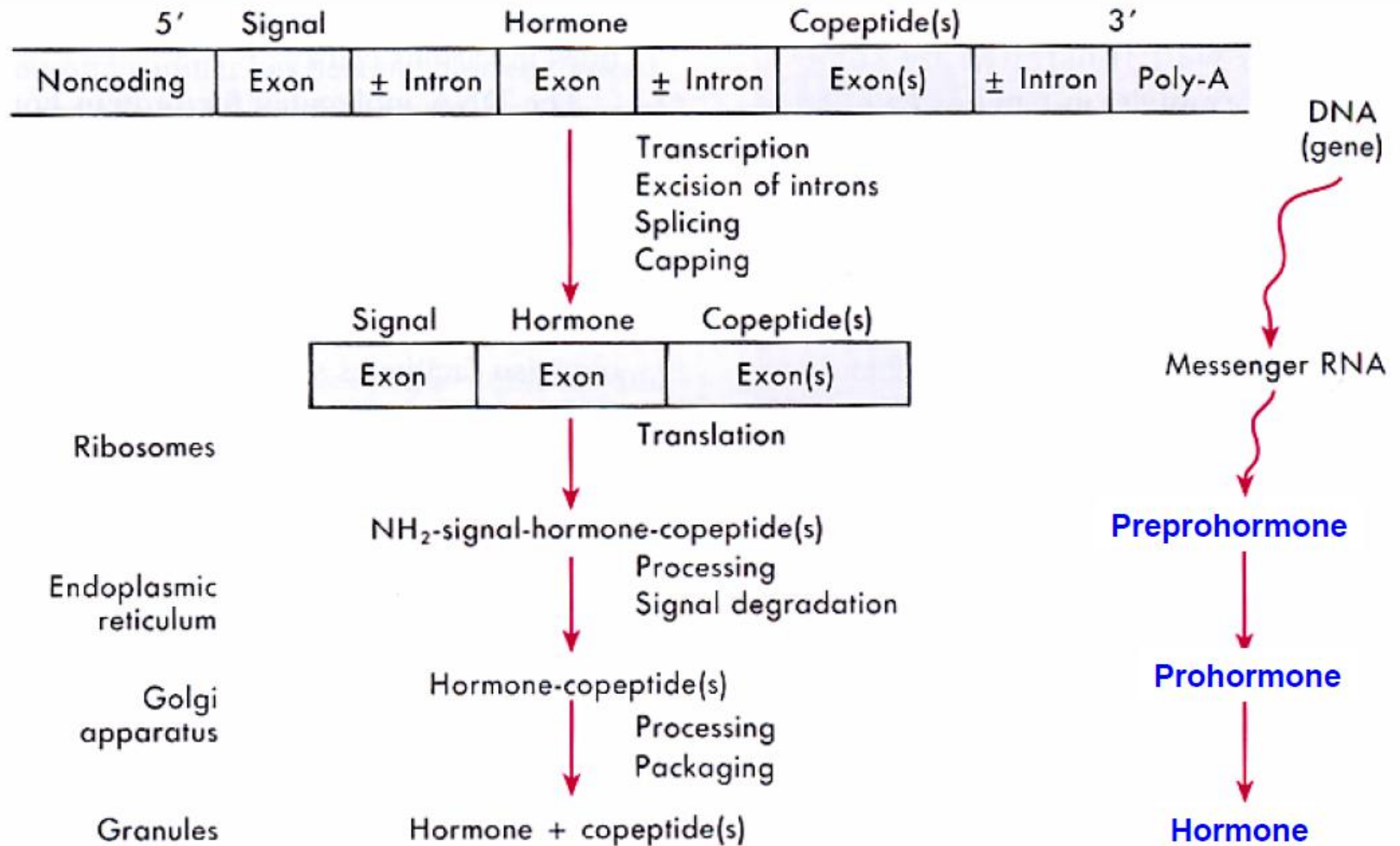
Hormone

■ Synthesis

- Polypeptide H
- Protein H



Peptide Hormone Synthesis





Typical synthesis of peptide hormones

- **Preprohormones (前激素元) - larger hormones produced on the ribosomes of the endocrine cells**
- **Prohormones (激素元) - 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**

Synthesis

Packaging

Storage

Secretion

Preprohormone

Prohormone

Hormone

Hormone
(and any "pro"
fragments)

↓
Prohormone

↓
Hormone

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Plasma membrane

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

pre-pro-insulin → **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

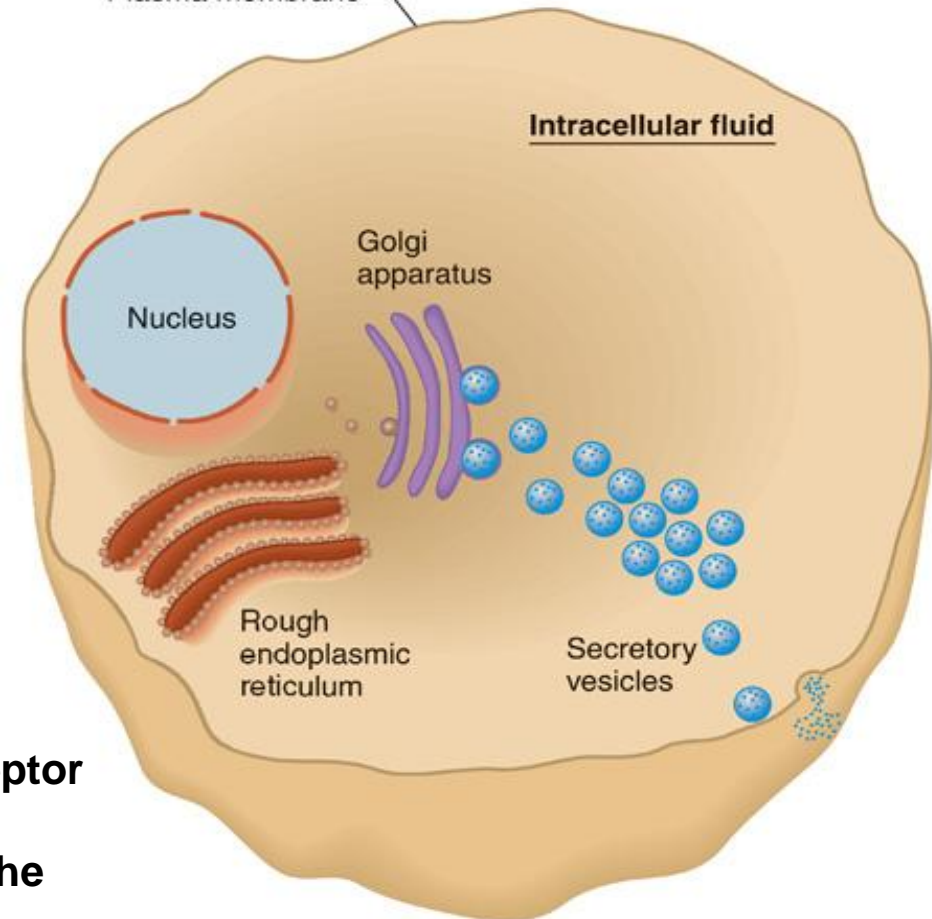


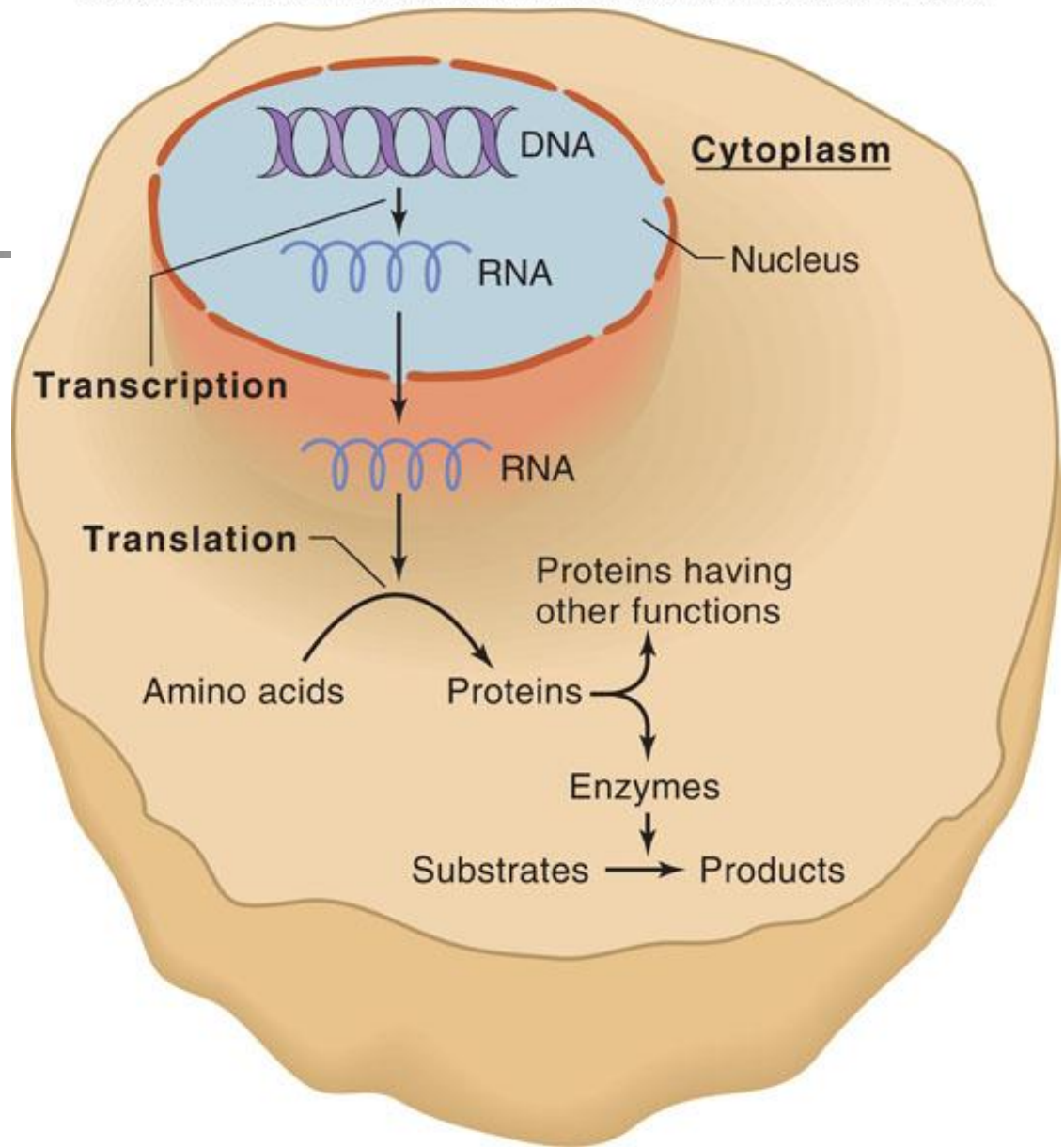
Figure 3-16

NUCLEUS

The DNA code is “transcribed” into mRNA.

RIBOSOMES

The mRNA is “translated” to give instructions for proteins synthesis.



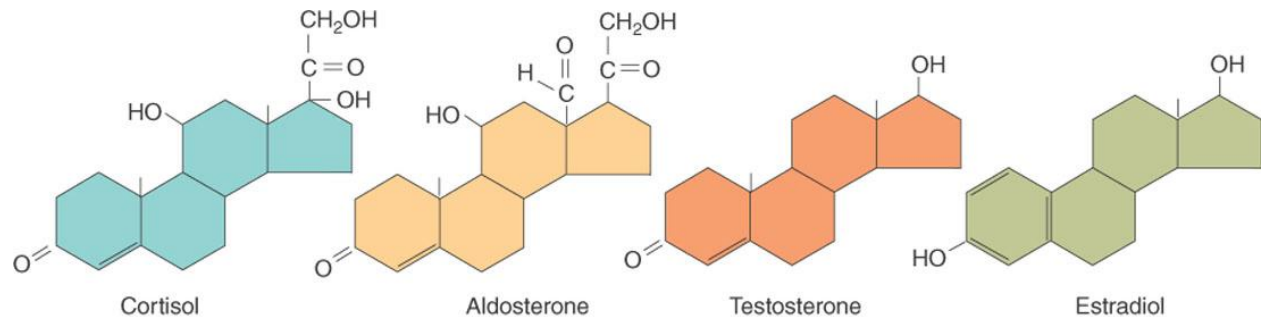
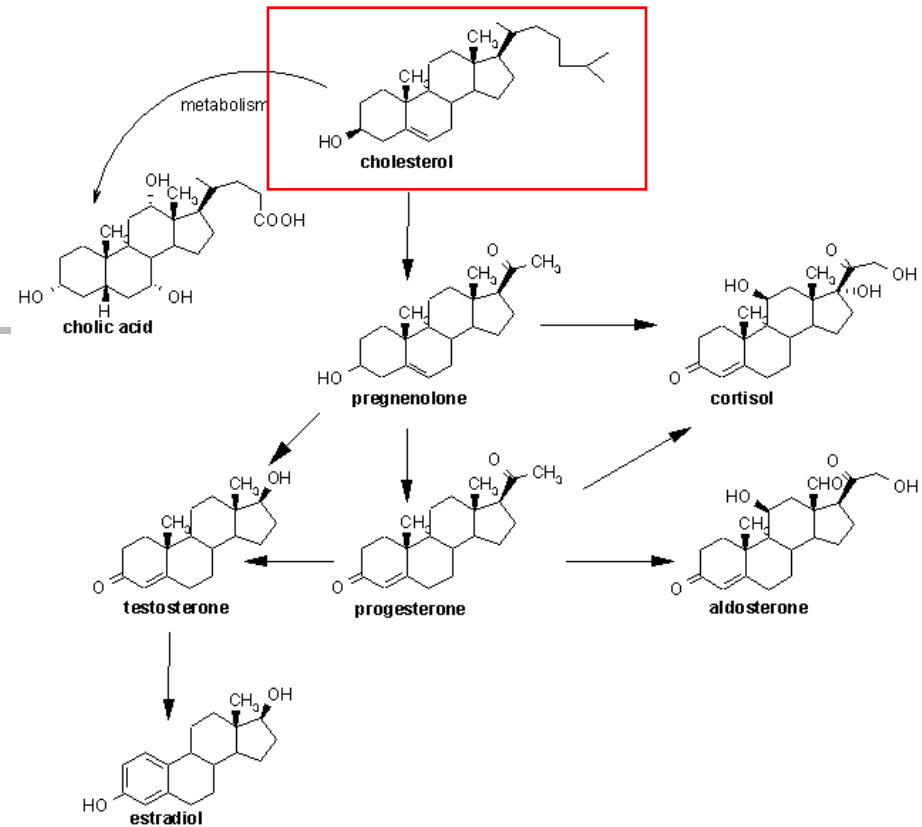
Hormone

■ Synthesis

■ Steroid hormones

■ From cholesterol (胆固醇)

■ Not stored





Hormone

- **Synthesis**

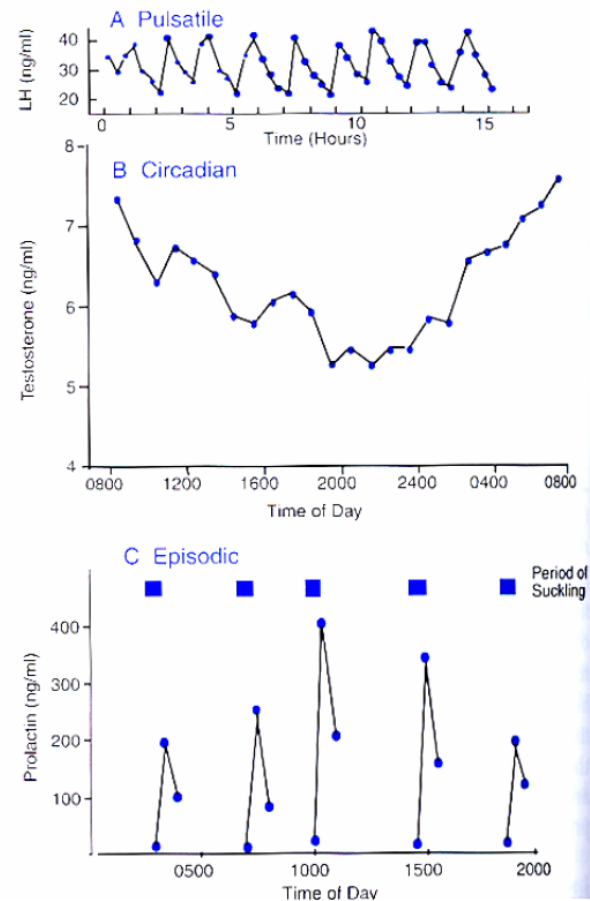
- **Amine hormones**

- **From tyrosine (酪氨酸)**

- **Be stored**

Hormone

- **Secretion (分泌)**
 - Concentrations of Hs in the blood
 - pg/mL ~ μ g/mL
 - Hormonal secretion rate
 - μ g/day ~ mg/day
 - Rhythmic secretion (pulses)
 - Diurnal (日周期)
 - daily, occurring in a 24-hour cycle
 - growth hormone, cortisol
 - Cyclic (月周期)
 - oestrogen, progesterone, LH





Hormone

- **Transport of Hs in the blood**
 - Peptides and catecholamine (儿茶酚胺)
 - water soluble
 - dissolve in blood
 - circulate in blood mainly in free form
 - Steroid and thyroid hormones (甲状腺激素)
 - circulate in blood mainly bound to plasma proteins
 - the free form is biologically active
 - the greater binding, the longer half-life



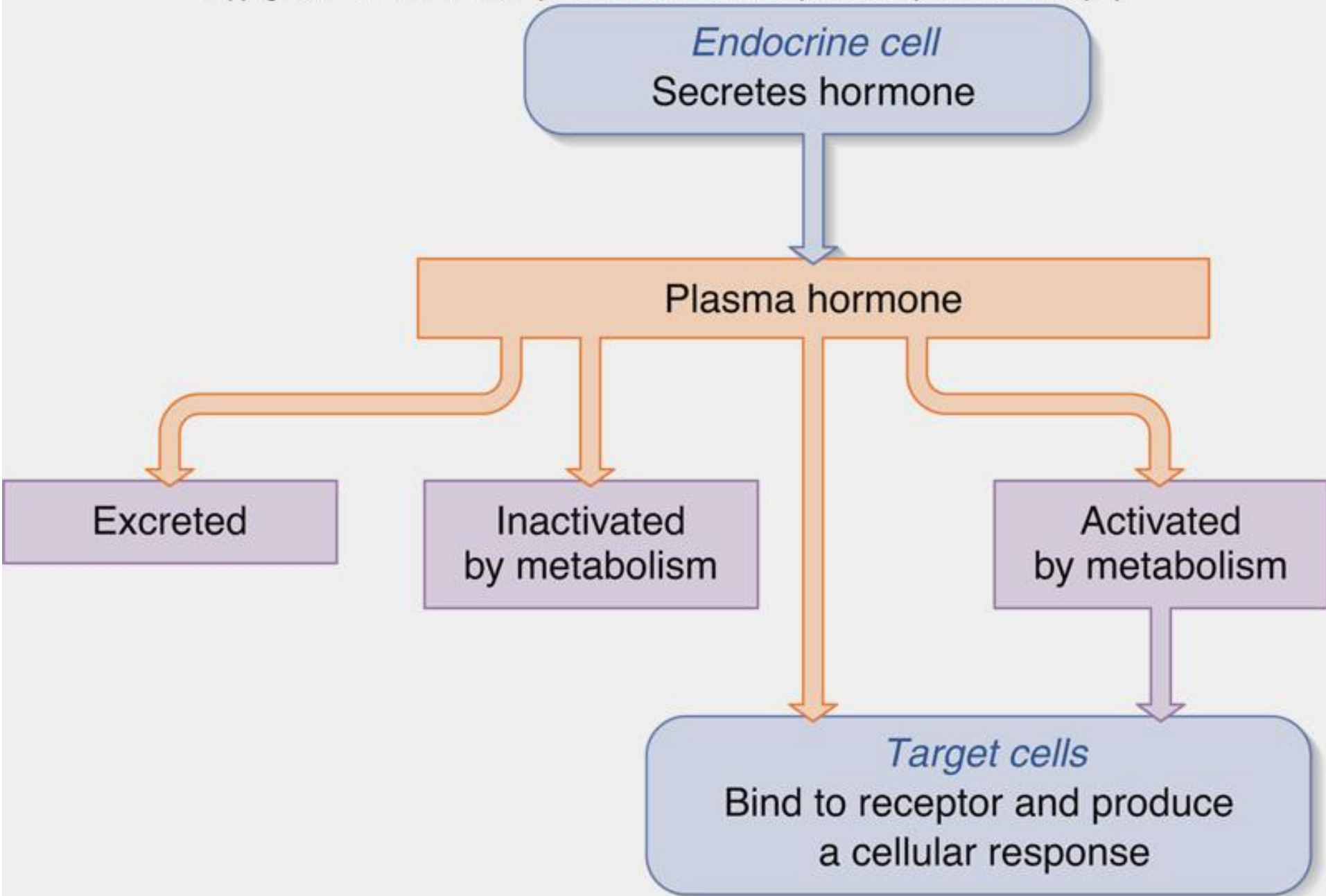
Half-life

- Persistence of a hormone in blood
- A time indicating half of its activity remaining
- Is brief
 - Free: min
 - Binding: mins, hrs, days
 - e.g. T4 (6 days); Insulin (0.006 days)
- But effects can last for several minutes to hours



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





Hormone

- **Clearance of Hs from the blood**
 - **Ways**
 - Metabolic destruction by the tissues
 - Binding with the tissues
 - Liver
 - Kidney



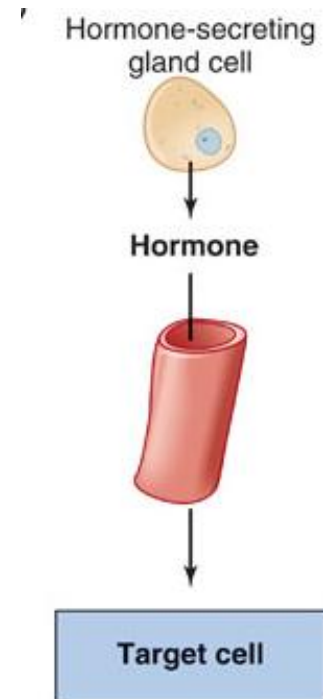
Modes of Action

内分泌方式

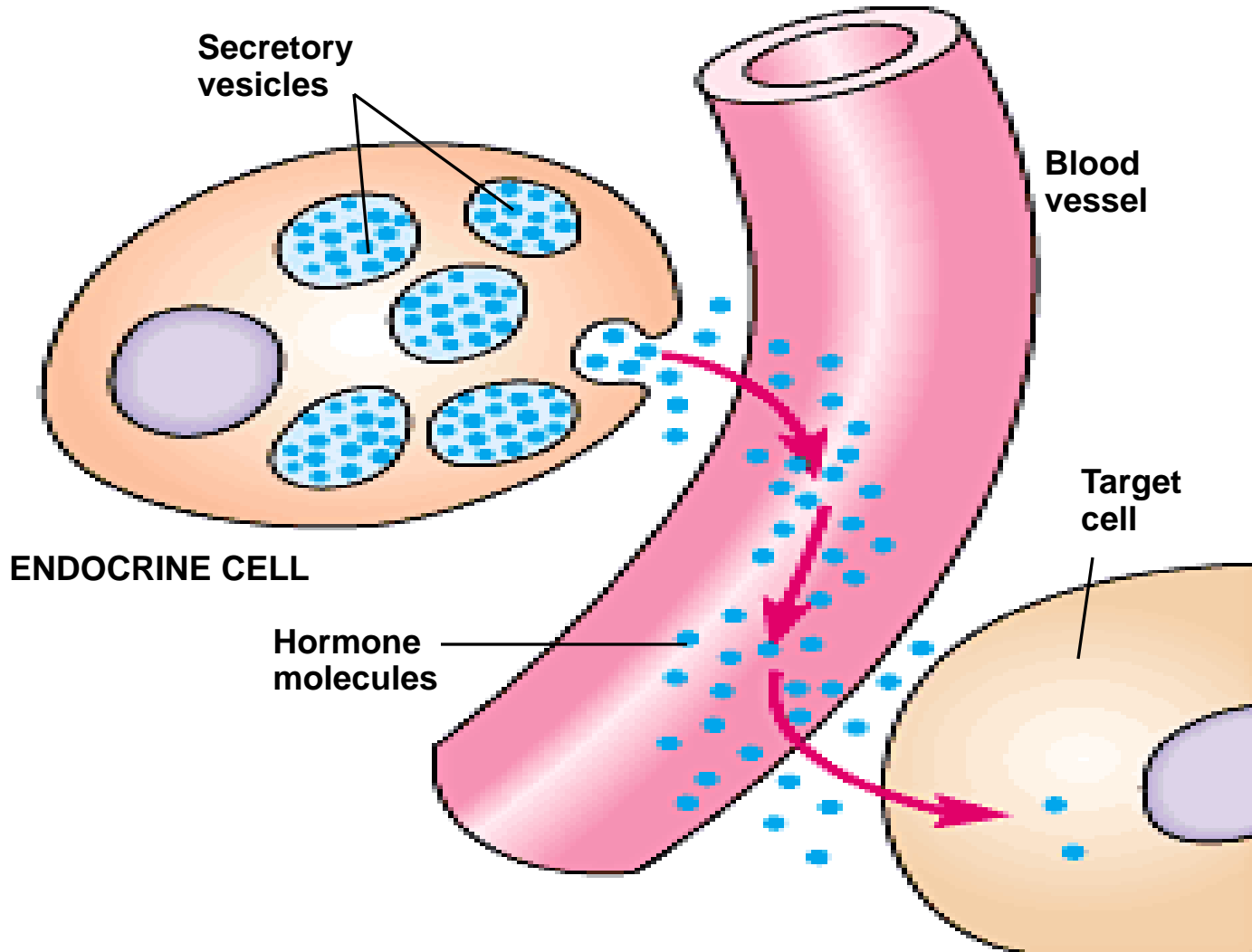
- **Can be categorized by the site of action relative to the site of secretion.**
 - **Endocrine (内分泌)**
 - **Paracrine (旁分泌)**
 - **Autocrine (自分泌)**
 - **Neurocrine (神经分泌)**

Endocrine secretion

- From gland via blood into a distance
- Substance released by cell into bloodstream that affects distant cells.
e.g. testosterone (睾酮) is secreted by Leydig cells in testis.

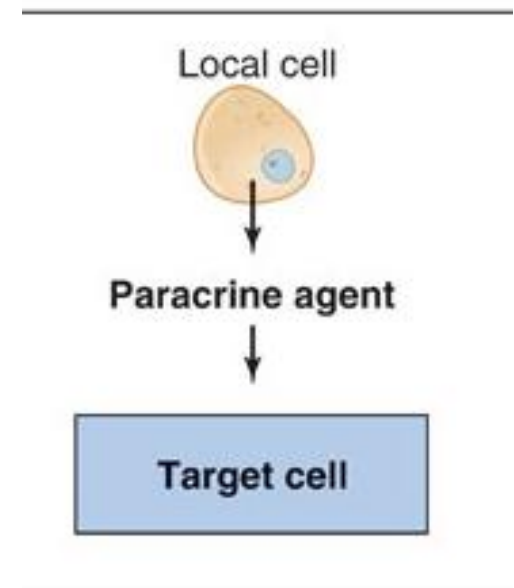


Hormone from an endocrine cell



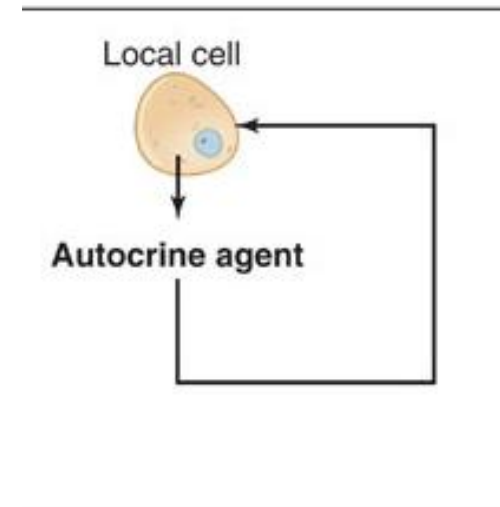
Paracrine secretion

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



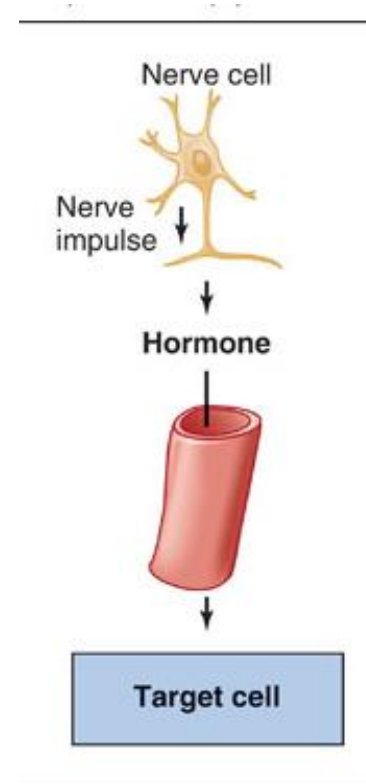
Autocrine secretion

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

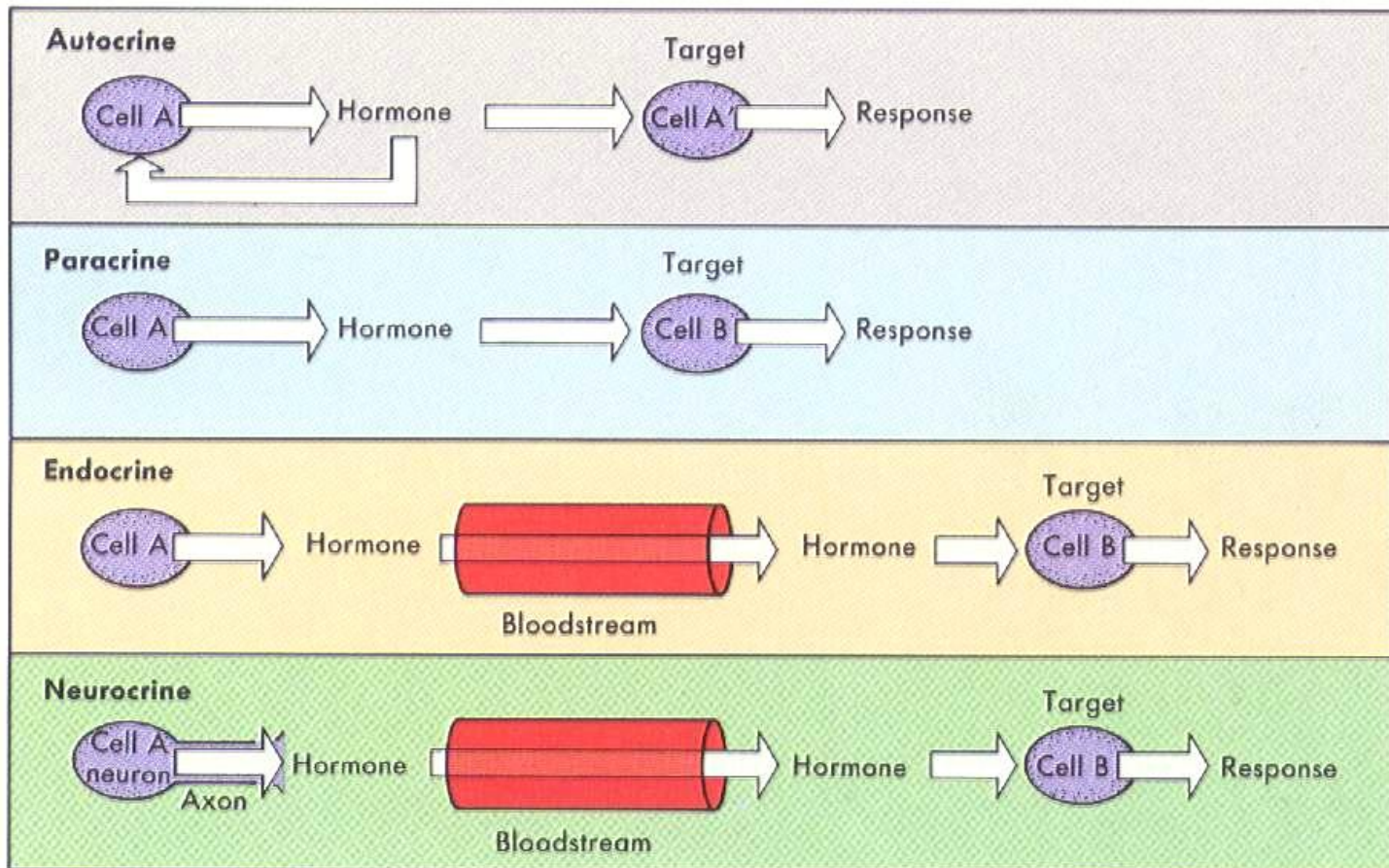


Neurocrine secretion

- **Secreted by nerve endings, via axonal transport and then via blood**



Endocrine route





A secretion may have several sites of action simultaneously.

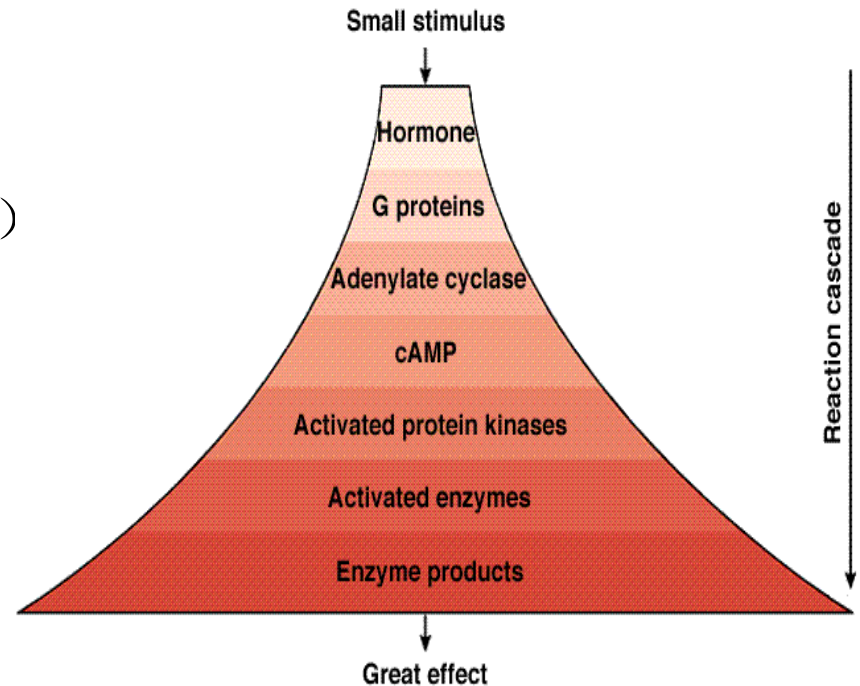
Example:

- **Norepinephrine (去甲肾上腺素)**
 - ***Autocrine* action causes negative feedback on secretion.**
 - **Simultaneously, *endocrine* action causes respiration rate to ↑, peripheral blood vessels to constrict, etc.**

Hormone

■ Characteristics

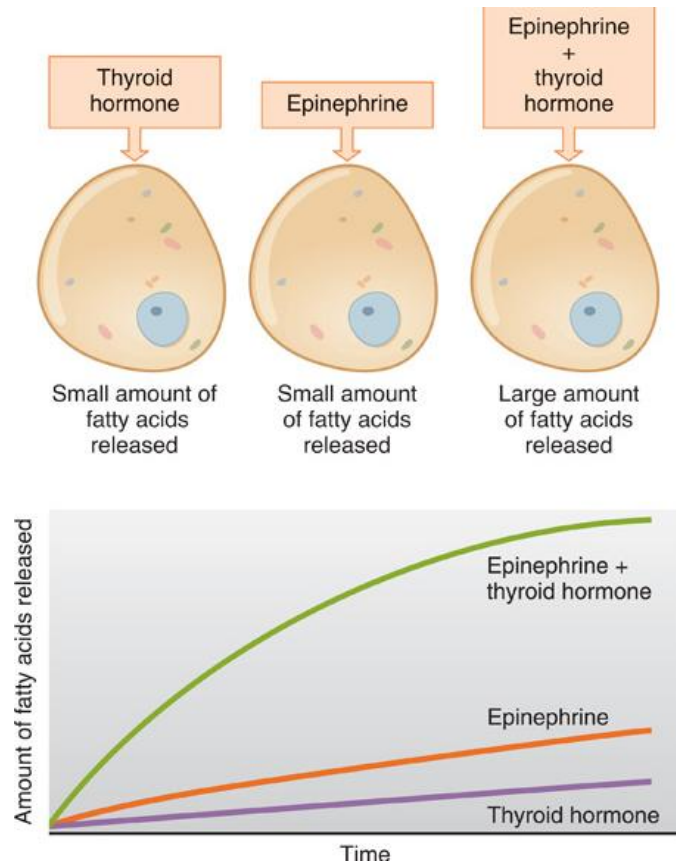
- Regulates **rate of reaction**
- Specificity (特异性)
- Amplification effect (放大效应)



Hormone

■ Characteristics

- Interaction between hormones
 - Synergistic action (协同作用)
 - Antagonistic action (拮抗作用)
 - **Permissive action (允许作用)**
 - **Hormone A must be present for the full strength of hormone B's effect.**
 - **Up-regulation of one hormone's receptors by another hormone**



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)

Hormone

- **Mechanism of hormone action (激素作用机制)**

- **Receptor (受体)**

- Membrane receptor
- Intracellular receptor

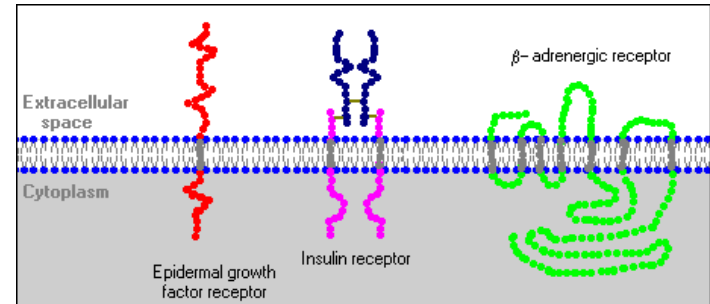
- **Regulation of Receptors**

- Up-regulation (上调)

- An increase in the number of a H's receptor
- Resulting from a prolonged exposure to a low concentration of the H
- ↑ target cell responsiveness to the H

- Down-regulation (下调)

- ↓ in number of receptors for a hormone in the target cell





Hormone

- **Mechanisms of hormone actions**
 - **Peptide/protein Hs**
 - Proteins and peptides cannot freely penetrate plasma membrane (**fixed receptor**)
 - Involve a **second messenger** (第二信使)
 - Bind to a specific receptor and activate the intracellular second messenger, e.g., ACTH, parathyroid hormones



Hormone

- **Mechanism of action**

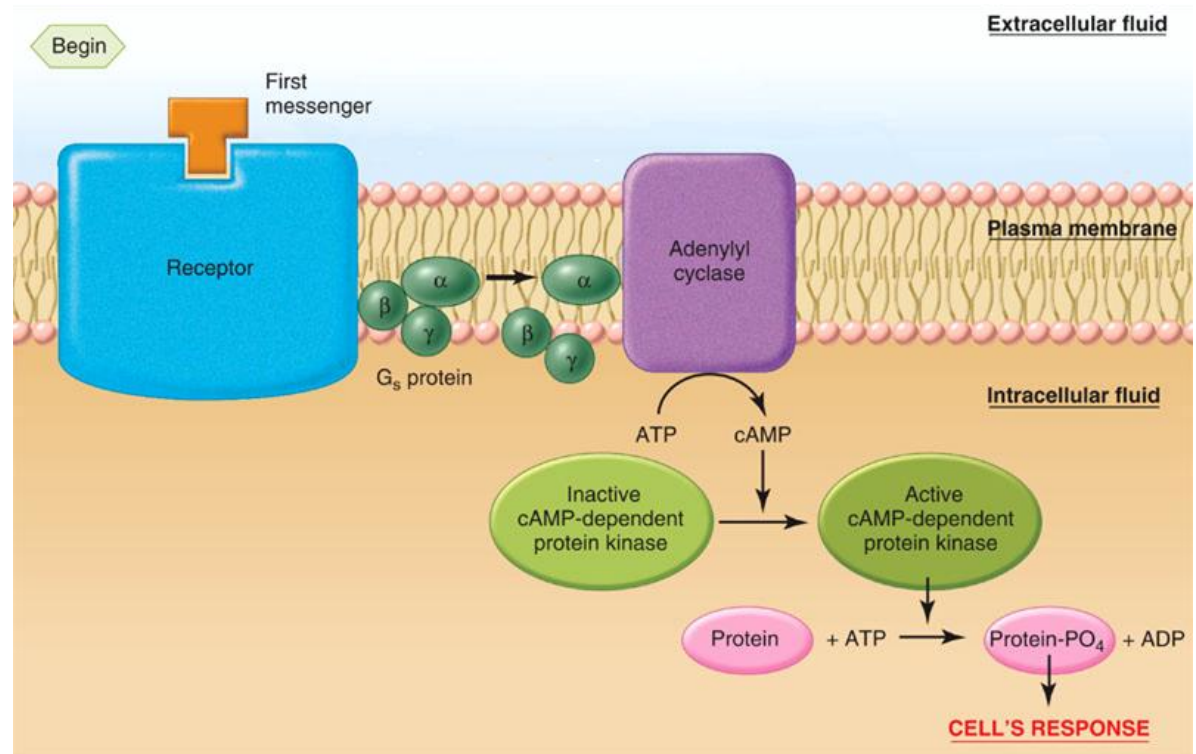
- **Peptide/protein Hs**

- **Second messenger mechanisms (第二信使学说)**

- AC-cAMP second messenger system
- Cell membrane phospholipids second messenger system
- Calcium-calmodulin (钙调蛋白) second messenger system

Hormone

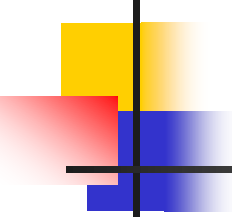
- Mechanism of action
 - Peptide/protein Hs
 - cAMP second messenger system





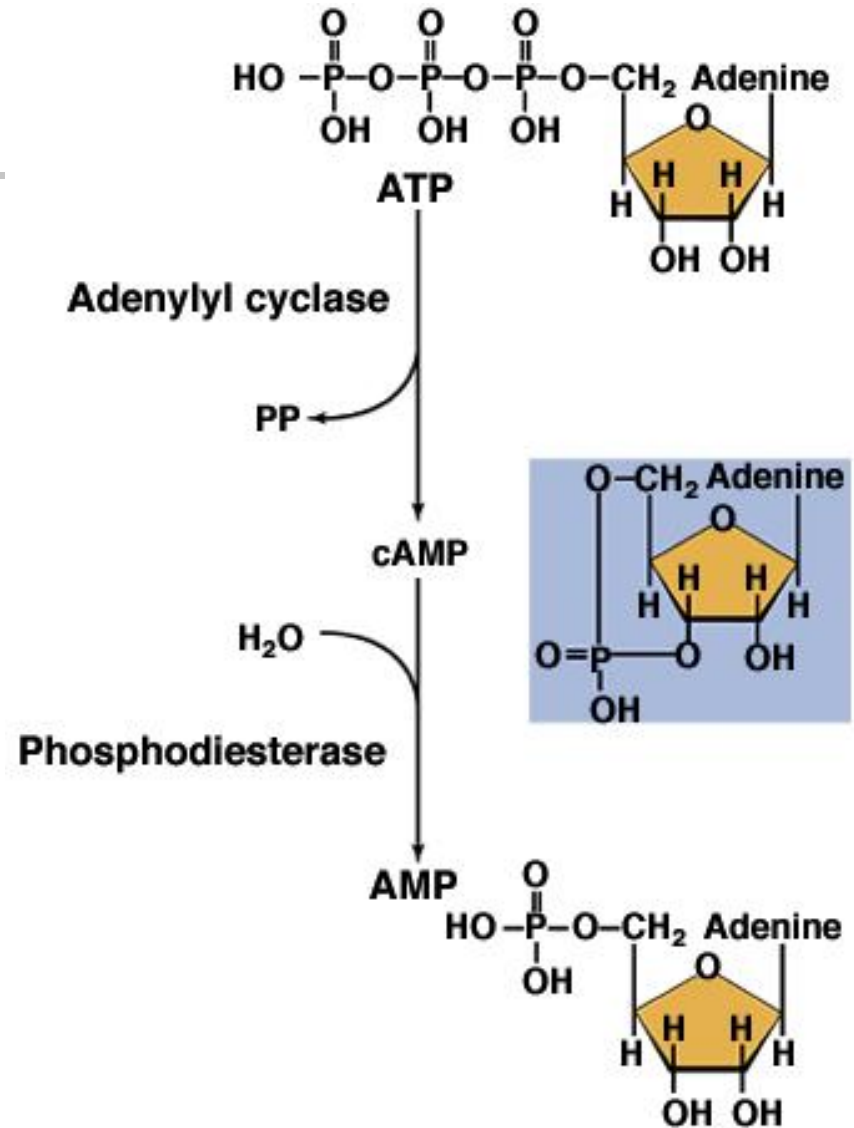
Cyclic AMP signaling-sequence of events

- 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



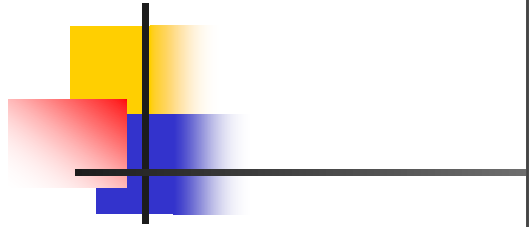
Adenylyl cyclase forms cAMP, a “second messenger” that activates enzymes used in cellular responses.

The phosphodiesterase enzymes “terminate” the second messenger cAMP.



Amplification effect

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Number of molecules

1

Messenger-receptor

1

Active adenylyl cyclase

100

cAMP

100

Active protein kinase

10,000


Phosphorylated enzyme

1,000,000

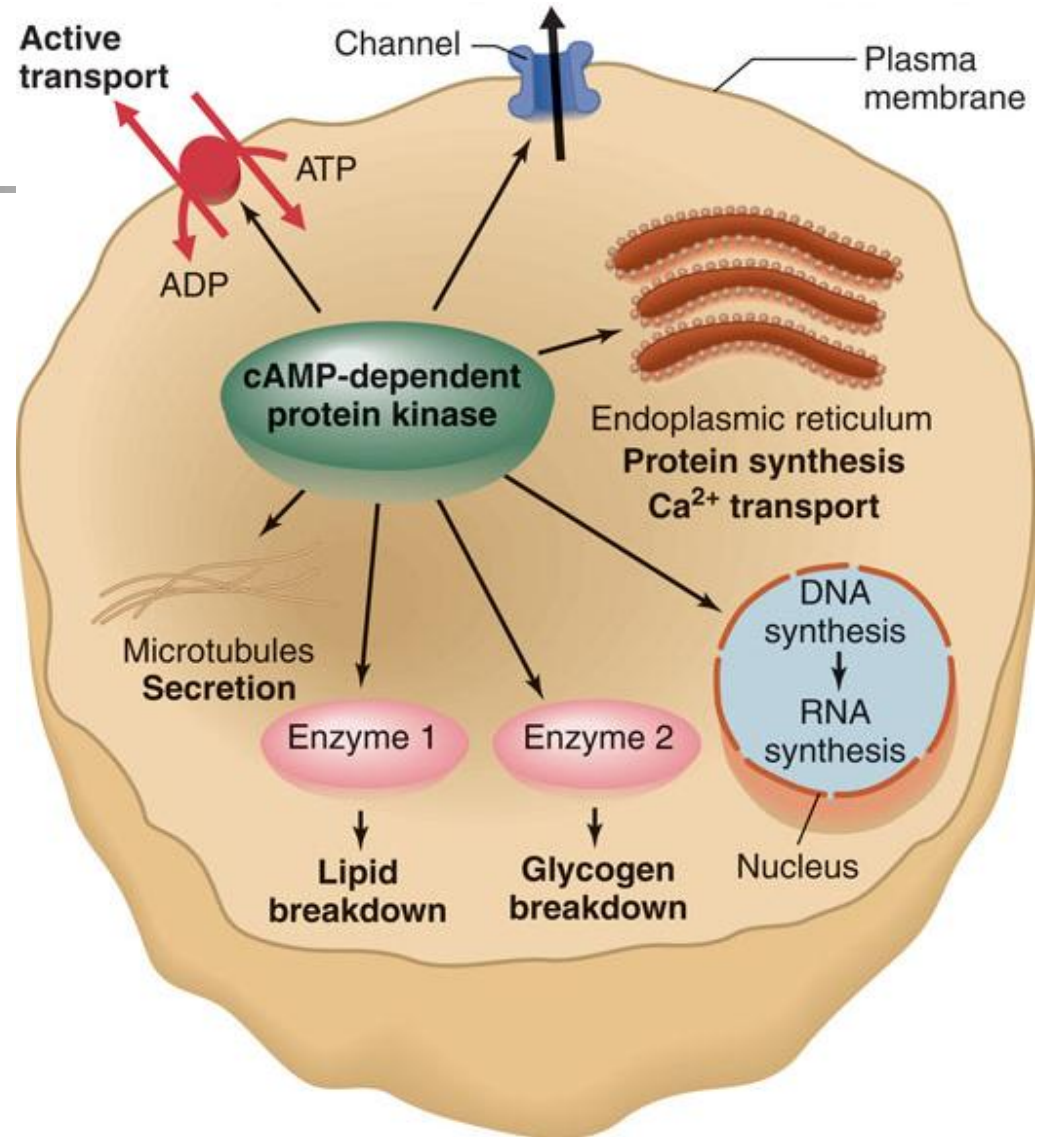
Products

Each protein kinase can catalyse hundreds of reactions

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

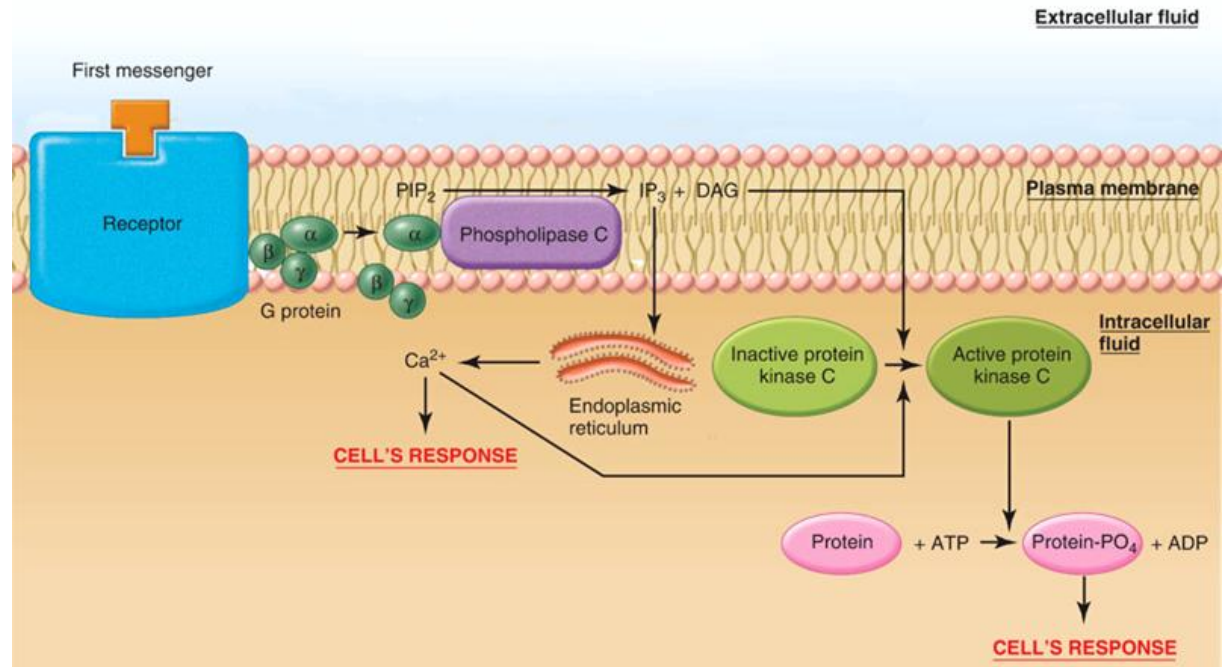


Cells can respond via the cAMP pathways using a diversity of cAMP-dependent enzymes, channels, organelles, contractile filaments, ion pumps, and changes in gene expression.



Hormone

- Mechanism of action
 - Peptide/protein Hs
 - Phospholipids second messenger system

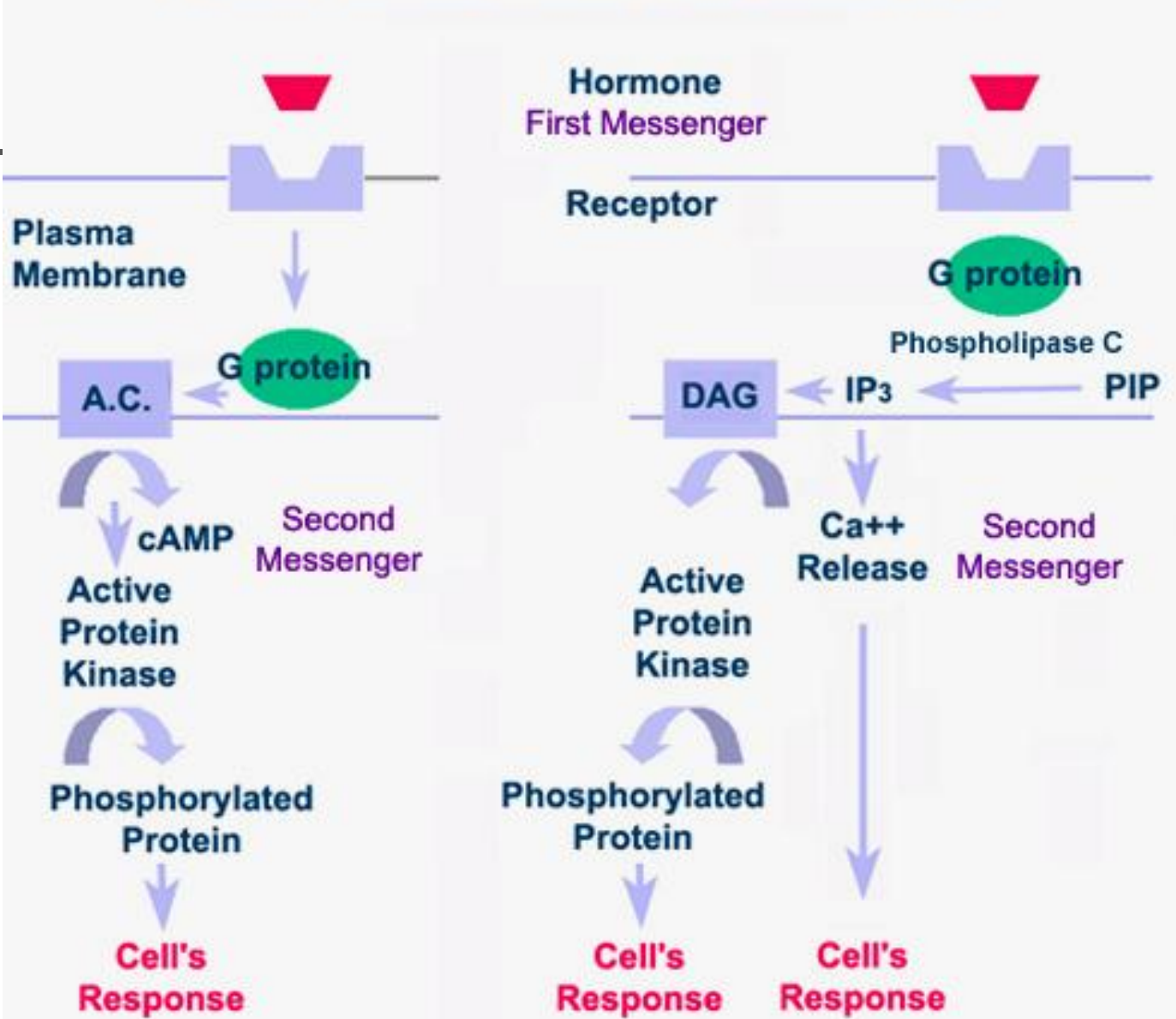




PIP-calcium signaling mechanism

- 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 specific enzymes' activity and ion channels or bind to the regulatory protein calmodulin;
- *Calmodulin* also activates specific enzymes to amplify the cellular response

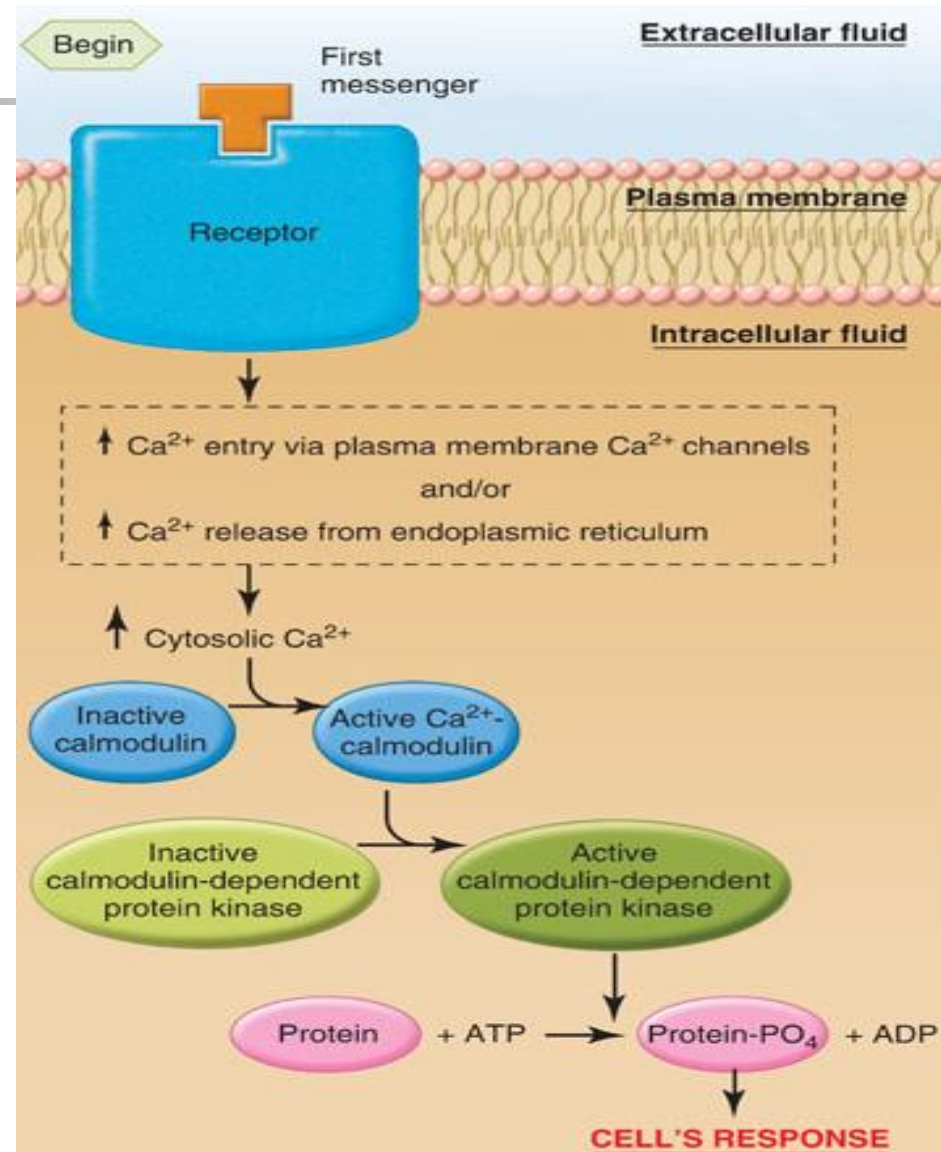
Peptide Hormone Action: Two Mechanisms



Hormone

- Mechanism of action
 - Peptide/protein Hs
 - Calcium-calmodulin second messenger system

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.





Hormone

- **Mechanism of action**
 - **Second messengers**
 - cAMP, cGMP, IP₃, DG, Ca²⁺

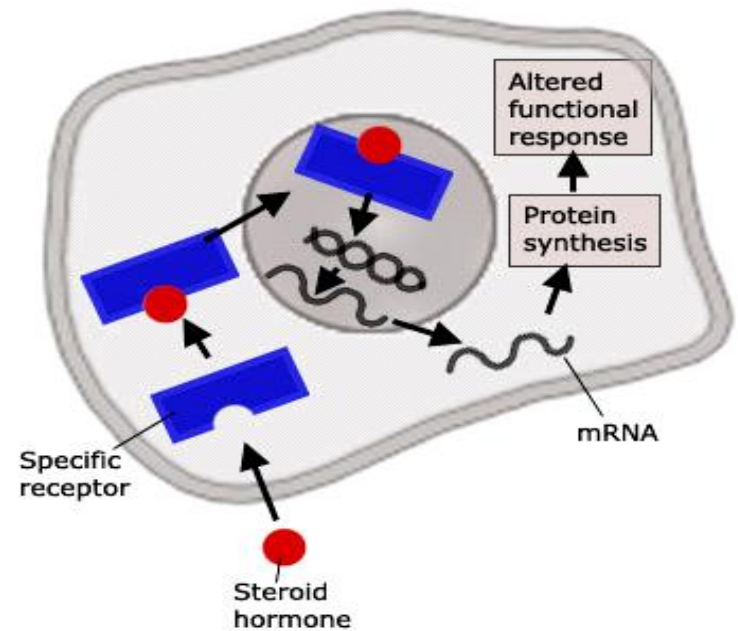
Second Messenger	Examples of Hormones Which Utilize This System
Cyclic AMP	<u>Epinephrine and norepinephrine</u> , <u>glucagon</u> , <u>luteinizing hormone</u> , <u>follicle stimulating hormone</u> , <u>thyroid-stimulating hormone</u> , <u>calcitonin</u> , <u>parathyroid hormone</u> , <u>antidiuretic hormone</u>
Protein kinase activity	<u>Insulin</u> , <u>growth hormone</u> , <u>prolactin</u> , <u>oxytocin</u> , erythropoietin, several growth factors
Calcium and/or phosphoinositides	<u>Epinephrine and norepinephrine</u> , angiotensin II, <u>antidiuretic hormone</u> , gonadotropin-releasing hormone, thyroid-releasing hormone.
Cyclic GMP	Atrial naturetic hormone, nitric oxide

Hormone

- Mechanism of action
 - Steroid hormones
 - Modulation of gene expression
 - Steroid hormones bind to intracellular receptors



Steroid hormone receptor



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

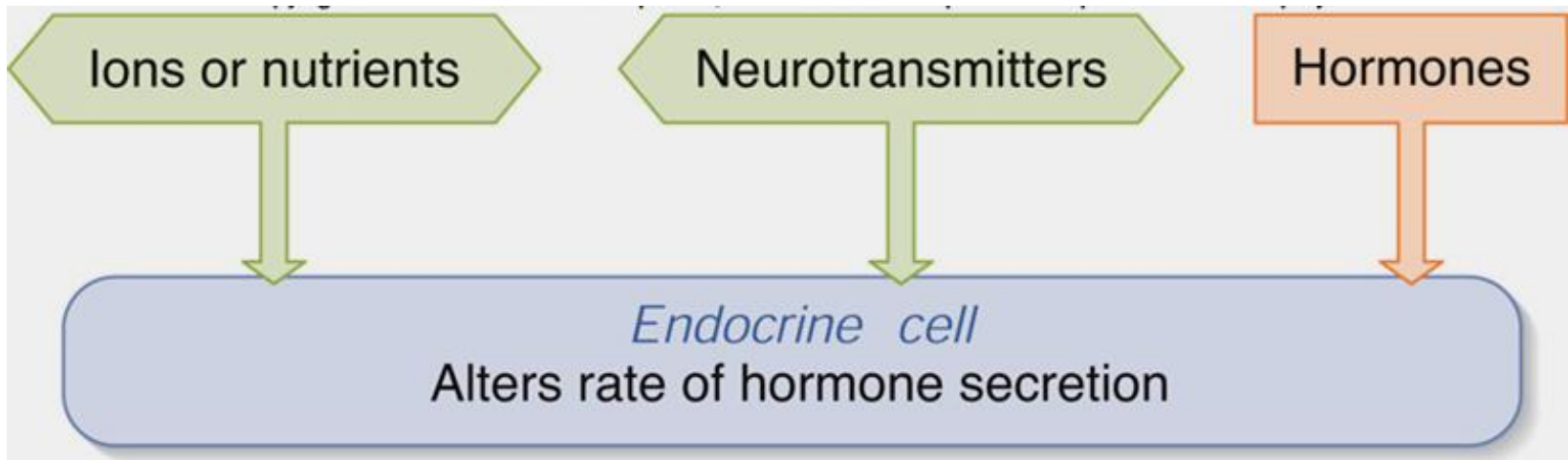


Sequence of events for steroid hormone binding

- **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**

Hormone

- **Control of H secretion** (激素分泌调控)
 - Three types of inputs to endocrine cells that stimulate or inhibit hormone secretion.



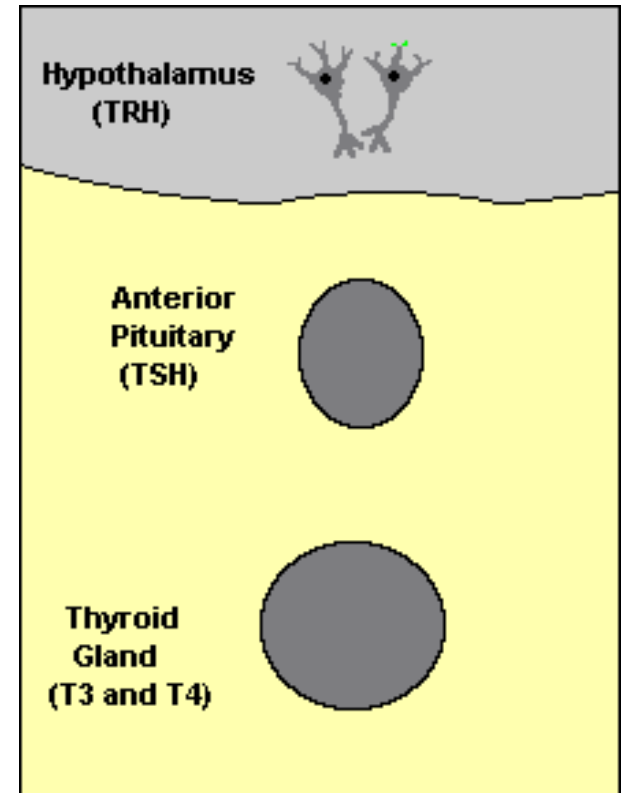


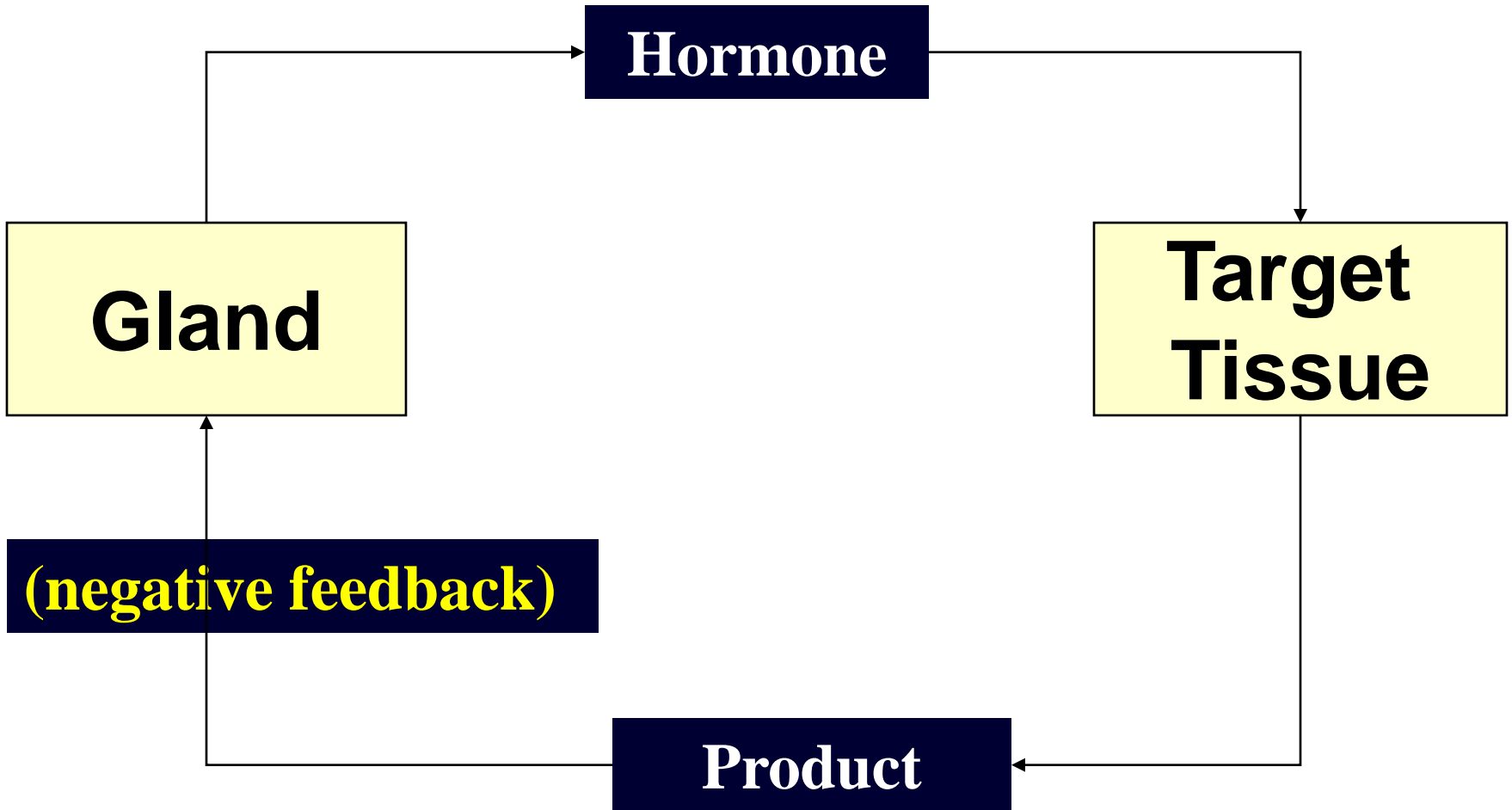
Hormone

- **Control of H secretion**
 - **By negative feedback (负反馈)**
 - By positive feedback (正反馈)

Regulation of hormone secretion

- 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.







Regulation of hormone secretion

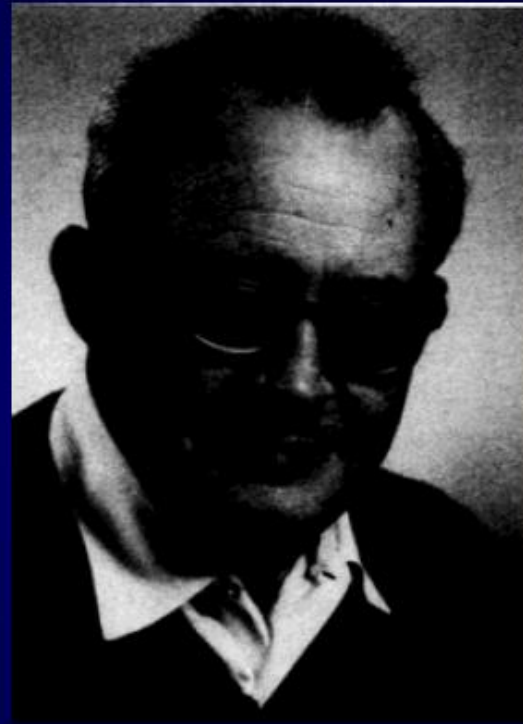
■ Positive Feedback

- 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.

Radioimmunoassay (RIA)

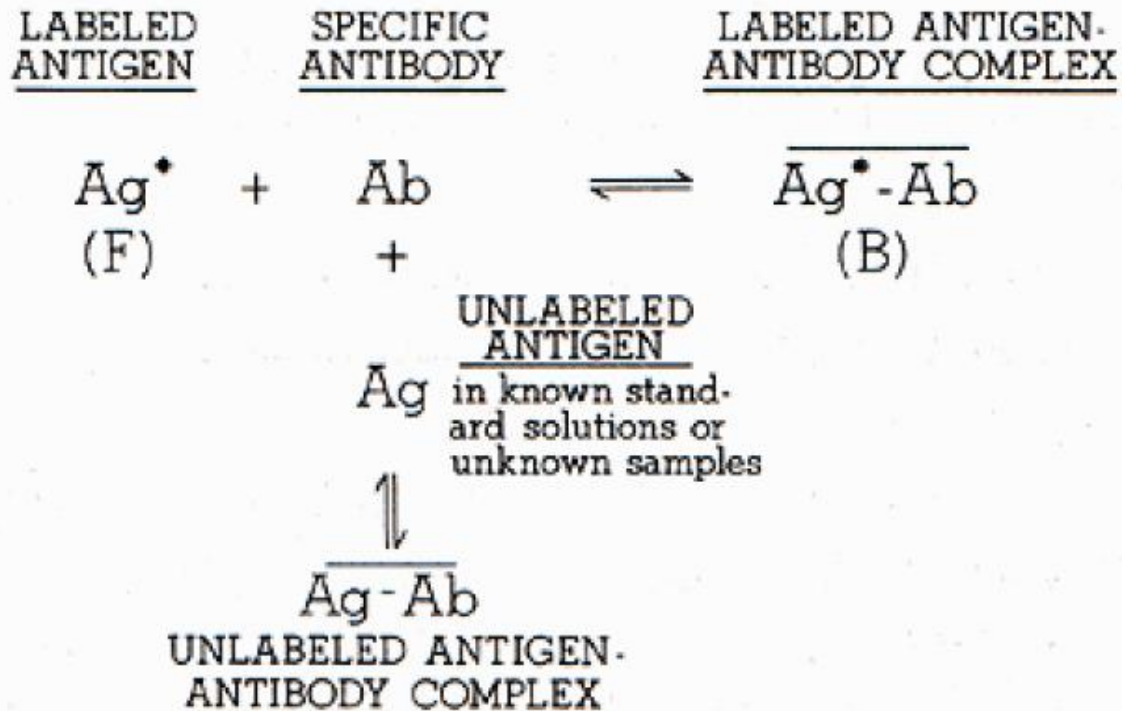


Dr. Rosalyn Yalow

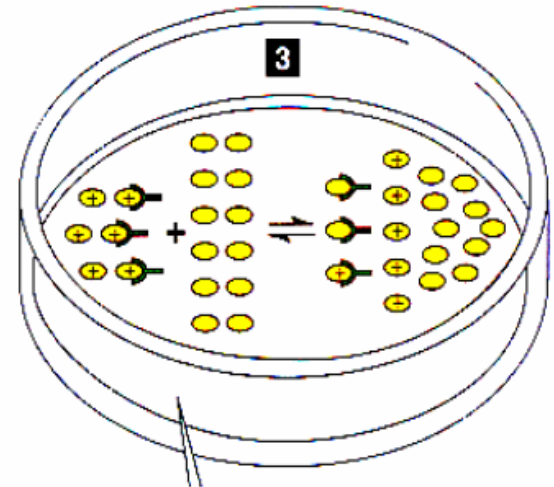
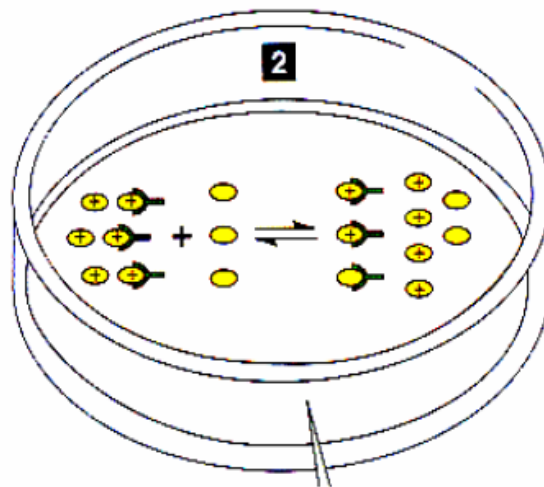
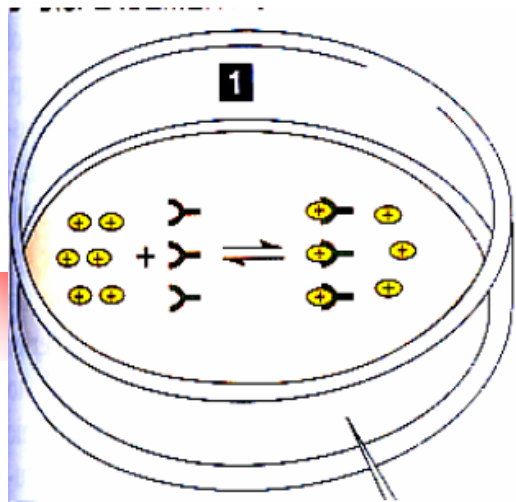


Dr. Solomon Berson

Radioimmunoassay (RIA)



(from the Nobel lecture by Dr. Rosalyn Yalow, 1977)

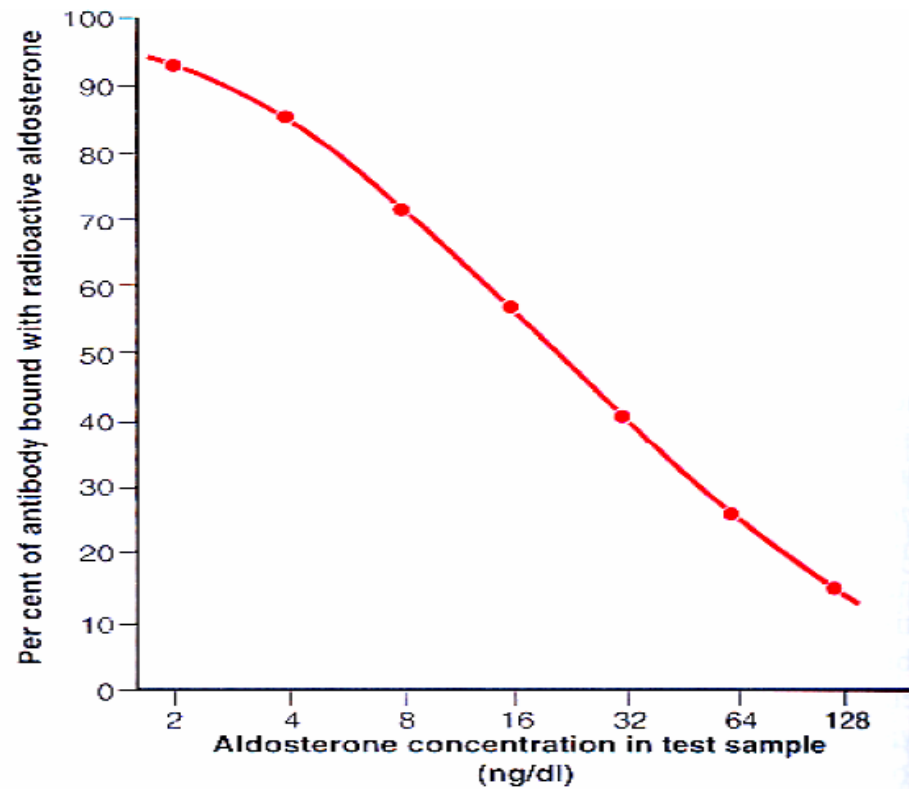


Y = Antibody

⊕ = Labeled hormone

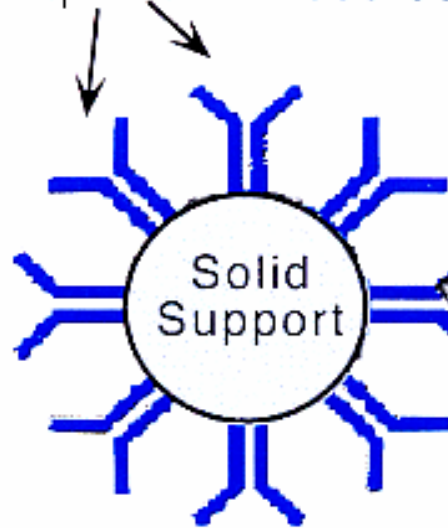
● = Unlabeled hormone

RIA



Enzyme-Linked Immunosorbent Assay (ELISA)

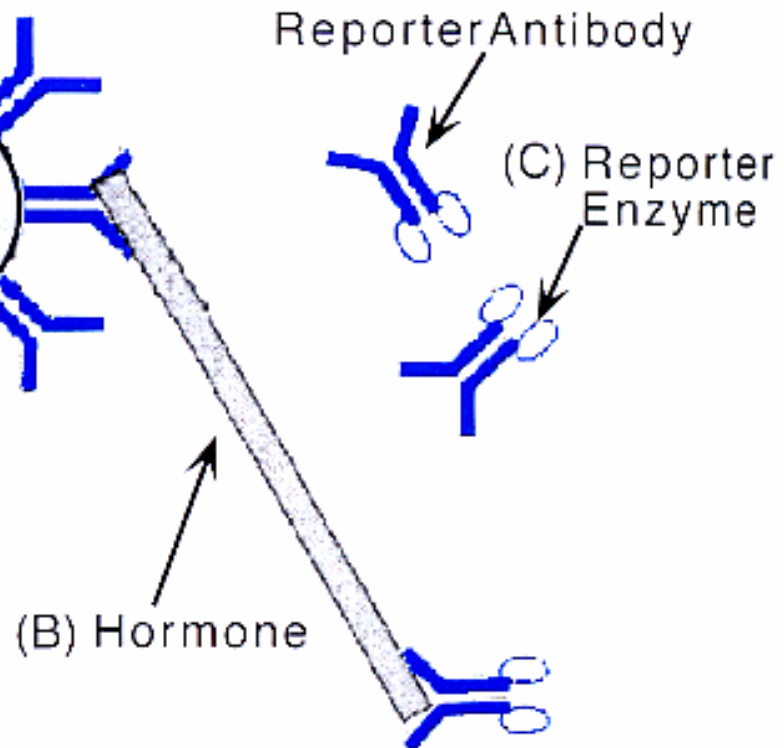
(A) Capture Antibodies



(B) Hormone

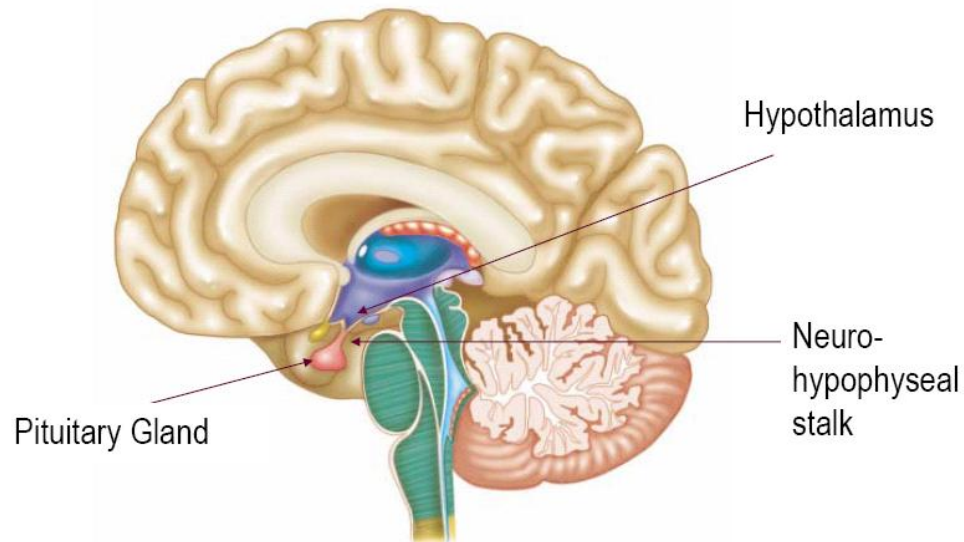
Reporter Antibody

(C) Reporter Enzyme



Hypothalamus and pituitary

下丘脑和垂体



Hypothalamus and pituitary

- **Hypophyseal portal system**

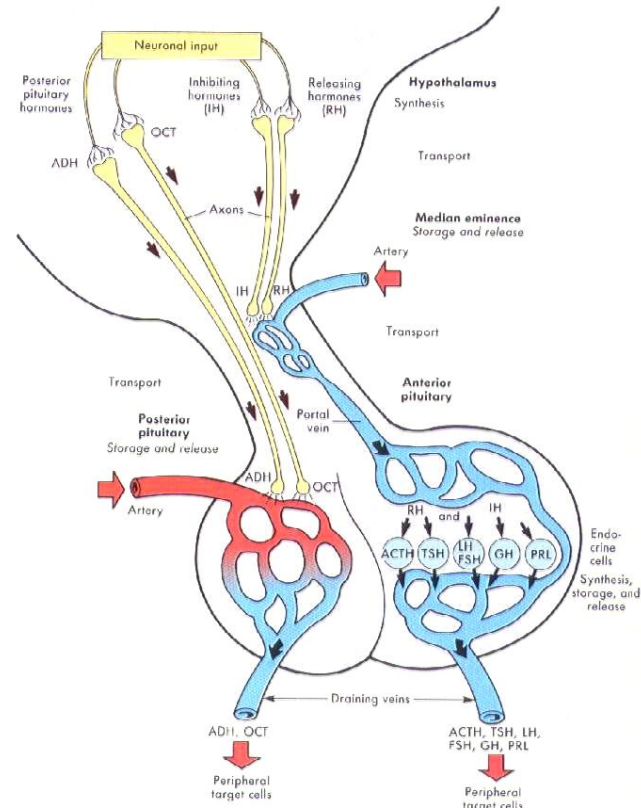
(垂体门脉系统)

- 下丘脑—腺垂体

- **Hypothalamohypophyseal tract**

(下丘脑垂体束)

- 下丘脑—神经垂体





Hypothalamus-Adenohypophysis system

■ Hypothalamus

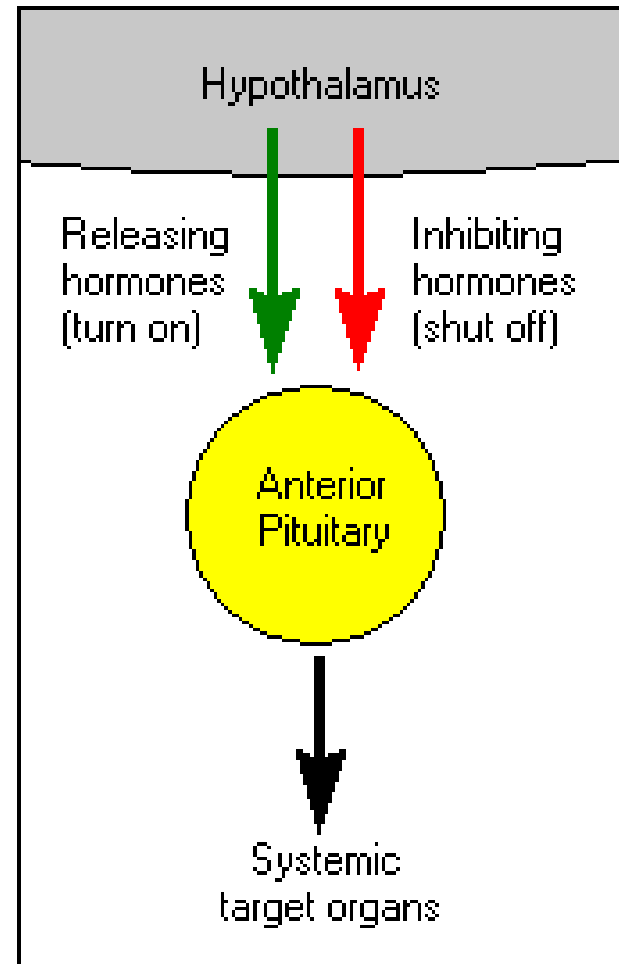
■ Neuroendocrine Cells (神经内分泌细胞)

■ Peptidergic neuron (肽能神经元)

- Magnocellular neuroendocrine cell
- Parvocellular neuroendocrine cell

Hypothalamus-Adenohypophysis system

- Hypothalamus
 - Hypophysiotrophic area
(下丘脑促垂体区)
 - Releasing H
 - Release-inhibiting H

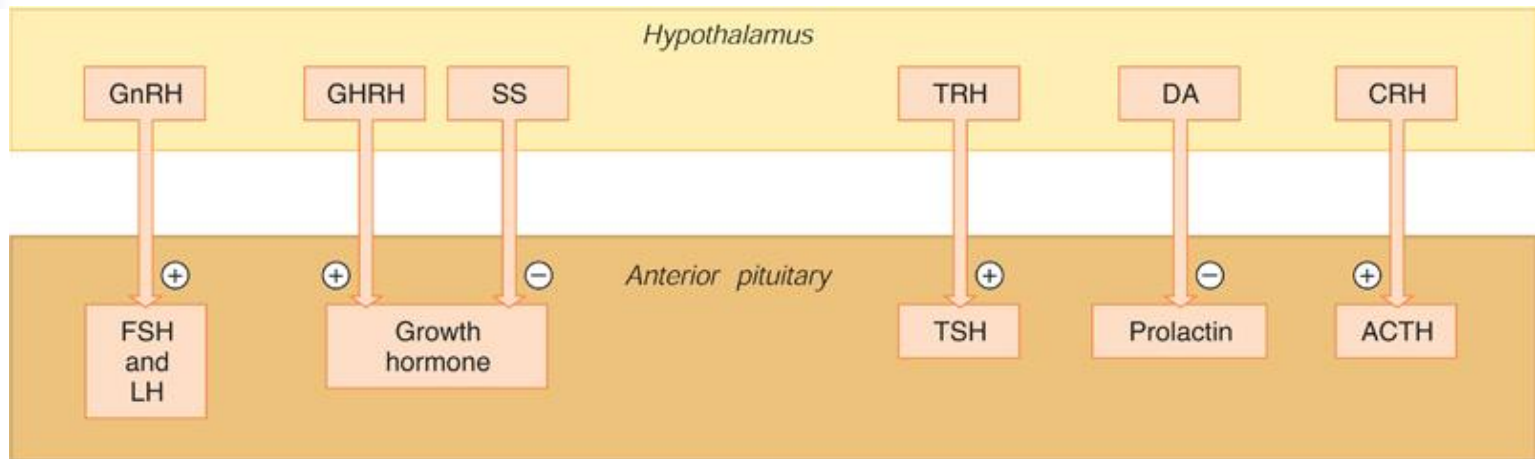




Hypothalamus-Adenohypophysis system

- **Hypothalamic regulatory peptide**
 - Thyrotropin-releasing hormone (TRH)
 - Gonadotropin-releasing hormone (GnRH)
 - Corticotropin-releasing hormone (CRH)
 - Growth hormone releasing hormone (GHRH)
 - Prolactin releasing factor (PRF)
 - Growth hormone release-inhibiting hormone (GHRIH, somatostatin)
 - Prolactin release-inhibiting hormone (PIH)
 - Melanophore-stimulating hormone releasing factor (MRF)
 - Melanophore-stimulating hormone release-inhibiting factor (MIF)

Relationships between hypothalamic and pituitary Hs



Major known hypophysiotropic hormones	Major effect on anterior pituitary
Corticotropin-releasing hormone (CRH)	Stimulates secretion of ACTH
Thyrotropin-releasing hormone (TRH)*	Stimulates secretion of TSH
Growth hormone-releasing hormone (GHRH)	Stimulates secretion of GH
Somatostatin (SS)	Inhibits secretion of GH
Gonadotropin-releasing hormone (GnRH)	Stimulates secretion of LH and FSH
Dopamine (DA)‡	Inhibits secretion of prolactin

*TRH can also stimulate the release of prolactin, but whether this occurs physiologically is unclear.

‡Dopamine is a catecholamine; all the other hypophysiotropic hormones are peptides.

Hypothalamus-Neurohypophysis System

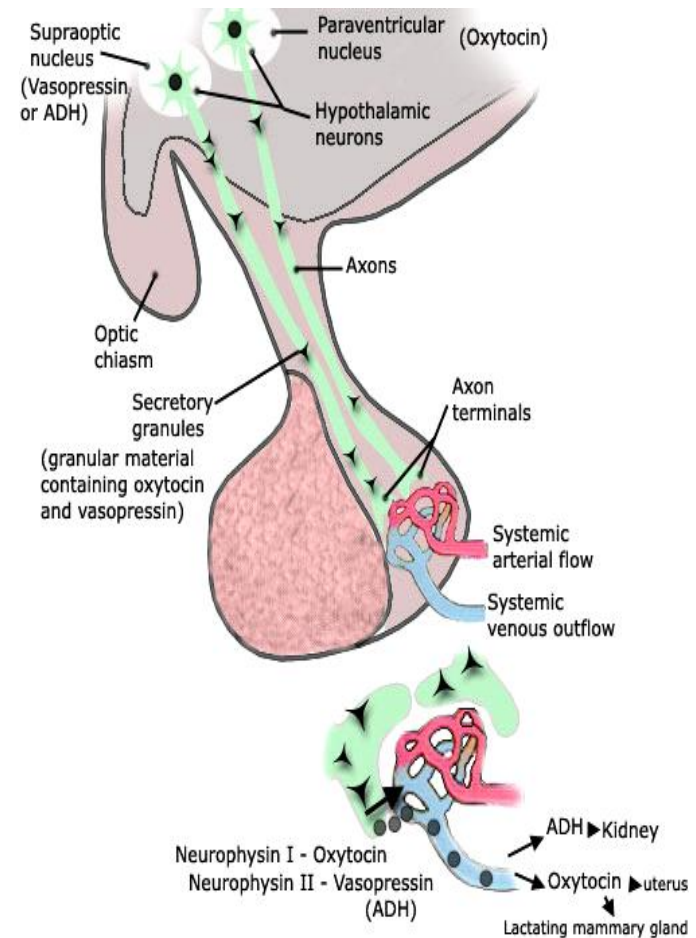
■ Hypothalamus

■ Supraoptic nucleus

(视上核)

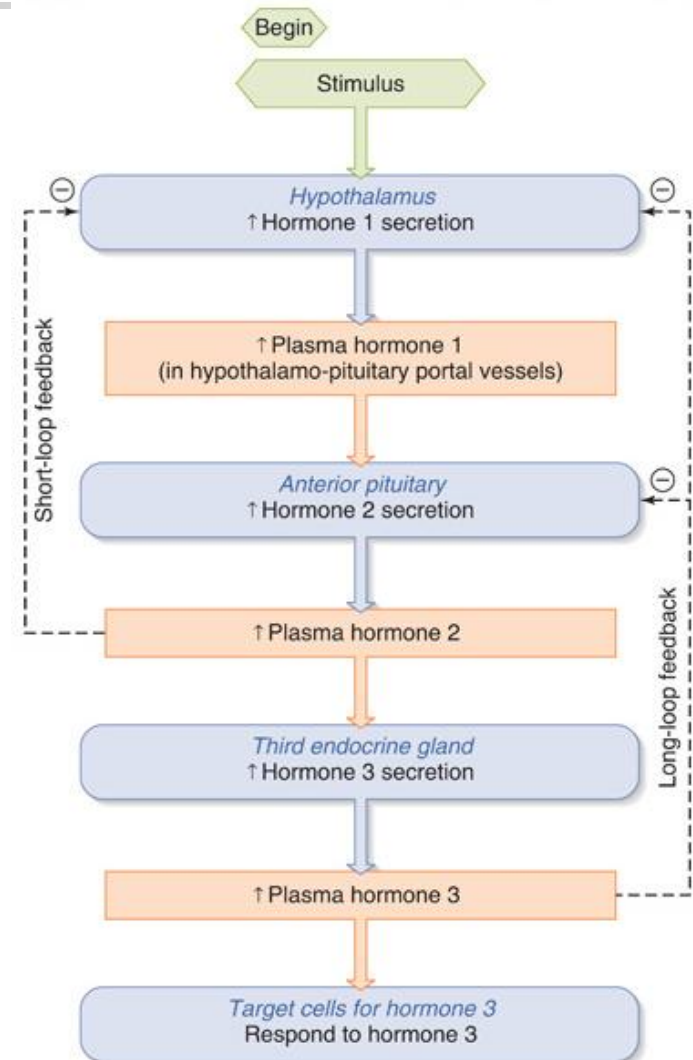
■ Paraventricular nucleus

(室旁核)



Regulation of hypothalamic H secretion

- Nervous regulation
 - NE, DA, 5-HT
- Hormonal regulation
 - Long-loop feedback
 - Short-loop feedback





To be continued.....