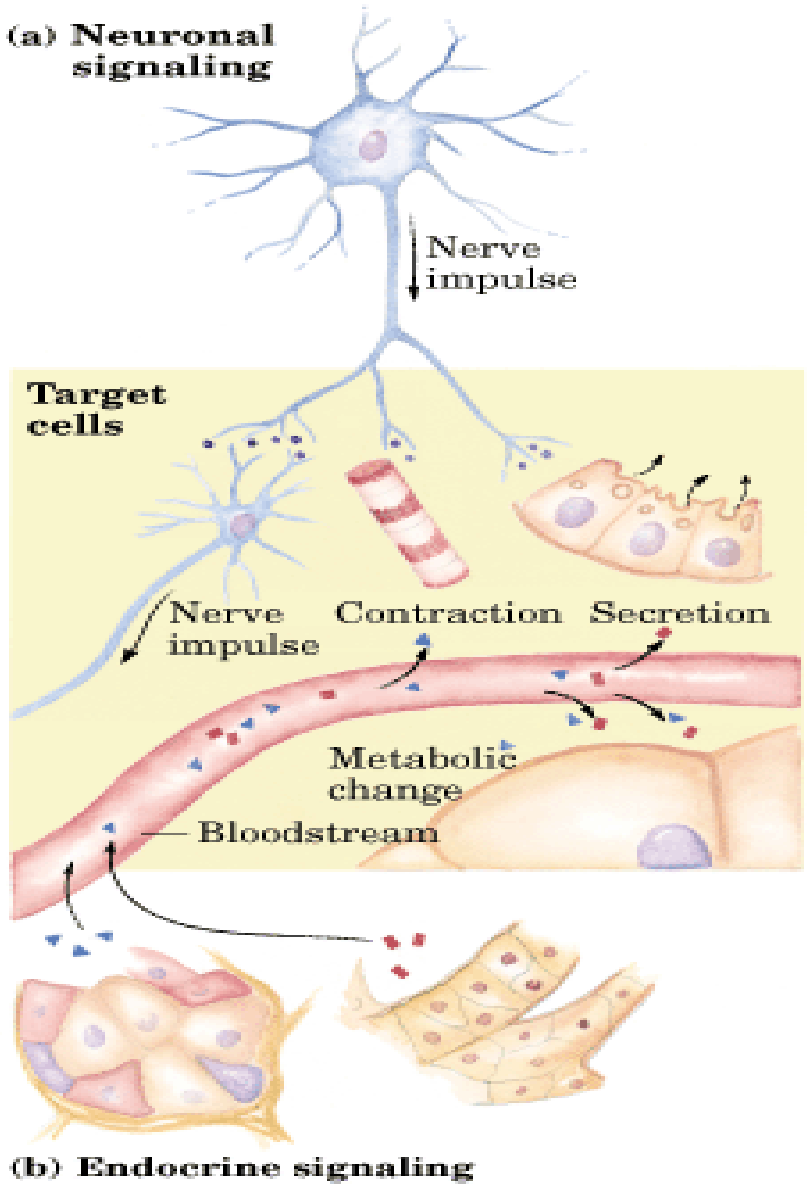
Chapter 11 Endocrinology

Dr. Huamin Xu（徐华敏）
huamin102@163.com
Rm 423, Boya Bld



Neuro-

Endocrine-

immune

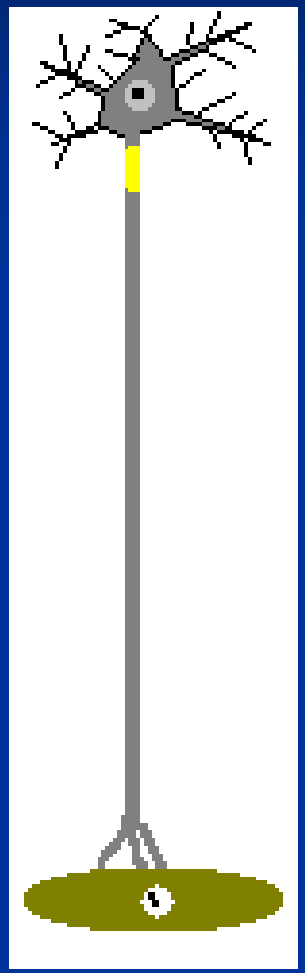
Network

-1977

Endocrine vs. Nervous Systems

- Major communication systems in the body
- Integrate stimuli and responses to changes in external and internal environment
- Both are crucial to coordinated functions of highly differentiated cells, tissues and organs
- Unlike the nervous system, the endocrine system is anatomically discontinuous.

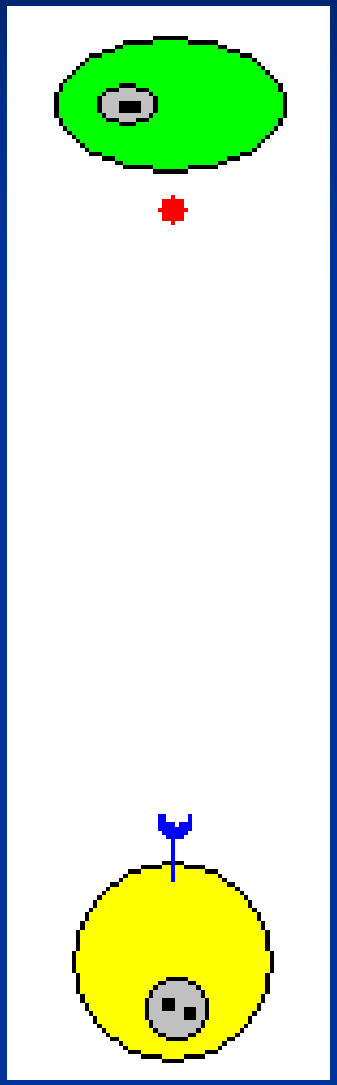
Nervous system



- **The nervous system** exerts point-to-point control through nerves, similar to sending messages by conventional telephone.

- Nervous control is electrical in nature and fast.

Hormones travel via the bloodstream to target cells



- **The endocrine system** broadcasts its hormonal messages to essentially all cells by secretion into blood and extracellular fluid.
- Like a radio broadcast, it requires a receiver to get the message –
- in the case of endocrine messages, cells must bear a ***receptor*** for the hormone being broadcast in order to respond.

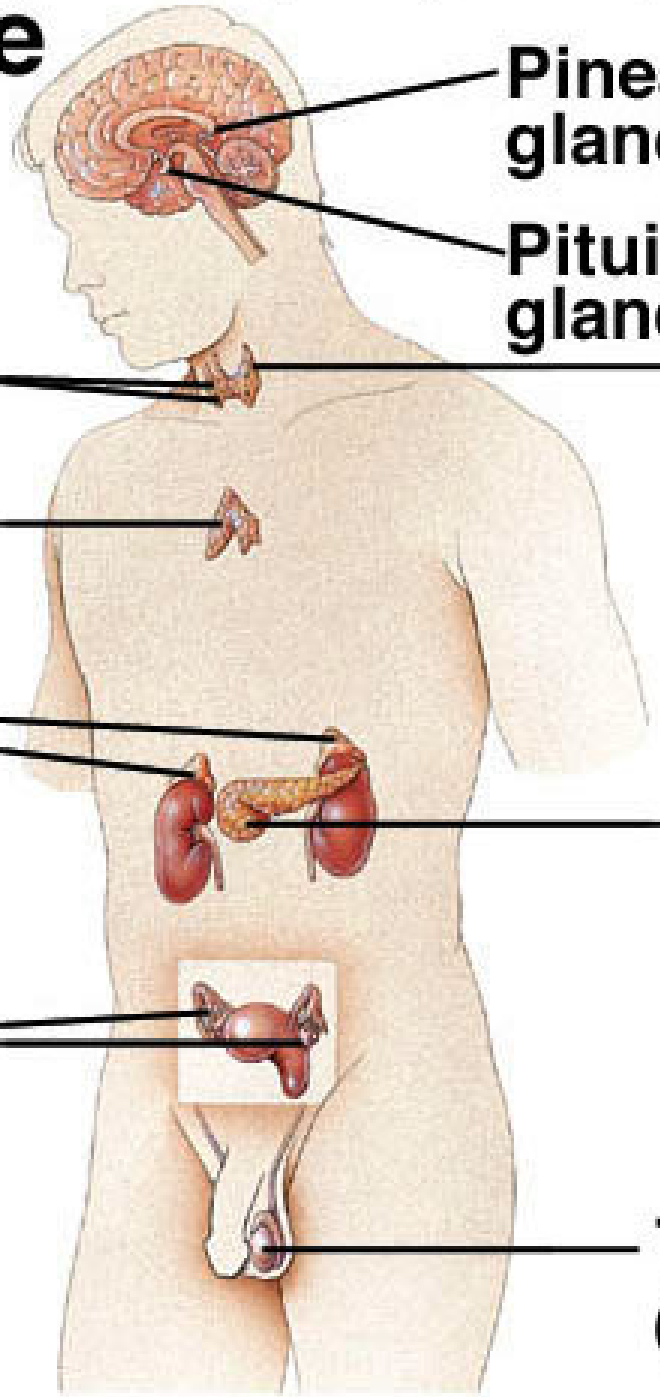
Section 1 Introduction

I. Organization of Endocrine System

The functions of the body are regulated by the nervous and the endocrine system.

The endocrine system consists of endocrine glands and cells that secrete hormones in various tissues.

Human Endocrine System



Pineal gland

Pituitary gland

Parathyroid glands (behind thyroid)

Thyroid gland

Thymus

Adrenal glands

Pancreas

Ovaries (in females)

Testes (in males)

Endocrine glands: Glands that do not use ducts to convey the secretion to a neighboring target, they are also called ductless glands.

The secretions, known **hormones**, circulate all over the body in the blood but may produce effects only in selected sites.

The **target organ(s)** may or may not be near the site of production of the hormone.

A **hormone** –

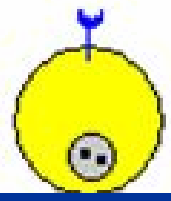
Definition

--chemical substance

--is secreted into the internal body fluids by one specialized cell or a group of cells and

--has a physiological control effect on other cells of the body.

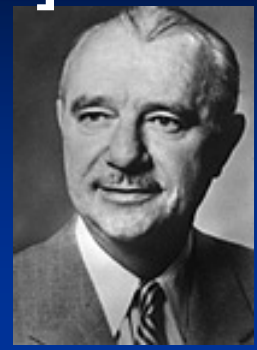
- **Functions**
  - Regulation of metabolism, growth and development, water and electrolyte balance, reproduction, and behavior



Bayliss & Starling discovered secretin [1902]
W.B.Hardy introduced the term hormone [1905]

- **Vincent du Vigneaud synthesized polypeptide hormones (oxytocin and vasopressin) [1955*]**

Vincent du Vigneaud
1901-1978



- **Frederick Sanger determined the structure of insulin [1958*]**

Frederick Sanger
1918-

- **Rosalyn Yalow developed radioimmunoassay for measurement of hormone concentrations [1977*]**

Rosalyn Yalow
1921- 2011

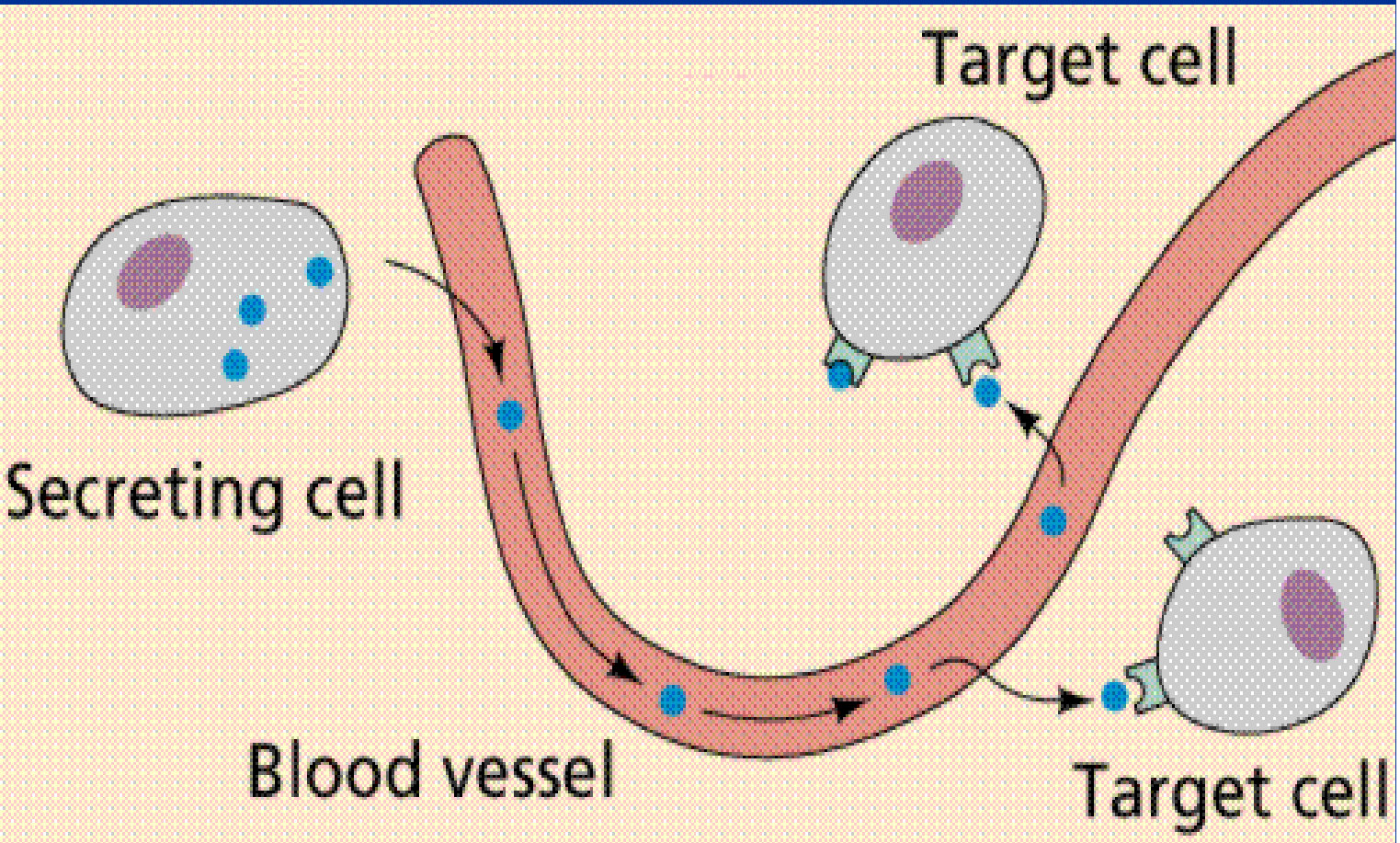
*** Nobel Prize year**

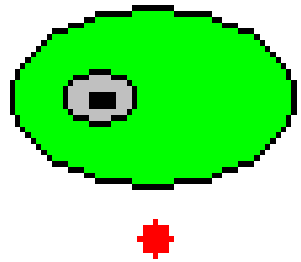
Patterns of the hormone action

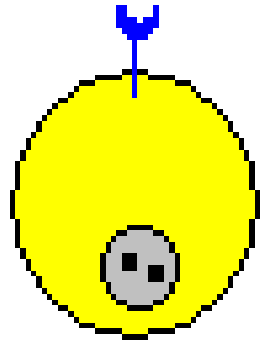
- Telecrine
- Paracrine
- Autocrine
- Neurocrine

Transportation of Hormones

1.Endocrine, or telecrine: glands or specialized cells release hormones into the circulating blood that influence the function of cells at another location in the body.

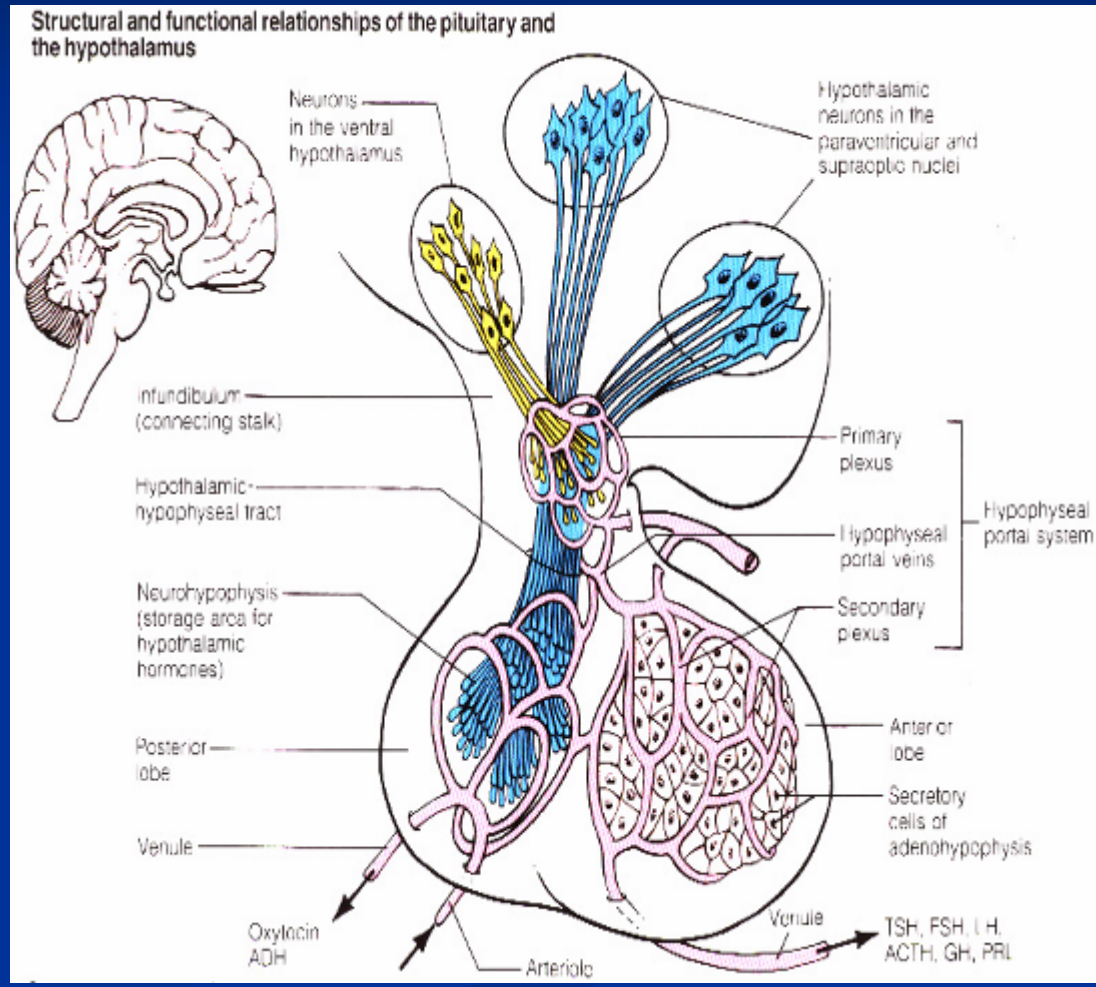




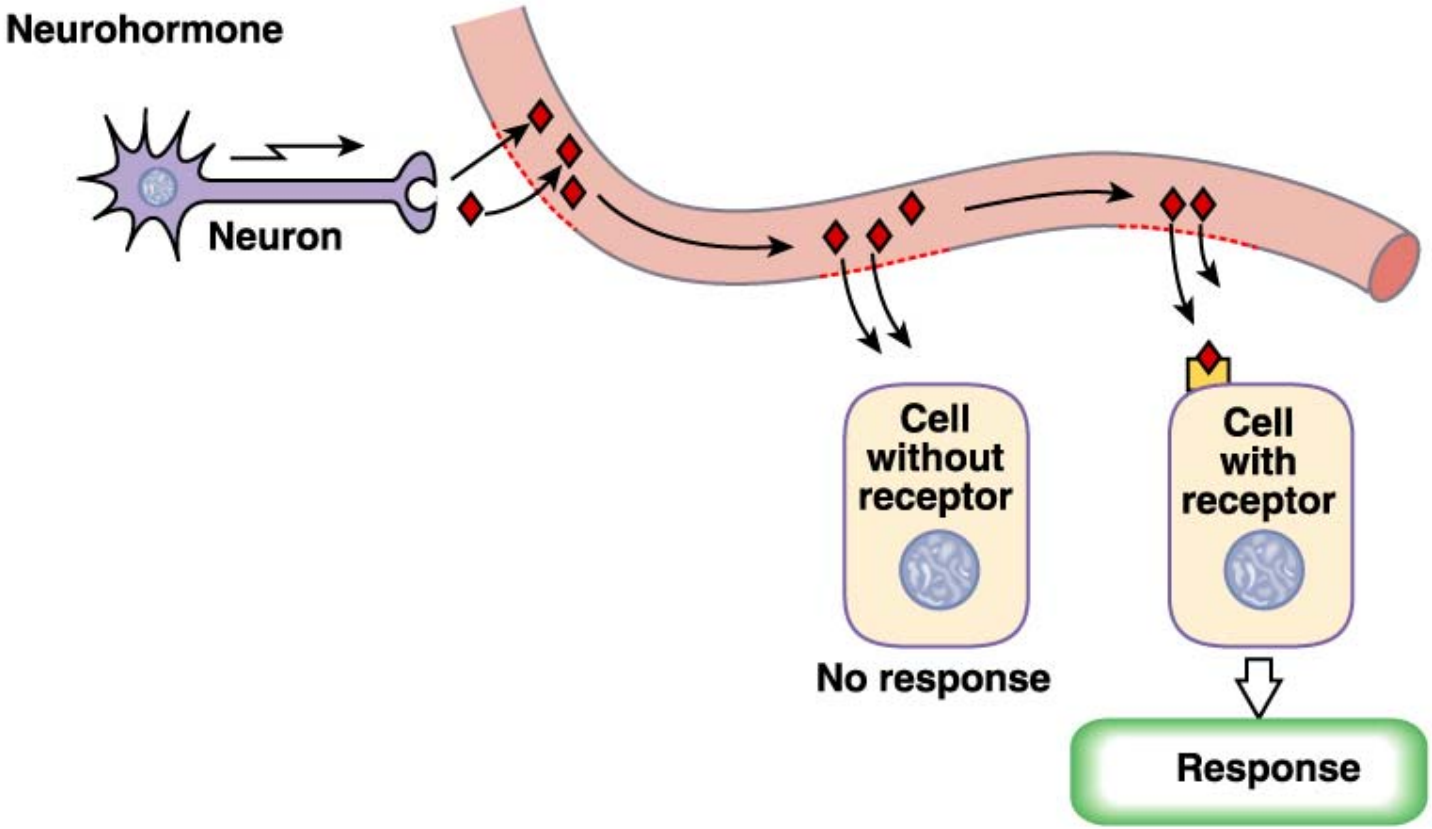


Transportation of Hormones

2, Neuroendocrine: neurons secrete substances (neurohormones) that reach the circulating blood and influence the function of cells at another location of the body.

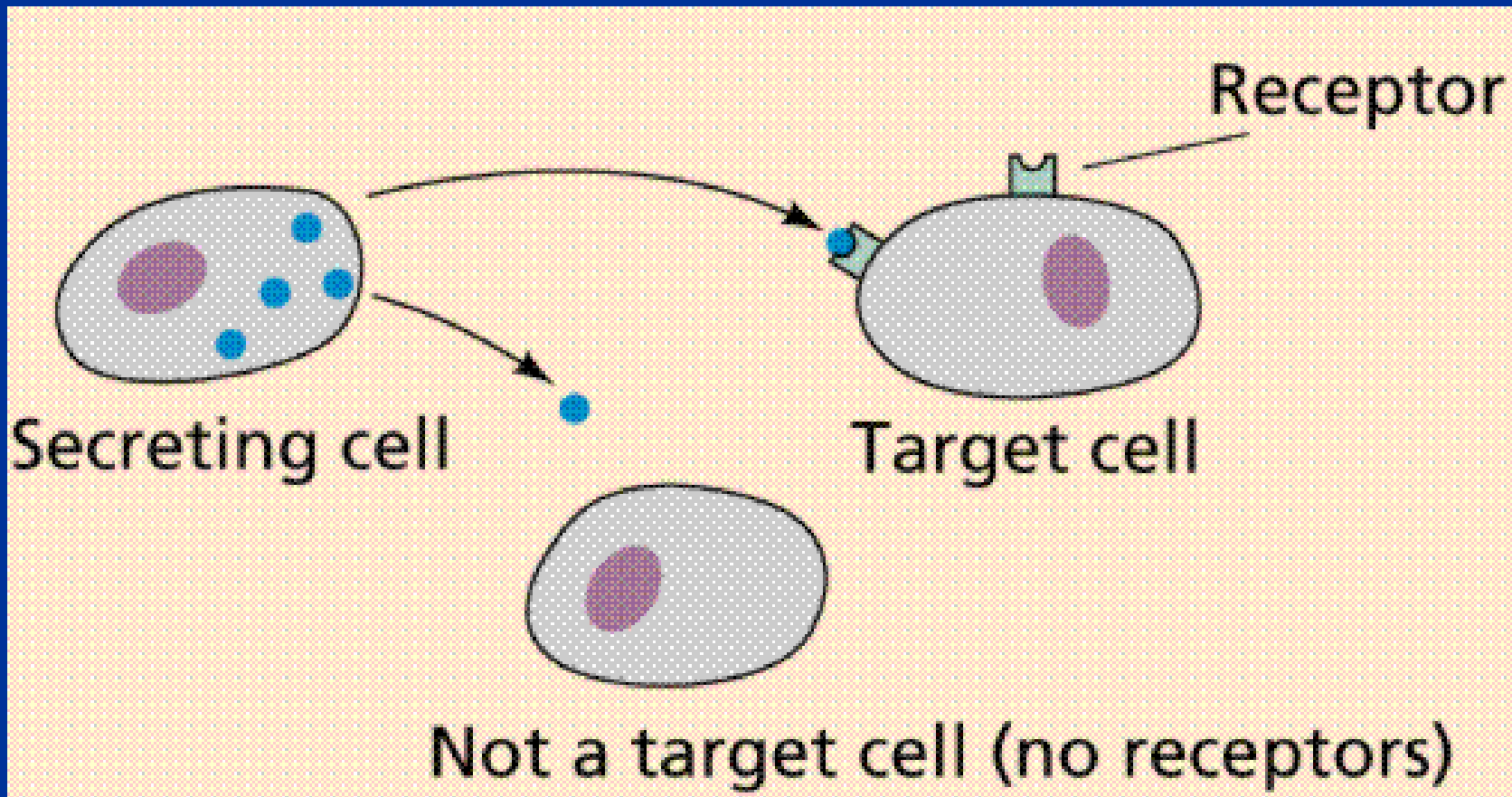


• Neurocrine

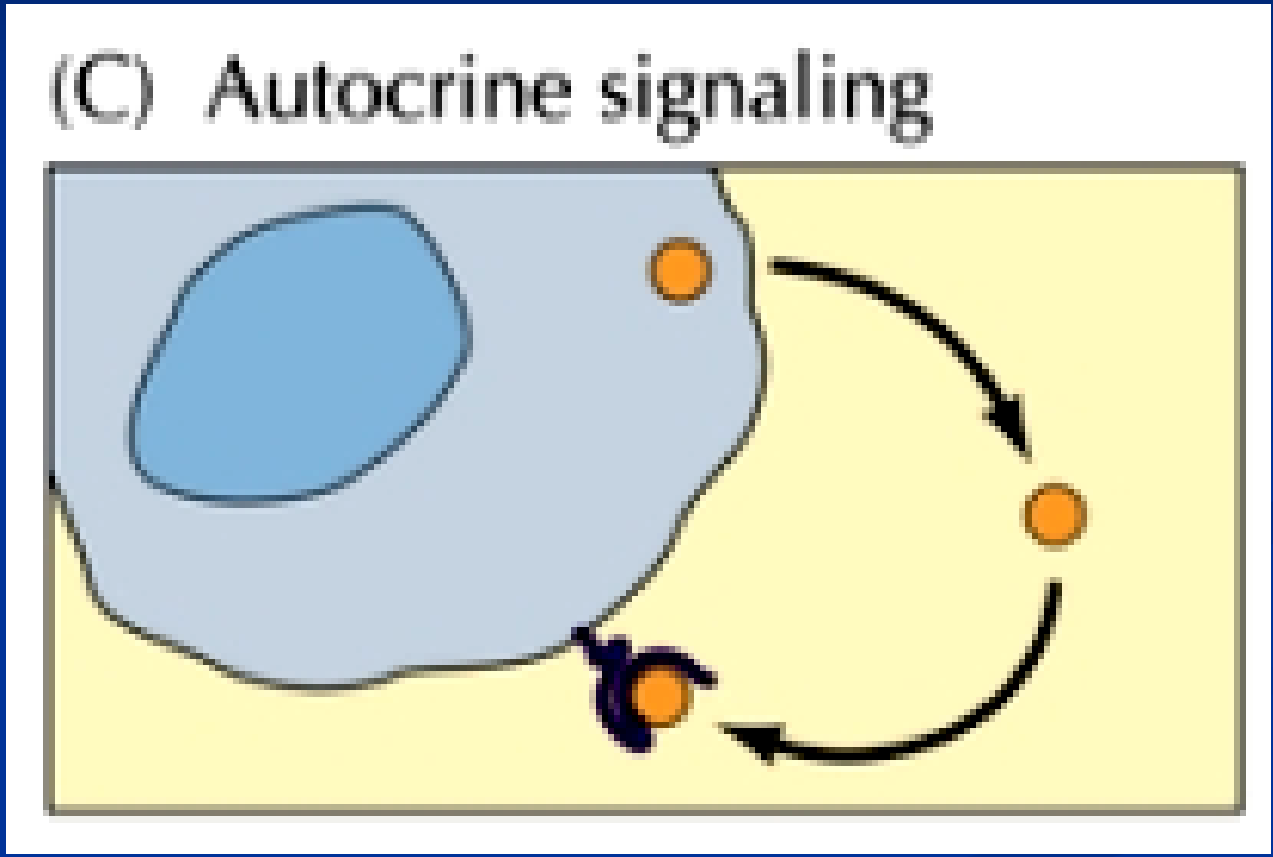

Neurohormone
Neuron
Cell without receptor
No response
Cell with receptor
Response

Transportation of Hormones

3. Paracrine, in which cells secret substances that diffuse into the extracellular fluid and affect neighboring cells.



- **Autocrine**



Chemical Classification of Hormones

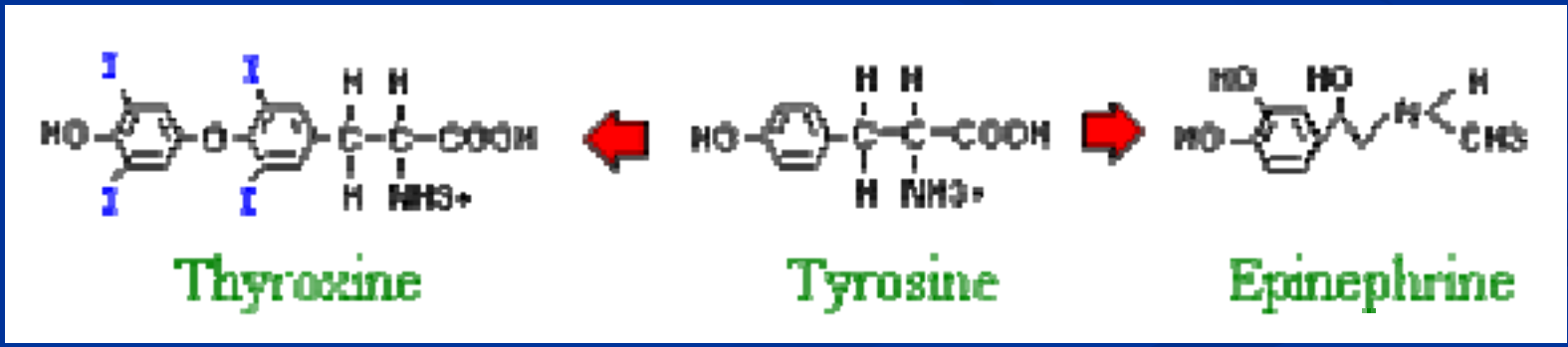
1. **Amine hormones**
2. **Peptide and protein hormones**
3. **Lipid hormones**

Steroids hormones

Fatty acid derivative-Eicosanoids

Amine Hormones

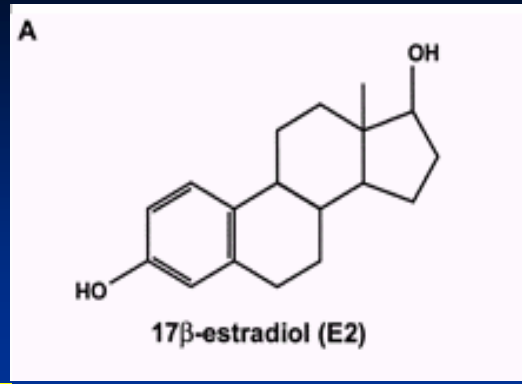
- **Derived from the amino acid**
  - **epinephrine and norepinephrine (tyrosine)**
  - **thyroid hormones (tyrosine)**
  - **Melatonin (tryptophane)**



Protein & Polypeptide Hormones

- Transcribed from genes
  - hypothalamic regulatory peptides, neurohypophysis hormones, adenohypophysis hormones
  - parathyroid hormone, insulin, calcitonin, gastrointestinal hormone

Steroids



- Derived from cholesterol
- Steroids are lipophilic molecules that freely cross membranes
  - glucocorticoids, mineralocorticoids androgens, estrogens & progesterone

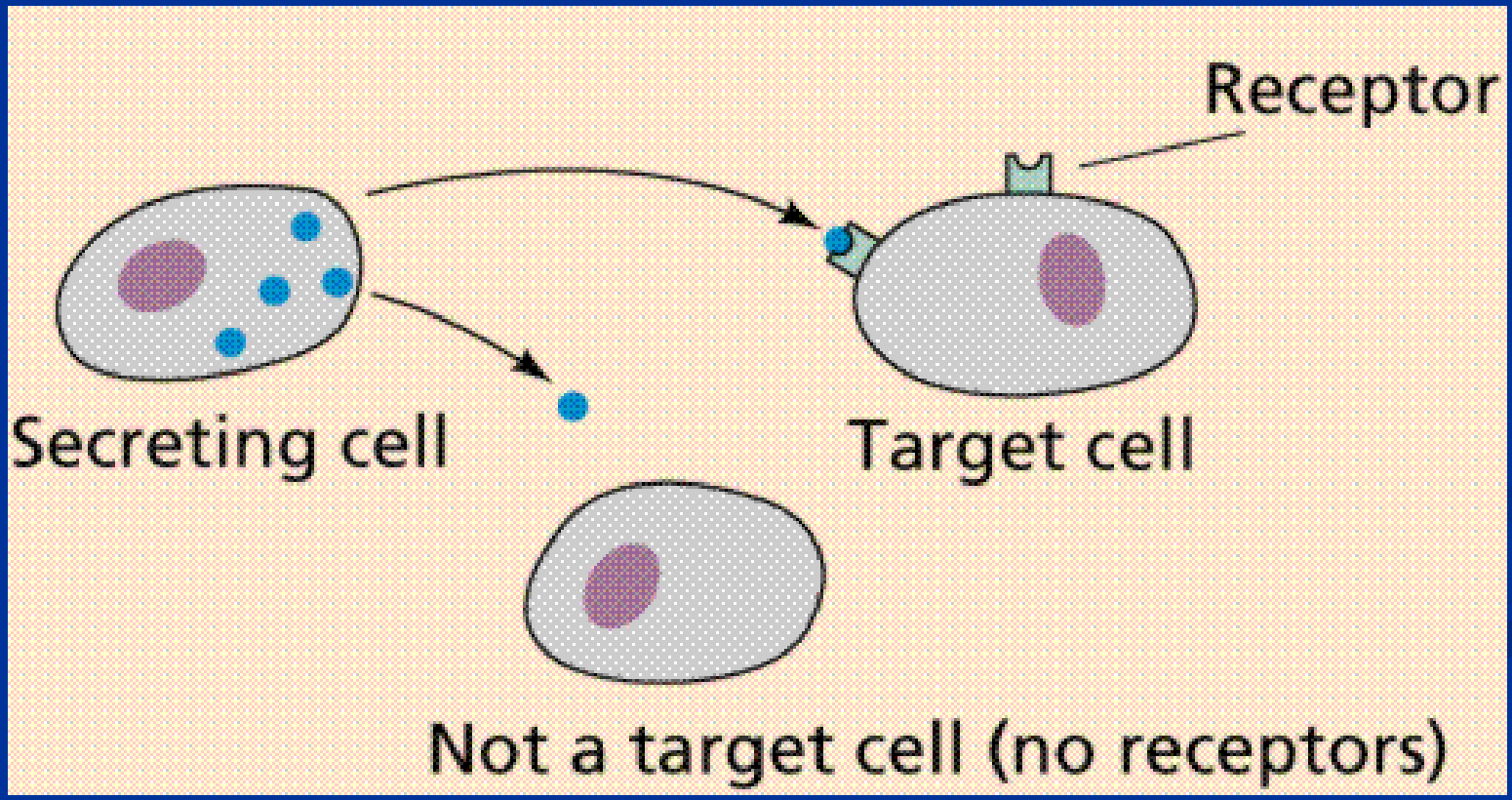
Characteristics of hormone action

1. Relative specificity
2. Message transmission
3. Biological amplification
4. Interaction of hormones

   (*permissive action*)

1. **Specificity**

The special feature of the target cells is the presence of **receptors** which can “attract” and interact with the hormone.



The receptors may be present either on the plasma membrane, or in the cytoplasm, or in the nucleus.

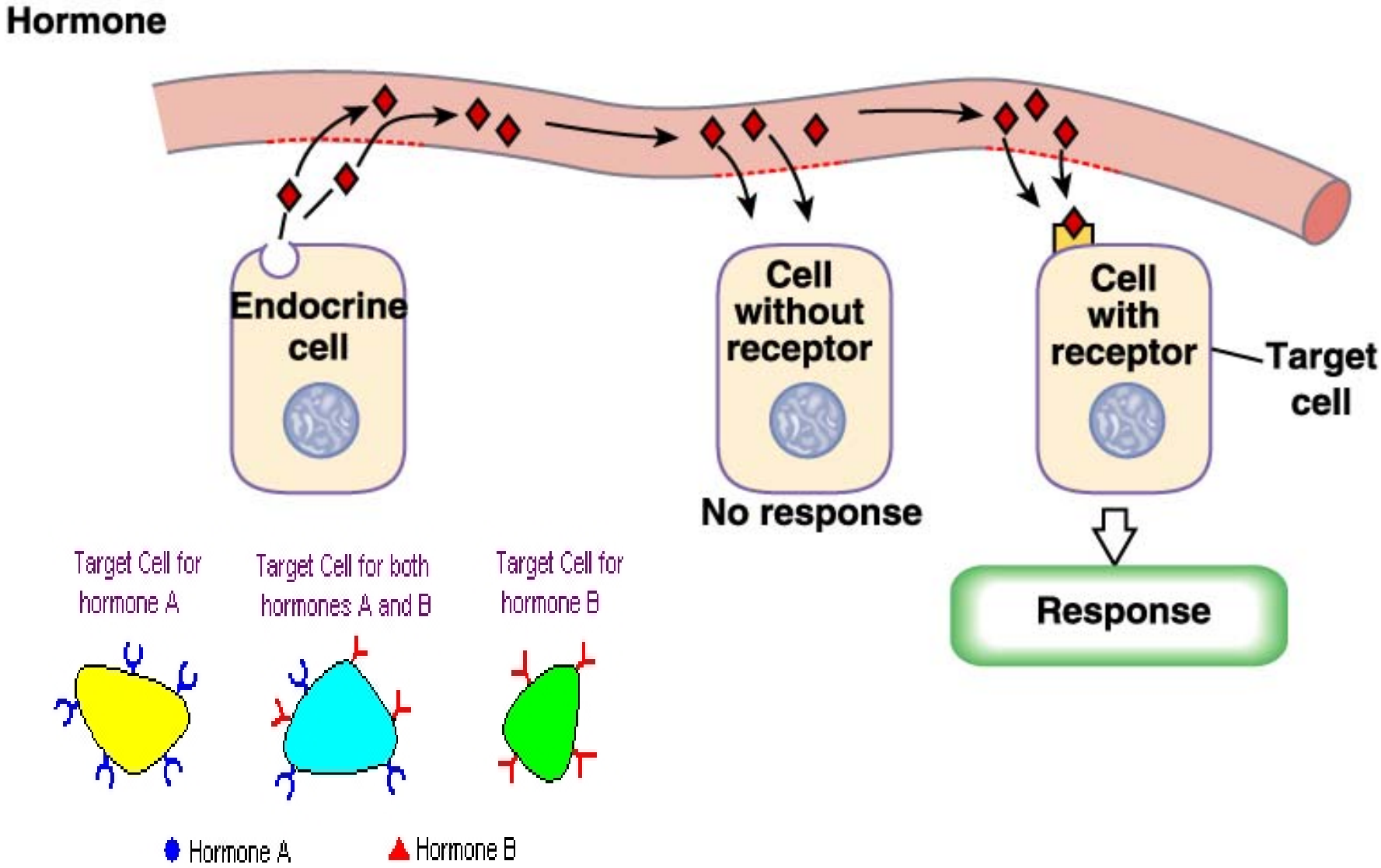
These receptor molecules are protein in nature and may contain carbohydrate or phospholipid moieties.

2. **Signal Transmission**

The role of the hormones is to transit the regulatory signals from the control (endocrine) system to the target cells (organs or glands).

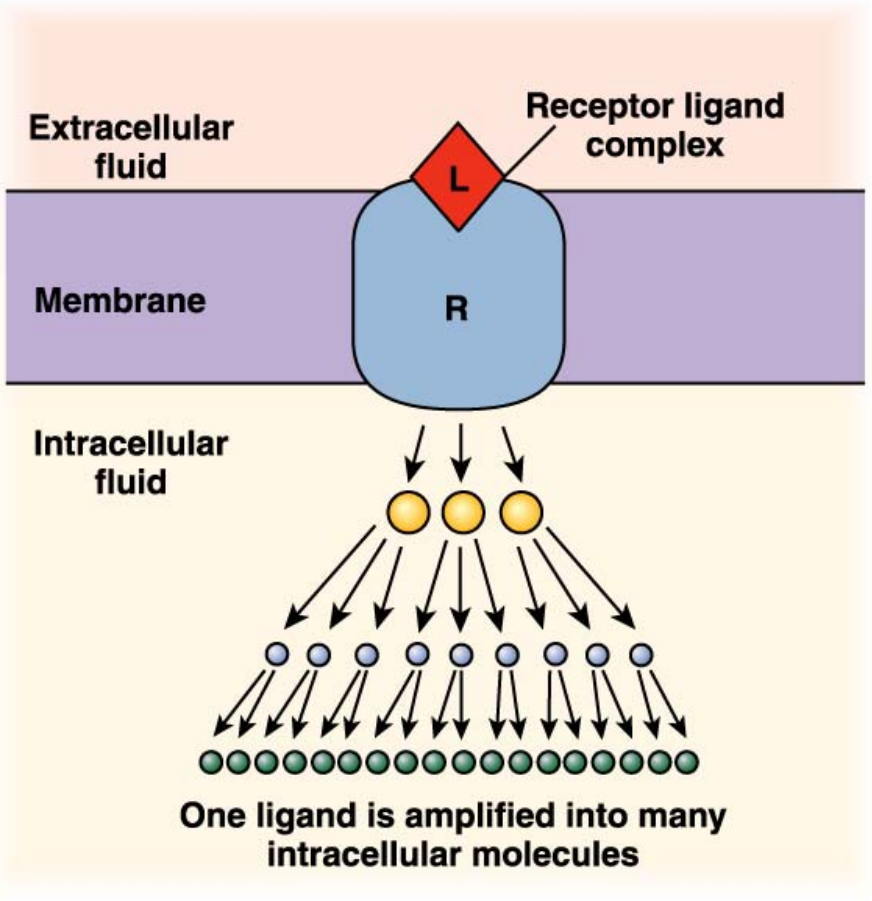
It could enhance or inhibit some function of the target.

Relative specificity & Message transmission

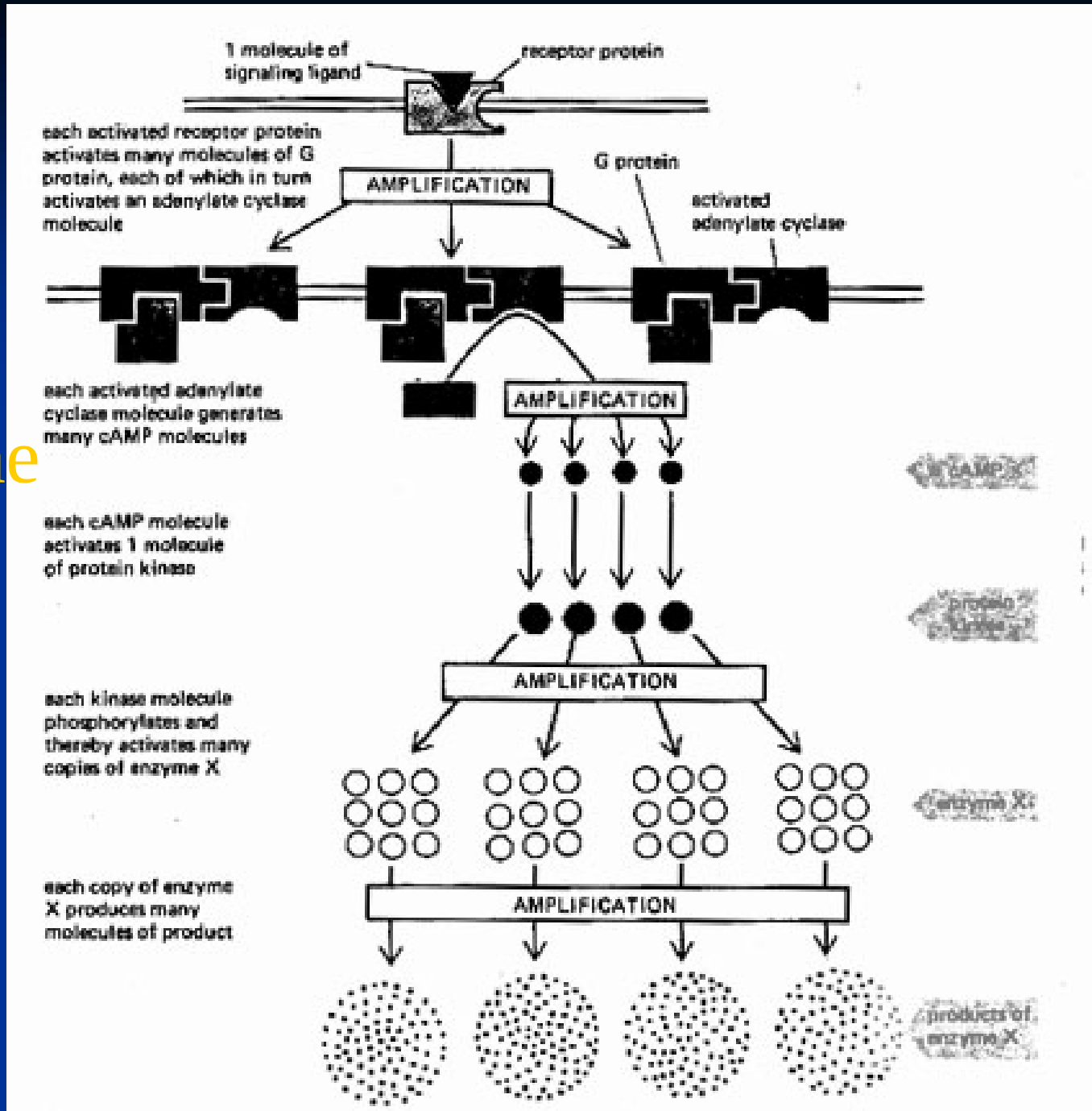


3. **High Biological Efficiency**

Low plasma concentration (nmol – pmol/L) ⟶ great regulatory function



Signal amplification during the transmembrane and intracellular transmission



4. **Interaction Between the Hormones**

(1) **Synergistic effects**. When two or more hormones work together to produce particular result their effect are said to be synergistic.

These effects may be **additive** or **complementary**.

Additive: Same effect of the hormones on one target organ, for example, epinephrine and norepinephrine on the heart rate

Complementary: Work on different stages of a physiological procedure, for example, FSH (initiation) and testosterone (maintenance) on spermatogenesis

(2) **Permissive effect**. A hormone is said to have a permissive effect on the action of a second hormone when it **enhances** the responsiveness of a target organ to the second hormone or when it **increases** the activity of the second hormone.

Estrogen – Expression of progesterone receptors on uterus – progesterone effect on the uterus.

Glucocorticoids – effects of catecholamines on cardiovascular system

(3) **Antagonist Effects**. In some situations the actions of one hormone antagonize the effects of another.

Lactation during pregnancy is prevented because the high concentration of estrogen in the blood inhibits the milk secretion and action of prolactin.

Mechanisms of hormone action

- All hormone action is receptor mediated.
- Hormones act through specific receptors that define tissue selectivity and response.

Mechanisms of Hormonal Action

The first step of a hormone's action is to bind to specific **receptors** at the target cell.

Locations for the different types of hormones:

1) On the **surface of the cell membrane**.

protein, peptide, and catecholamine hormones

2) In the **cell cytoplasm**.

steroid hormones

3) In the **cell nucleus**.

thyroid hormones (T_3 and T_4)

(一) Cell membrane receptors

- **Cell membrane receptors:**

  Includes receptors for amine, protein, and peptide hormones (except thyroid hormone)

Second Messengers (Sutherland;1965)

for Mediating Intracellular Hormonal Functions

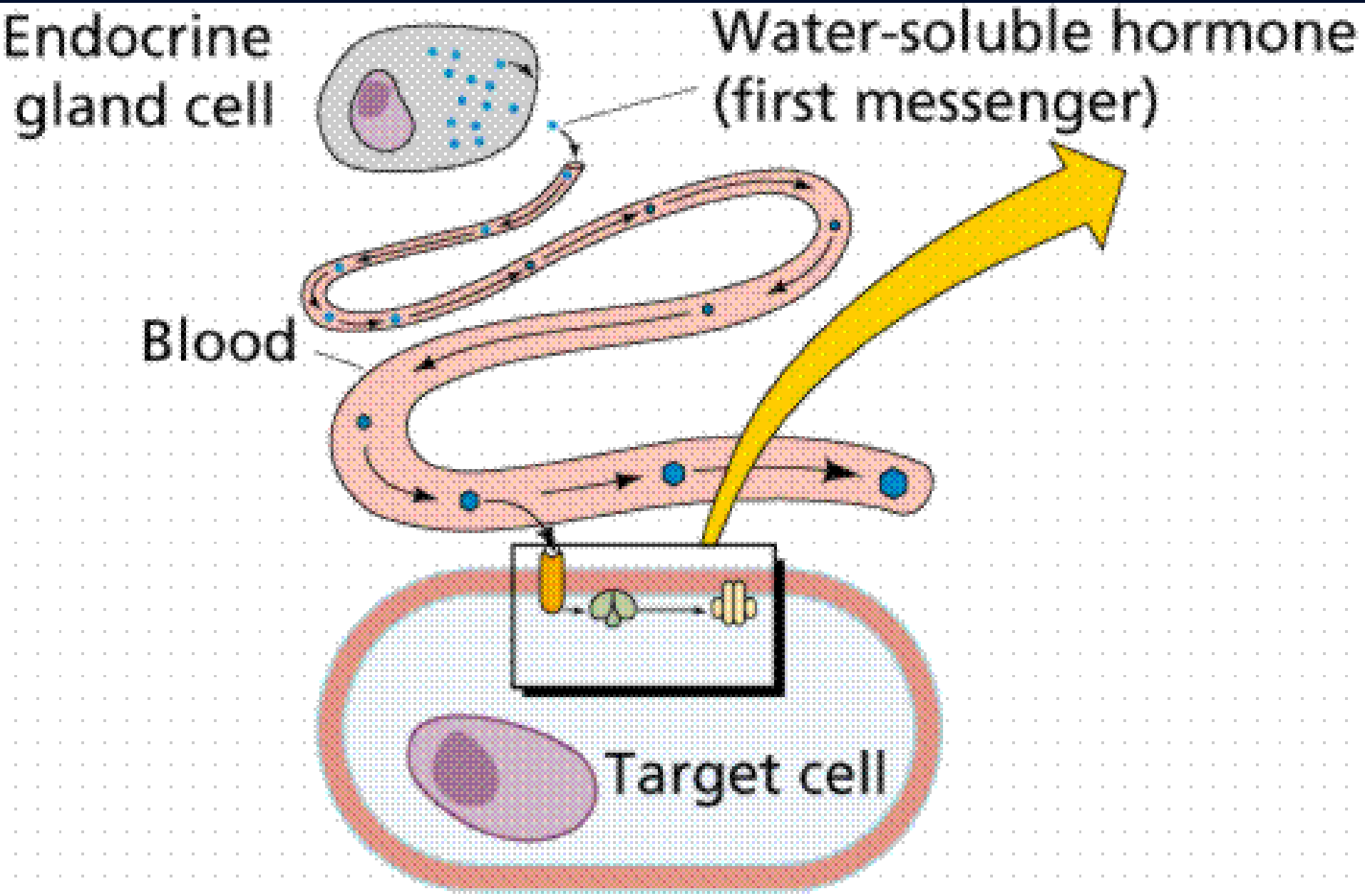
Hydrophilic hormones (proteins, peptides and catecholamine)

--bind the receptors on the membrane,

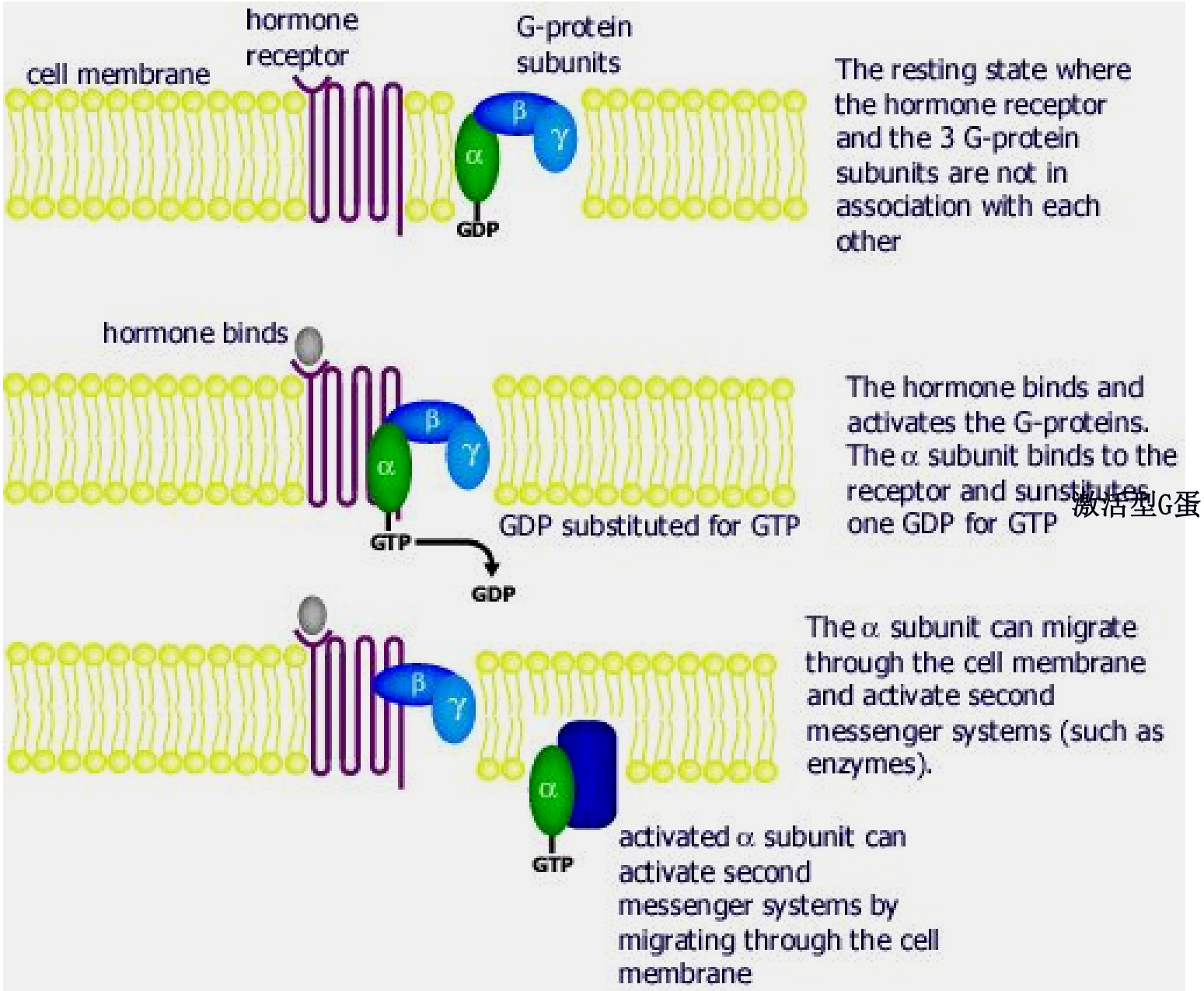
--activate some enzyme on the membrane

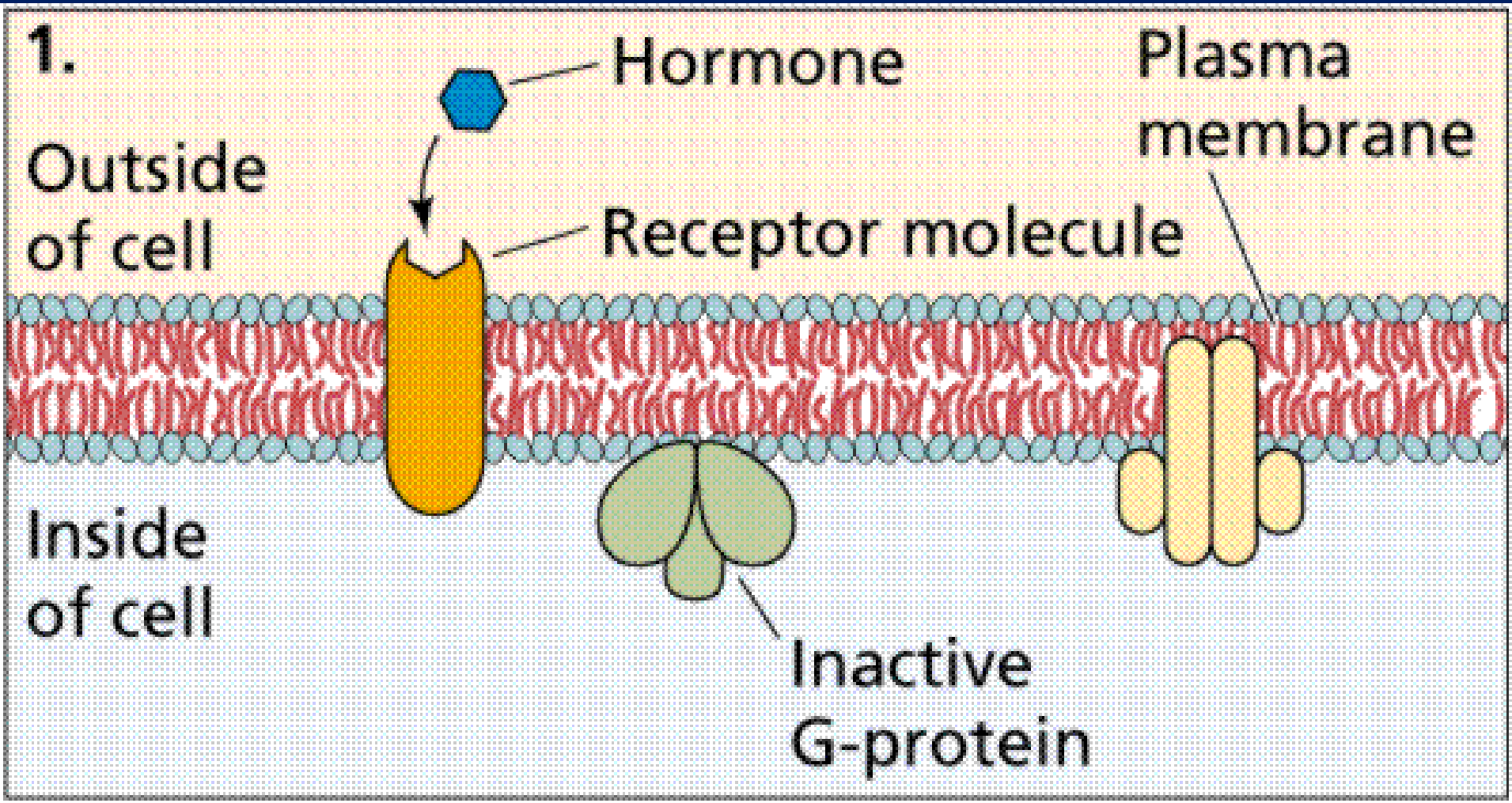
-- regulate the concentration of some messengers (**second messengers**) in the cytoplasm. .

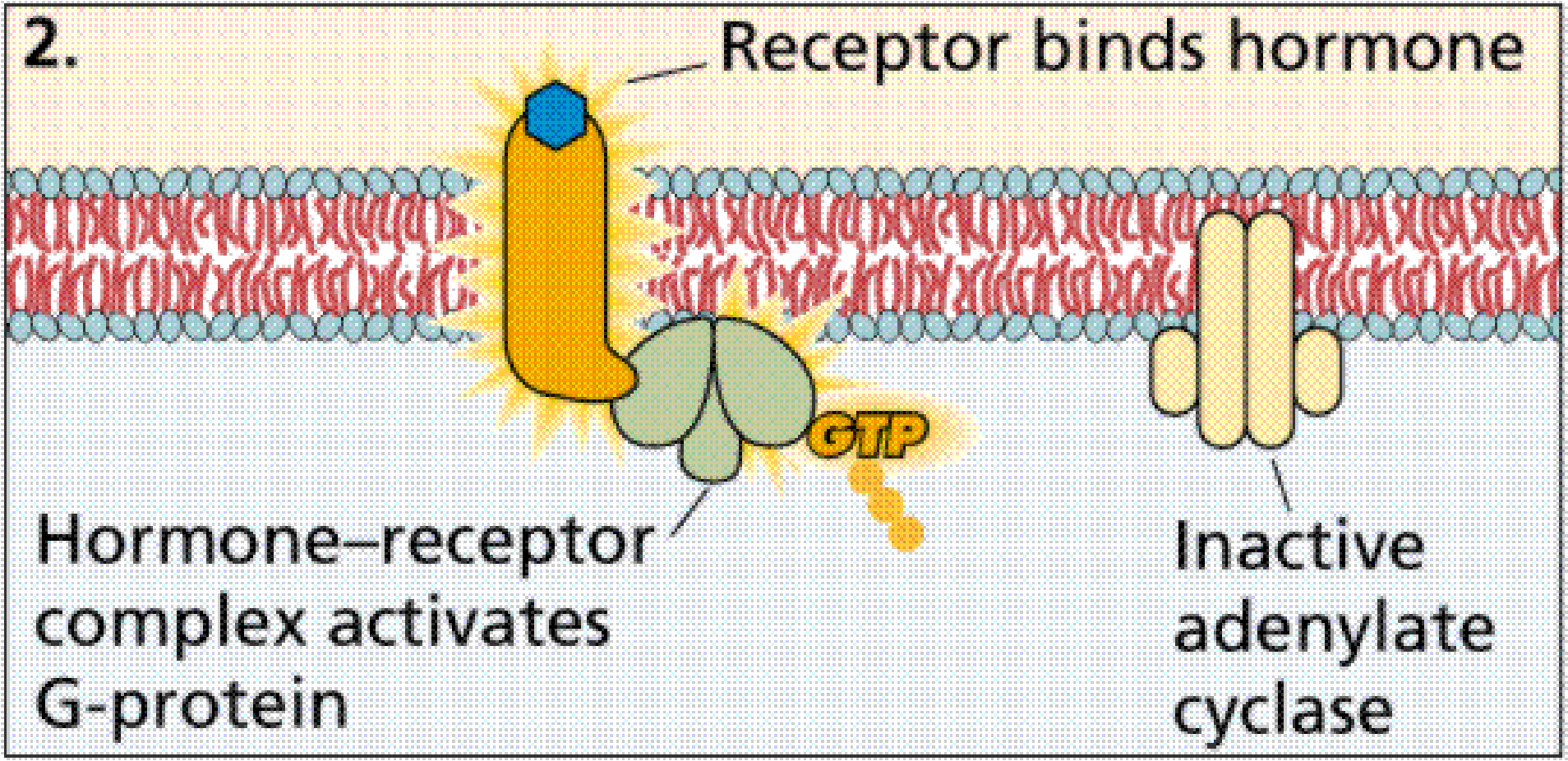
Earl W. **Sutherland**, Jr.
Vanderbilt University
1915--1974

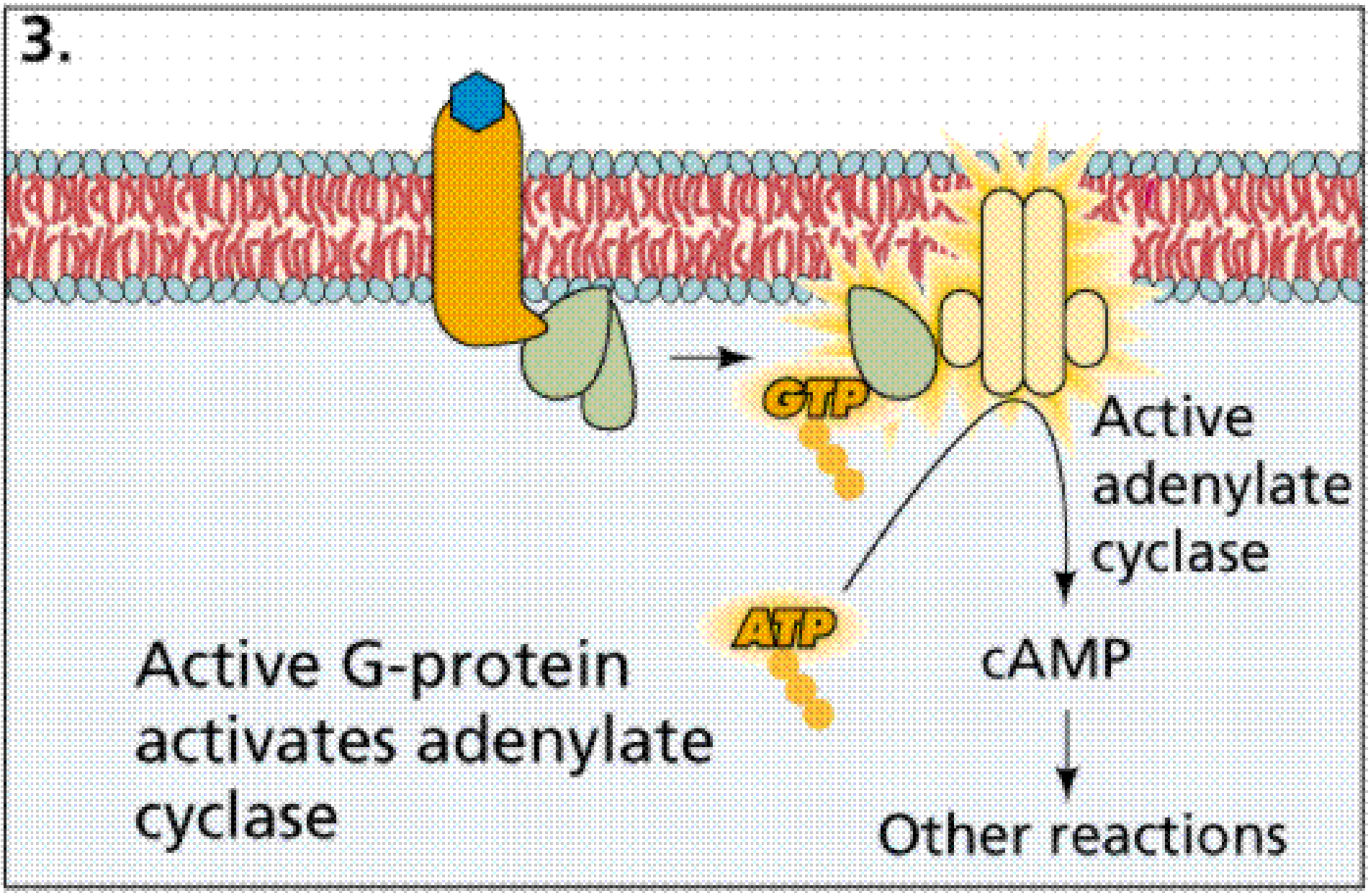

Endocrine gland cell
Water-soluble hormone (first messenger)
Blood
Target cell

G-protein coupled receptor pathway



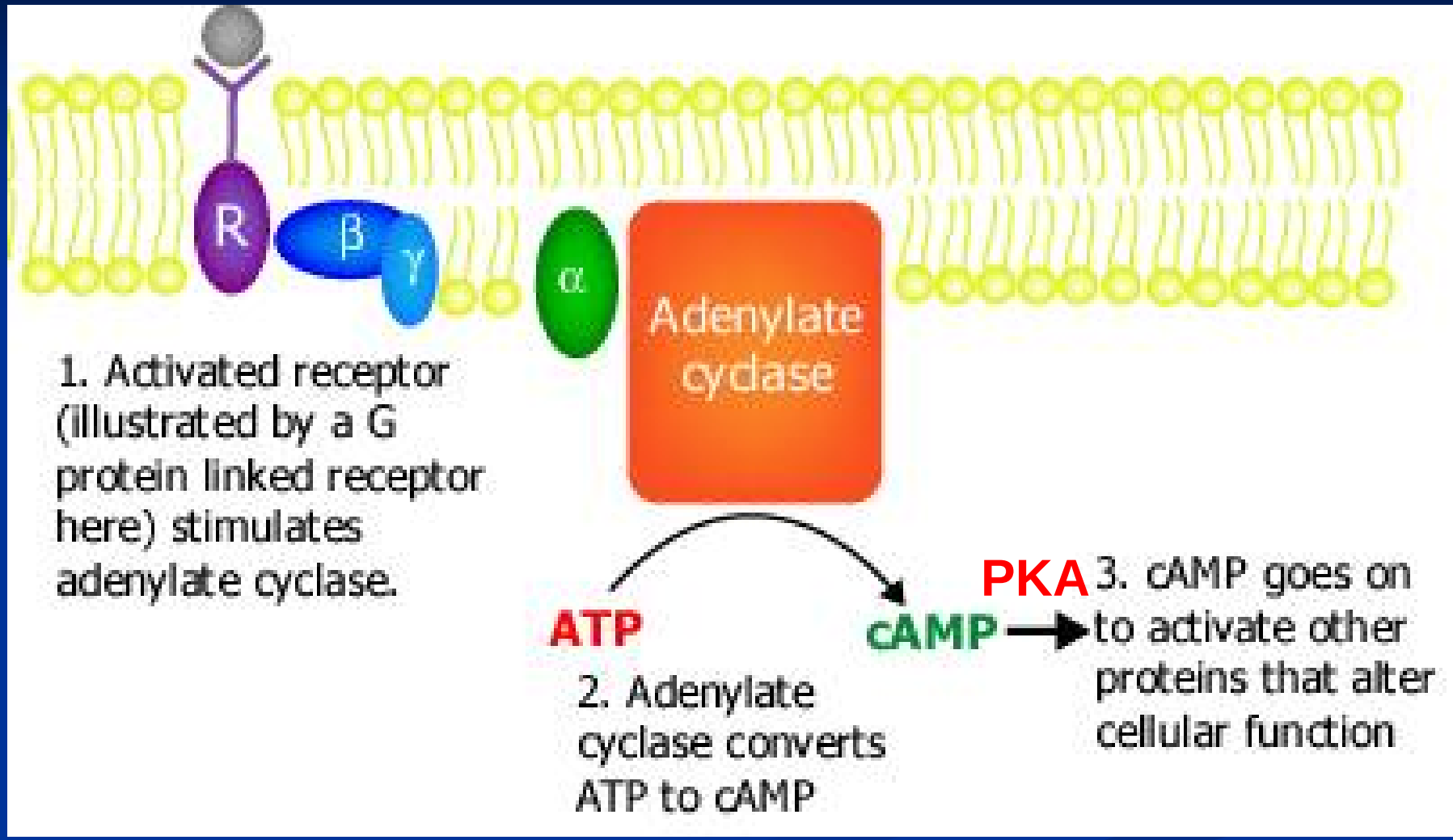

1.
Hormone
Plasma membrane
Outside of cell
Receptor molecule
Inside of cell
Inactive G-protein


2.
Receptor binds hormone
GTP
Hormone–receptor complex activates G-protein
Inactive adenylate cyclase


3.
GTP
Active
adenylate
cyclase
ATP
cAMP
Active G-protein
activates adenylate
cyclase
Other reactions

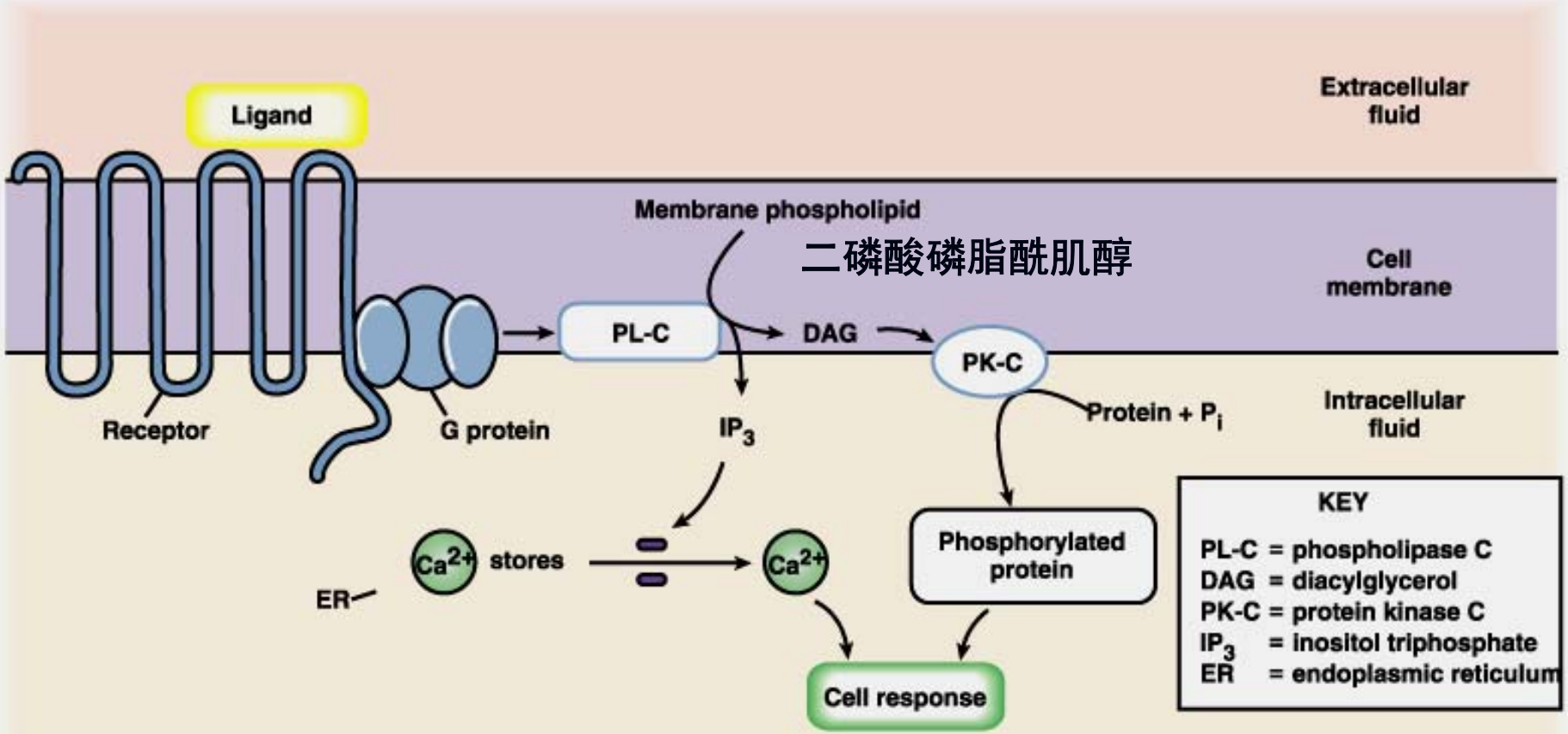
There are at least three kinds of second messengers: cAMP, Calcium ions and products of membrane phospholipid metabolism.

cAMP as second messenger



CRH, GHRH, TSH, Glucagon, E, LH…

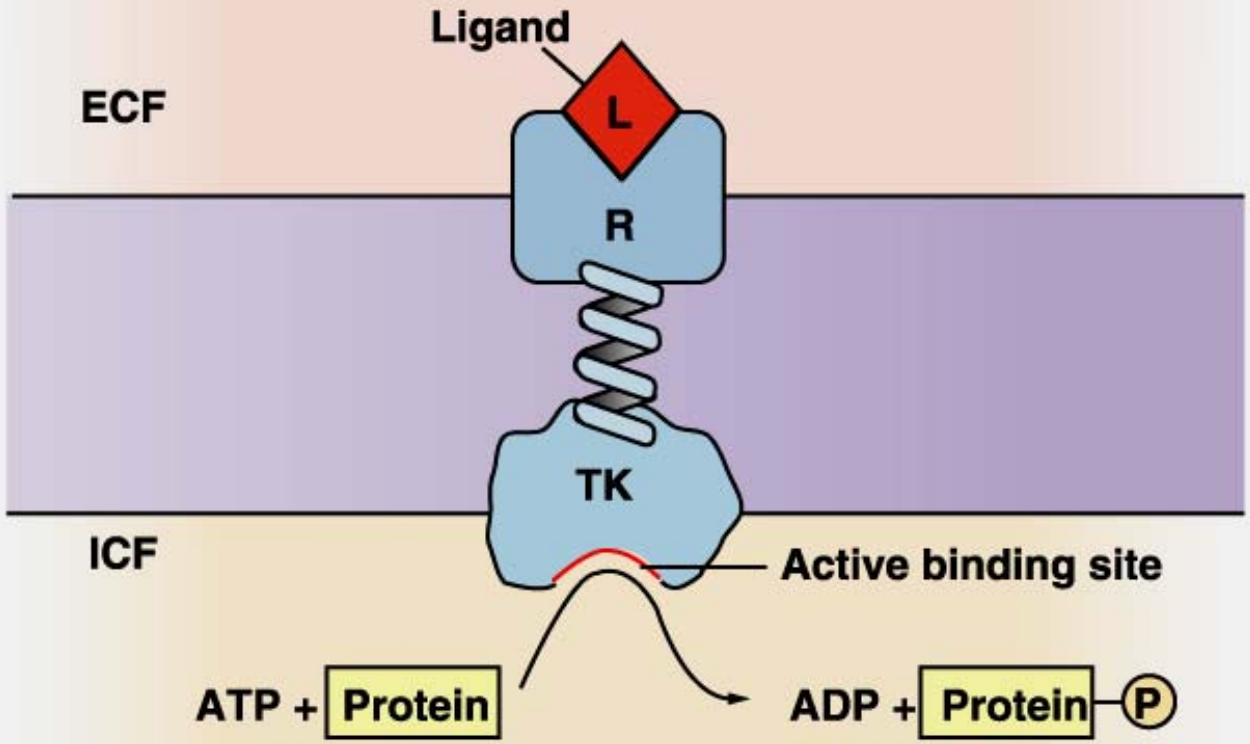
IP_3, DG & Ca^{2+} as second messenger



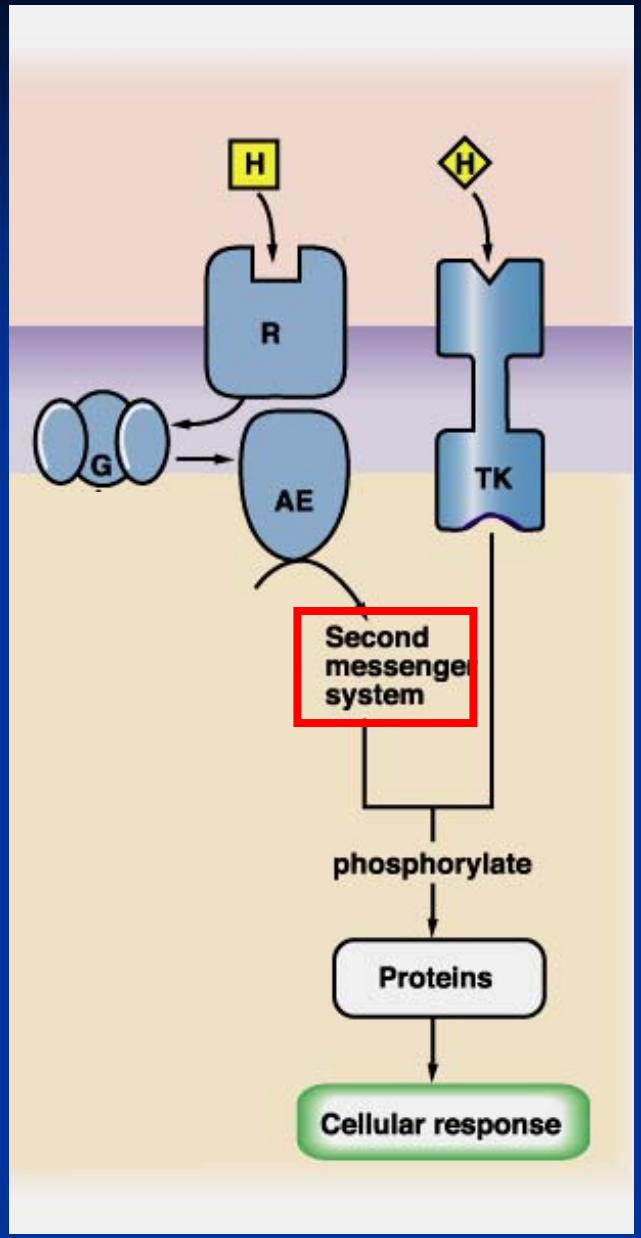
GnRH, TRH, OXT, VP …

Enzyme coupled receptor pathway

Tyrosine kinase receptor
Guanylyl cyclase receptor



GH, IGF-I, Insulin…



(1) AC-cAMP-PKA

(2) PLC-IP3/DG-CaM/PKC

(3) GC-cGMP-PKG

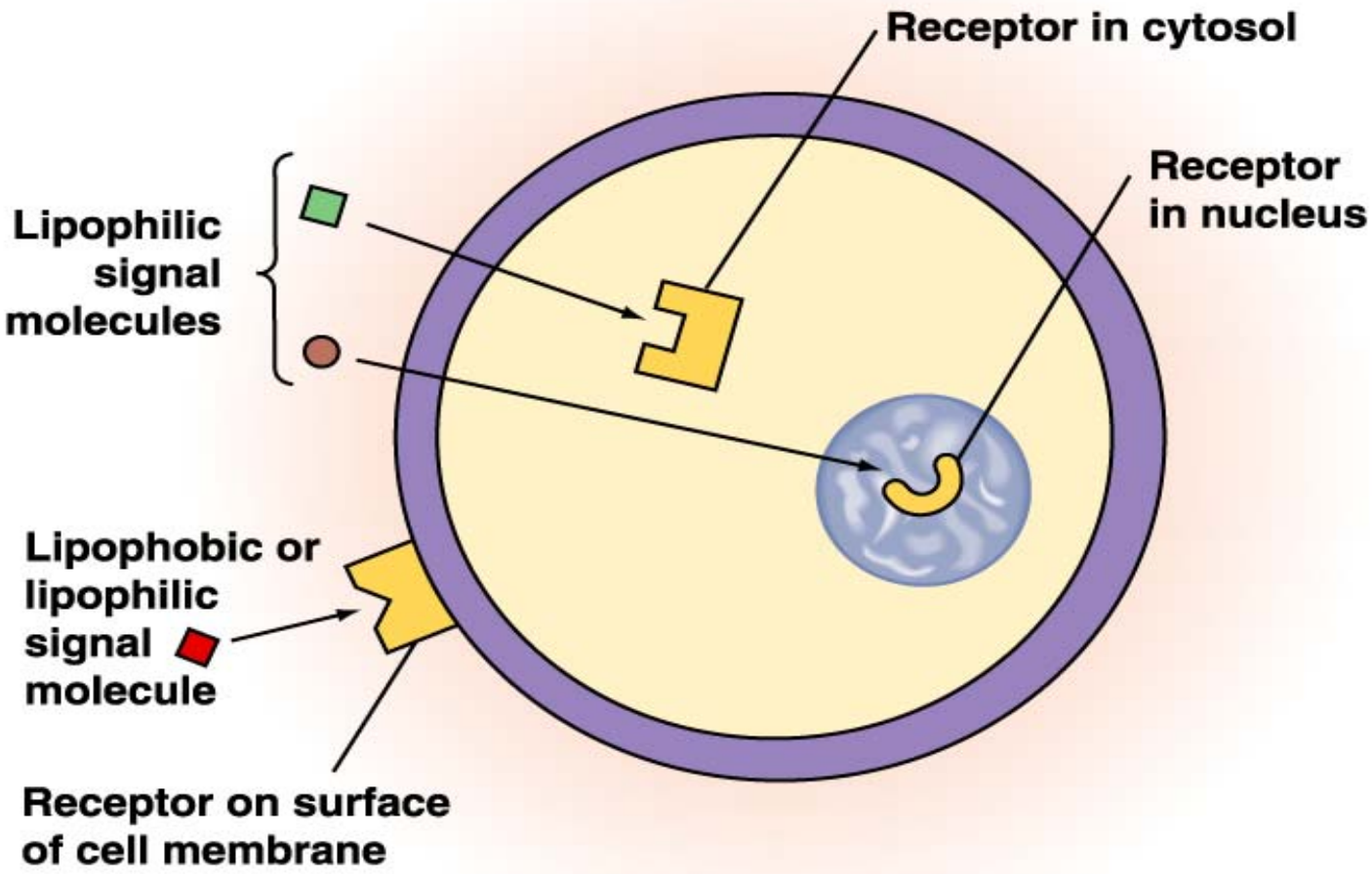
(4) Tyrosine kinase (TK)

(二) Intracellular receptors

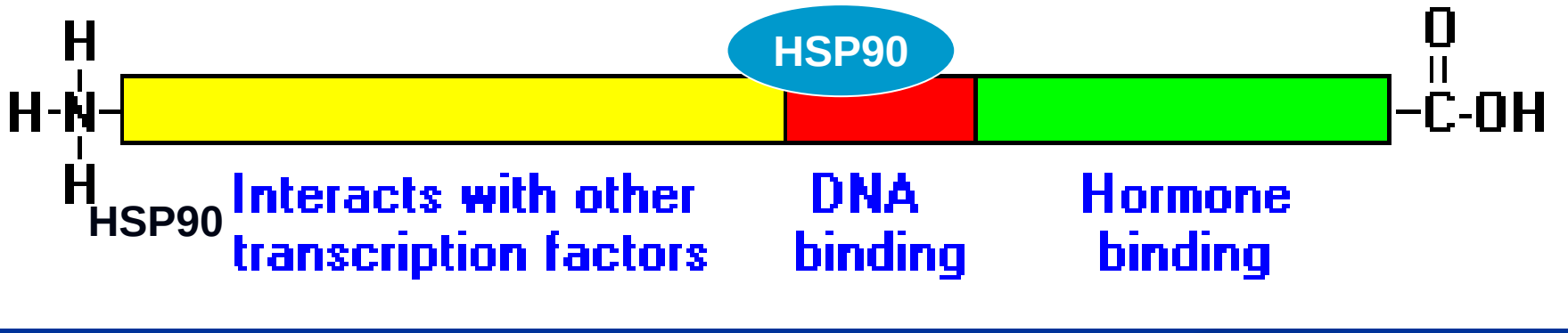
- **Intracellular receptors:**

  Includes receptors for steroid and thyroid hormones

Steroid/thyroid hormone mechanism



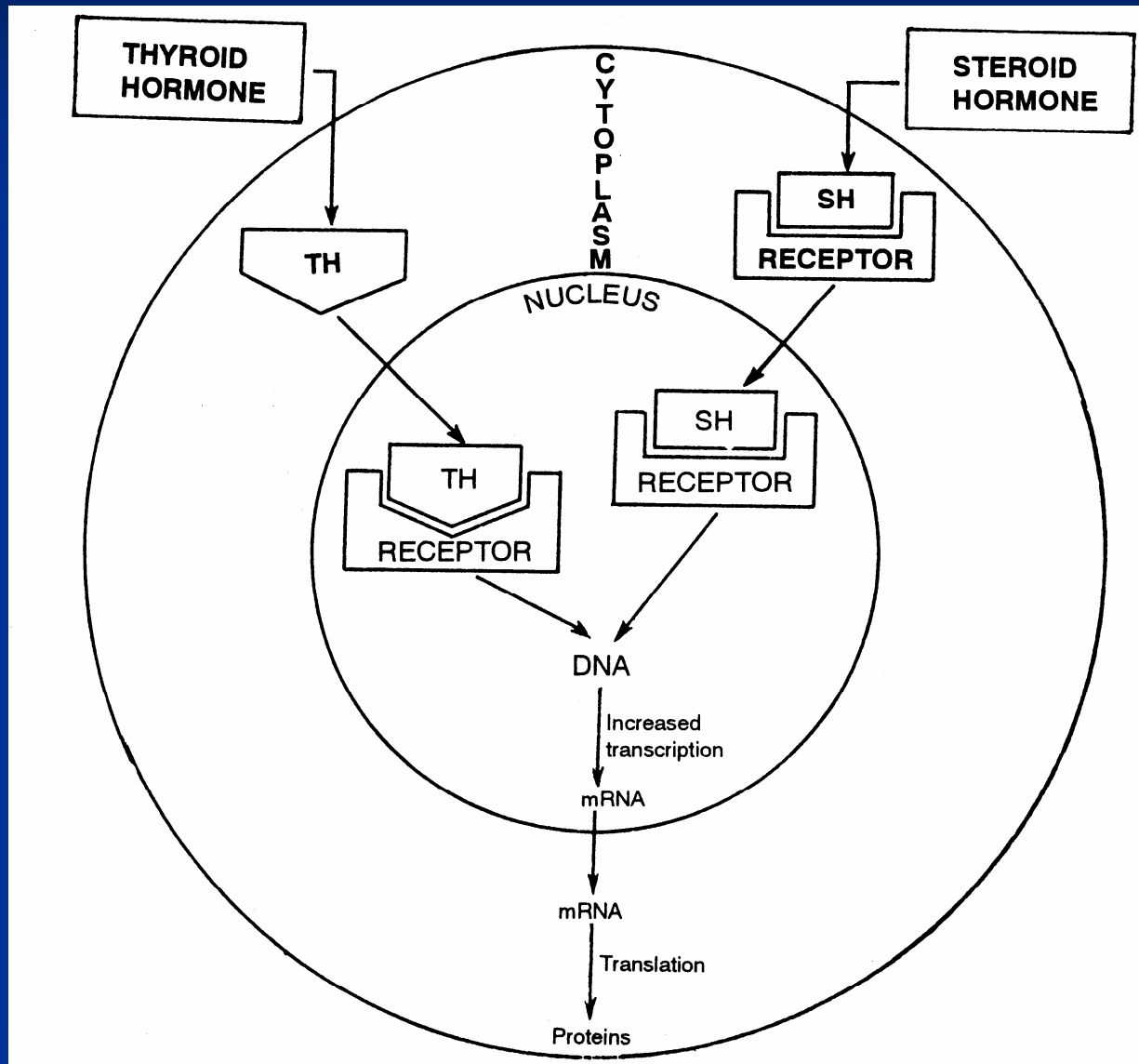
Steroid Receptor Domains



Hormones That Act Mainly on the Genetic Machinery of the Cell

(1)Steroid hormones increase protein synthesis

(2) Thyroid hormones increase gene transcription in the cell nucleus



Regulation of hormone secretion

1. *Hypothalamic-pituitary-gland axis*
2. *Feedback through metabolites*
3. *Nervous regulation*

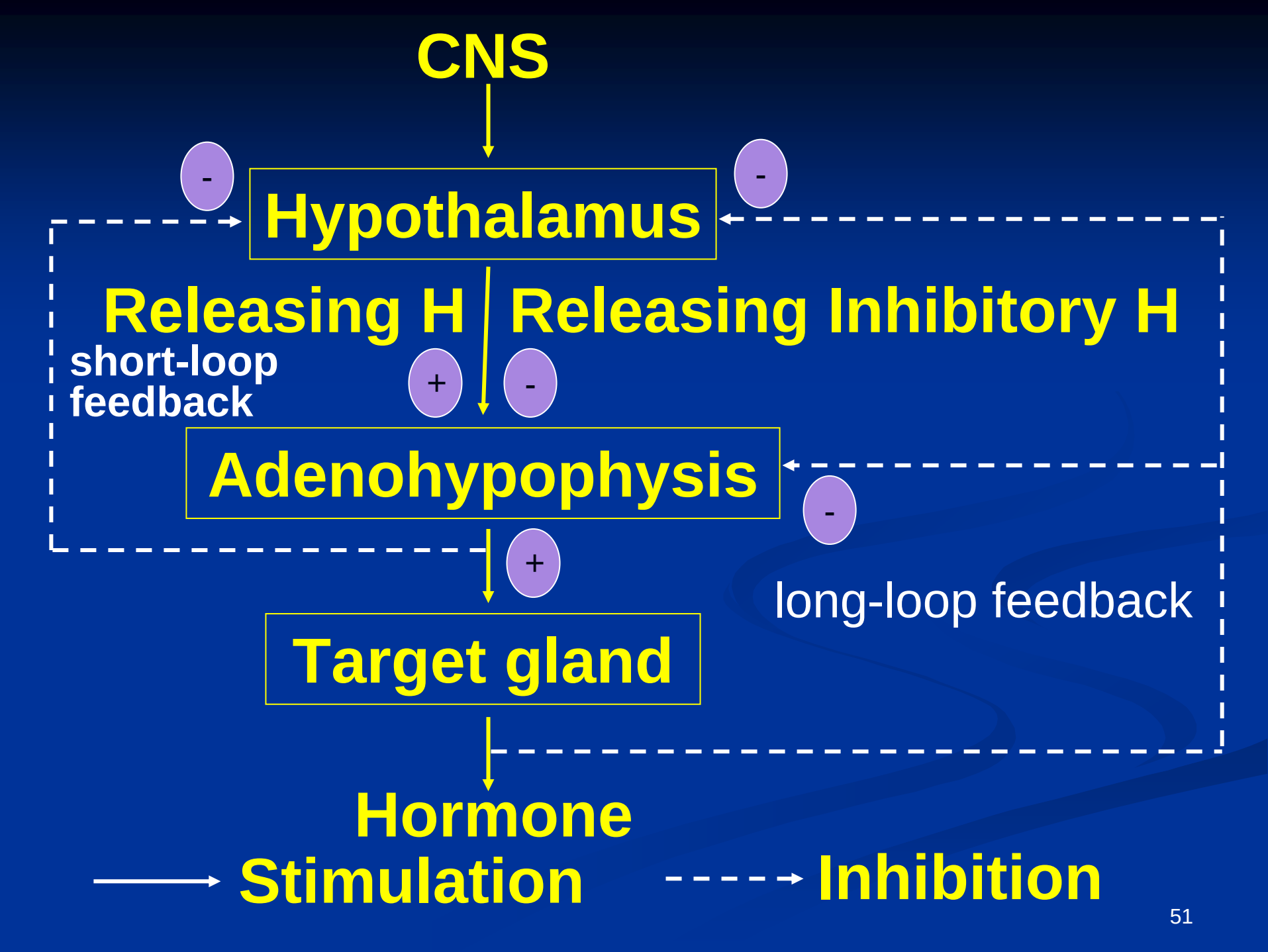
(一) *Hypothalamic-pituitary-gland*

- **Three main axes involving hypothalamus and pituitary control much of endocrine system**

  - Hypothalamic-Pituitary-Thyroid axis (HPT)

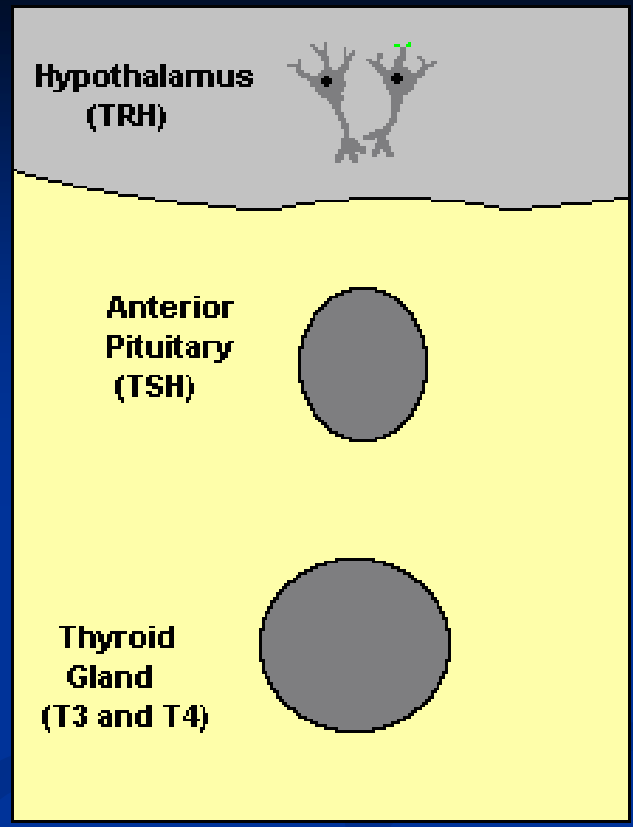
  - Hypothalamic-Pituitary-Adrenal axis (HPA)

  - Hypothalamic-Pituitary-Gonadal axis (HPG)


CNS
-
-
Hypothalamus
Releasing H
Releasing Inhibitory H
short-loop feedback
+
-
Adenohypophysis
-
+
long-loop feedback
Target gland
Hormone
Stimulation
Inhibition

Negative Feedback

- Most common control mechanism
- Feedback to hypothalamus (and pituitary) limits releasing signal



Positive Feedback

- Less common mechanism
- Used when signal amplification is needed

(二) *Feedback through metabolites*

- ✓ Glucose
- ✓ Na^+ K^+
- ✓ Ca^{2+}

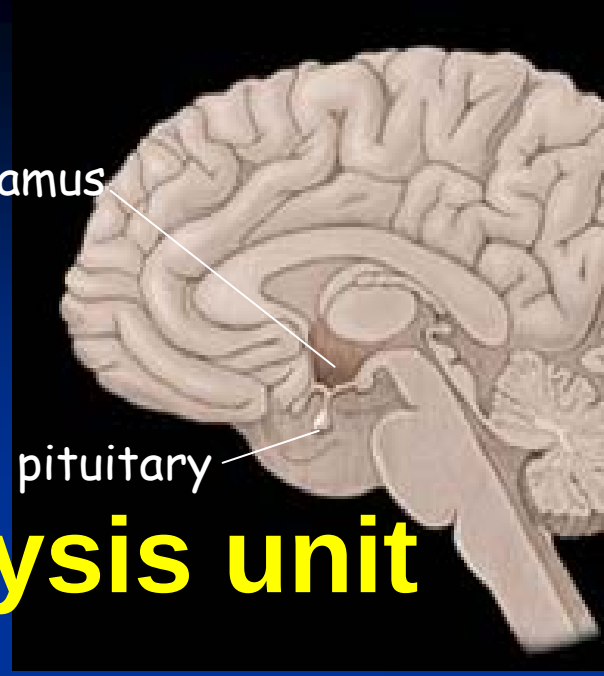
(三) *Nervous regulation*

- ✓ Sympathetic nerve
- ✓ Parasympathetic nerve

Summary of Section 1

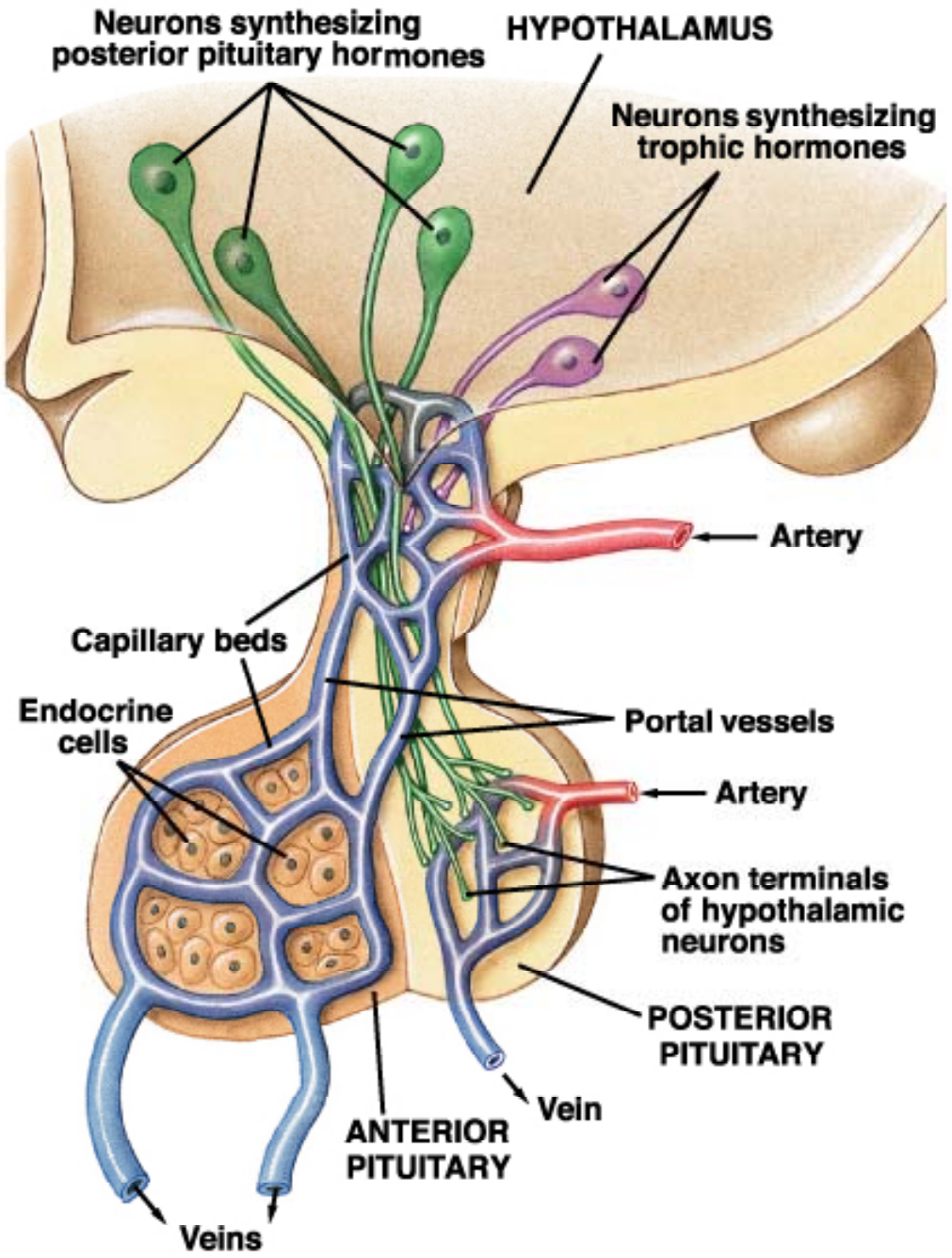
- ✓ Definition of the endocrine (system) hormone, permissive action
- ✓ Chemical classification of hormone
- ✓ Patterns and Feature of hormonal action
- ✓ Mechanisms of hormonal action

Section 2
Hypothalamus and Pituitary Gland

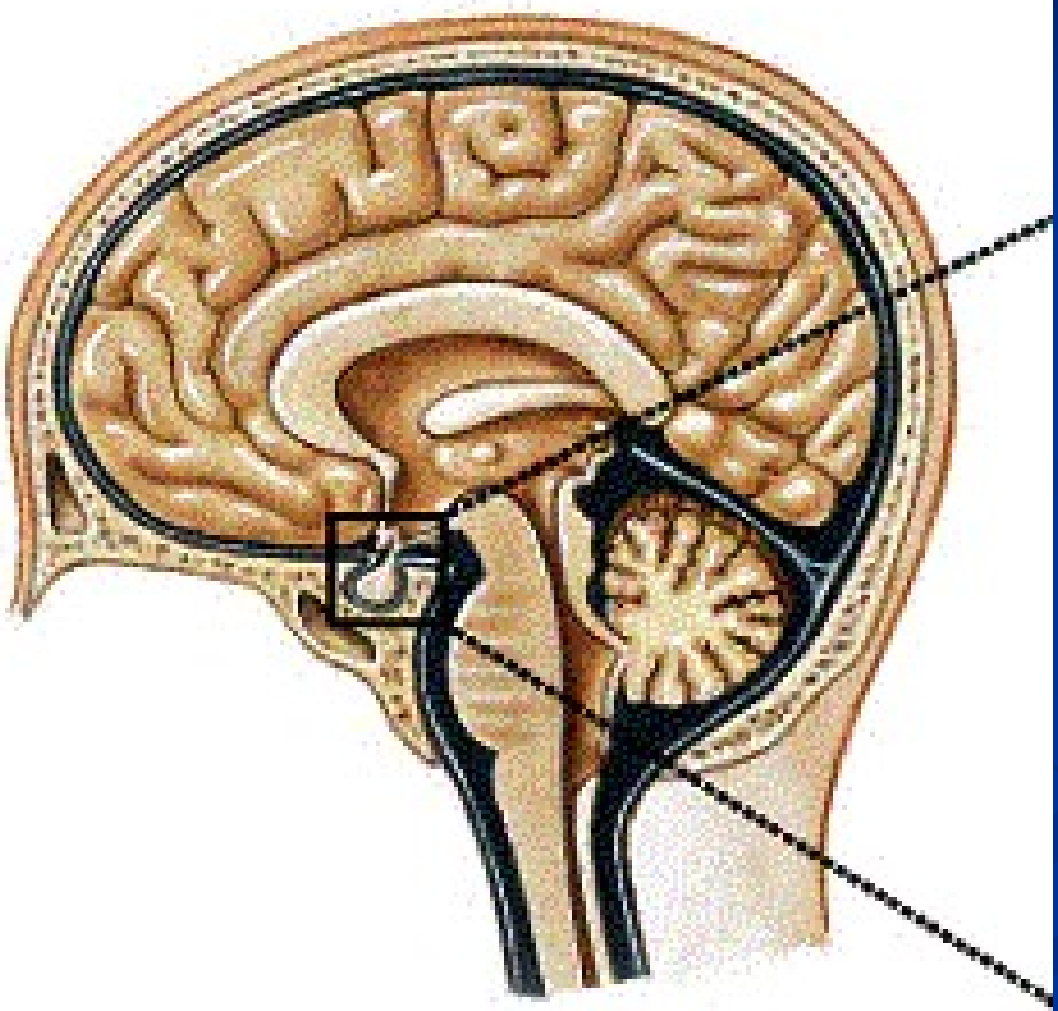


- **Hypothalamus-hypophysis unit**
  - **hypothalamo-adenohypophysis system**
  - **hypothalamo-neurohypophysis system**

I. Anatomical and Functional Connection Between the Hypothalamus and Pituitary (hypothalamo-hypophyseal portal system and tract)

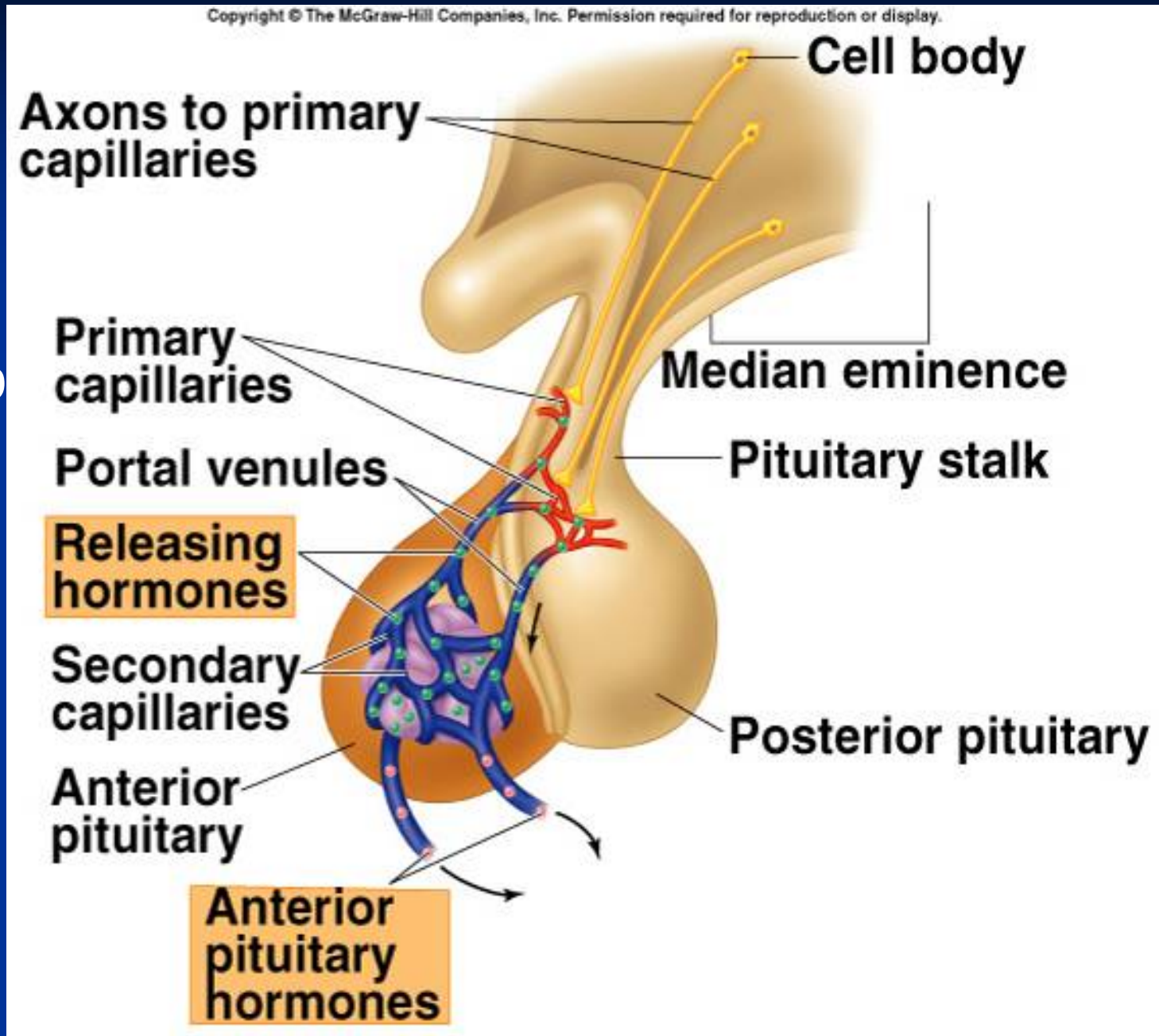


Location of the Pituitary



1. The Pituitary Gland

Anterior pituitary, also known as the **adenohypophysis**,



Important peptide hormones that secreted by the anterior pituitary and the targets:

TSH, Thyroid stimulating hormone

ACTH, Adrenocorticotropin hormone

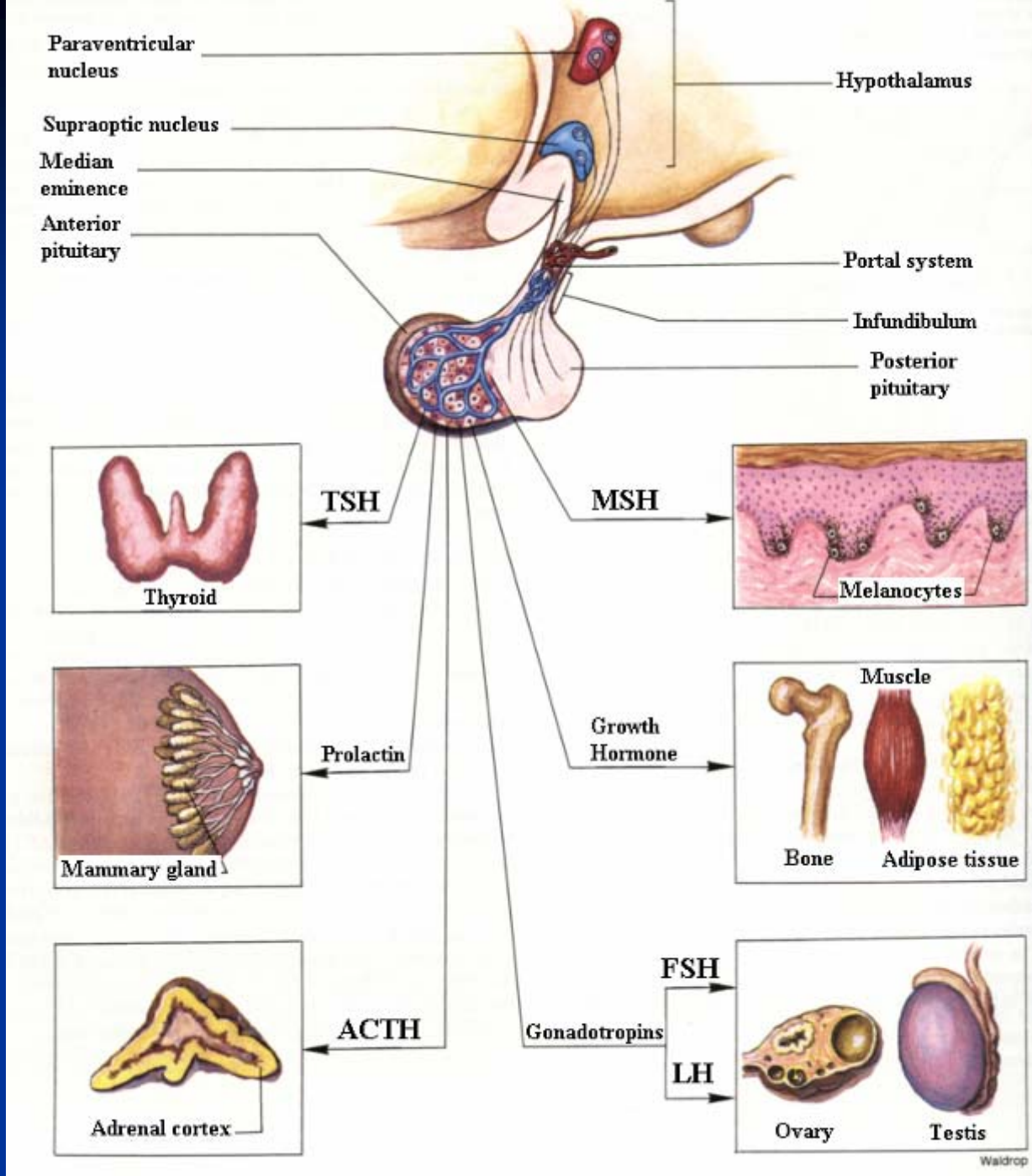
FSH, Follicle-stimulating hormone

LH, Luteinizing hormone

MSH, Melanophore-stimulating hormone

GH, Growth Hormone;

PRL, Prolactin



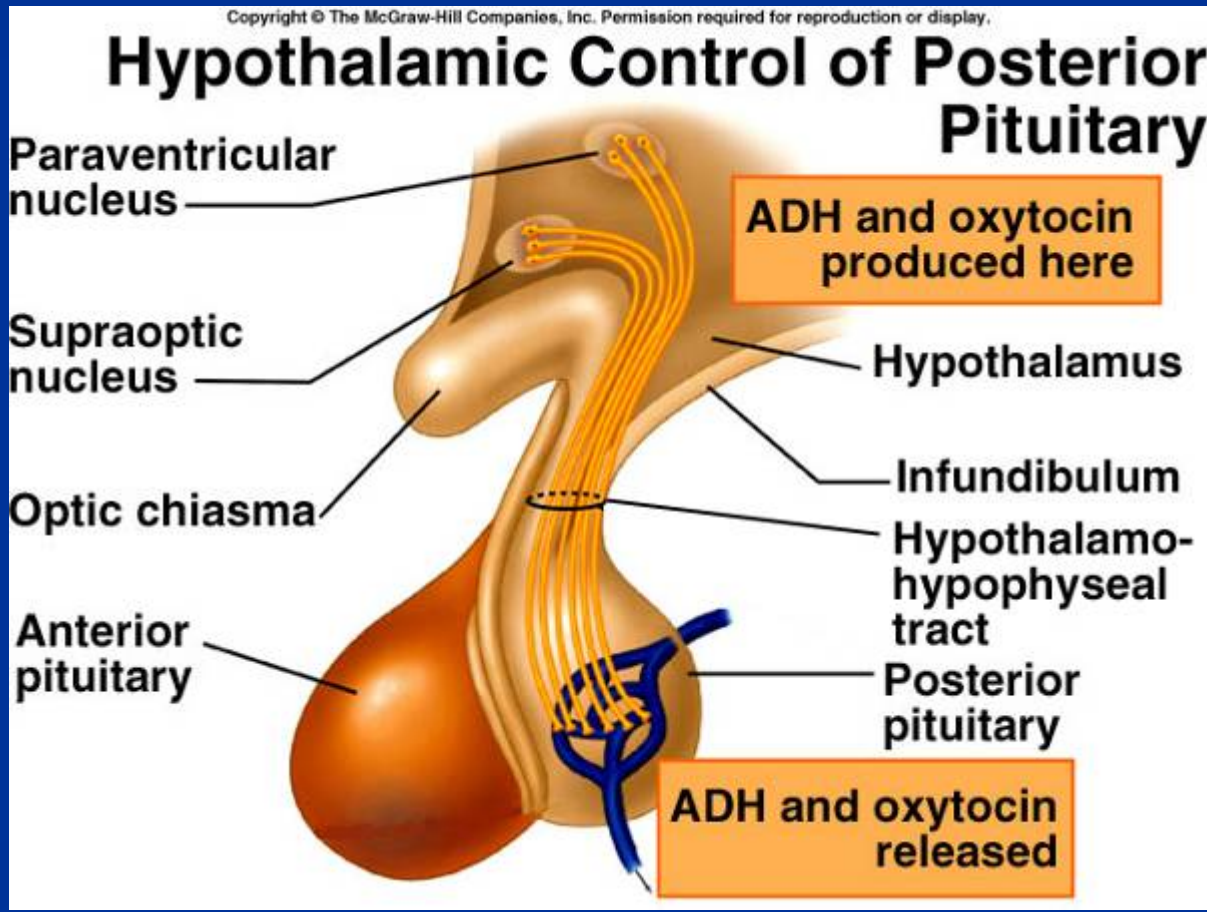
The **posterior pituitary**, also known as the **neurohypophysis**.

Two important peptide hormones that secreted by the posterior pituitary,

ADH

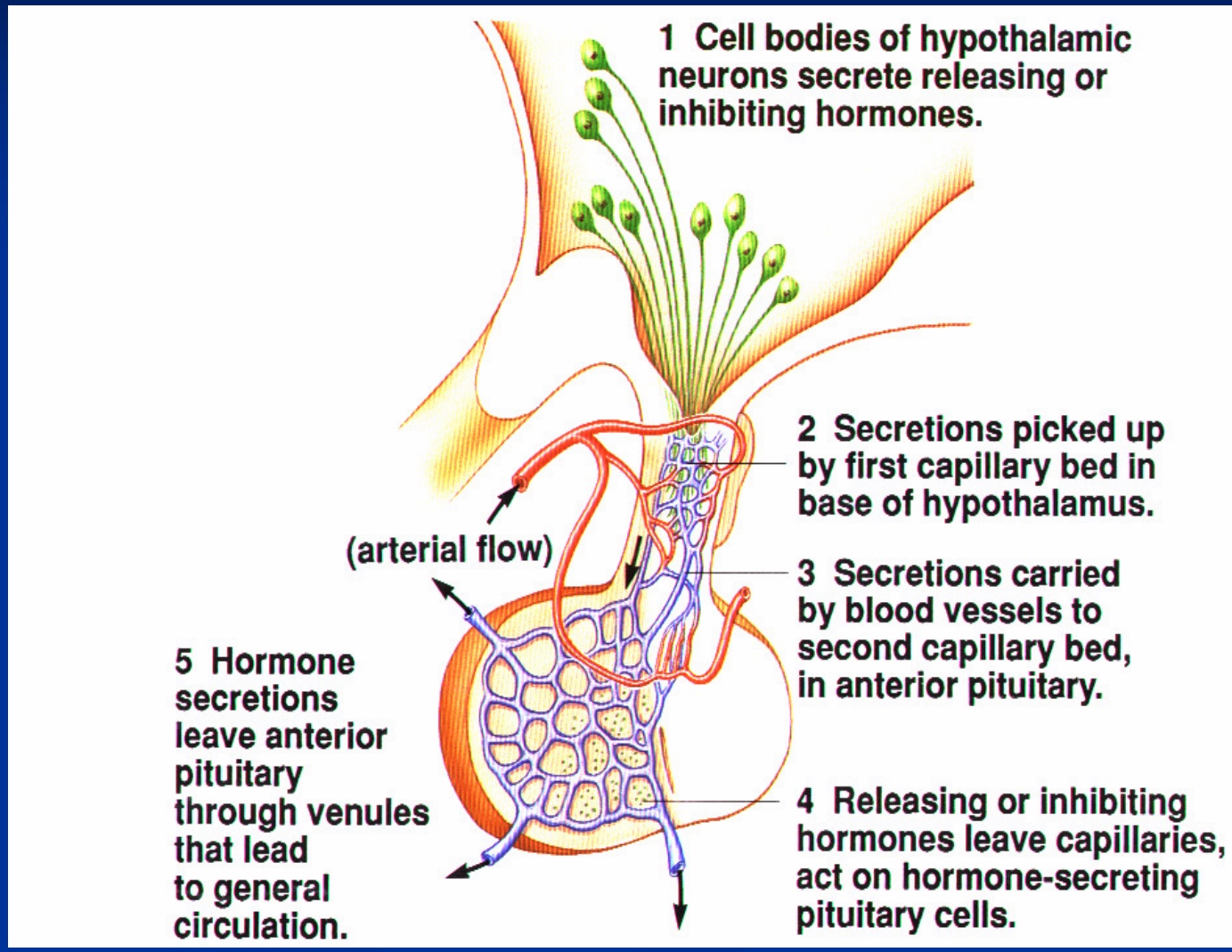
(or vasopressin)

oxytocin

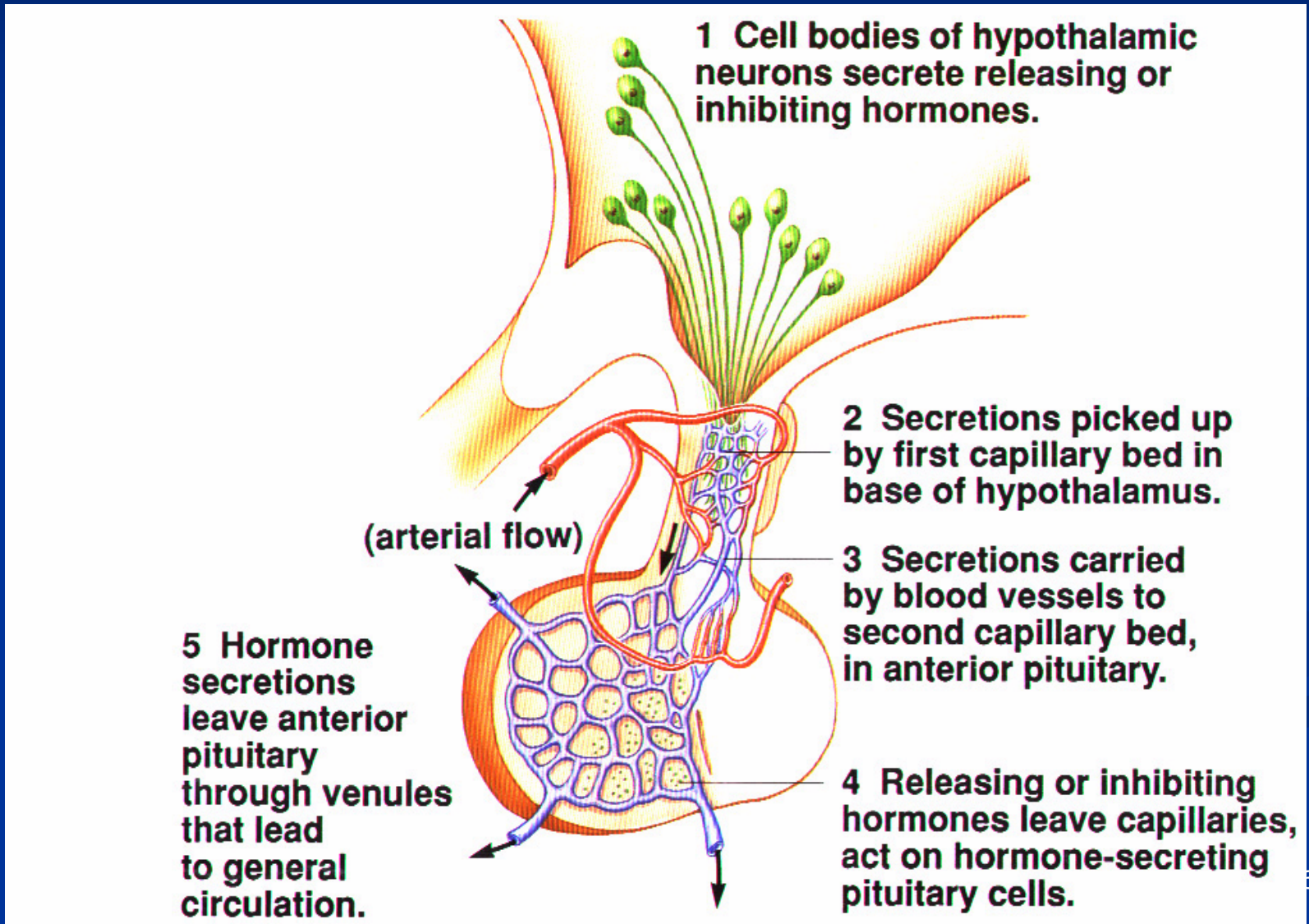


2. Relationship Between the Hypothalamus and Anterior Pituitary

Neurons in the hypothalamus secreted **releasing hormones** into the blood vessels of the hypothalamo-hypophyseal portal system.



These **releasing hormones** regulate the anterior pituitary to secrete its hormones in the general circulation.



3. Hormones Secreted by the Hypothalamus and Their Effects on Anterior Pituitary

Corticotropin-releasing hormone (CRH) – Stimulates secretion of ACTH (adrenocorticotropic hormone)

Gonadotropin-releasing hormone (GnRH) Stimulates secretion of FSH (follicle-stimulating hormone) and LH (luteinizing hormone)

Thyrotropin-releasing hormone (TRH)-stimulates secretion of TSH (thyroid-stimulation hormone)

Melanocyte-stimulating hormone release inhibiting factor (MIF)-inhibits secretion of MSH (Melanocyte-stimulating hormone)

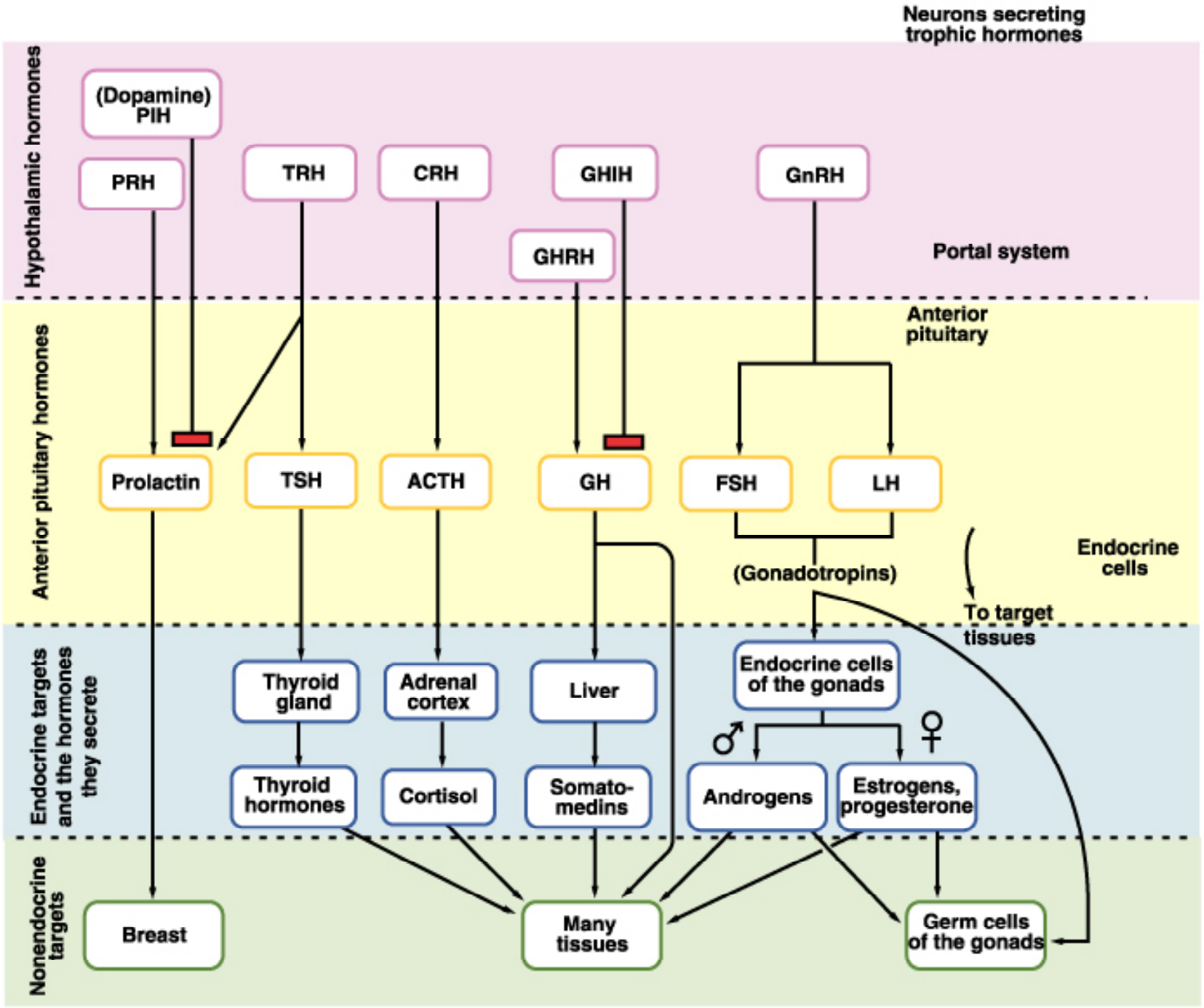
Melanocyte-stimulating hormone releasing factor (MRF)-stimulate secretion of MSH

Growth hormone release inhibiting hormone (GHRIH) or Somatostatin (SS) – inhibits secretion of growth hormone

Growth hormone-releasing hormone (GHRH)– stimulates growth hormone secretion

Prolactin-inhibiting factor (PIF)- inhibits prolactin secretion

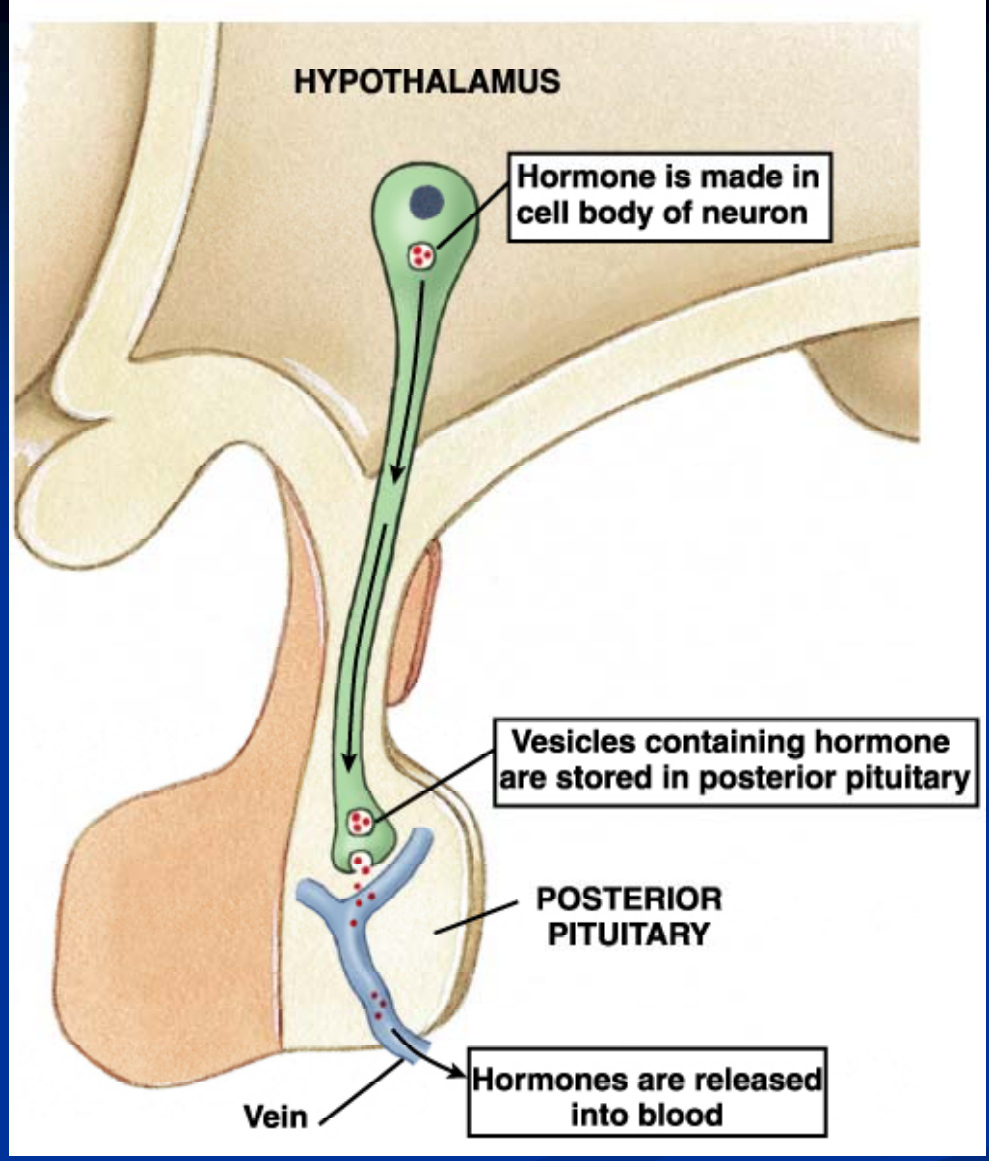
Prolactin-releasing factor (PRF)-stimulates prolactin section


Neurons secreting trophic hormones
Hypothalamic hormones
(Dopamine) PIH
PRH
TRH
CRH
GHIH
GHRH
GnRH
Portal system
Anterior pituitary
Anterior pituitary hormones
Prolactin
TSH
ACTH
GH
FSH
LH
(Gonadotropins)
Endocrine cells
To target tissues
Endocrine targets and the hormones they secrete
Thyroid gland
Adrenal cortex
Liver
Endocrine cells of the gonads
♂
♀
Thyroid hormones
Cortisol
Somato-medins
Androgens
Estrogens, progesterone
Nonendocrine targets
Breast
Many tissues
Germ cells of the gonads

4. Hormones Secreted from the Posterior Pituitary

vasopressin and oxytocin

produced in neuron cell bodies within the supraoptic and paraventricular nuclei of the hypothalamus

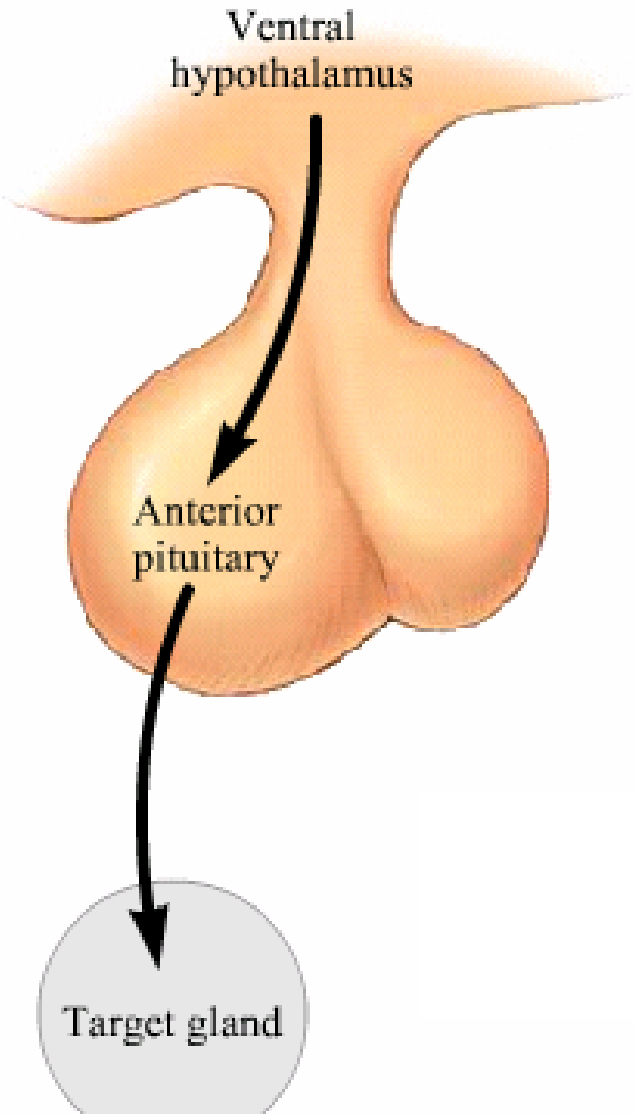


transported to the posterior pituitary by nerve fibers of the hypothalamo-hypophyseal tract.

II. Physiological Function of Hormones Secreted From Anterior and Posterior Pituitary

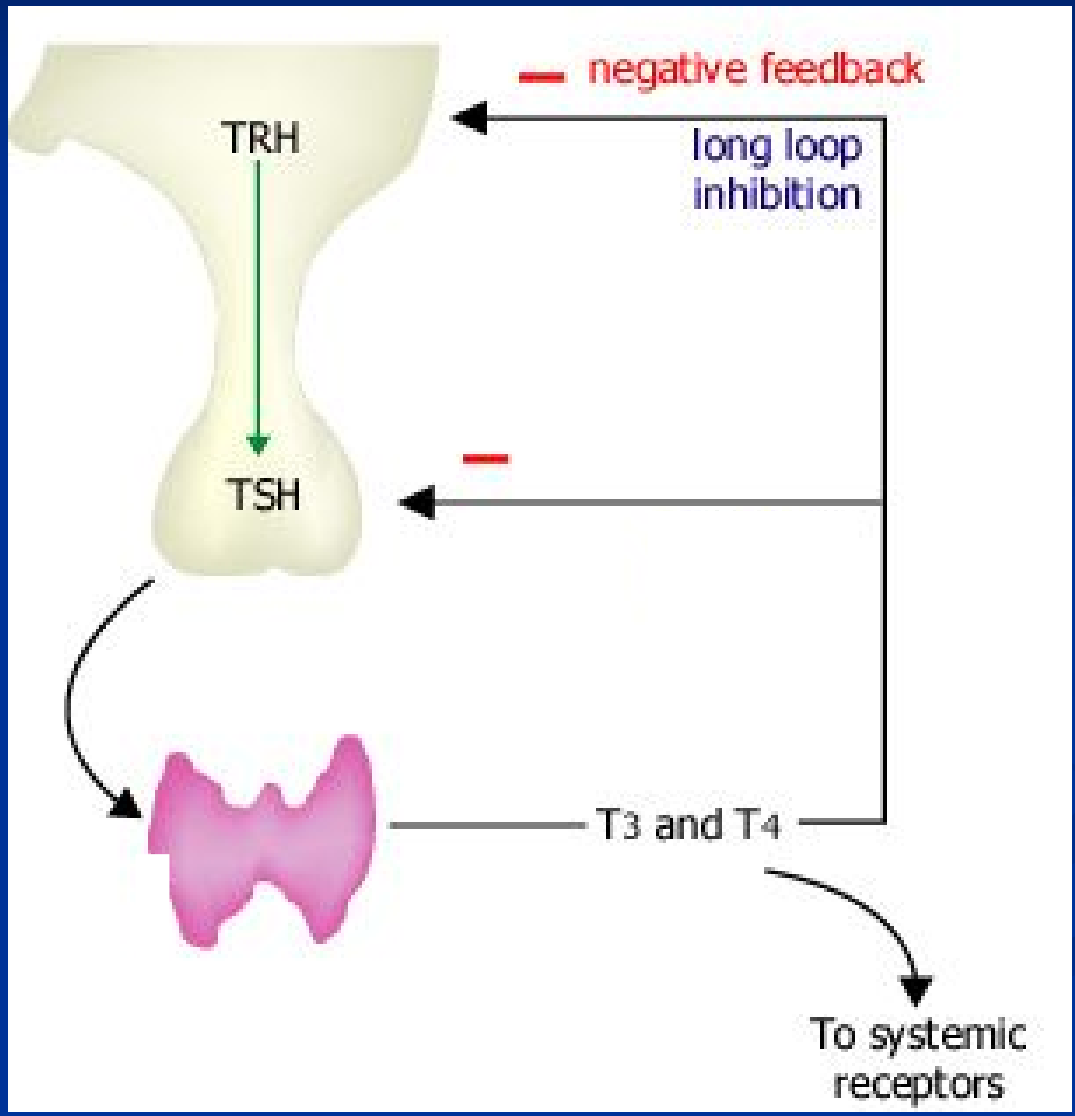
Adenohypophysis hormone

- TSH (thyroid stimulating hormone)
- ACTH (adrenocorticotropic hormone)
- FSH (follicle stimulating hormone)
- LH (luteinizing hormone)
- GH (growth hormone)
- PRL (prolactin)
- MSH (melanophore stimulating hormone)

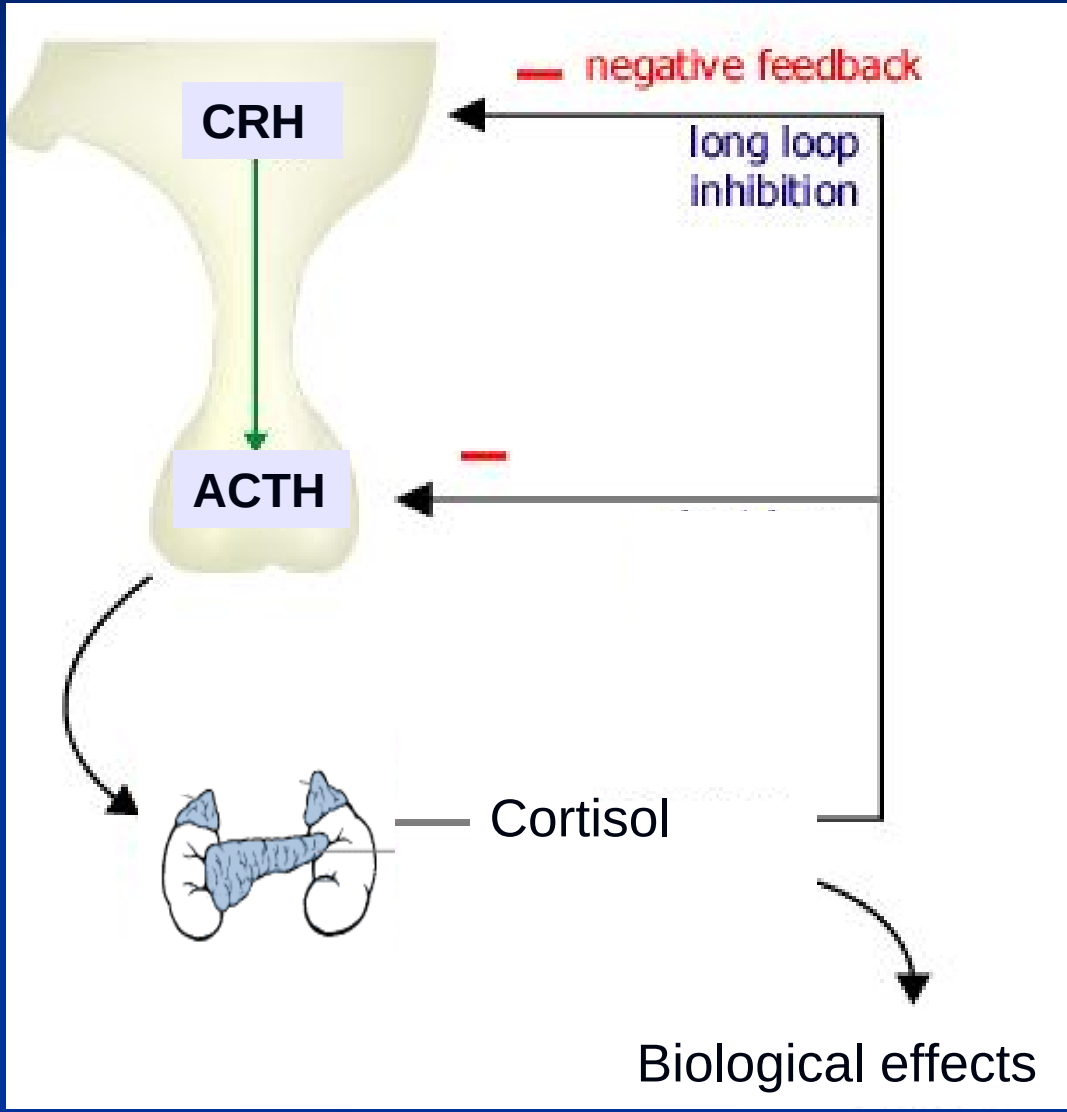


TRH	GnRH	CRH
↓	↓	↓
TSH	FSH, LH	ACTH
↓	↓	↓
TH	Estrogen progesterone testosterone	Cortisol and other adrenocortical hormones

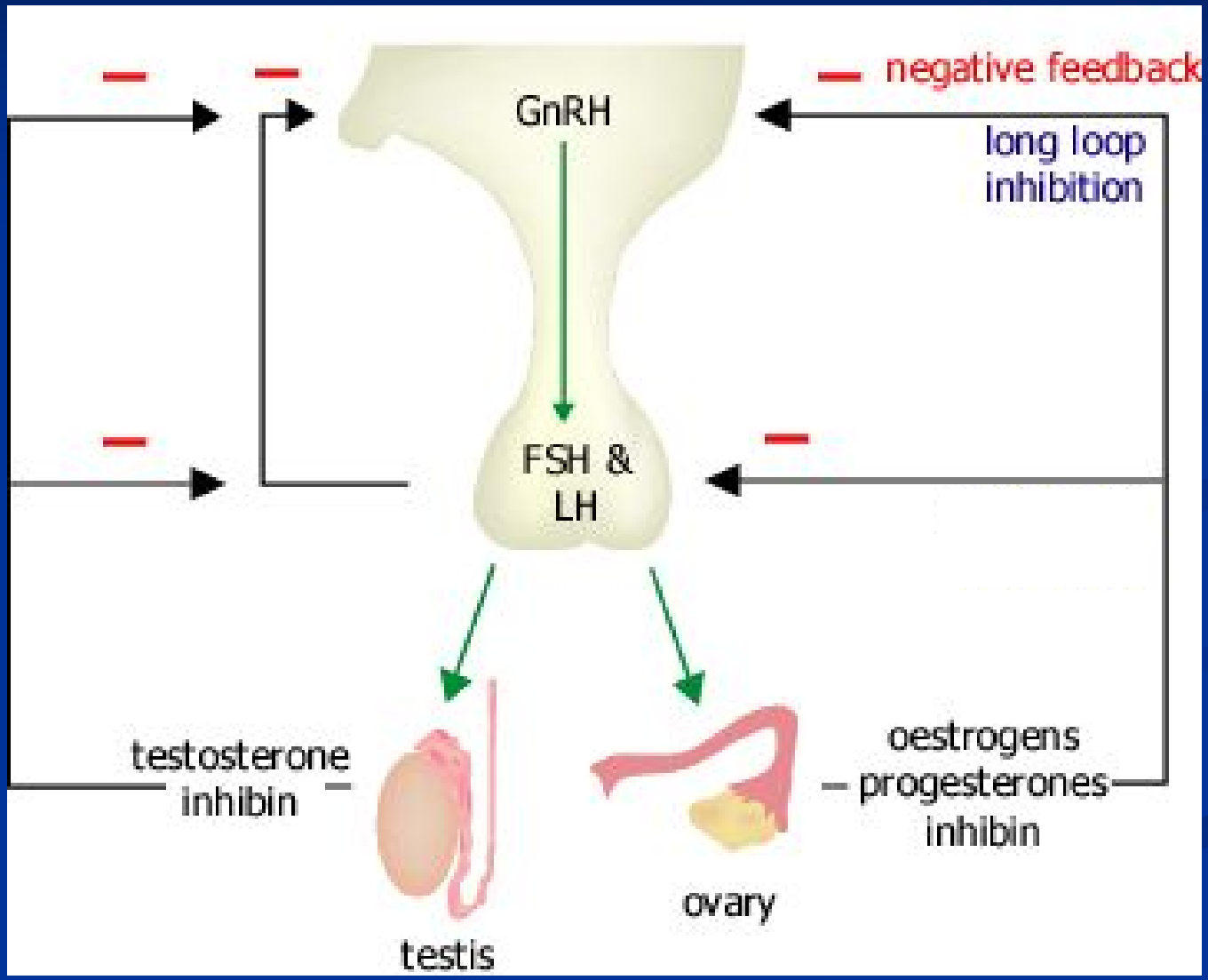
Hypothalamus-Adenohypophysis-Thyroid Axis



Hypothalamus-Adenohypophysis-Adrenocortical Axis



Hypothalamus-Adenohypophysis-Gonadal Axis

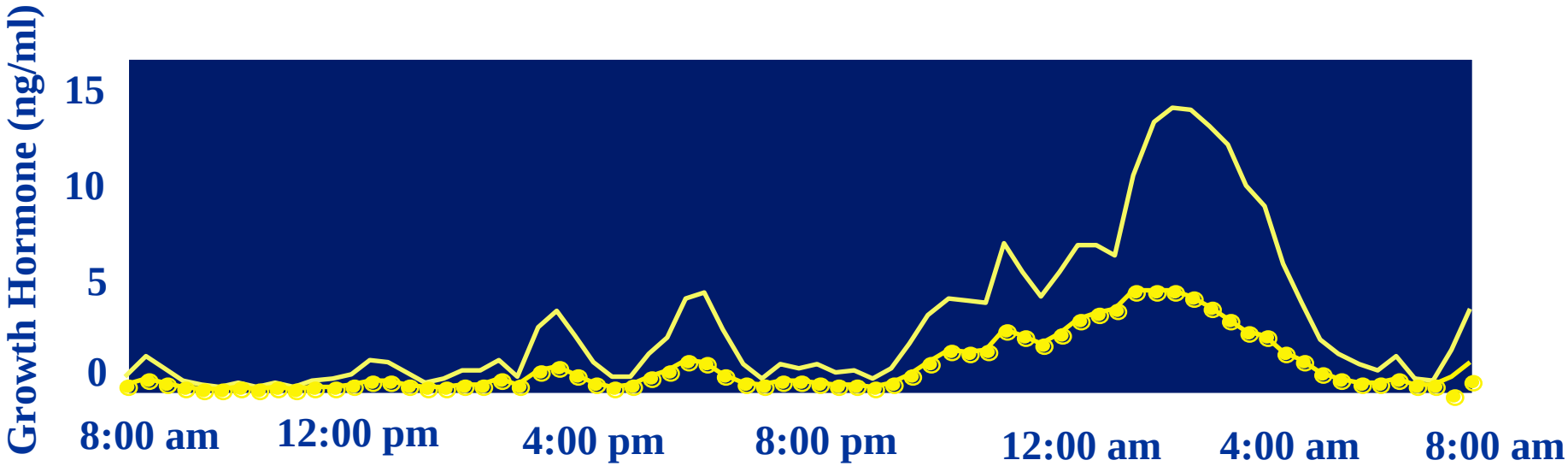


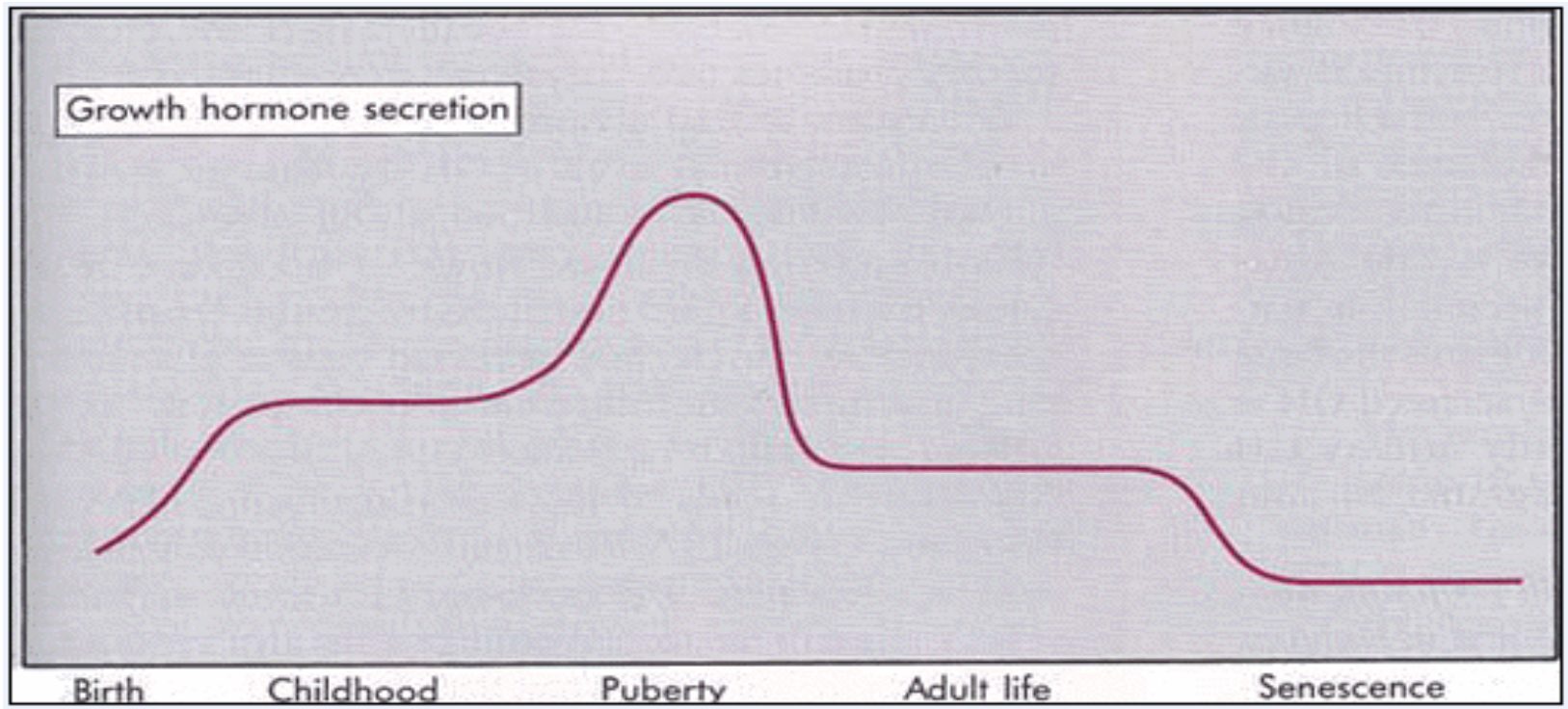
Adenohypophysis hormone

- TSH (thyroid stimulating hormone)
- ACTH (adrenocorticotropic hormone)
- FSH (follicle stimulating hormone)
- LH (luteinizing hormone)
- GH (growth hormone)
- PRL (prolactin)
- MSH (melanophore stimulating hormone)

Growth hormone

- General introduction
  - 8.5mg/g
  - 191 aa; MW: 22kD
  - hGH: male < 5μg/L, female<10μg/L
  - Half time :6-20 min
  - Pulsatile secretion:
    - produced in small bursts (1-4h)


Growth Hormone (ng/ml)
15
10
5
0
8:00 am
12:00 pm
4:00 pm
8:00 pm
12:00 am
4:00 am
8:00 am


Growth hormone secretion
Birth
Childhood
Puberty
Adult life
Senescence

1.Growth Hormone

(1)Physiological functions of growth hormone.

1) Growth effect

Growth hormone stimulates cell division, especially in muscle and epiphyseal cartilage of long bones.

The result is muscular growth as well as linear growth.

GH also stimulates growth in several other tissues, e.g.

skeletal muscle, heart, skin, connective tissue, liver, kidney, pancreas, intestines, adrenals and parathyroids.

Hypersecretion of GH leads to cause **gigantism** in children and **acromegaly** in adult.

Hyposecretion of GH results in **dwarfism** during childhood.

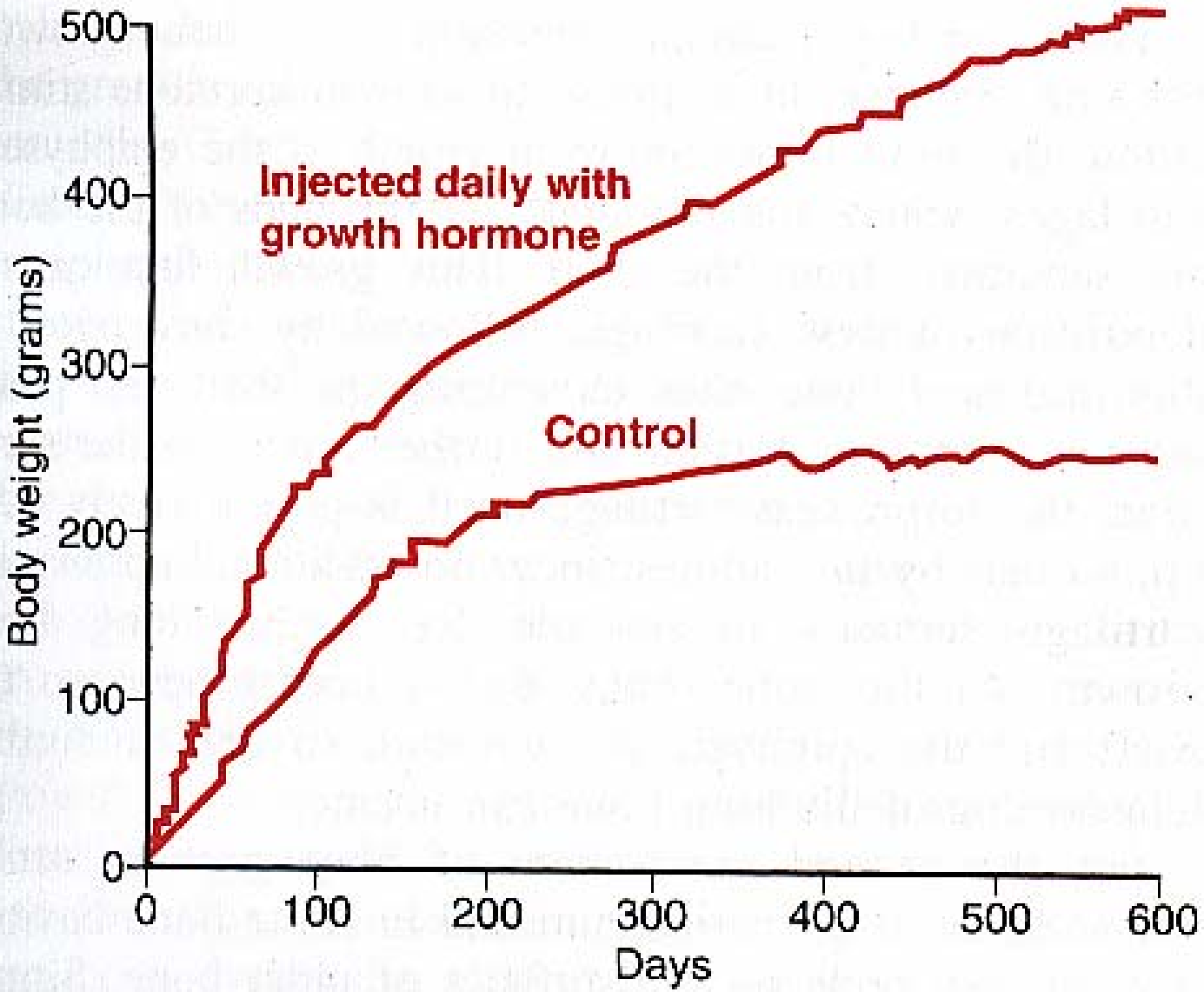


FIGURE 75–5

Comparison of weight gain of a rat injected daily with growth hormone with that of a normal littermate.

Effect of hypophysectomy on growth of the immature rhesus monkey.

Both monkeys were the same size and weight 2 years previously, when the one on the left was hypophysectomized.

Effect of growth hormone treatment for 4 days on the proximal tibial epiphysis of the hypophysectiomized rat.

Note that increased width of the unstained cartilage plate in the tibia of the right, compared with the control in the left.

Growth Hormone Excess

- in childhood leads to GIGANTISM

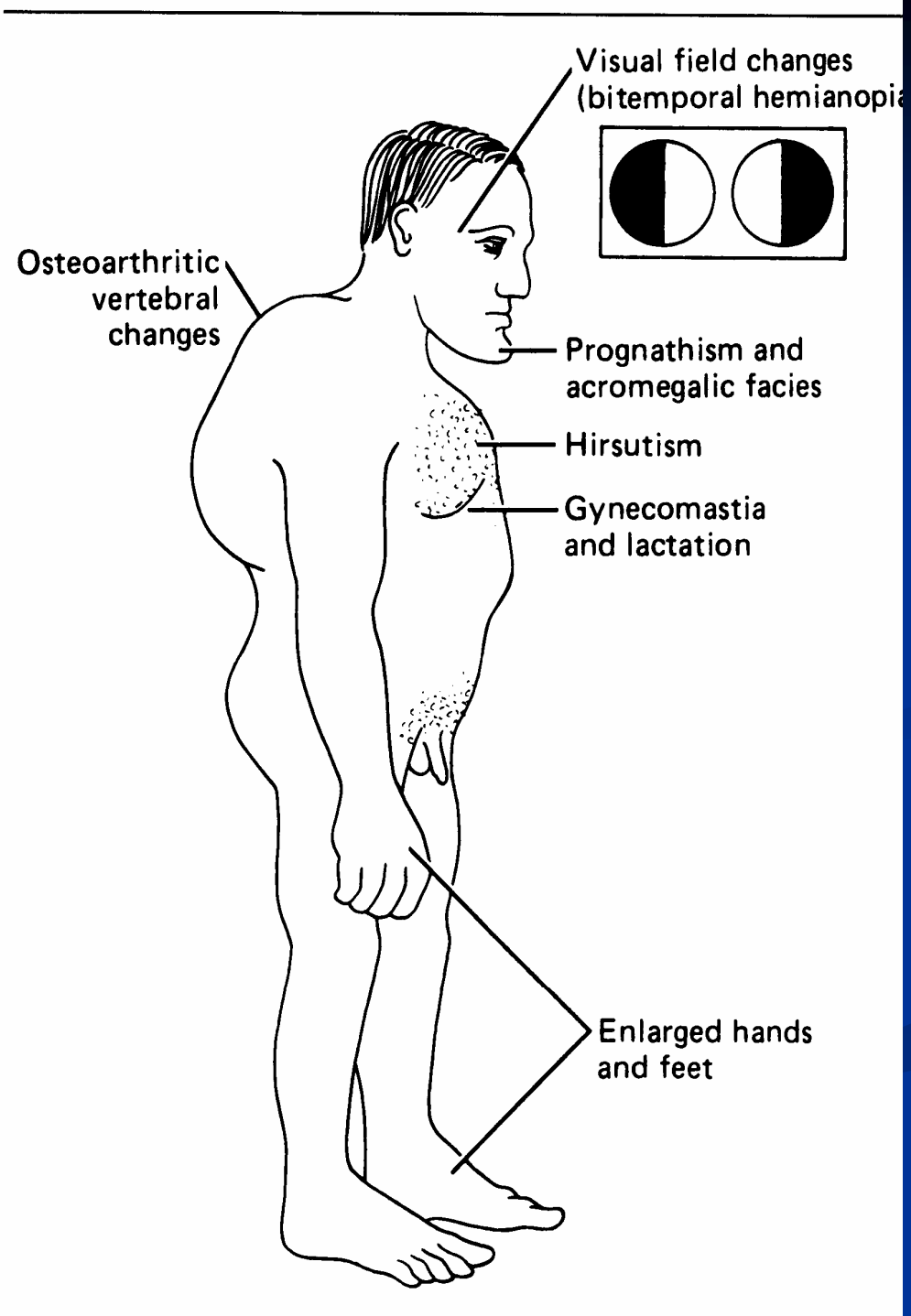
If an acidophilic tumor occur after adolescence –

that is , after the epiphyses of the lone bones have fused with shafts

– the person cannot grow taller,

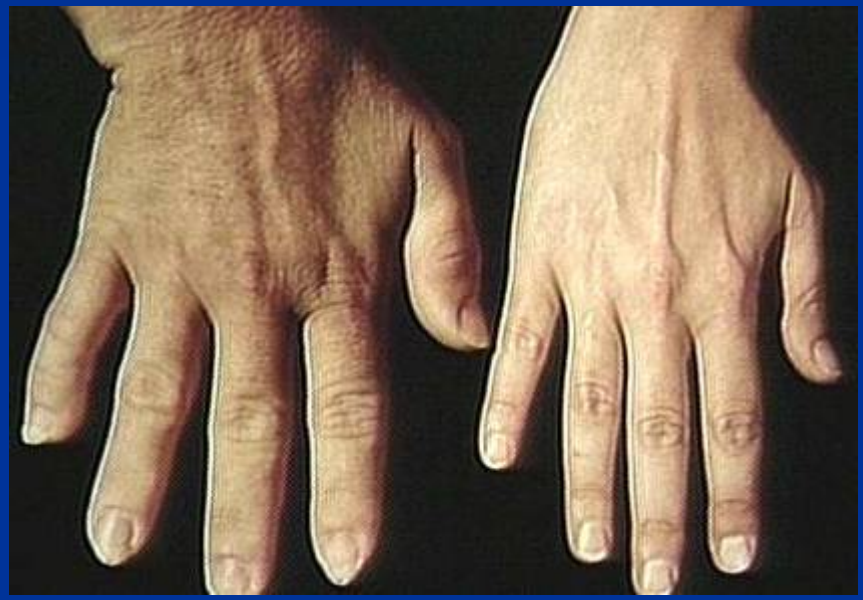
but the soft tissue can continue to grow and the bones can grow in thickness.

This condition is known as **acromegaly**.

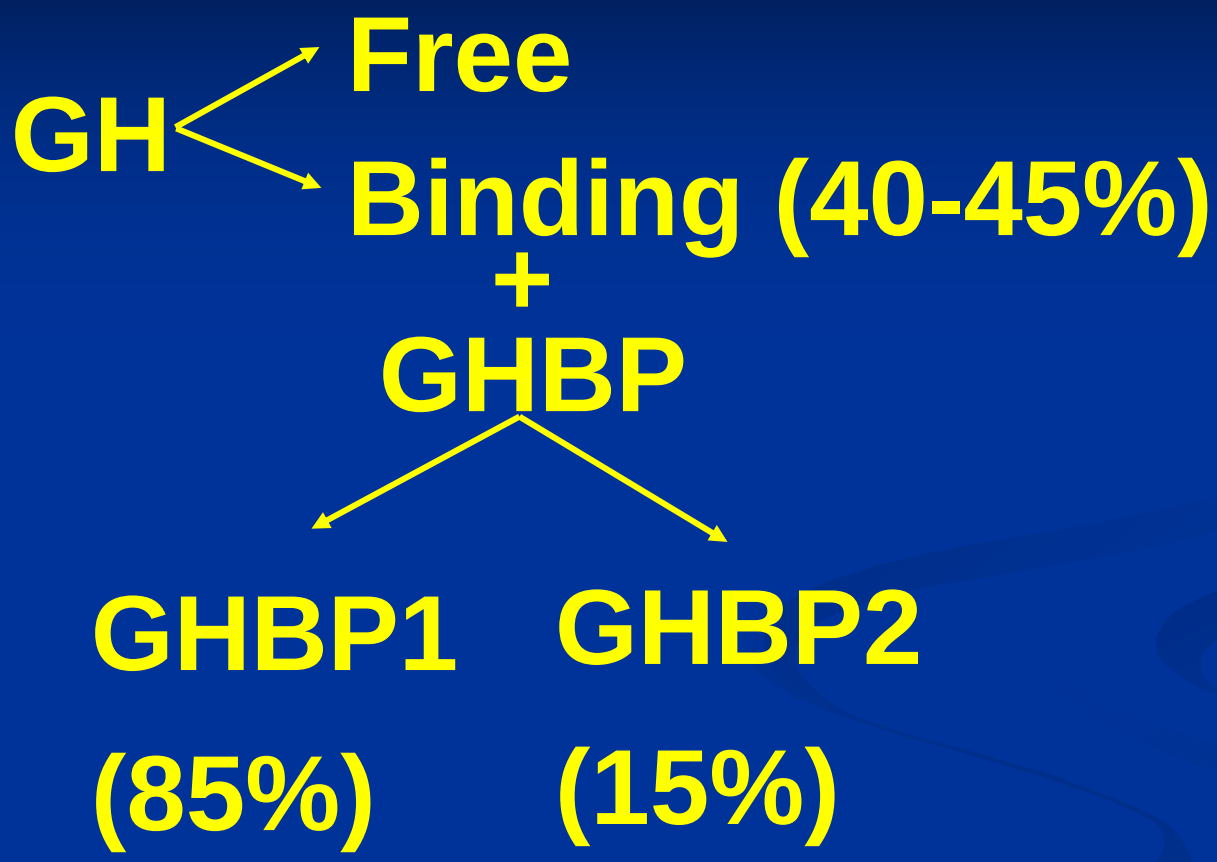


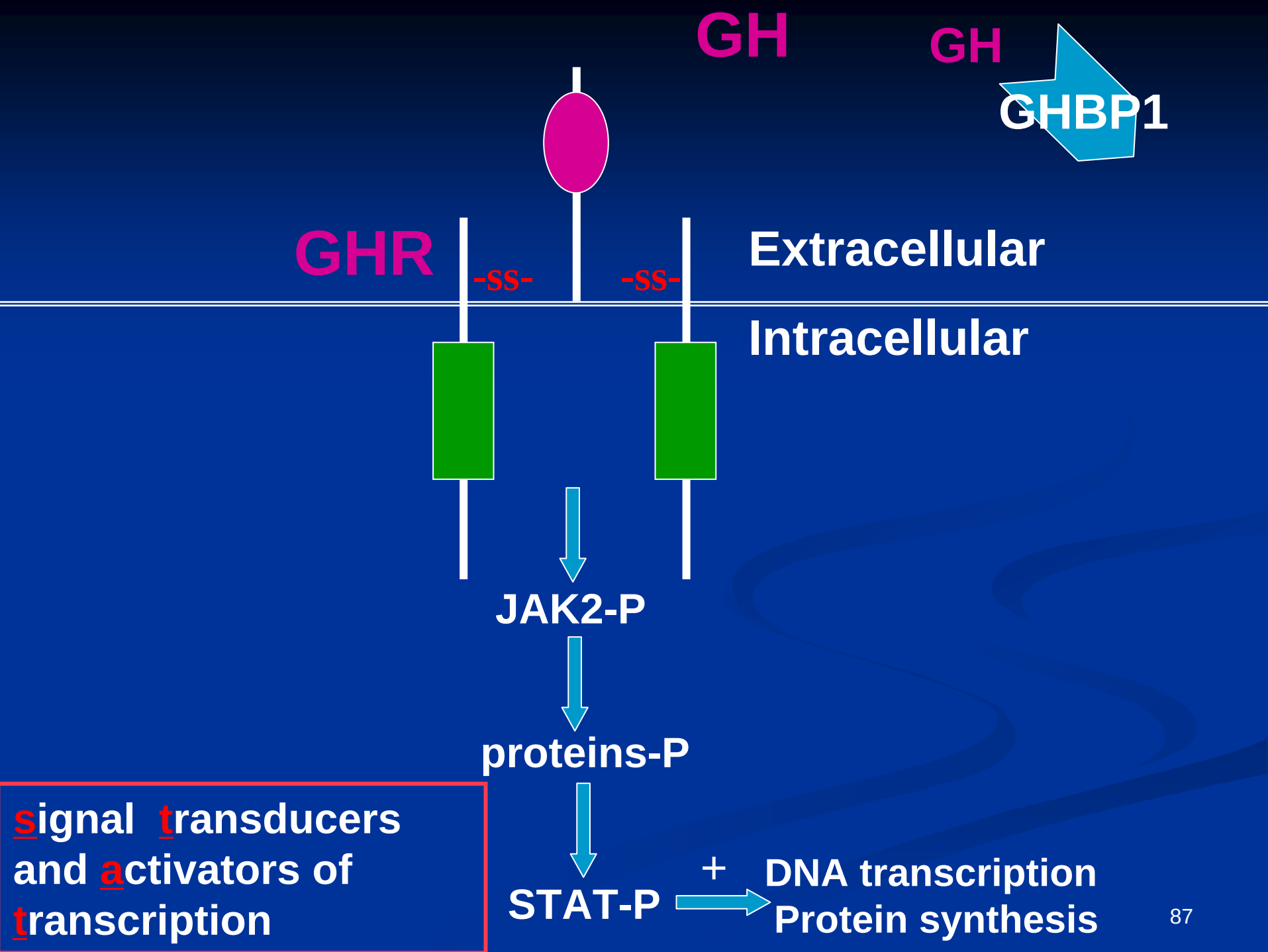
Growth Hormone Excess

- in adulthood leads to ACROMEGALY



Mechanisms of GH action

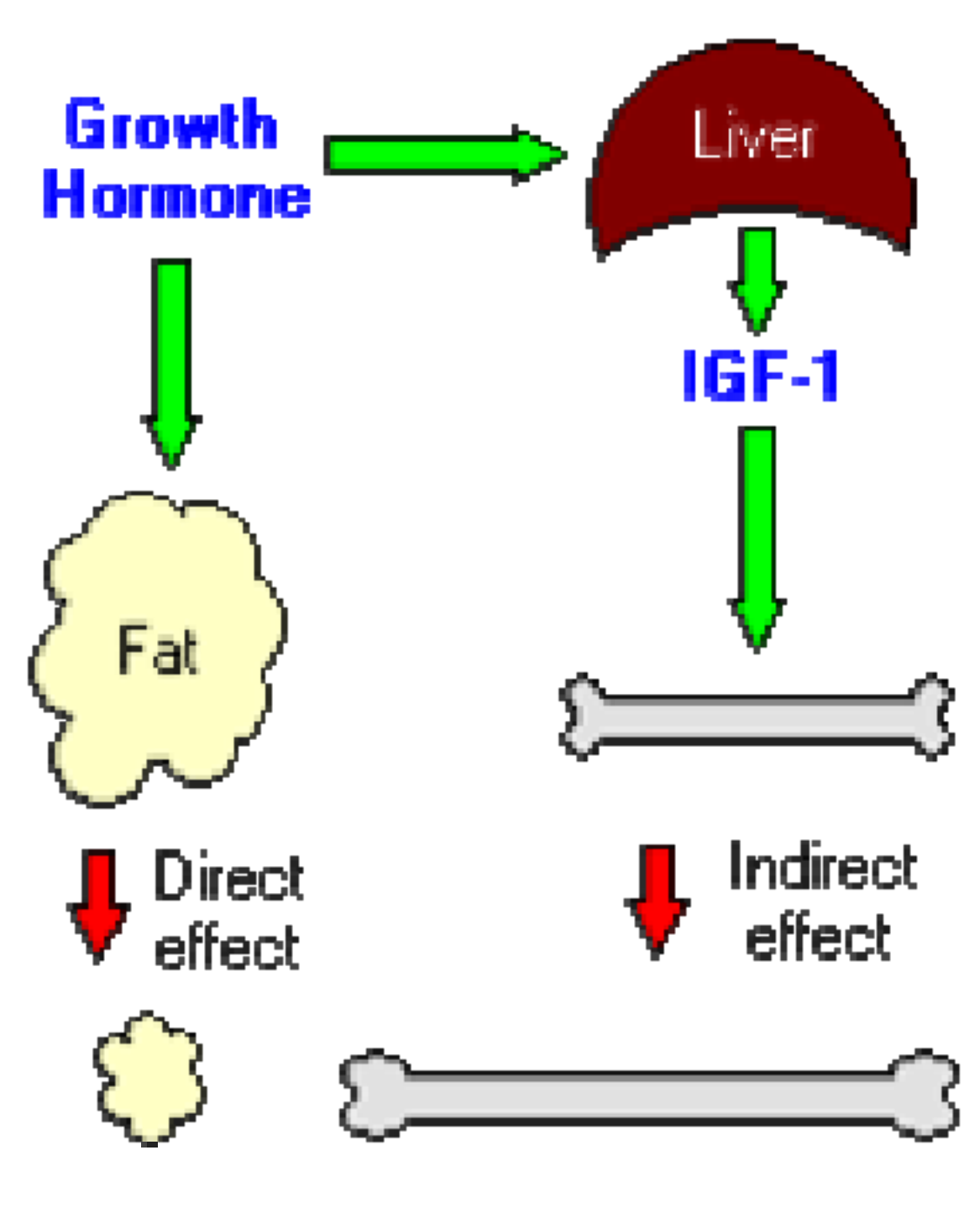




signal transducers and activators of transcription

Receptor mechanism of the growth hormone effect

GH ⟶ somatomedins (SM)（also called insulin-like growth factor, IGF) in the liver⟶ growth of bone and other peripheral tissues.

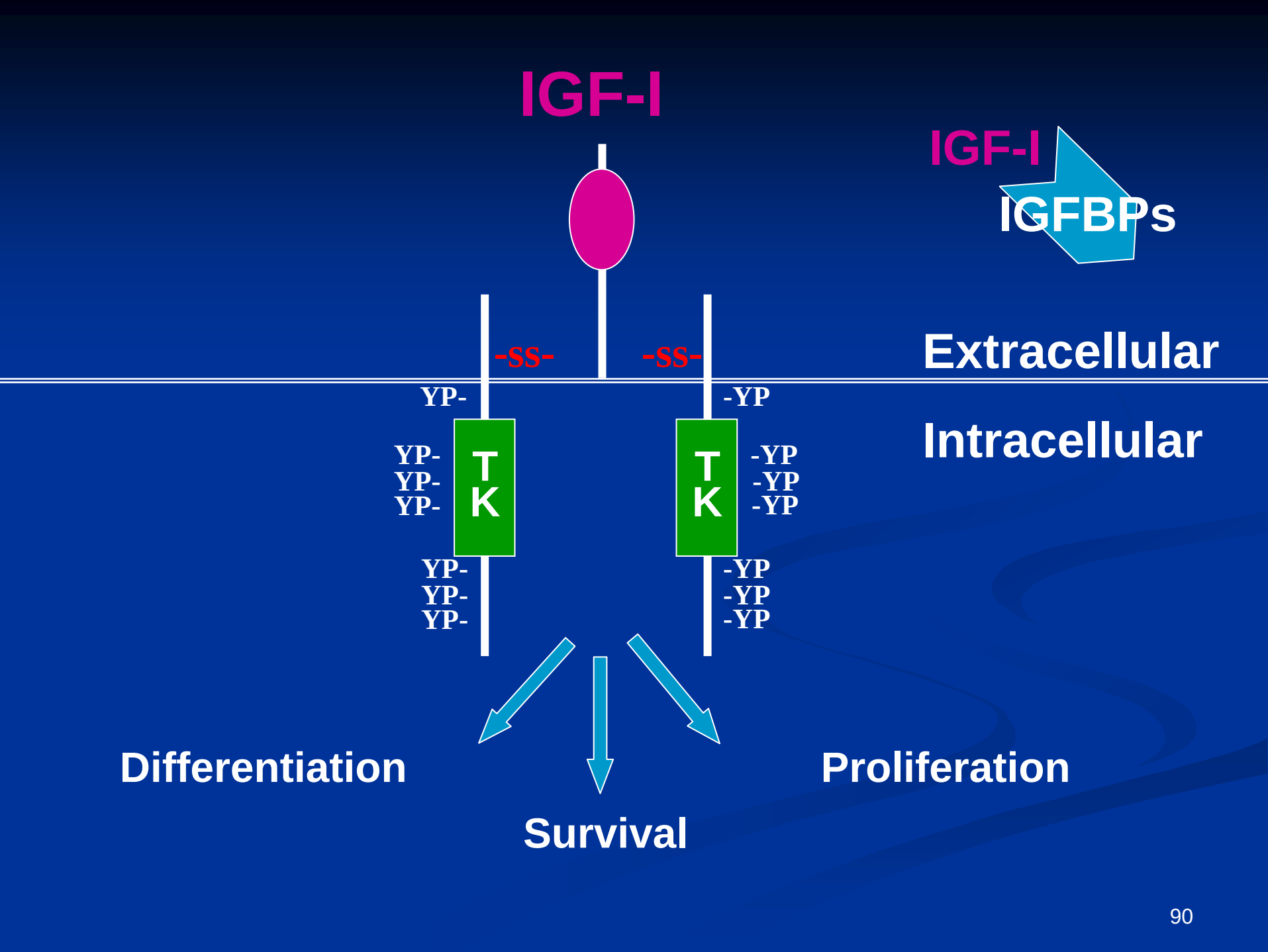


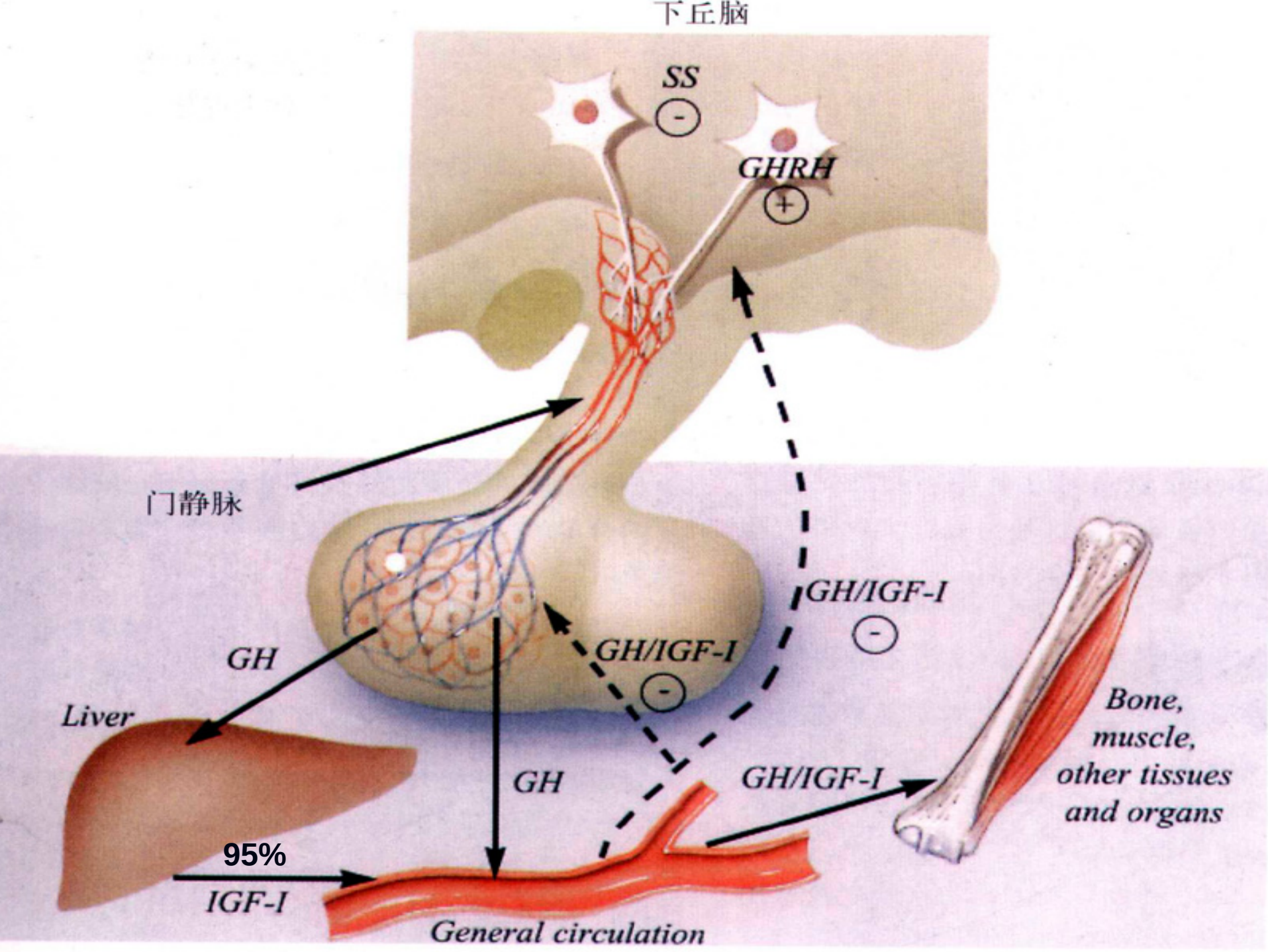
- **GH exert much of its effects through intermediate substances called "somatomedins", also called "*insulin-like growth factors*" (IGF)**

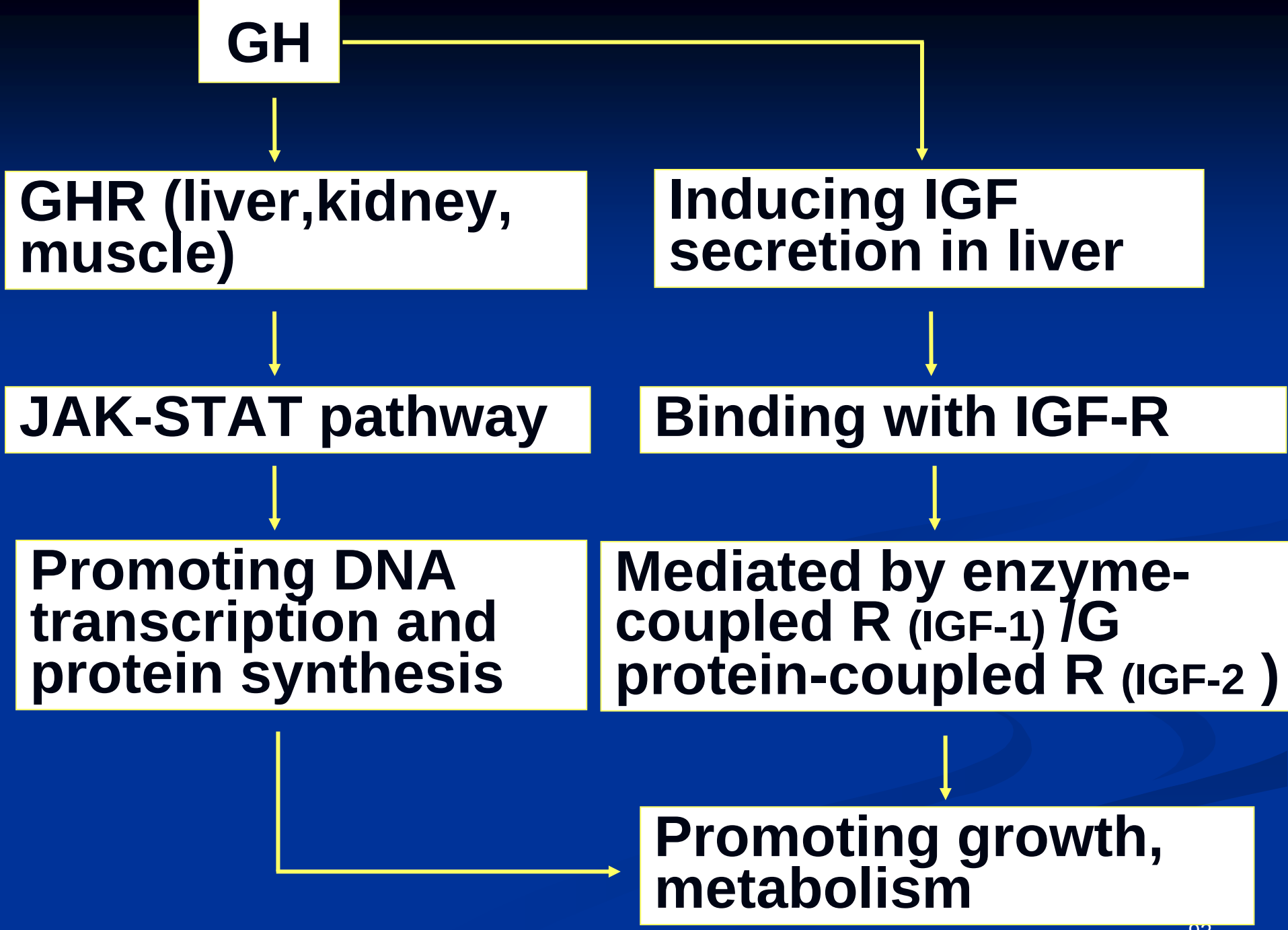
somatomedin (SM):

IGF I: adult

IGF II: fetus, cancer


IGF-I
IGF-I
IGFBPs
-SS-
-SS-
Extracellular
Intracellular
YP-
YP-
YP-
YP-
YP-
YP-
-YP
-YP
-YP
-YP
-YP
-YP
T
K
T
K
Differentiation
Survival
Proliferation


下丘脑
SS
GHRH
门静脉
GH/IGF-I
GH
GH/IGF-I
Liver
Bone,
muscle,
other tissues
and organs
GH
GH/IGF-I
95%
IGF-I
General circulation


GH
GHR (liver,kidney, muscle)
Inducing IGF secretion in liver
JAK-STAT pathway
Binding with IGF-R
Promoting DNA transcription and protein synthesis
Mediated by enzyme-coupled R (IGF-1) /G protein-coupled R (IGF-2)
Promoting growth, metabolism

2) Metabolic effects of GH

A, On Protein metabolism

Enhance amino acid transport to the interior of the cells and increase RNA translation and nuclear transcription of DNA to form mRNA, and so increase rate of protein synthesis.

GH also reduces the breakdown of cell proteins by decreasing catabolism of protein.

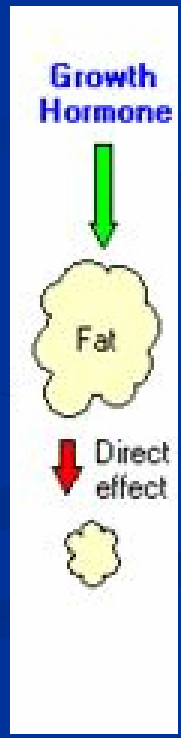
- ↑protein deposition
  - ↑AA transport through the cell membranes
  - ↑ RNA translation
  - ↑DNA transcription
- ↓ Catabolism of protein and AA

B, On fat metabolism

Cause release of fatty acids from adipose tissue and then increasing the concentration of fatty acids.

Therefore, utilization of fat is used for providing energy in preference to both carbohydrates and proteins.

- ↑Fat utilization for energy



C. On glucose metabolism

Decreases cellular uptake of glucose and glucose utilization,

leads to increase of the blood glucose concentration.

- ↓Carbohydrate utilization
  - ↓Glucose uptake
  - ↑Glucose production by the liver

pituitary glycosuria

(2) Regulation of GH secretion

The plasma concentration of GH changes with age. 5 – 20 years old, 6ng/ml; 20 – 40 years old, 3ng/ml; 40 – 70 years old, 1.6ng/ml.

The change of GH concentration within one day.

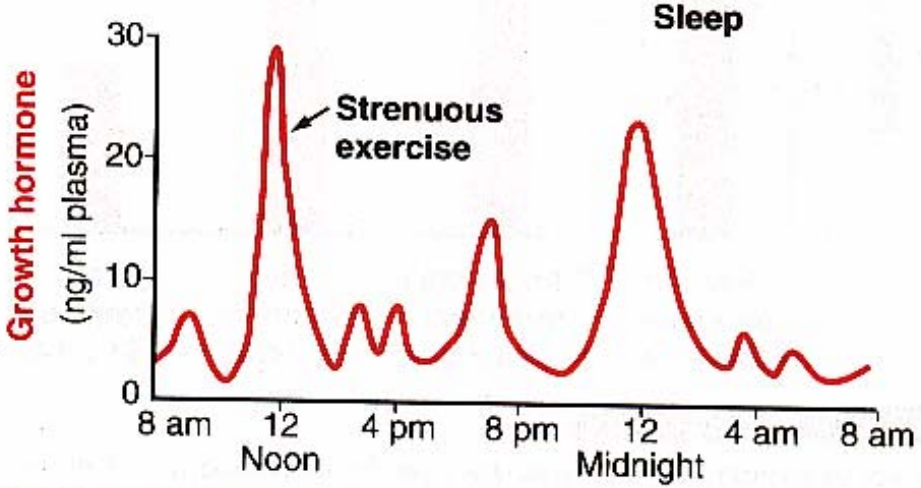


FIGURE 75 – 6

Typical variations in growth hormone secretion throughout the day, demonstrating the especially powerful effect of strenuous exercise and also the high rate of growth hormone secretion that occurs during the first few hours of deep sleep.

Regulation of GH secretion

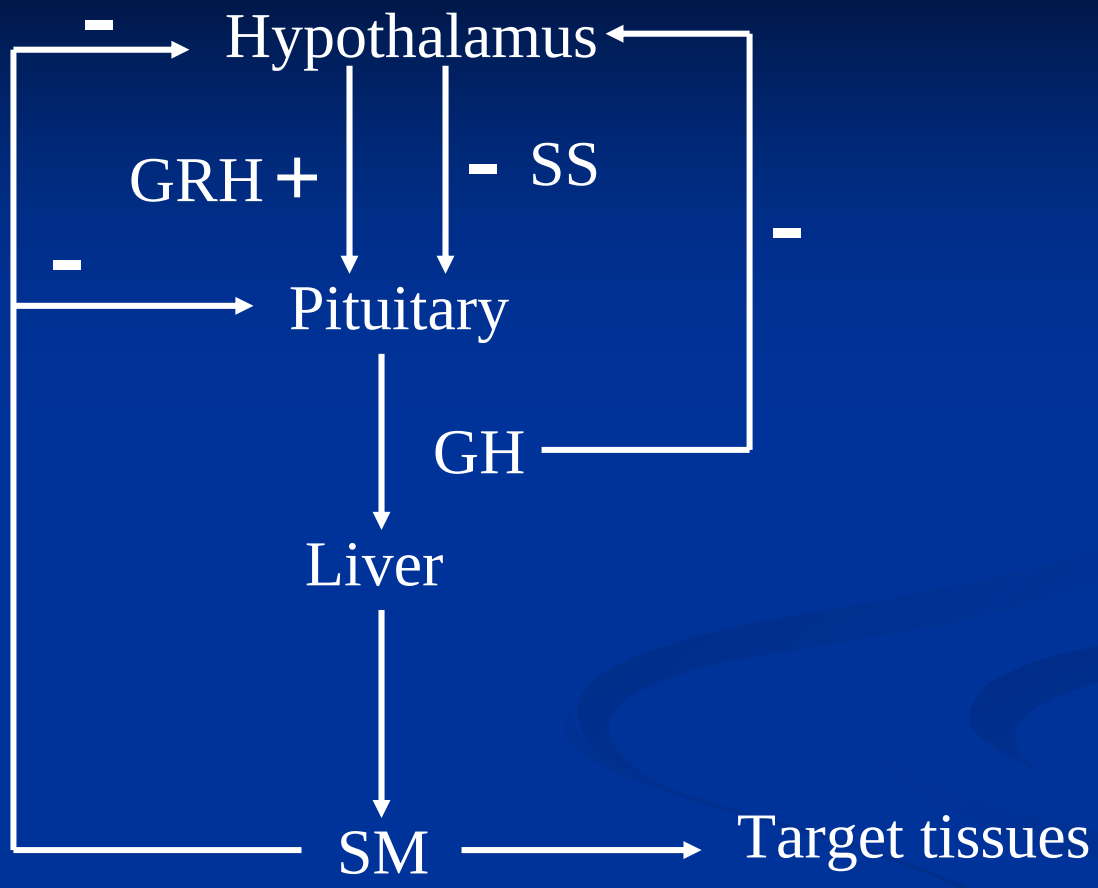
1)Hypothalamic regulation

- GHRH: normal
- GHIH: excess (stress)

2)Feedback regulation

3)The other mechanisms

1) Role of hypothalamus and feedback mechanism



+ increase the secretion; - inhibit the secretion

2) Other factors that affect the GH secretion

A, Starvation, especially with severe protein deficiency

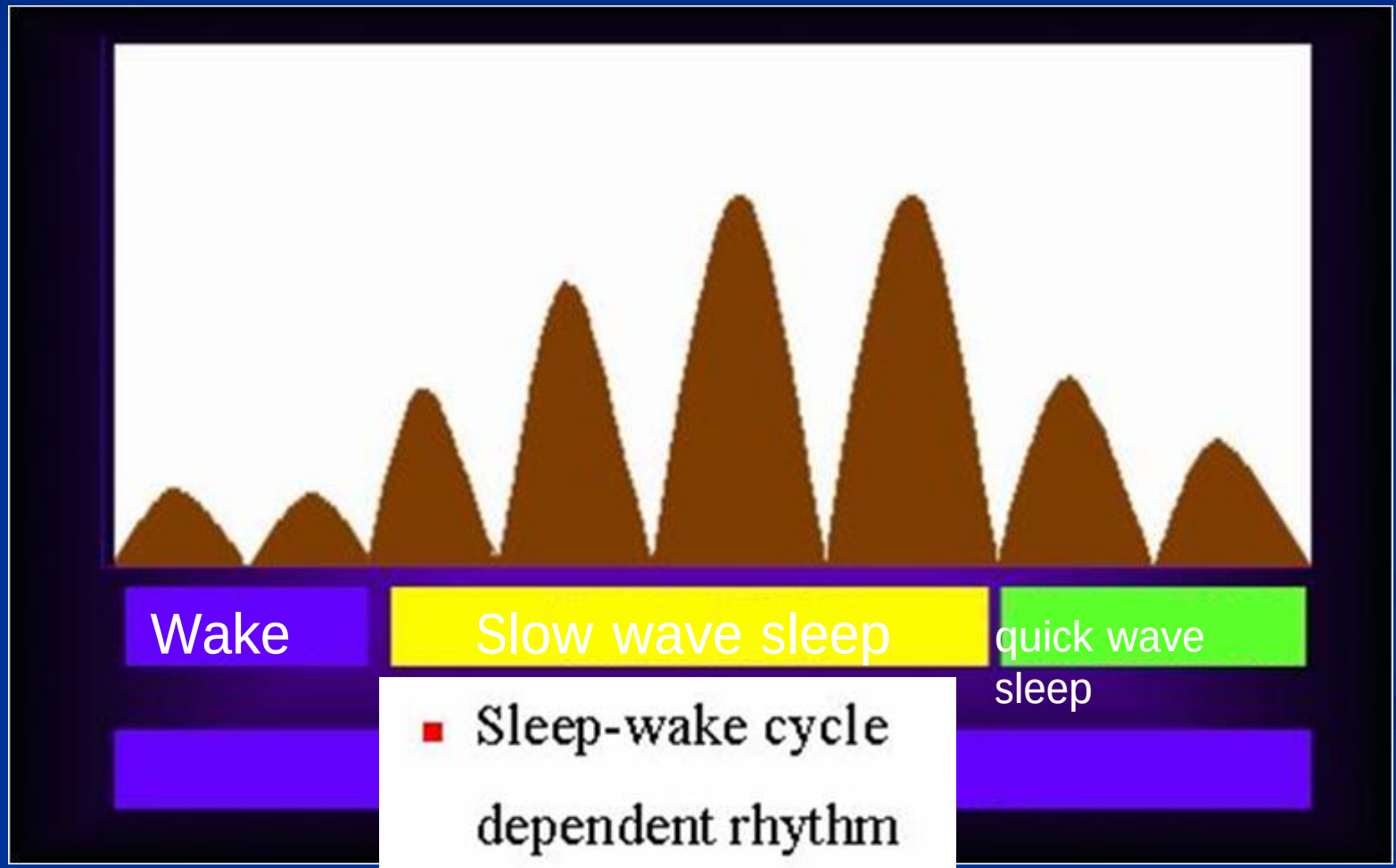
B, Hypoglycemia or low concentration of fatty acids in the blood

C, Exercise

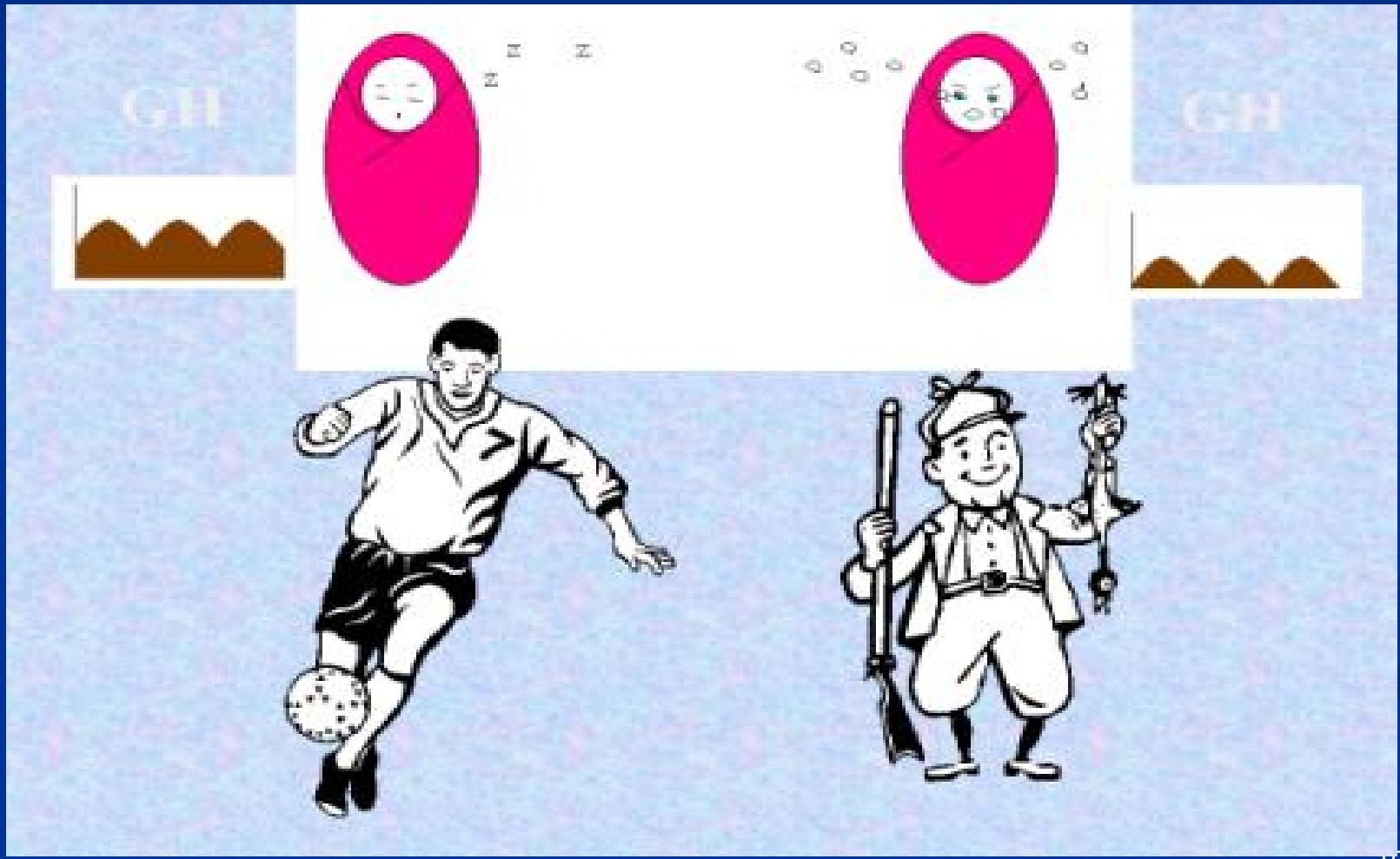
D, Excitement

E, Trauma

The other mechanisms



The other mechanisms



The other mechanisms

Stress

Hormones

2. Prolactin (PRL)

(1)Physiological function of PRL

1) On breast: stimulate the development and milk secretion

In women, breasts development at **puberty** is stimulated by estrogen, progesterone, growth hormone, cortisol, insulin, thyroid hormones and prolactin.

During pregnancy, great growth of breast tissues occurs by stimulation of estrogen, progesterone and prolactin but estrogen and progesterone inhibit the secretion of milk.

Immediately after the baby is born, the sudden loss of estrogen and progesterone secreted by the placenta allows the lactogenic effect of PRL to assume its nature milk promoting role, initiating milk secretion.

After birth of the baby, the level of PRL secretion returns to the normal level before pregnancy but each time the mother nurses her baby causes a 10 to 20 fold surge in PRL secretion that lasts for about 1 hour. Lactation is maintained for nursing period.


Prolactin (plus
several other hormones)

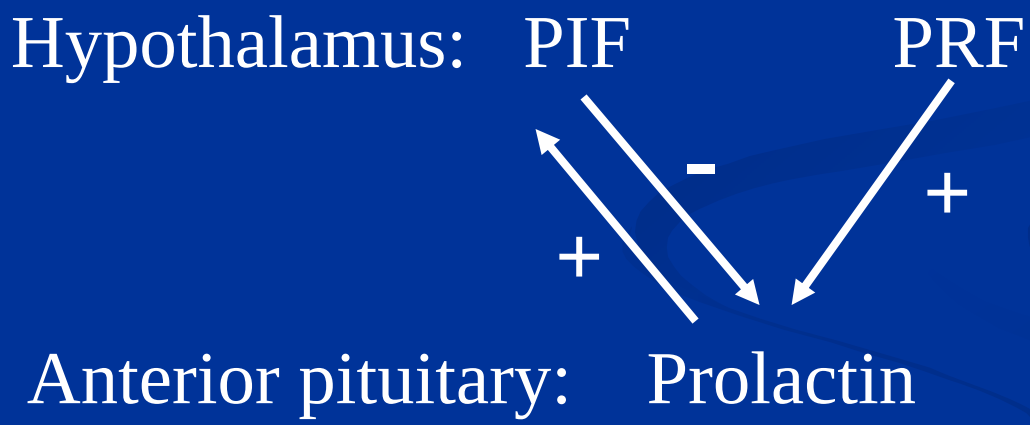
2) Effect on sexual organs

In women, PRL combined with PRL receptors in granulosa cells stimulates production of LH receptors. Through LH receptors, LH promotes ovulation and then formation of corpus luteum. (permissive effect)

In male, PRL promotes growth of prostate glands and seminal vesicle, enhancing the effect of LH on the interstitial cells producing testosterone.

(2) Regulation of PRL secretion

1) Hypothalamic hormones and feedback mechanism



+ increase the secretion; - inhibit the secretion

2) Milk rejection reflex

Sucking, tactile stimulation

↓

Afferent nerve (somatic nerve)

↓

Centers including spinal cord and hypothalamus

PRF secretion

↓

PRL secretion

↓

Milk production increase

Oxytocin secretion

↓

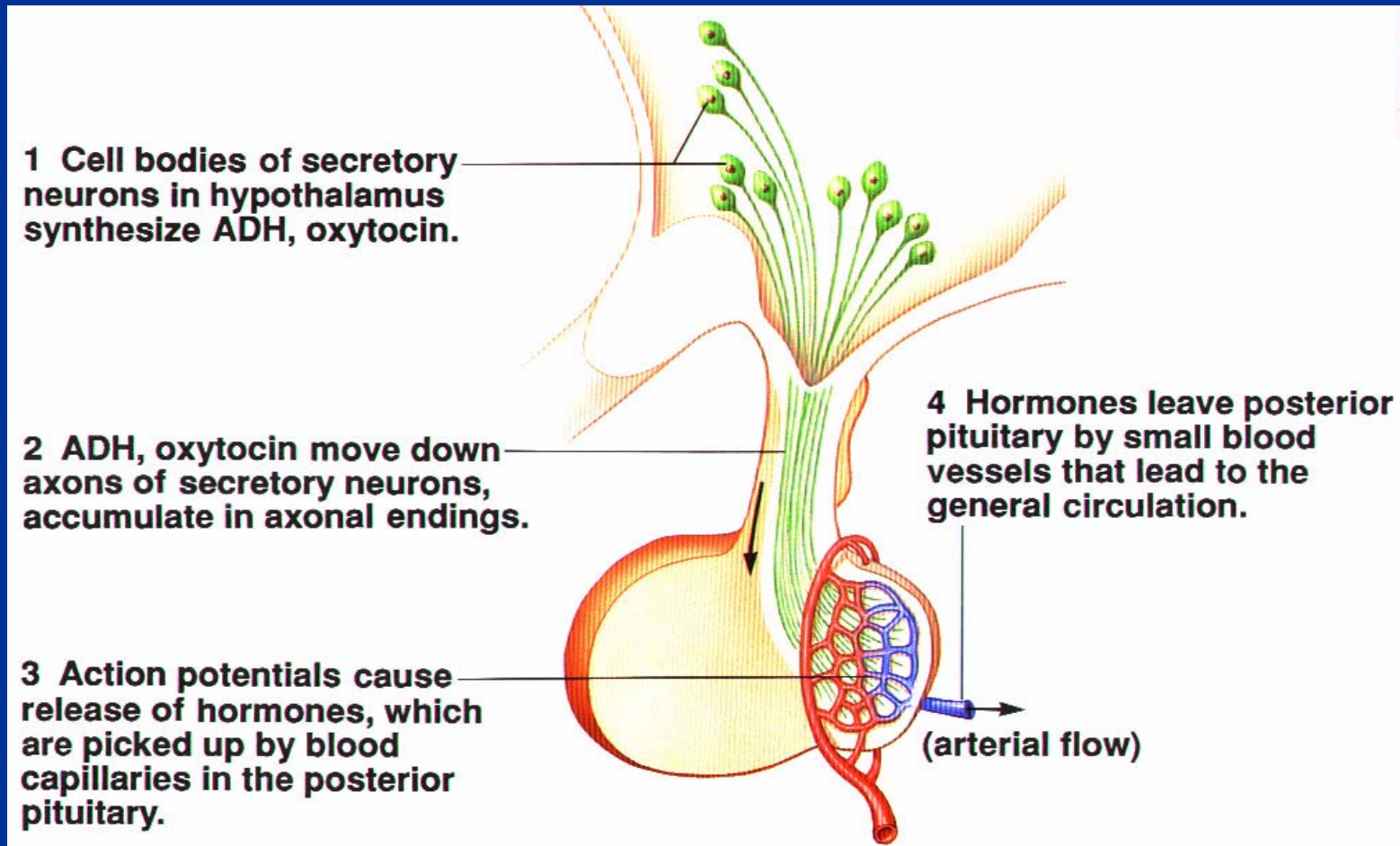
Myoepithelial cells contraction of mammary glands

↓

Milk flows

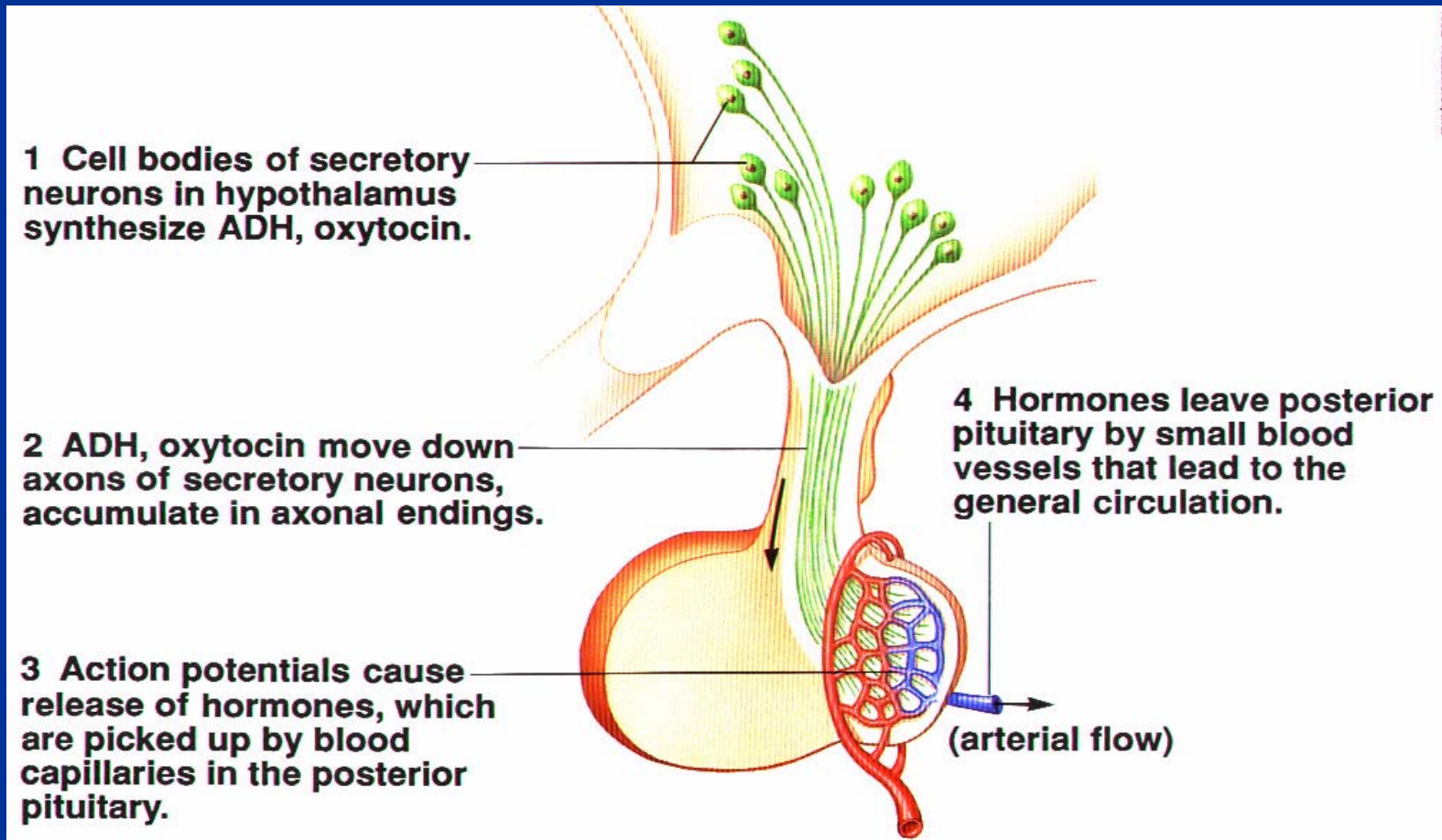
3. Synthesis and Release of Vasopressin (VP) and Oxytocin (OXT)

Cells in neurohypophysis do not synthesize hormones but act simply as supporting structure for nerve fibers.

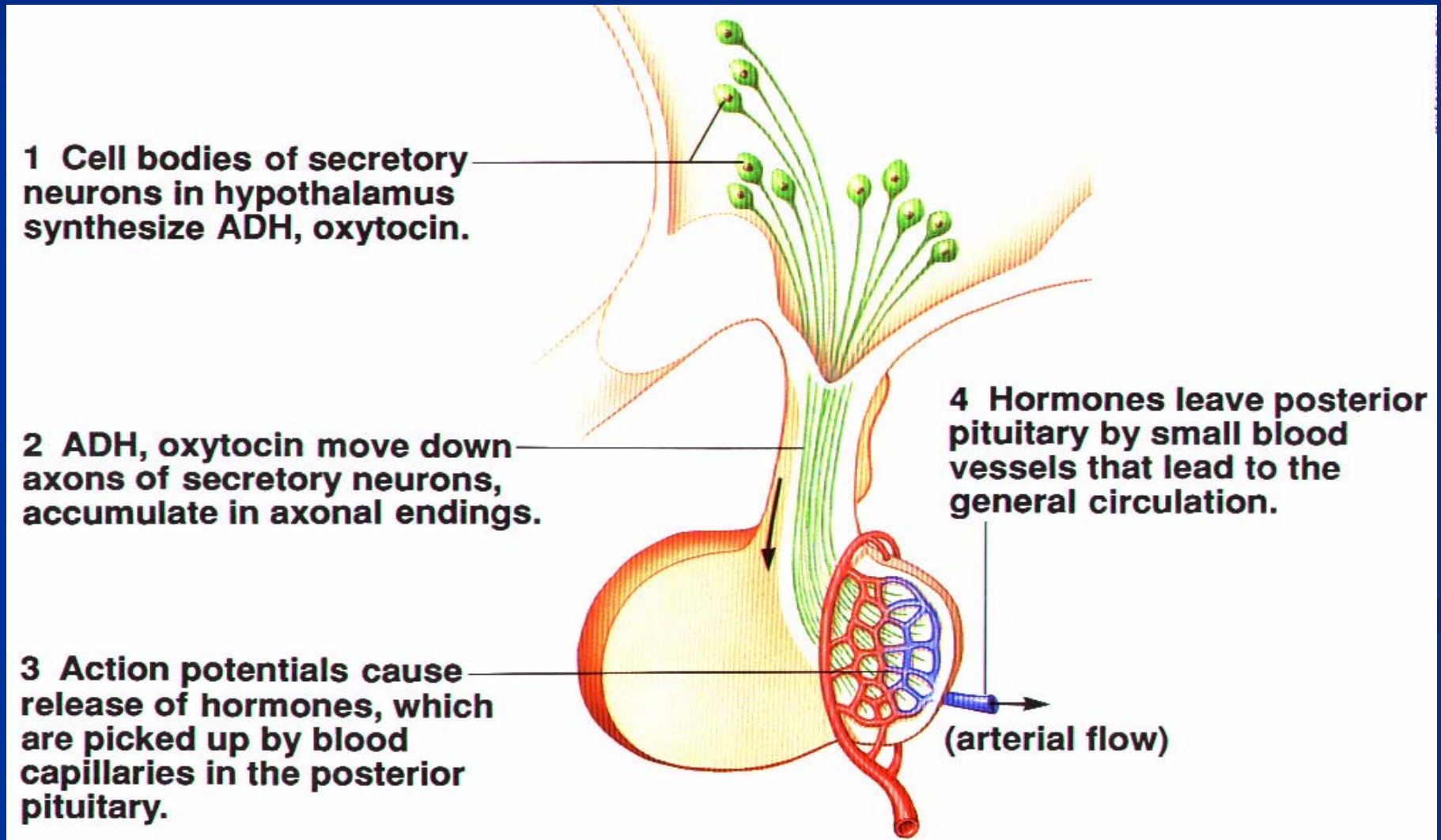


Vasopressin (VP), also called ADH, and oxytocin (OXT) are initially synthesized in the cell bodies of the supraoptic and paraventricuar nuclei of hypothalamus

and are transported down to the nerve endings in the neurohypophysis by hypothalamic hypophyseal tract.



When nerve impulses are transmitted downward along the fibers from nuclei, the hormone is immediately released from secretary granules in the nerve endings by exocytosis and is absorbed into adjacent capillaries.



(1)Roles of ADH

1) Antidiuretic effect (refer to chapter 8)

2) Pressure effect. High concentration of ADH have a potent effect of constricting the arterioles everywhere in the body, raise the resistance blood flow and blood pressure

Effects of ADH

Dehydration

Lowers blood volume and pressure

Osmotic concentration of blood increases

Osmoreceptors

ADH synthesized by neurosecretory cells in hypothalamus

ADH

ADH released from posterior pituitary into blood

Increased water retention

Increased vasoconstriction (in some vertebrates) leading to higher blood pressure

Reduced urine volume

Negative feedback

Negative feedback

Vasopressin

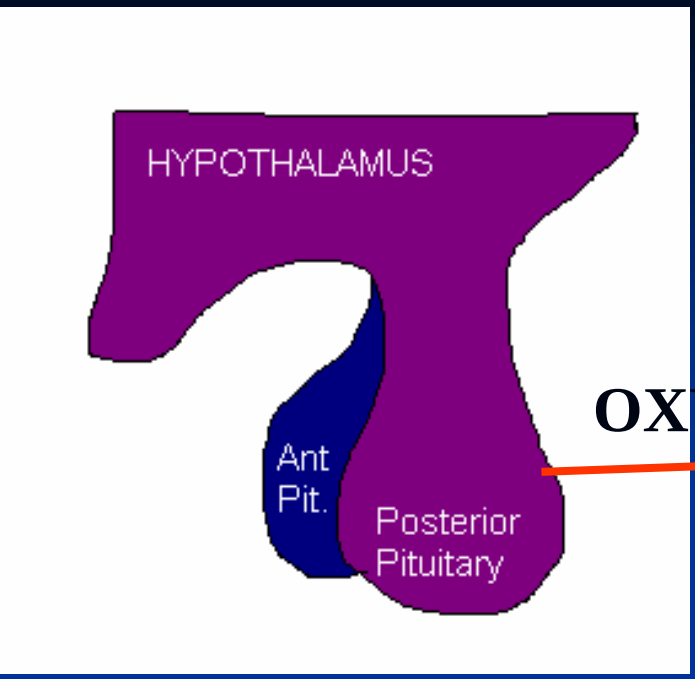
- Antidiuretic hormone V_2-receptor: collecting duct
- Vasopressor hormone V_1-receptor: vascular smooth muscle

(2) Role of Oxytocin (OXT)

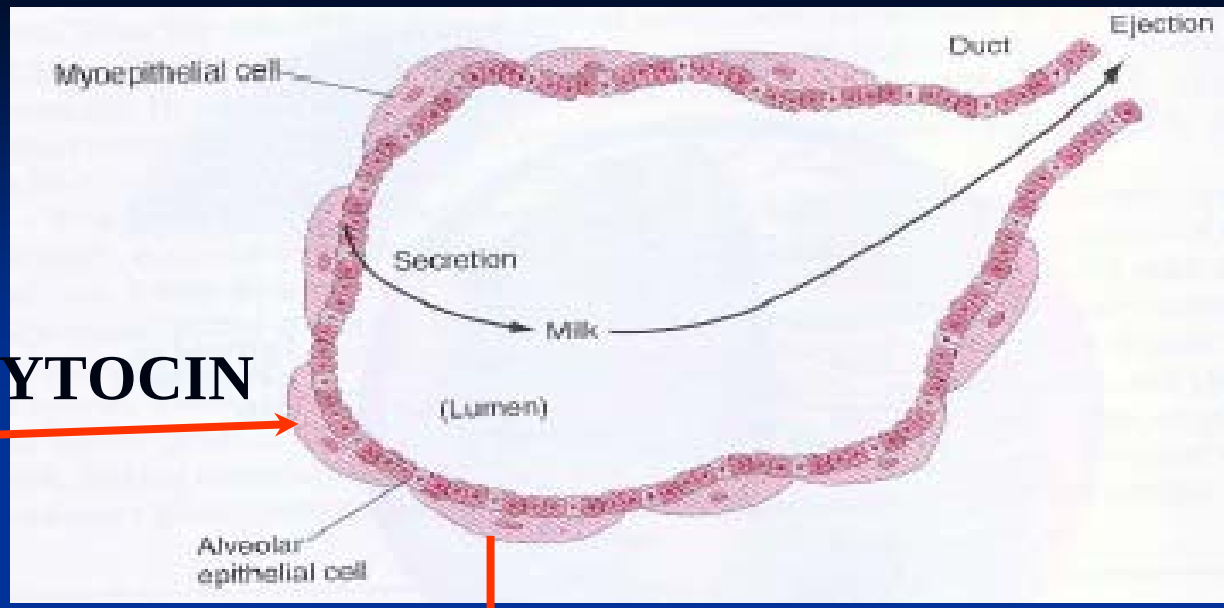
1) Effect on mammary glands.

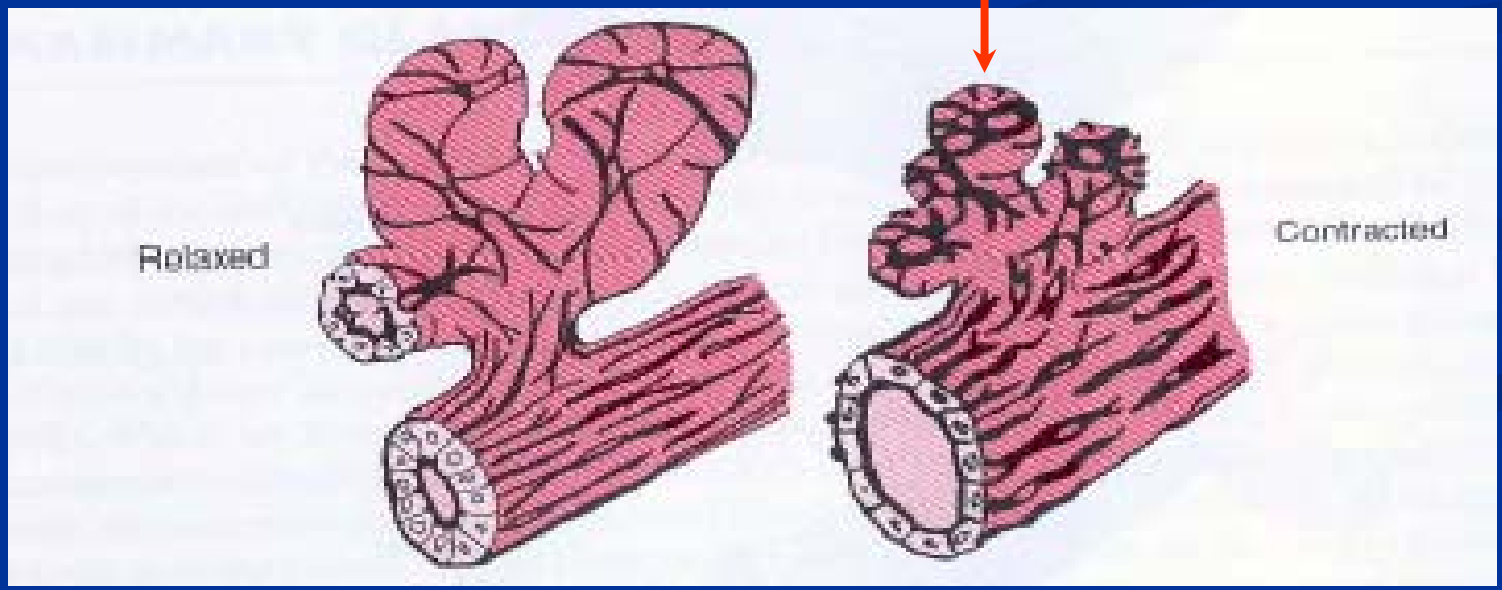
Cause the contraction of the myoepithelial cells that surround the outer walls of the alveoli of the mammary glands, press the milk from the alveoli to the duct and make it flow out --- milk ejection

Unconditioned and conditioned reflex


HYPOTHALAMUS
Ant Pit.
Posterior Pituitary

OXYTOCIN

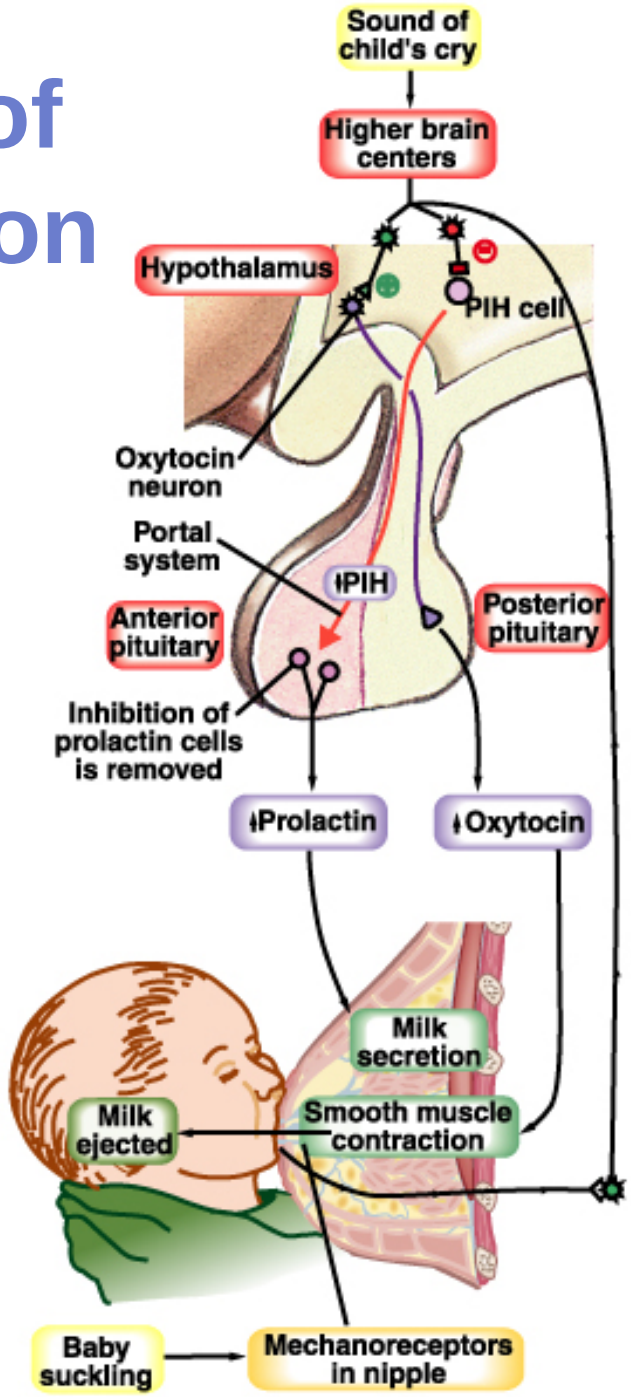

Myoepithelial cell
Duct
Ejection
Secretion
Milk
(Lumen)
Alveolar epithelial cell


Relaxed
Contracted

Milk ejection reflex

- Nipple stimulation produces neural stimulation of hypothalamus
- Transmits through hypothalamohypophysial tract
- Stimulates oxytocin release
- Oxytocin causes constriction of mammary glands
- Milk ejection rewards suckling infant

Regulation of OXT secretion



2) Effect on uterus

OXT powerful stimulate the smooth muscle contraction, especially that towards the end of gestation.

It is believed that OXT is at least partially responsible for causing birth of the baby

Summary of Section 2

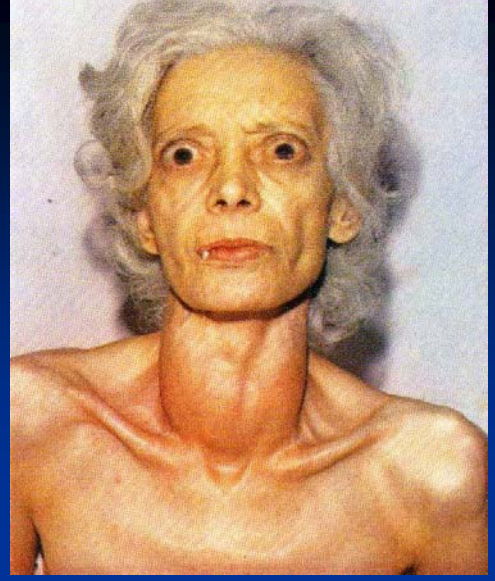
- ✓ Hypothalamus-hypophysis unit
- ✓ Adenohypophysis
- ✓ GH, PRL
- ✓ Neurohypophysis
- ✓ VP & OXT

Section 3

The Thyroid Gland

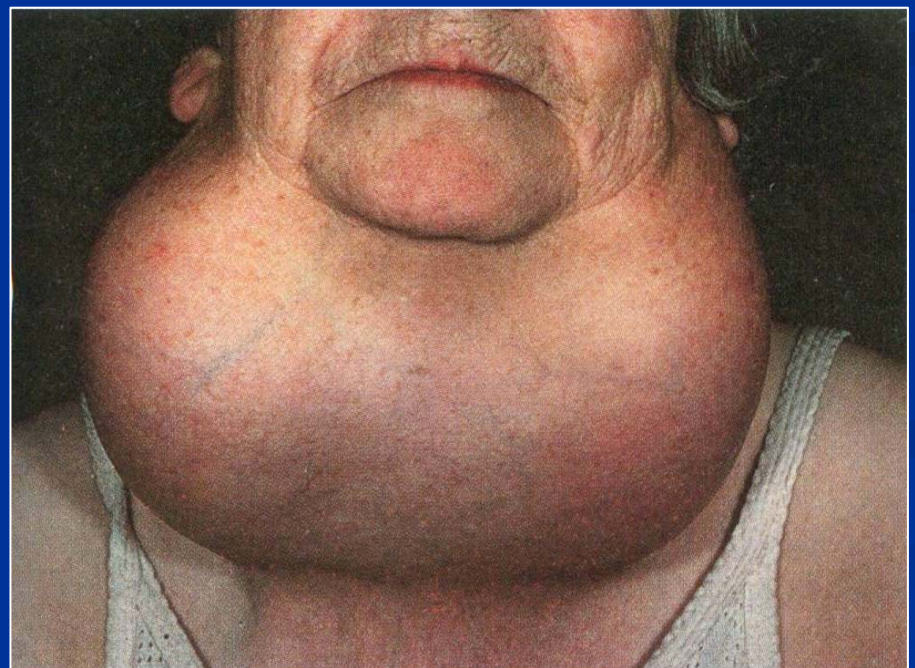
Learning issues

- Formation, Secretion & Transport of the thyroid hormone
- Functions of the thyroid hormones
- Regulation of thyroid hormone secretion
- Diseases of the thyroid

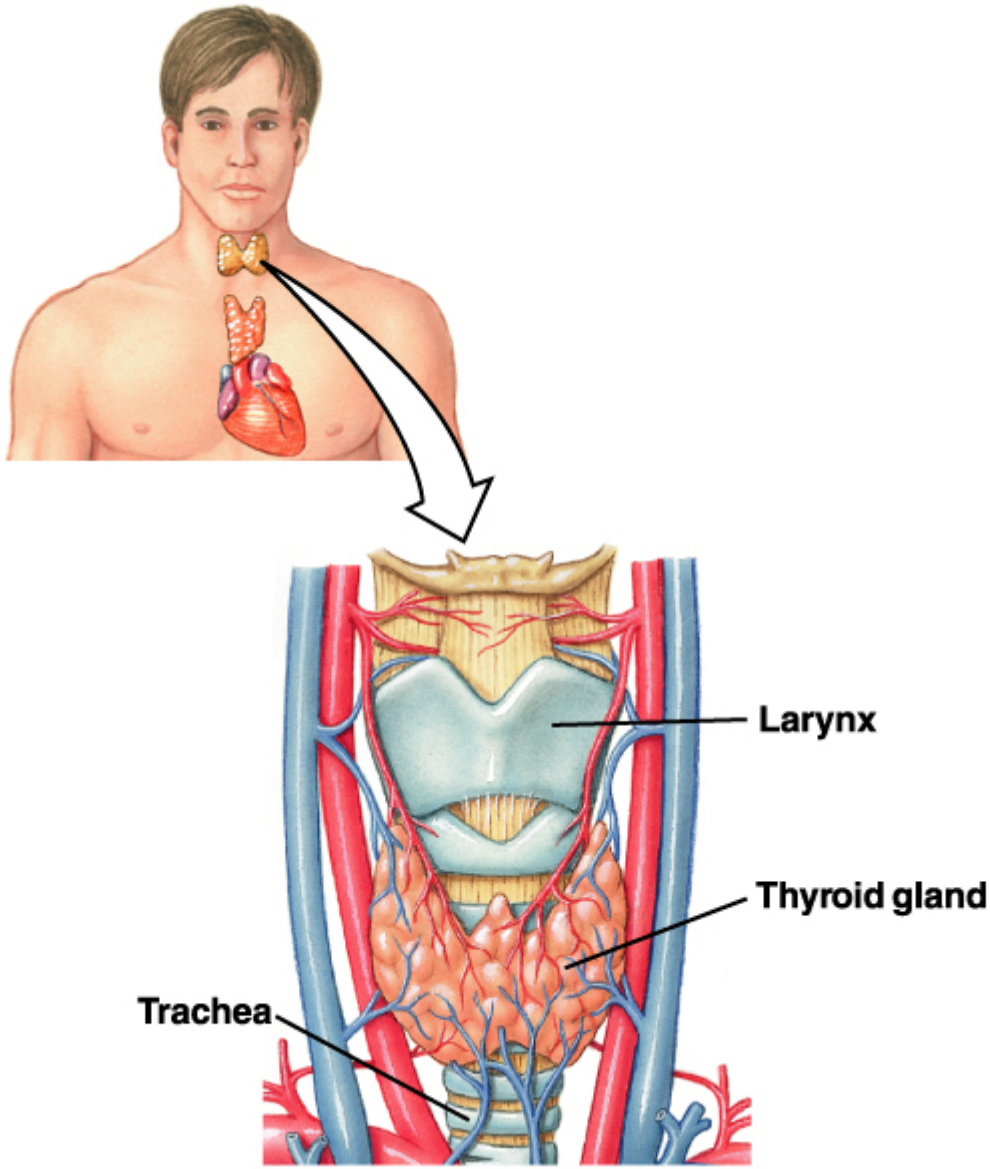


Hyperthyroidism

Overt hypothyroidism after thyroidectomy



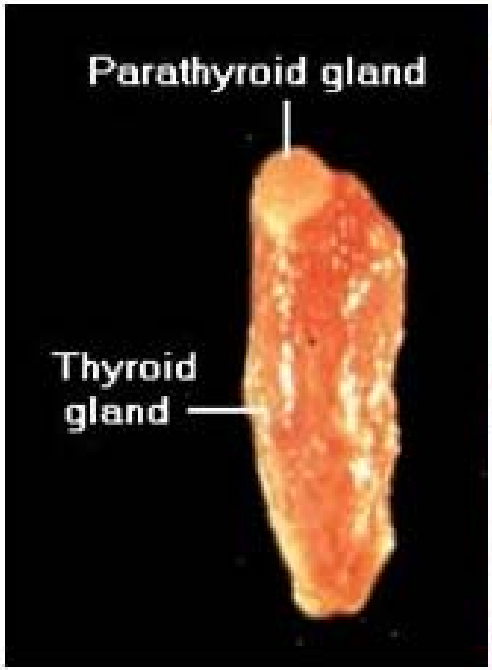
Goiter

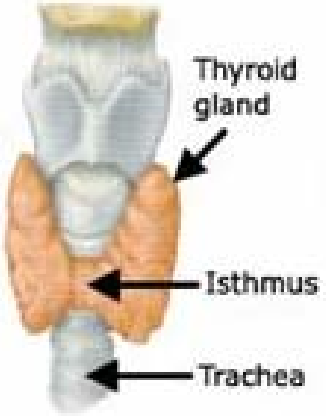

Larynx
Thyroid gland
Trachea

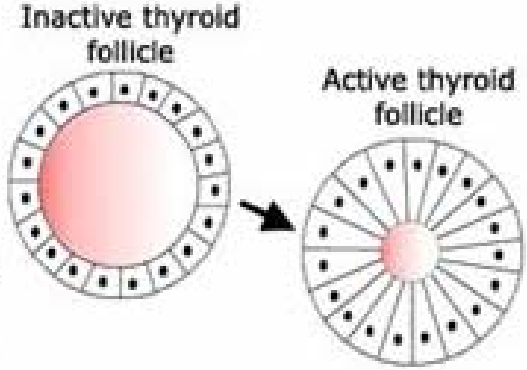
1.Thyroid Gland: Hormones and Iodine Metabolism

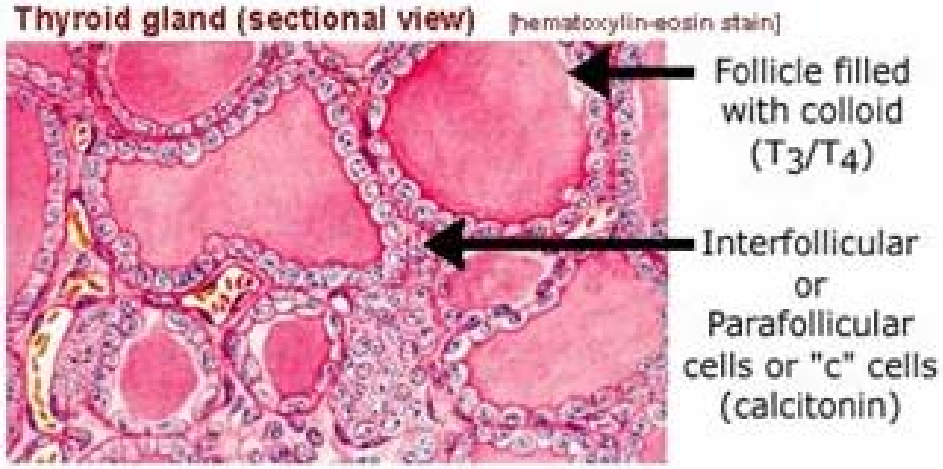
- C-cells – calcitonin (covered later)
- Follicule cells
  - Amine hormones:
  - thyroxine, T_1, T_2 & T_3(triiodothyronine)
    - ↑ growth
    - ↑ metabolism
    - Thermogenic

The Thyroid Gland

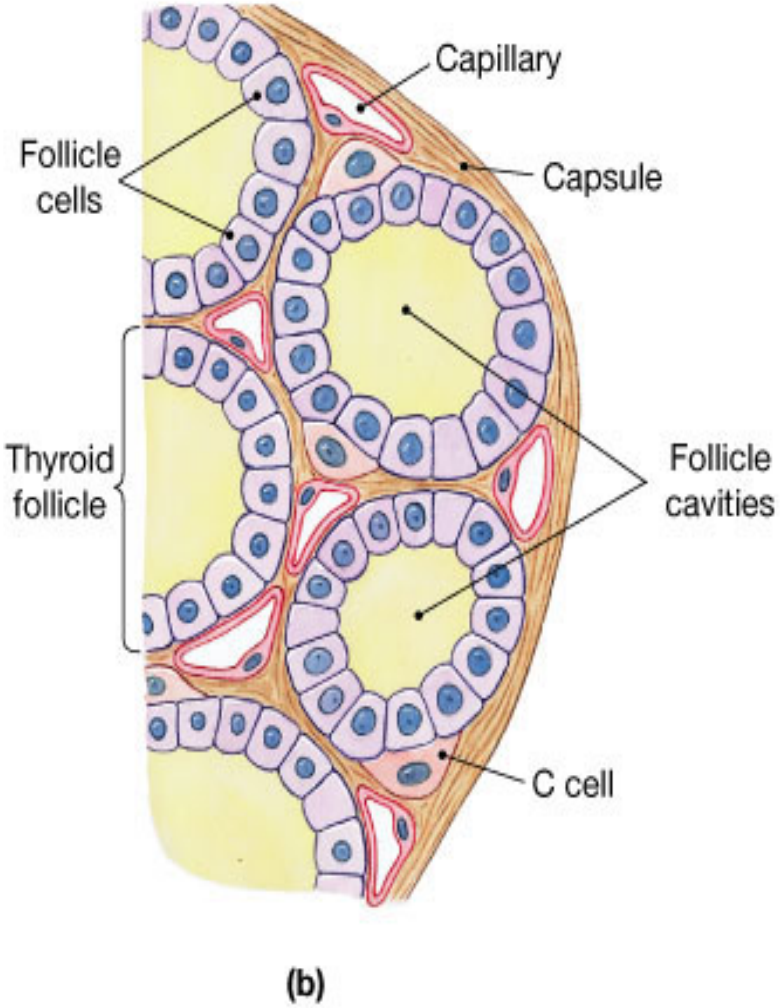


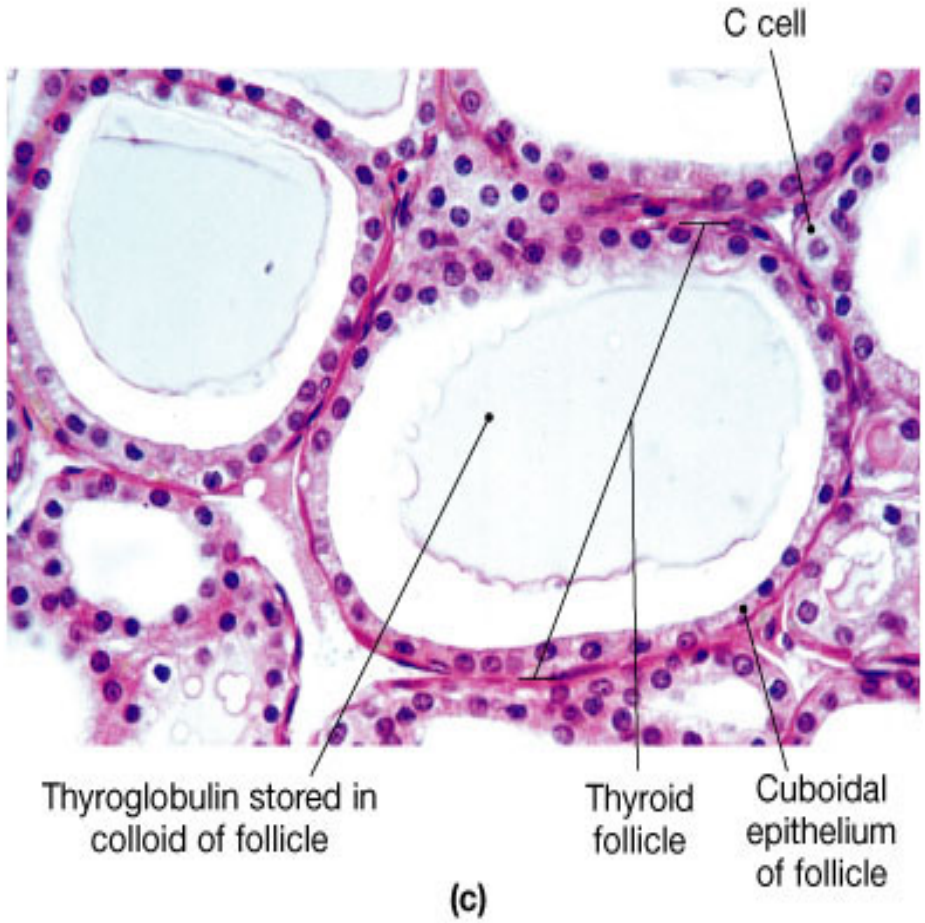




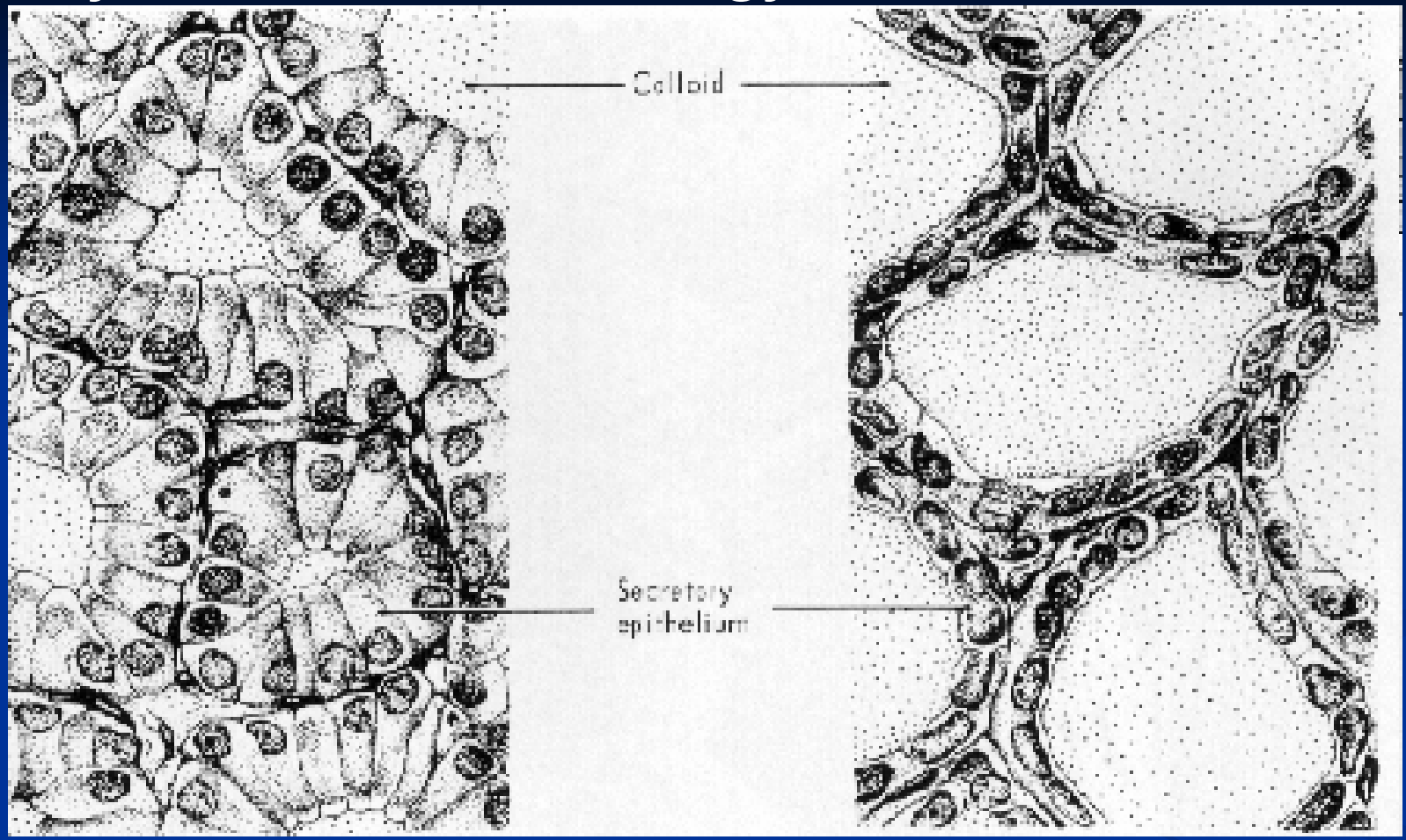


Thyroid Gland Histology 1





Thyroid Gland Histology 2



active gland

- ***columnar epithalium***
- ***reduced colloid***

inactive gland

- ***cuboidal epithalium***
- ***abundant colloid***

Biosynthesis and metabolism of thyroid hormone

- **Thyroxin, 3,5,3’,5’-tetraiodothyronine (T4)**
- **3,5,3’-triiodothyronine (T3)**
- **3,5,5’-triiodothyronine (rT3)**
- **Iodide and thyroglobulin (TG)**

Synthesis

(一) Uptake of the iodide (I^-) by follicle cells

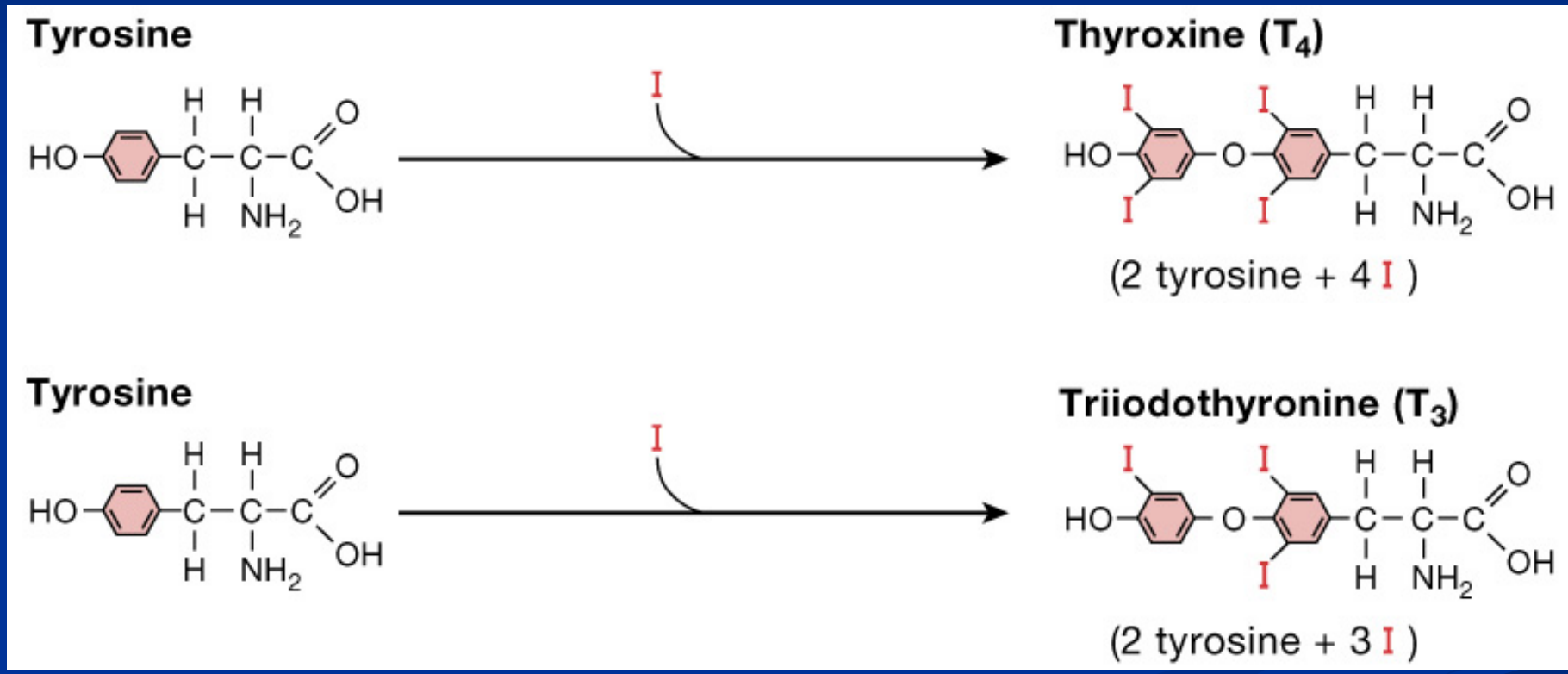
(二) Activation of I^- (thyroperoxidase)

(三) Iodination of tyrosine from thyroglobulin and synthesis of TH

MIT+DIT ⟶ T3

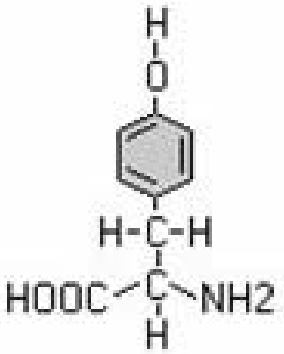
DIT+DIT ⟶ T4

Thyroxine and its precursors: Structure & Synthesis

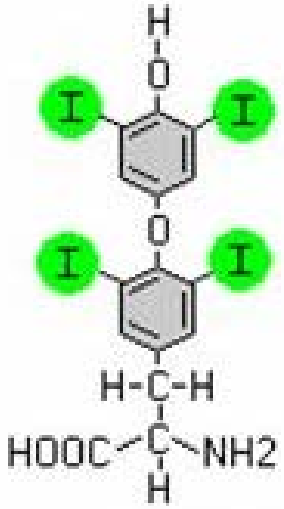


The Thyroid Hormones

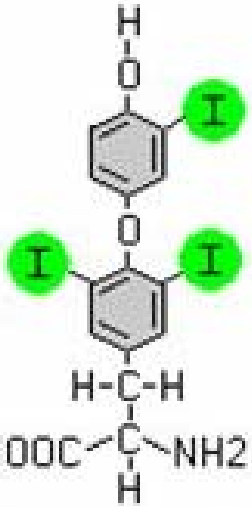
- **Types**



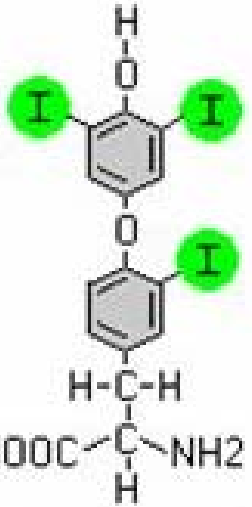
Tyrosine



Thyroxine (T4)



Triiodothyronine (T3)



"Reverse T3" (inactive)

The Thyroid Hormones

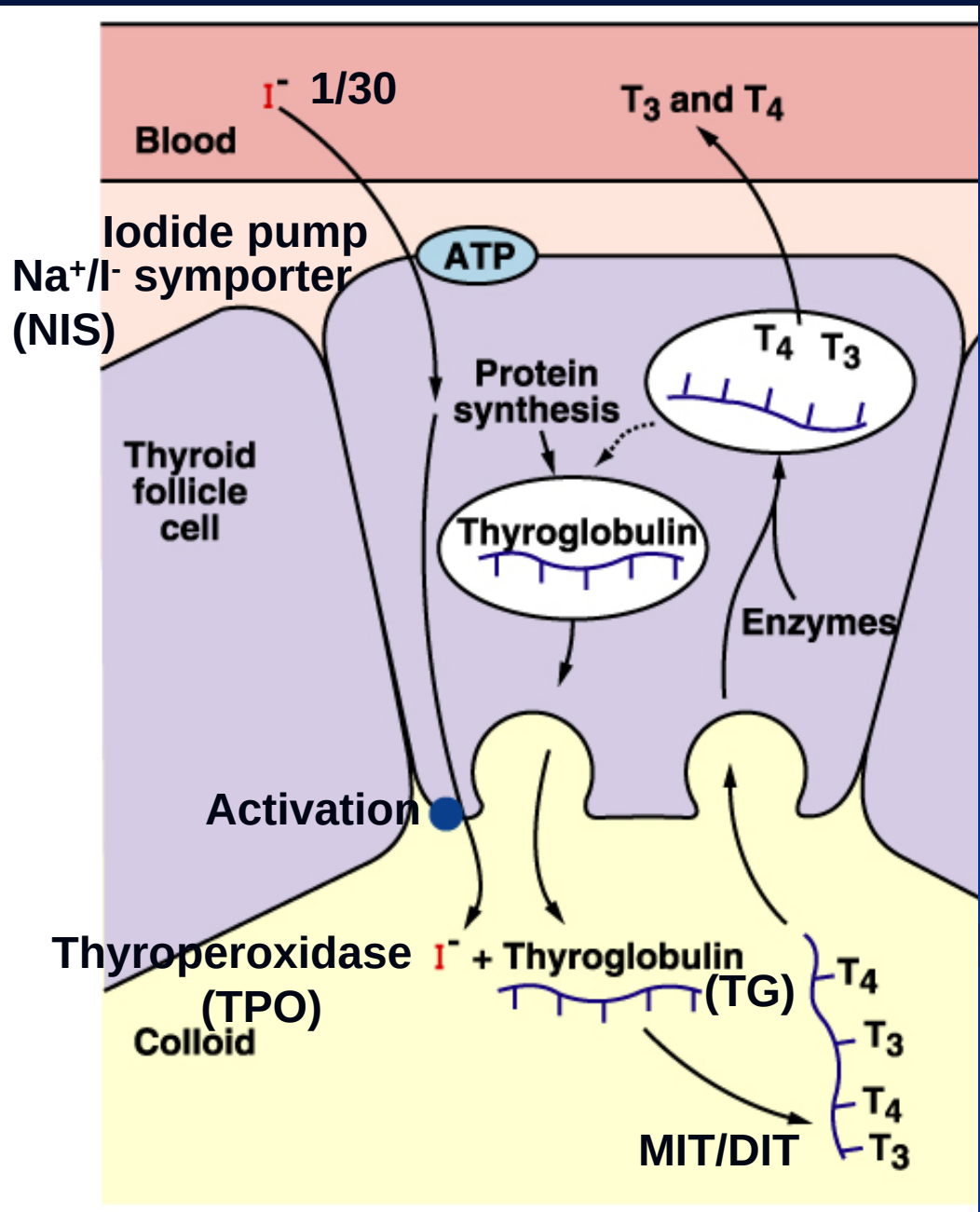
- **Concentration**
  - Thyroxine(T_4): 93%
  - Triiodothyronine(T_3): 7%
  - $T_4 \rightarrow T_3$
- **Activity**
  - $T_3 = 5\ T_4$

The Thyroid Hormones

- **Synthesis**
  - **Materials**
    - **Iodine (in the form of iodide—I^-)**
      - 50mg/year
      - Iodized table salt (1 sodium iodide/100,000 NaCl)
    - **Tyrosine**
      - Thyroglobulin (TG): 70 tyrosines

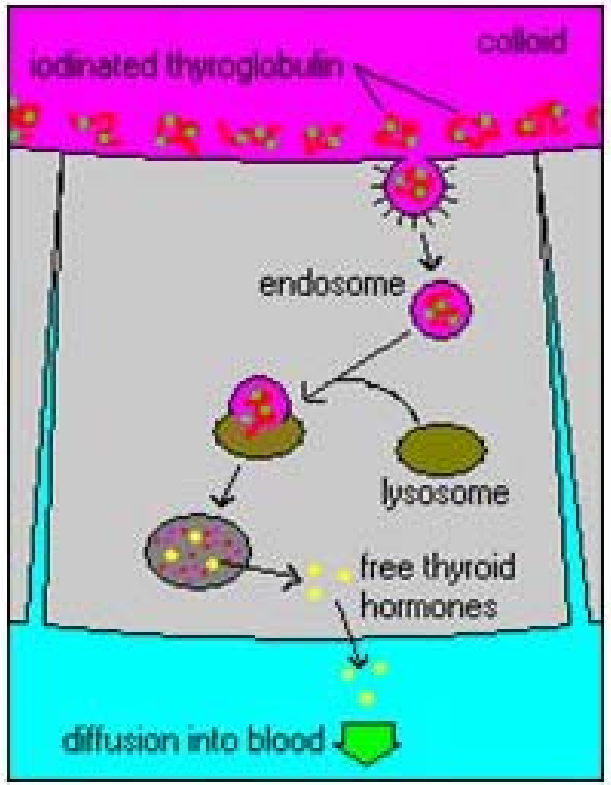
Synthesis

- Iodide trapping
  - Iodide pump
- Oxidation of the iodide ion
  - Peroxidase: $I^- \rightarrow I^0$ or I_3^-
- Iodination of tyrosine
  - Peroxidase
  - MIT and DIT
- Formation of T_3 , T_4



The Thyroid Hormones

- **Storage**
  - **In the follicles**
  - In the form of TG (30 T_4)
  - For 2 ~3 months
- **Release**
  - **TSH**
  - Proteinase(lysosome)



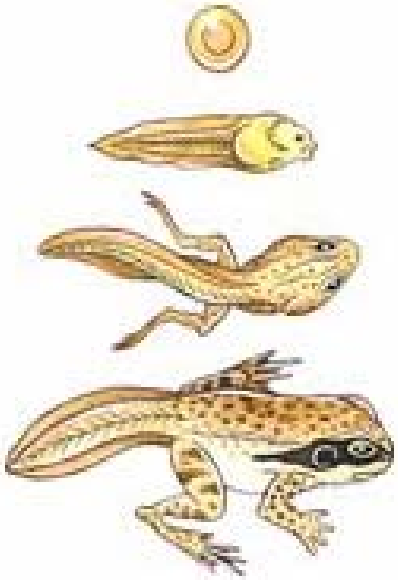
The Thyroid Hormones

- **Transport**
  - **Bound to plasma proteins: T_4 (slow release)**
    - **Thyroxine-binding globulin(TBG): mainly**
    - Thyroxine-binding prealbumin
    - Albumin
  - **Free: T_3**
- **Concentration in plasma**
  - T_3: 1.2 ~3.4 nmol/L
  - T_4: 85 ~142 nmol/L

2. Physiology functions of thyroid hormone

The Thyroid Hormones

- **Physiological functions**
  - **Effect on growth**
    - Mainly in growing chidren
      - ↑ Skeletal growth
      - ↑Growth and development of brain (fetus and baby)
    - Tadpole → frog
    - Cretinism



Maturation of the CNS is absolutely dependent on TH in the perinatal period

TH deficiency caused cretinism

The Thyroid Hormones

- **Physiological functions**
  - **Effects on metabolism**
    - **Stimulation of carbohydrate metabolism**
      - ↑ Uptake of glucose
      - ↑ Glycolysis
      - ↑ Gluconeogenesis
      - ↑ Rate absorption of G
      - ↑ Insulin secretion
    - Hyperthyroidism: G ↑

The Thyroid Hormones

- **Physiological functions**
  - **Effects on metabolism**
    - **Stimulation of fat metabolism**
      - Lipid mobilization from the fat tissue
      - ↑Free fatty acid concentration in the plasma
      - ↑Oxidation of free fatty acid

The Thyroid Hormones

- **Physiological functions**
  - **Effects on metabolism**
    - **Protein metabolism**
      - ↑ Protein synthesis (normal)
      - ↑ Protein catabolism (hyperthyroidism)
    - **Hypothyroidism: myxedema**

The Thyroid Hormones

- **Physiological functions**
  - **Effects on metabolism**
    - ↑BMR
      - 60 ~100%
    - Hyperthyroidism
      - Intolerance to heat

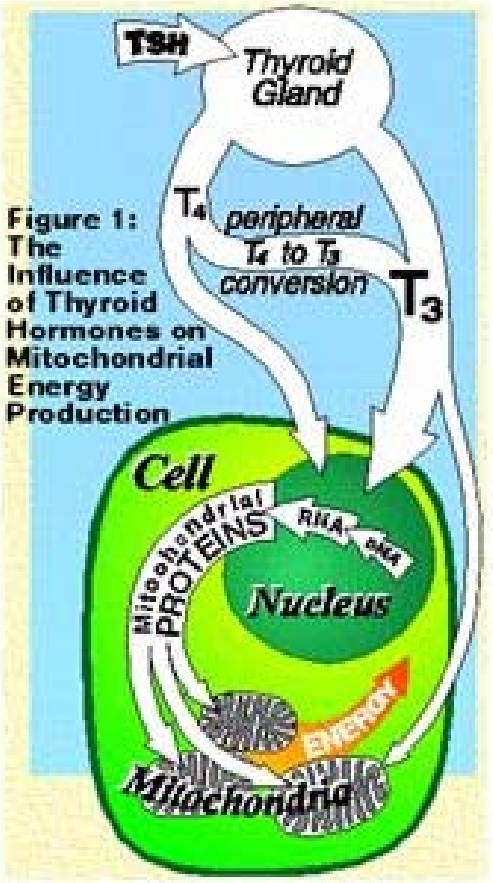


Figure 1: The Influence of Thyroid Hormones on Mitochondrial Energy Production

The Thyroid Hormones

- **Physiological functions**
  - **Effects on the cardiovascular system**
    - ↑ Blood flow and cardiac output
    - ↑ HR
    - ↑Heart strength
    - Normal mean arterial pressure

The Thyroid Hormones

- **Physiological functions**
  - **↑ Respiration**
  - ↑Gastrointestinal motility
  - Excitatory effects on the CNS

The Thyroid Hormones

- **Physiological functions**
  - **Effect on the function of the muscles**
    - Weakened (↑ ↑ T_3,T_4)
    - Fine muscle tremor (↑ ↑ T_3,T_4)
    - Sluggish(↓ ↓ T_3,T_4)
  - **Effect on sleep**
    - Constant tiredness (↑ ↑ T_3,T_4)
    - Difficult to sleep (↑ ↑ T_3,T_4)

The Thyroid Hormones

- **Physiological functions**
  - Effect on other endocrine glands
  - Effect on sexual function

Fraternal twins, age 8 years. The boy has congenital hypothyroidism.

- If treatment is started at birth, the prognosis for normal growth and development is good, and mental retardation can generally be avoided; for this reason, screening tests for congenital hypothyroidism are routine in all states of the USA and most other developed countries.
- Adult hypothyroidism, myxedema. the BMR falls to about 40%. The hair is coarse and sparse, the skin is dry and yellowish (carotenemia), and cold is poorly tolerated.The voice is husky and slow, memory is poor

Hyperthyroidism

- Hyperthyroidism is characterized by nervousness; weight loss; hyperphagia; heat intolerance; increased pulse pressure; a fine tremor of the outstretched fingers; a warm, soft skin; sweating; and a increased BMR as high as +80%.

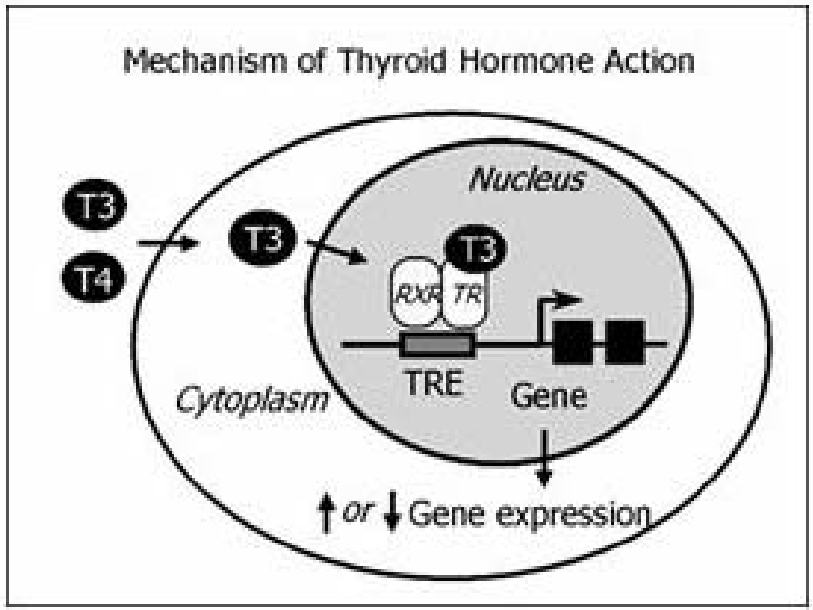
Graves disease

•much more common in women, is an autoimmune disease.

•producing protrusion of the eyeballs (**exophthalmos)**

The Thyroid Hormones

- **Mechanisms of action**
  - ↑Transcription of large numbers of genes
  - ↑Synthesis of great numbers of proteins



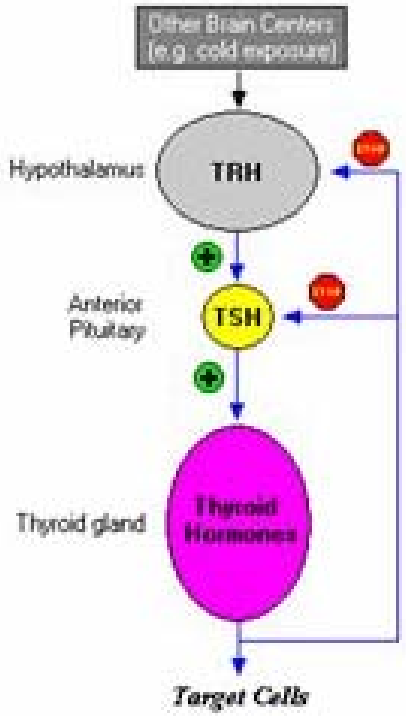
3 .The regulation of thyroid hormone secretion

Regulation of TH secretion

1. Hypothalamic-pituitary control- TRH and TSH
2. Feedback regulation of TH on pituitary and hypothalamus
3. Autoregulation of thyroid
4. Effect of autonomic nervous system on thyroid

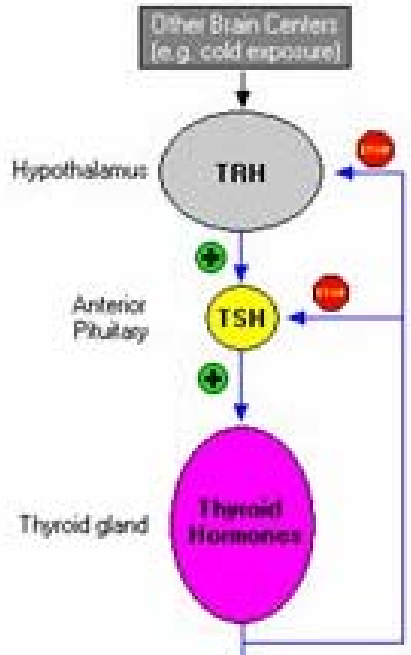
The Thyroid Hormones

- **Regulation of thyroid hormone secretion**
  - **Hypothalamus-adenohypophysis-thyroid axis**
    - **TRH**
      - Tripeptide amide
      - **↑ TSH secretion**
      - Cold: ↑TRH release



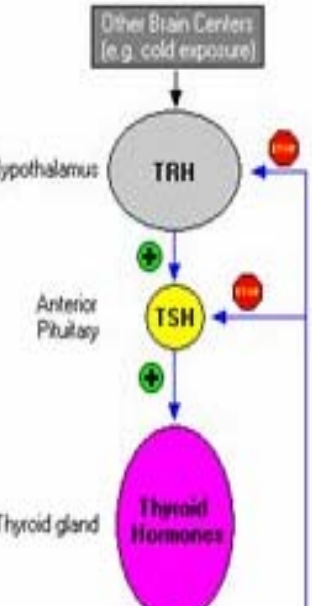
The Thyroid Hormones

- **Regulation of thyroid hormone secretion**
  - **Hypothalamus-adenohypophysis-thyroid axis**
    - TSH
      - Glycoprotein
      - ↑ T_3, T_4 synthesis and release
      - ↑ Size of the thyroid cells
      - cAMP mediated mechanism



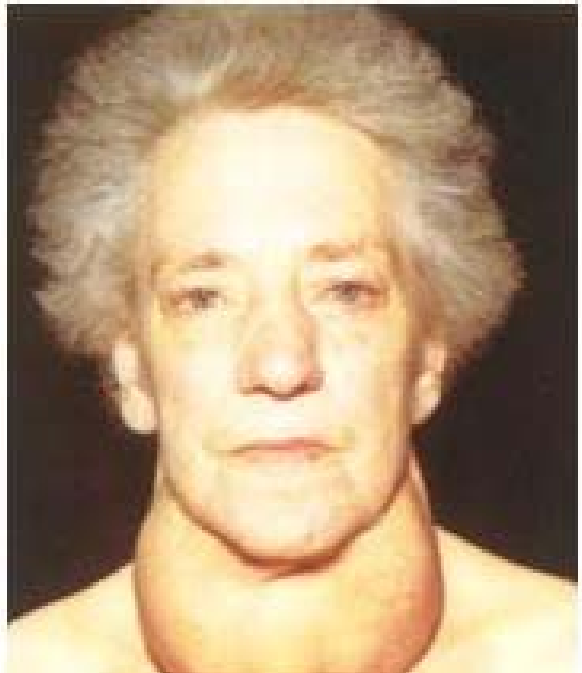
The Thyroid Hormones

- **Regulation of thyroid hormone secretion**
  - **Hypothalamus-adenohypophysis-thyroid axis**



Feedback effect of thyroid hormone

- **Negative** feedback



The Thyroid Hormones

- **Regulation of thyroid hormone secretion**
  - **Autoregulation**
    - **Wolff-Chaikoff effect**

Feedback Mechanisms of Thyroid Hormones

T_3 and T_4 ⟶ **inhibitory protein** in anterior pituitary

reduces production and secretion of TSH,

decrease response of pituitary to TRH.

Because of the negative mechanism, the concentration of free thyroid hormone in the blood can be maintained within a normal range.

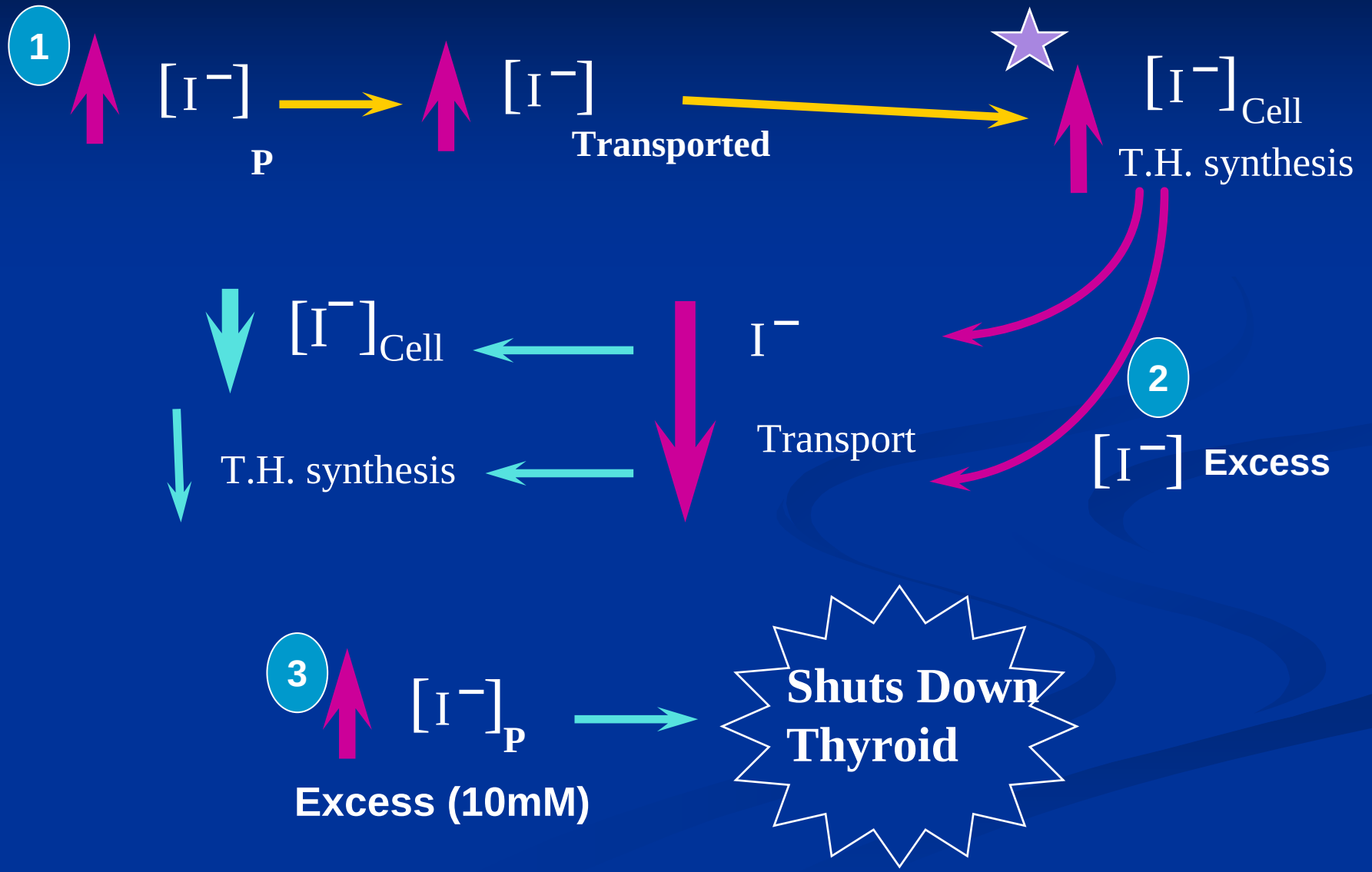
3. Autoregulation of Thyroid Hormone Secretion

Without control of TSH, the thyroid gland can adapt itself function to iodide uptake, which is the autoregulation of thyroid gland.

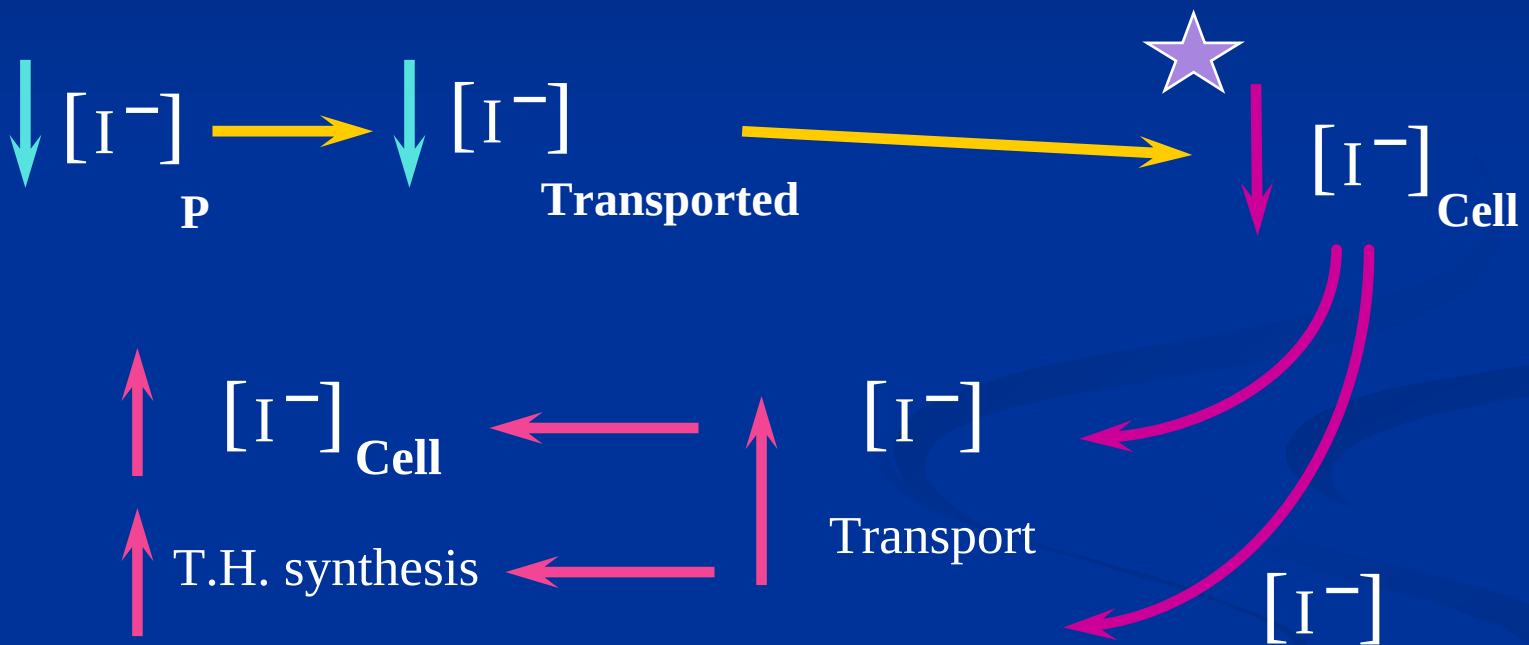
In normal individuals, large doses of iodide act directly on the thyroid gland to produce a mild and transit inhibition of hormone synthesis.

When iodine is insufficient, the thyroid gland increases formation of hormones.

Wolff-Chaikoff Effect



Autoregulation of Hormone Release



Summary of Section 3

- ✓ Biosynthesis & metabolism of TH
- ✓ Biological effects of TH
- ✓ Regulation of TH secretion

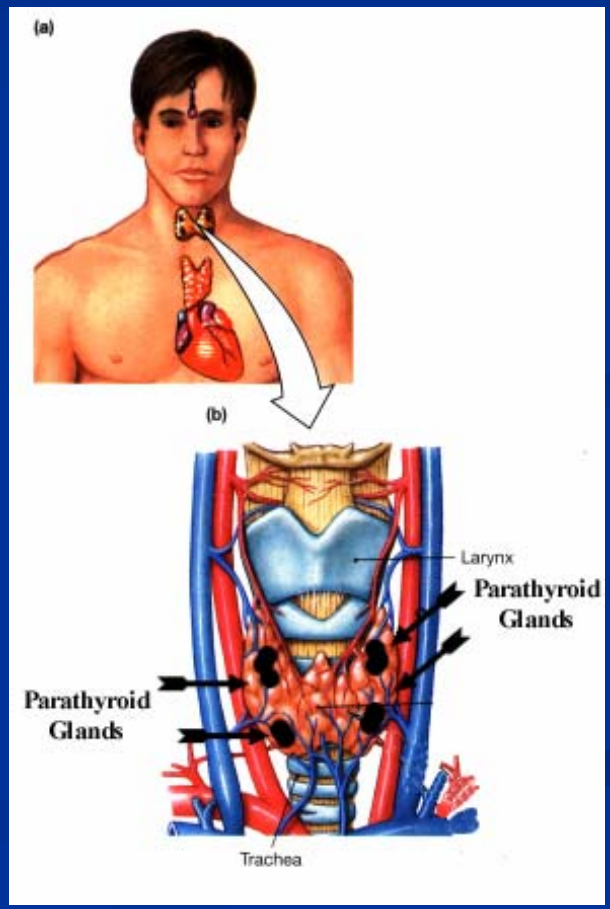
Section 4 Hormones related to calcium and phosphate metabolism

- **Half of the calcium in the blood is ionized (biologically active form)**
- **Is bound to proteins**
- **Is complexed with anions: phosphate and sulfate**
- **Blood Ca^{2+} homeostasis is produced through the interaction of bones, kidney, and small intestine**

- **Parathyroid hormone**
- **Calcitonin**
- **1,25-dihydroxyvitamin D_3**

1.Parathyroid Gland Anatomy

- Four Parathyroid glands are usually found posterior to the thyroid gland
- Total weight of parathyroid tissue is about 150mg
- Parathyroid hormone (PTH) is made by these glands



Parathyroid hormone, PTH

-- Is the major hormone for the

- regulation of serum Ca & P (phosphorus)

- 84 aa, MW 9500

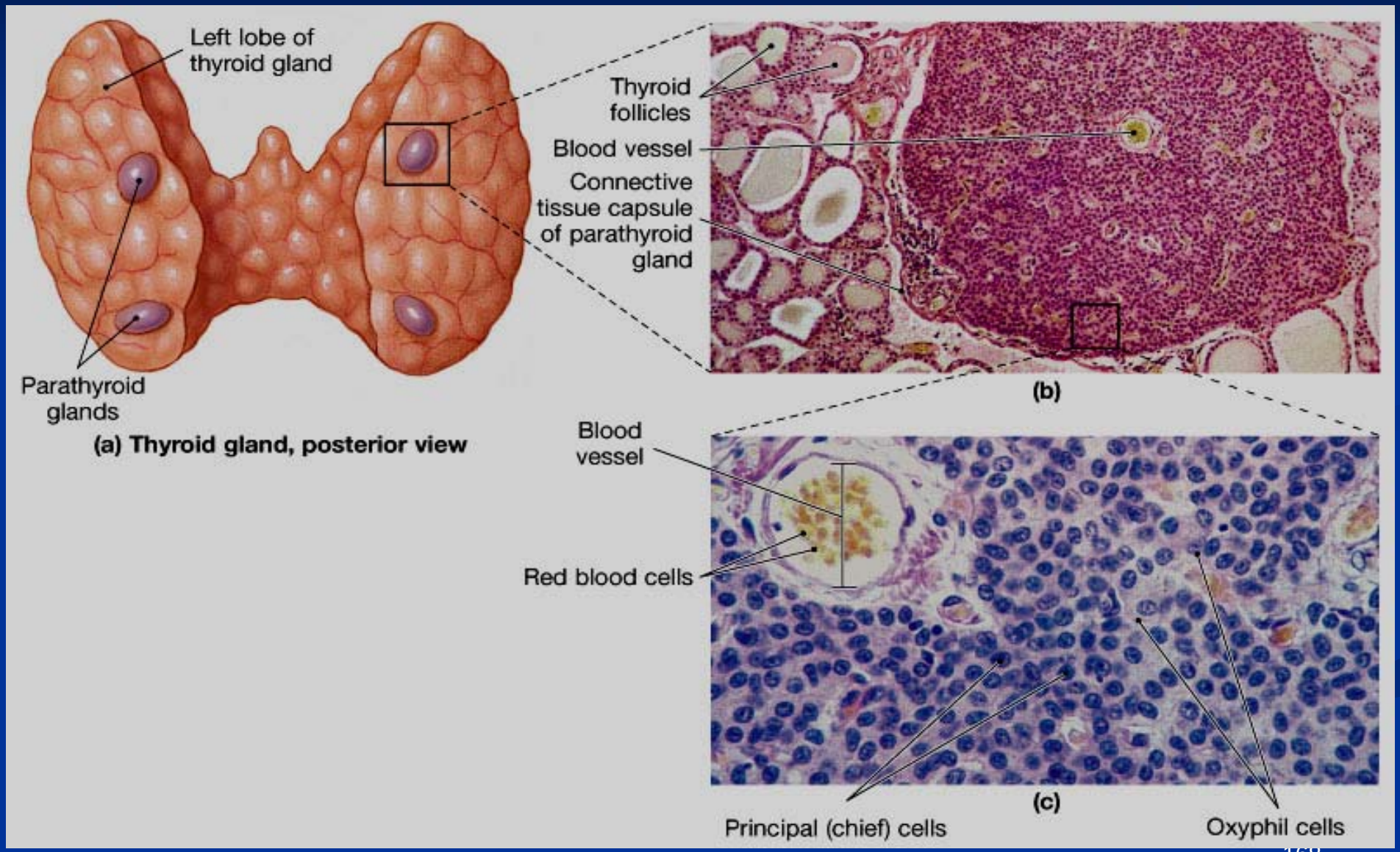
- Circadian rhythm

- Half life: 20-30 min

Biosynthesis, Storage & Secretion of PTH

- PTH is synthesized as the preprohormone (Preproparathyroid Hormone) by parathyroid gland chief cells
- The active form of PTH is cleaved from the preprohormone before release from the gland
- PTH is synthesized continously (it is either released from the gland or degraded)
- PTH is released by exocytosis in response to reduced plasma calcium
- Vitamin D feeds back to reduce PTH secretion as a secondary mechanism

Parathyroid glands



(一) Biological effects of PTH

(Ca^{2+}↑ & Phosphate↓)

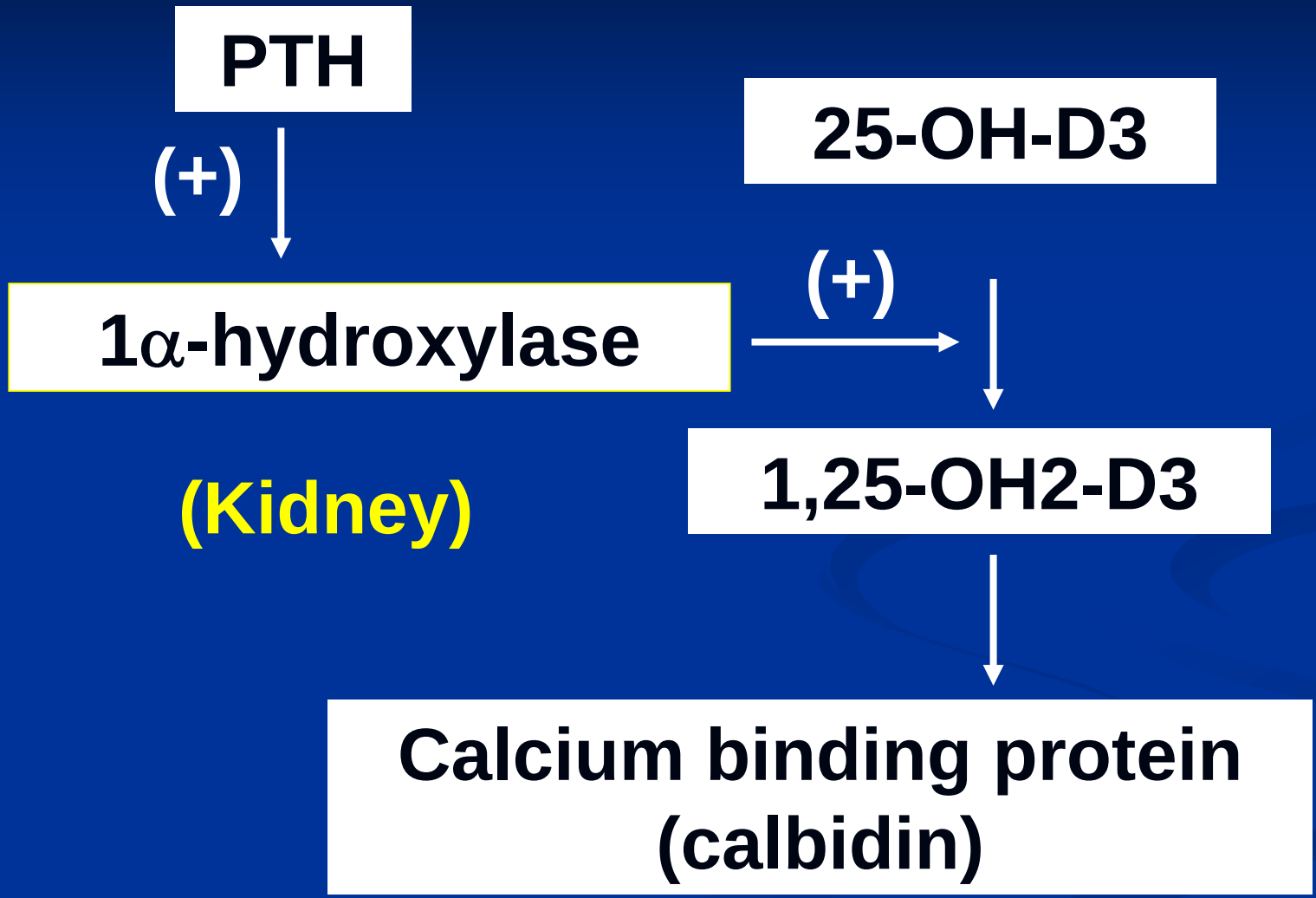
(kidney, bone and intestine)

99% of stored calcium

Biological Activity of PTH

- BONE
  - PTH stimulates bone osteoclasts to increase growth & metabolic activity
  - PTH stimulated bone releases calcium & phosphate into blood
- KIDNEY
  - PTH increases reabsorption of calcium & reduces reabsorption of phosphate
  - Net effect of its action is increased calcium & reduced phosphate in plasma
- INTESTINE
  - Increases calcium reabsorption via vitamin D

Increased intestinal Ca^{2+}/P absorption

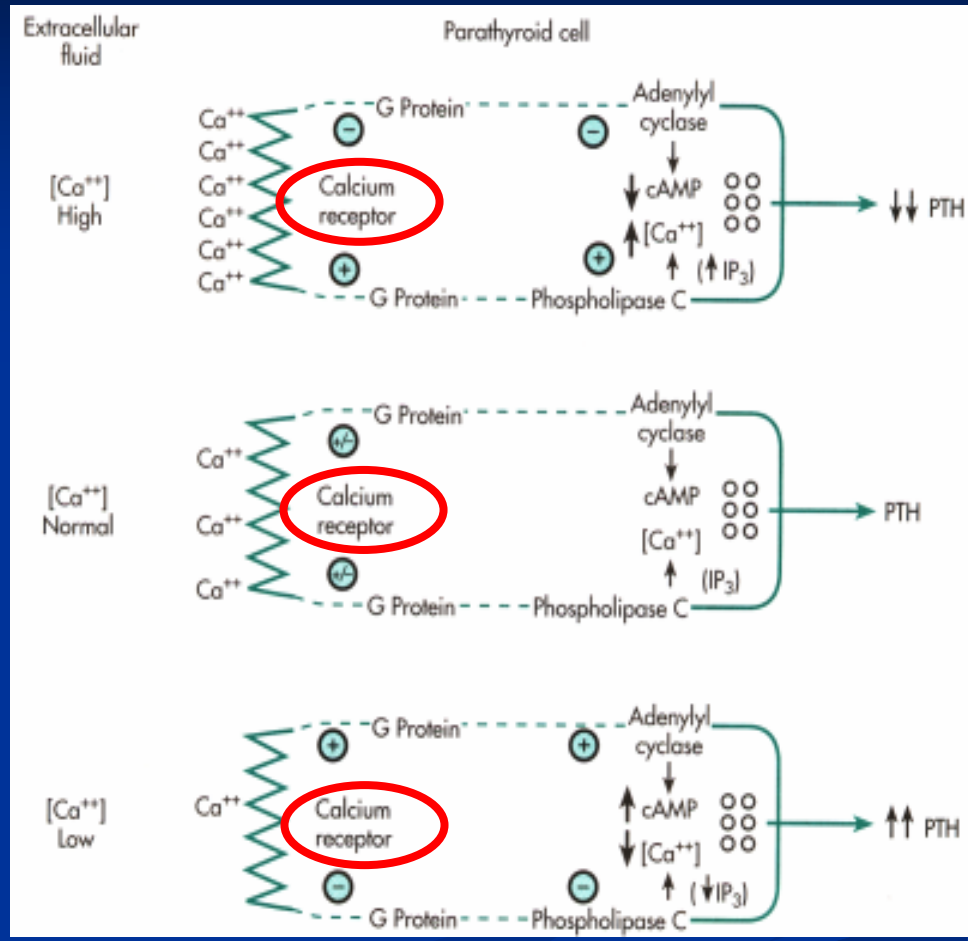


(二) Regulation of PTH secretion

1. Blood Ca^{2+} level

   Negative feedback

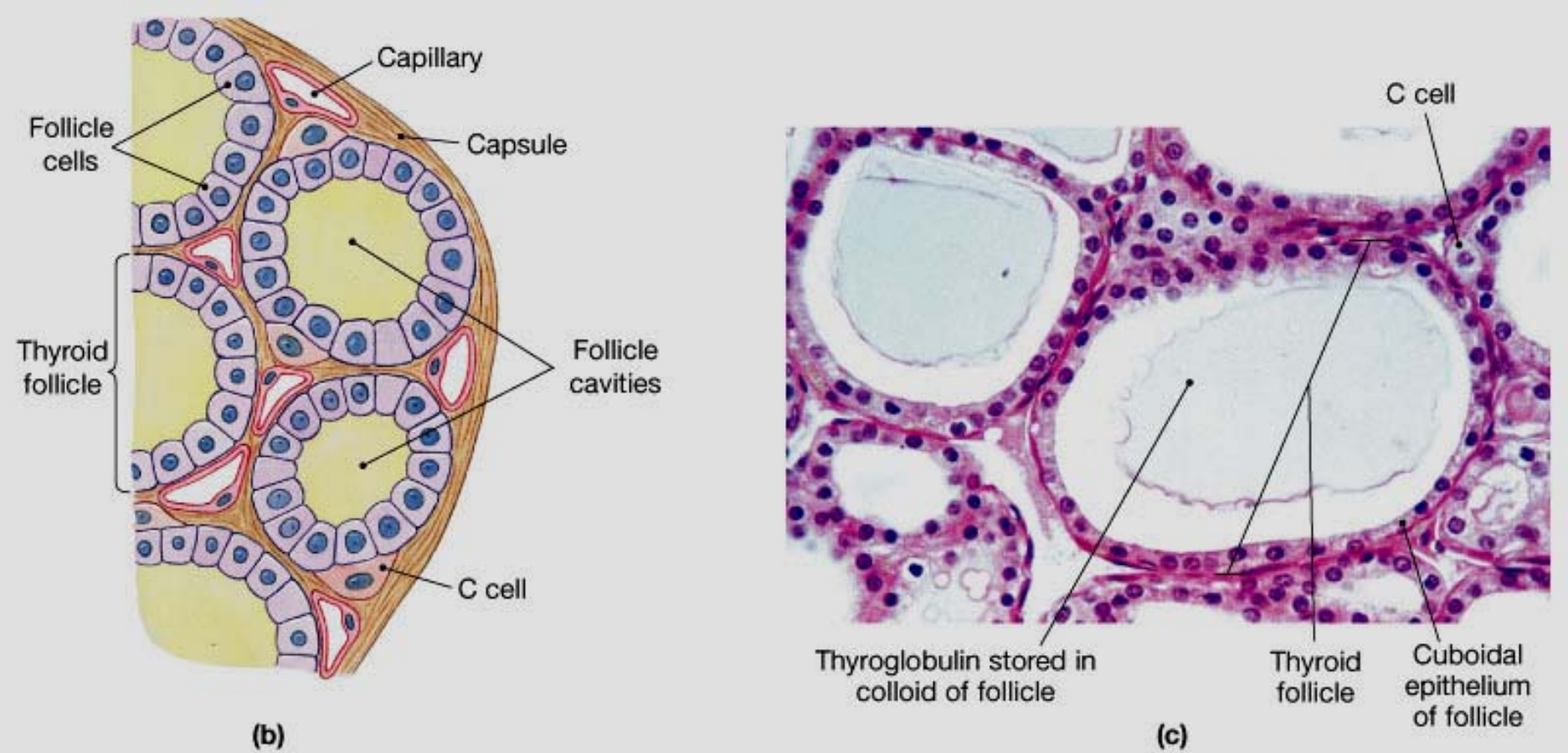
   1 min



2. Blood phosphate↑ or Mg^{2+}↓

3. GHIH

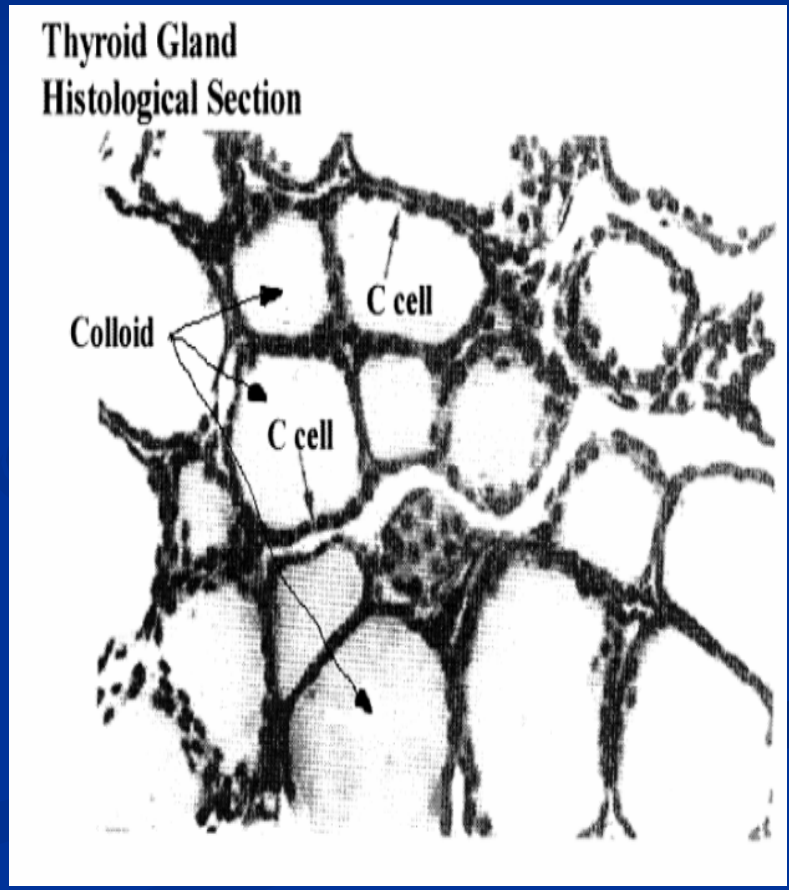
二. Calcitonin, CT



- 32 aa, MW 3500
- Half life: <1h

Calcitonin

- Calcitonin is a peptide hormone secreted by the parafollicular or "C" cells of the thyroid gland
- It is synthesized as the preprohormone & released in response to high plasma calcium
- Calcitonin acts on bone osteoclasts to reduce bone resorption.
- Net result of its action is a decline in plasma calcium & phosphate



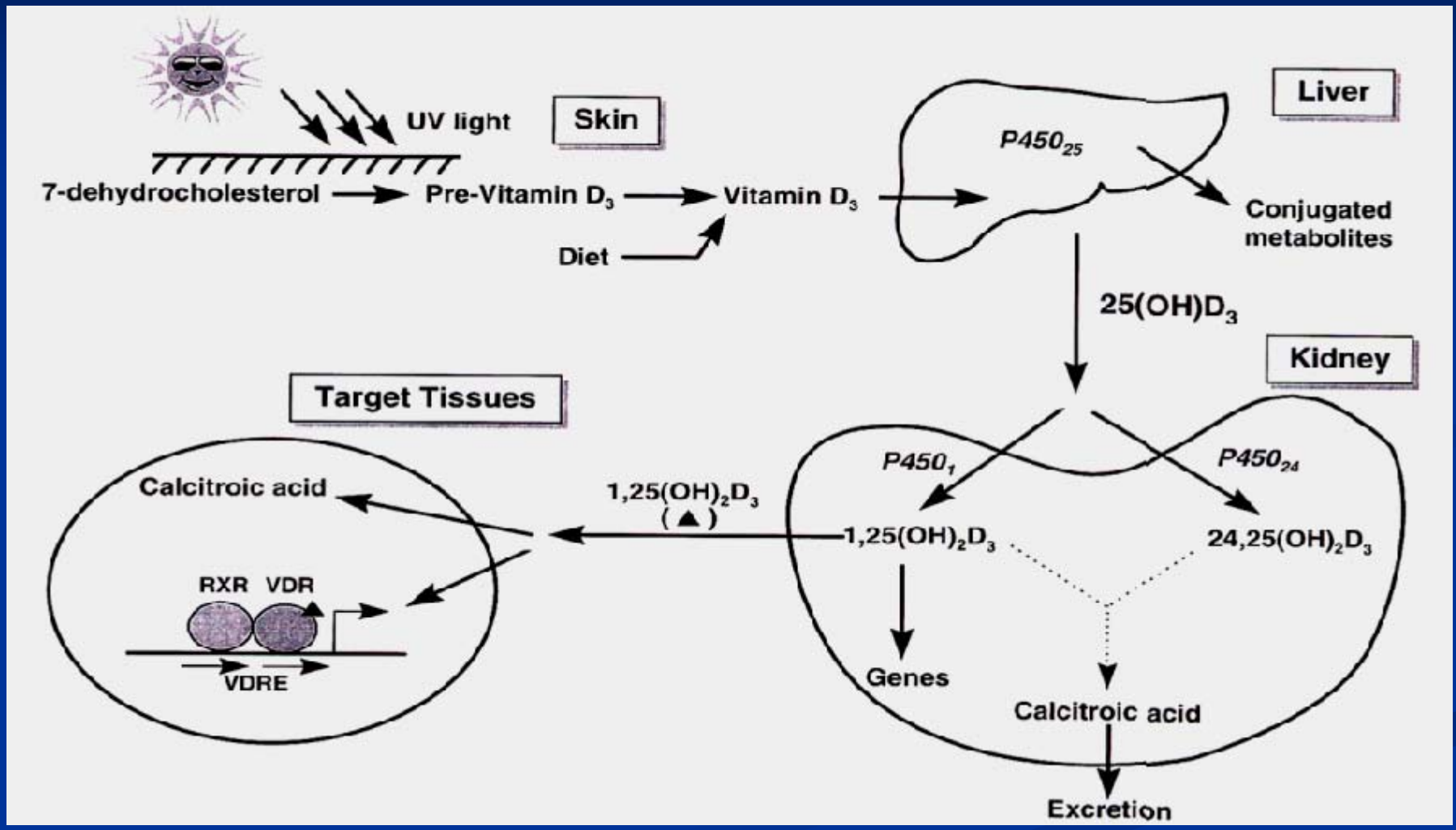
Regulation of CT secretion

1. Blood Ca^{2+} level
2. The others mechanism:

   Gastrin, secretin, glucagon…

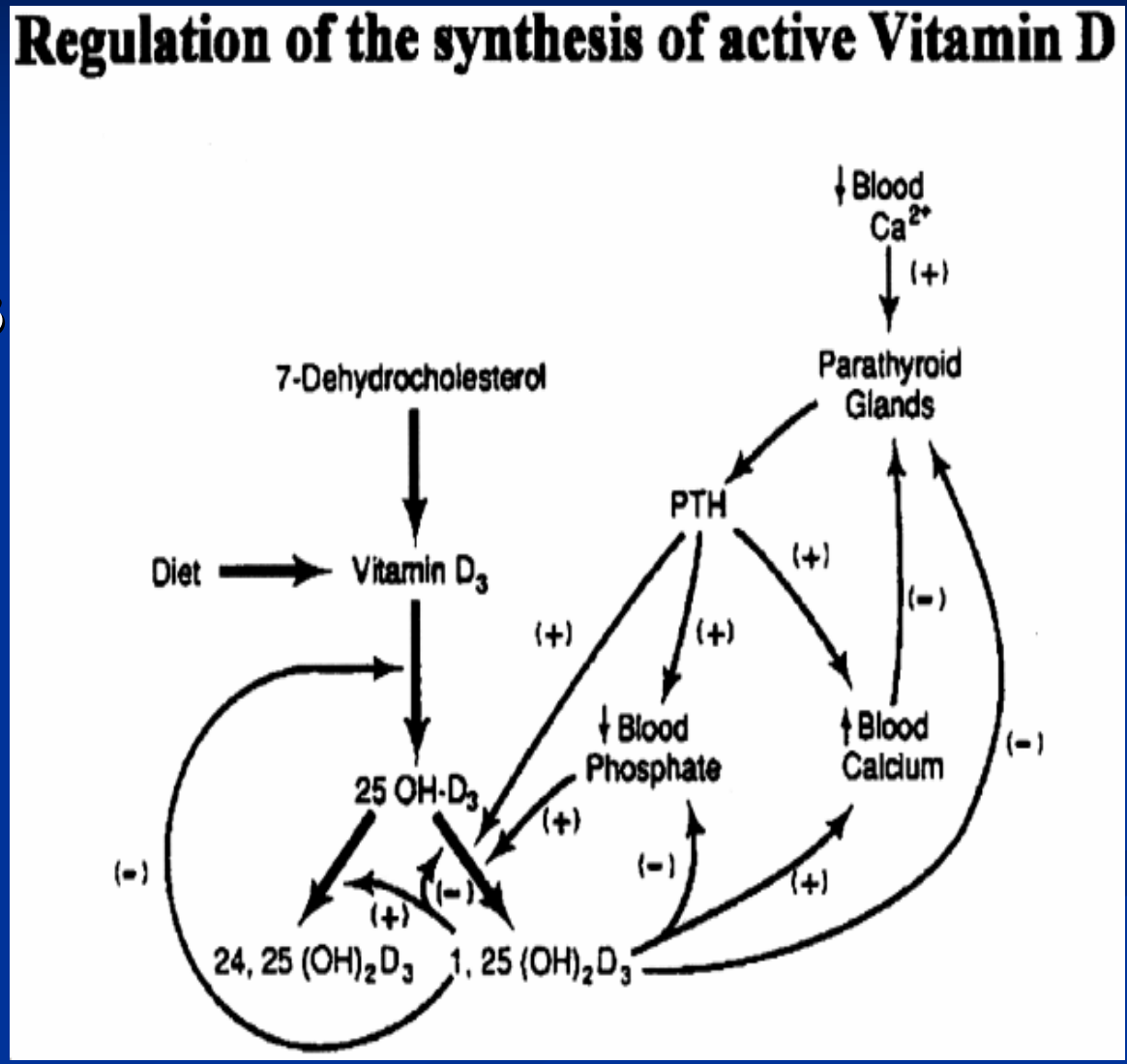
   Blood Mg^{2+} ↑

三. 1,25-dihydroxyvitamin D_3

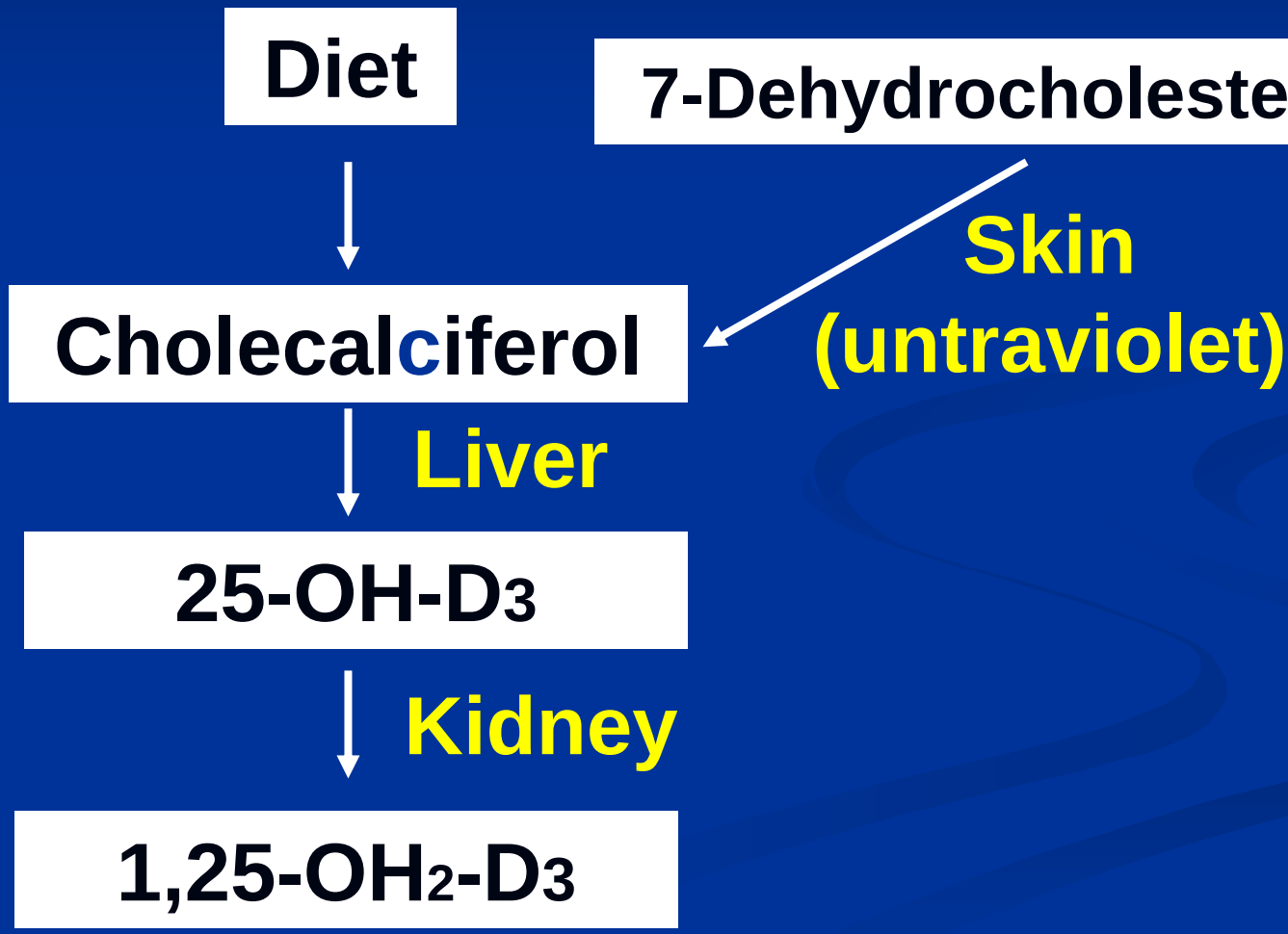


Vitamin D

- Vitamin D3 is may be obtained from the diet or made in the skin
- It is converted to the active form (1,25-OH-D3 by sequential enzymatic reactions in the liver and kidney (stimulated by PTH)
- Vitamin D3 stimulates intestinal calcium uptake, increased bone calcium resorption & increased kidney phosphate uptake



(一) Synthesis of 1,25-$(OH)_2D_3$
- is derived from cholesterol



(二) Biological effects of 1,25-$(OH)_2D_3$

(Ca^{2+}↑ & Phosphate ↑)

(kidney, bone and intestine)

1. Increased intestinal Ca^{2+} and phosphate absorption

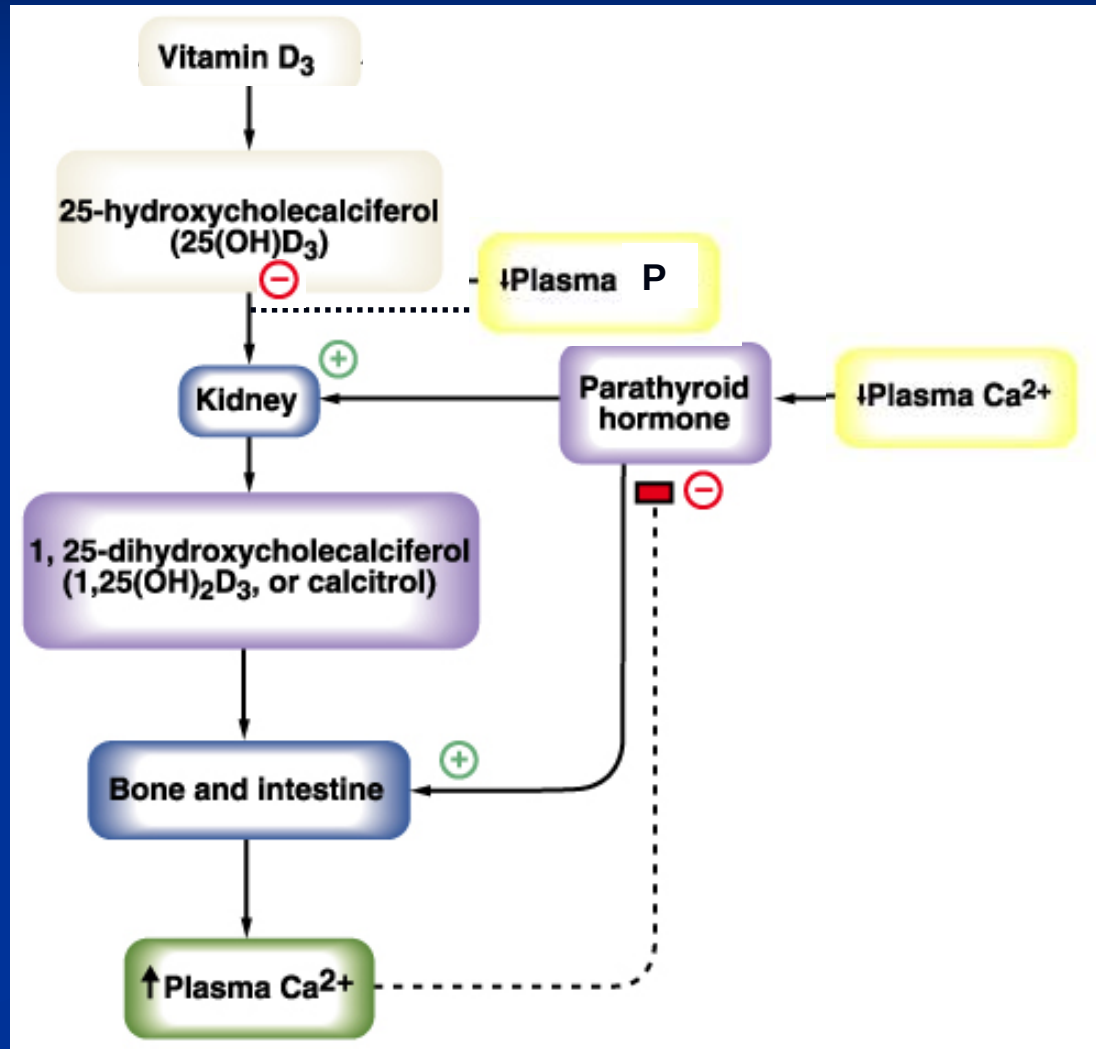
   Ca^{2+} -binding protein (calbindin)

2. Increased bone resorption
   - stimulated osteoclast (main) and osteoblast

3. Increased renal resorption

(三) Regulation of 1,25-$(OH)_2D_3$ secretion

1. Blood Ca^{2+} & phosphate
2. PTH
3. Hormones
   - e.g. Estrogen



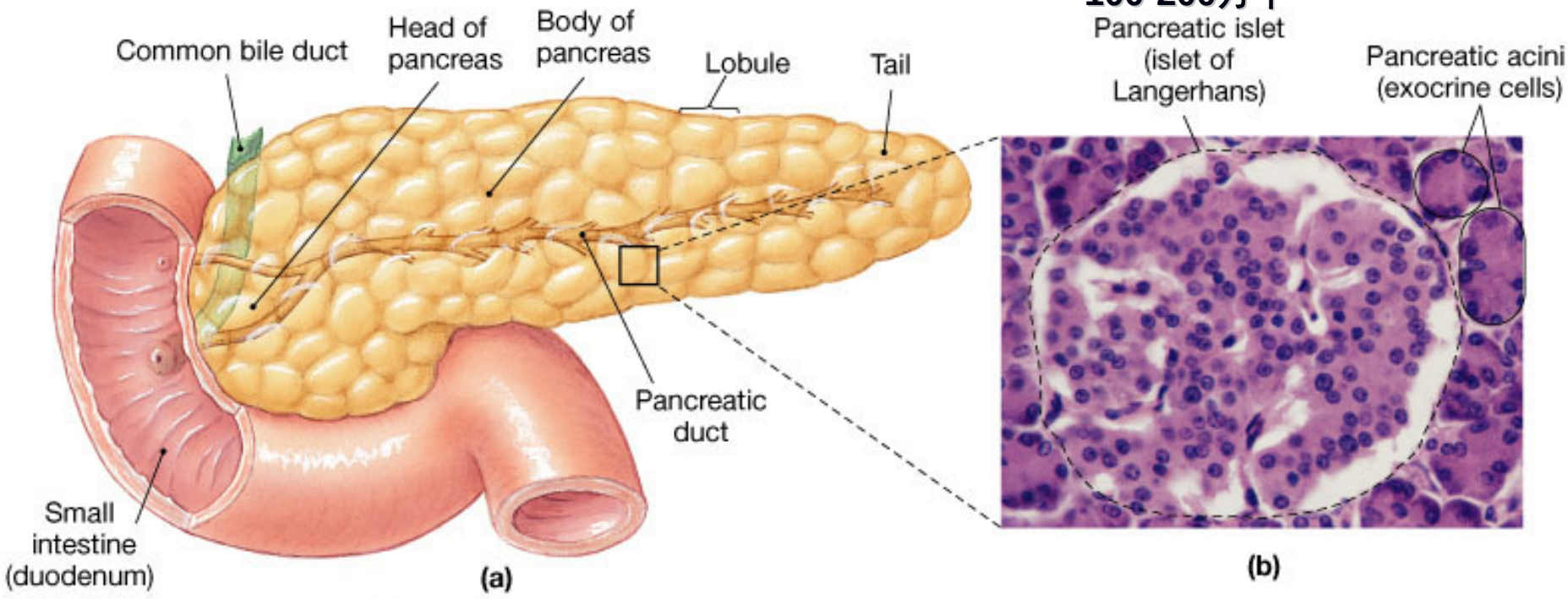
	PTH	Vitamin D	Calcitonin
Stimulus	Serum $[Ca^{2+}]$ ↓	Serum $[Ca^{2+}]$ ↓	Serum $[Ca^{2+}]$ ↑
Action on:			
Bone	mobilization ↑	mobilization ↑	mobilization ↓
Kidney	Ca^{2+} resportion ↑ P resportion ↓	Ca^{2+} /P resportion ↑	Ca^{2+} /P resportion ↓
Intestine	Ca^{2+}/P absorption ↑	Ca^{2+}/P absorption ↑	
Overall effect on:			
Serum $[Ca^{2+}]$	↑	↑	↓
Serum [phosphate]	↓	↑	↓

Summary

- PTH & calcitonin release are regulated by plasma Ca levels
- Bone Ca & phosphate serve as a ready reserve for maintenance of plasma levels
- Bone, kidney & intestine participate in the regulation of plasma calcium
- PTH, Vitamin D, & calcitonin balance plasma [Ca++] for bone synthesis, muscle contraction, & cell signaling
- Endocrine diseases result from pathway or glandular hypo or hyper secretion

Section 6
Endocrine function of Pancreatic Islets

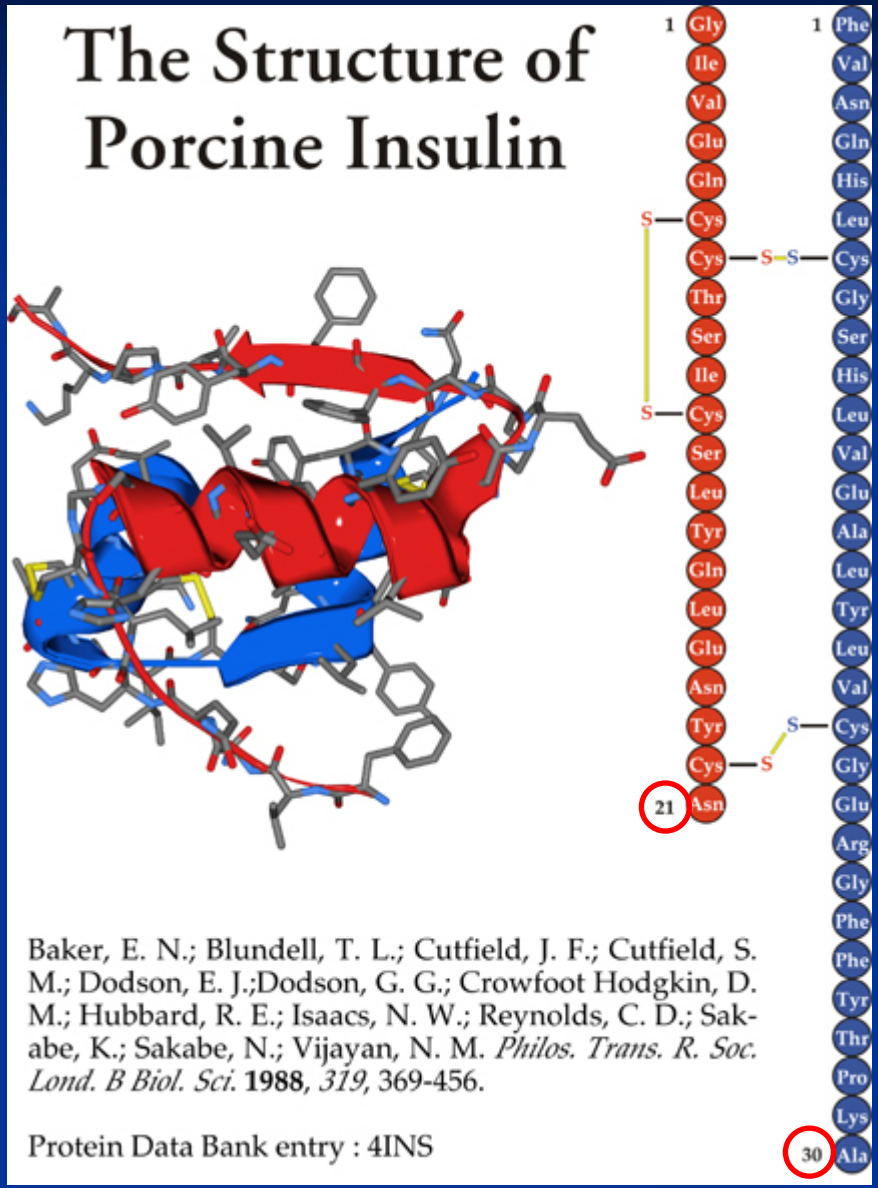
100-200万个


Common bile duct
Head of pancreas
Body of pancreas
Lobule
Tail
Pancreatic duct
Small intestine (duodenum)
(a)
Pancreatic islet (islet of Langerhans)
Pancreatic acini (exocrine cells)
(b)

Cell types of the islet of Langerhans

Type of Cell	Function
A cells (25%)	Secrete glucagon
B cells (60-70%)	Secrete insulin
D cells (5%)	Secrete somatostatin
D1 cells	Secrete vasoactive intestinal peptide
F (PP) cells	Secrete pancreatic polypeptide

Insulin



- Discovered in 1922 by Banting and Best
- Consist of A & B chains linked by 2 disulfide bonds

  (plus additional disulfide in A)
- 51aa
- Half time: 5-8 min

The discovery of insulin.

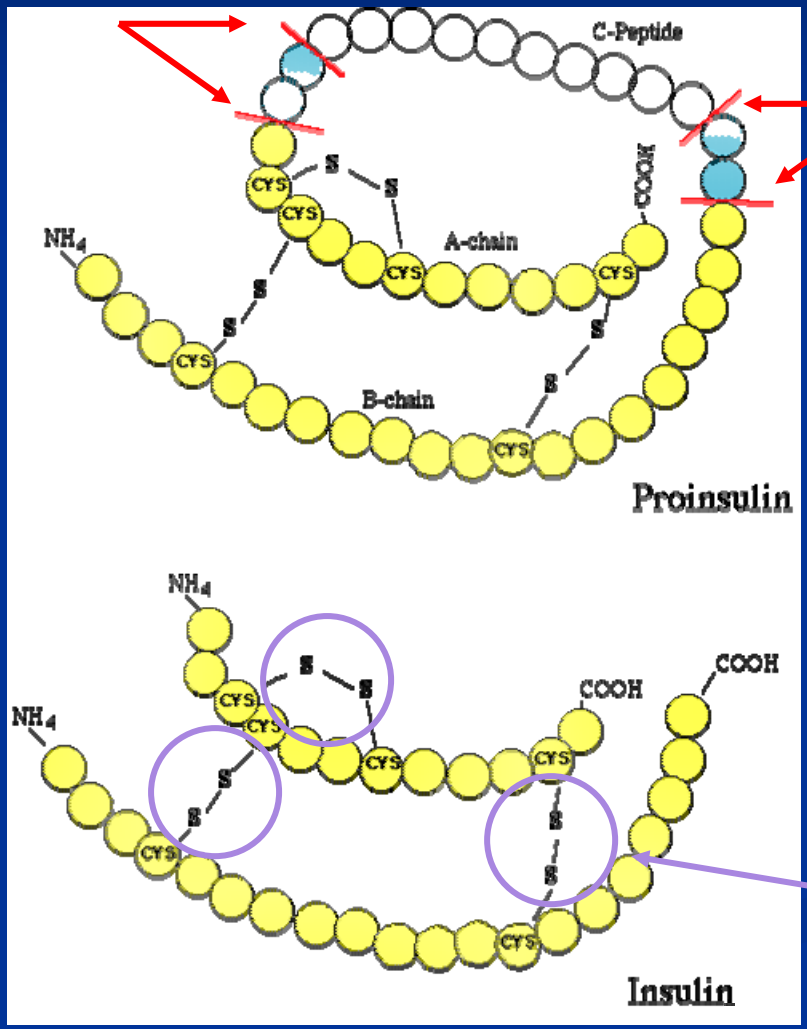
F.G. Banting shared the 1923 Nobel Prize with J.J.R. MacLeod for the discovery of insulin.

When the pancreatic duct was closed by ligatures, the cells of the pancreas which secrete trypsin degenerate, but that the Islets of Langerhans remain intact. Banting and Best tied off the pancreatic ducts of several dogs for 7 weeks. A solution was extracted from them. The injection of this extract into diabetic dogs (ie, dogs whose pancreas had been removed) quickly restored the health of the dogs.

Chemistry of Insulin

synthesis as a prohormone (proinsulin):

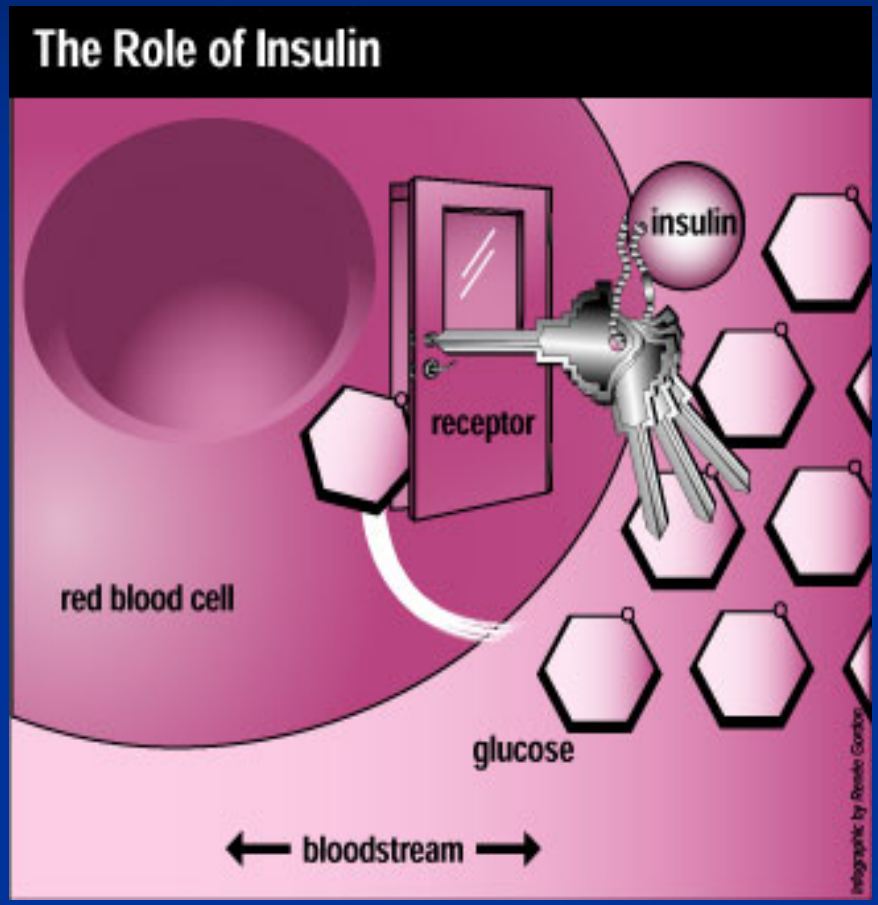
cleavage (Lys-Arg)



cleavage (Arg-Arg)

3 S-S bonds required for biological activity

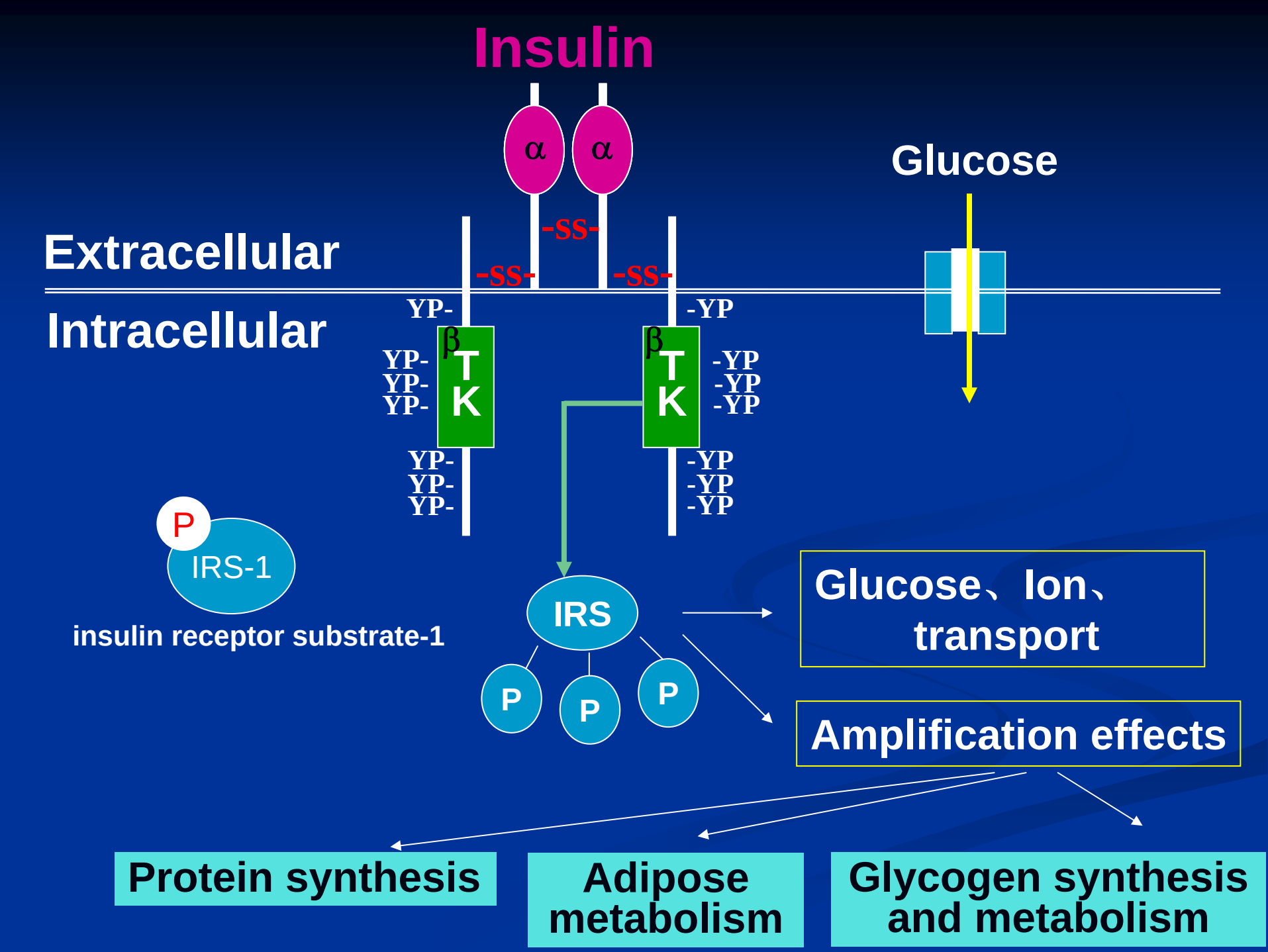
The Role of Insulin

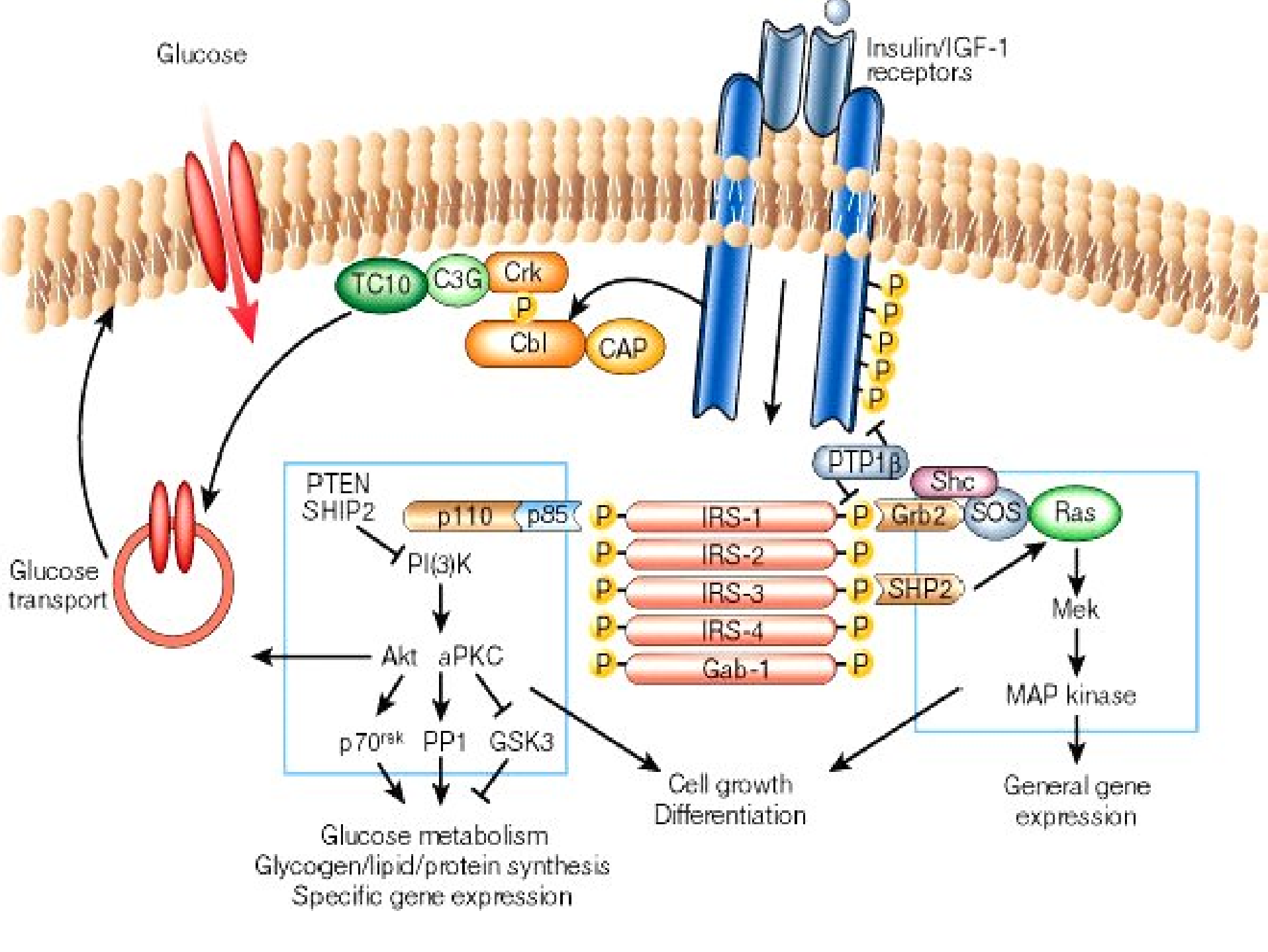


Tyrosine Kinase receptors are the locks in which the insulin key fits

- Involved in ***signal transduction***

(insulin hormone being 1st messenger)


Insulin
α
α
-SS-
-SS-
-SS-
Extracellular
Intracellular
Glucose
YP-
-YP
β
T
K
YP-
YP-
YP-
-YP
-YP
-YP
P
IRS-1
insulin receptor substrate-1
IRS
P
P
P
Glucose、Ion、transport
Amplification effects
Protein synthesis
Adipose metabolism
Glycogen synthesis and metabolism

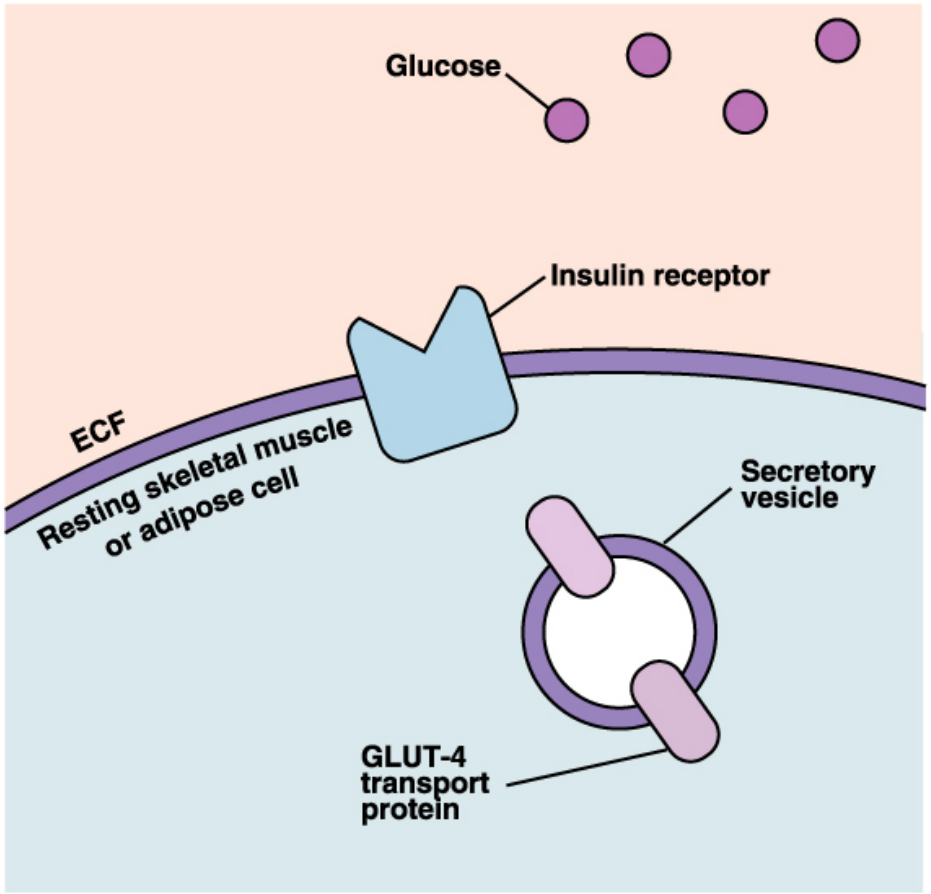

Glucose
Insulin/IGF-1 receptors
TC10
C3G
Crk
P
Cbl
CAP
P
P
P
P
P
PTP1β
Shc
Grb2
SOS
Ras
PTEN
SHIP2
p110
p85
PI(3)K
IRS-1
IRS-2
IRS-3
IRS-4
Gab-1
SHP2
Mek
MAP kinase
Glucose transport
Akt
aPKC
p70rsk
PP1
GSK3
Cell growth
Differentiation
General gene expression
Glucose metabolism
Glycogen/lipid/protein synthesis
Specific gene expression

Distinct biological effects of insulin:

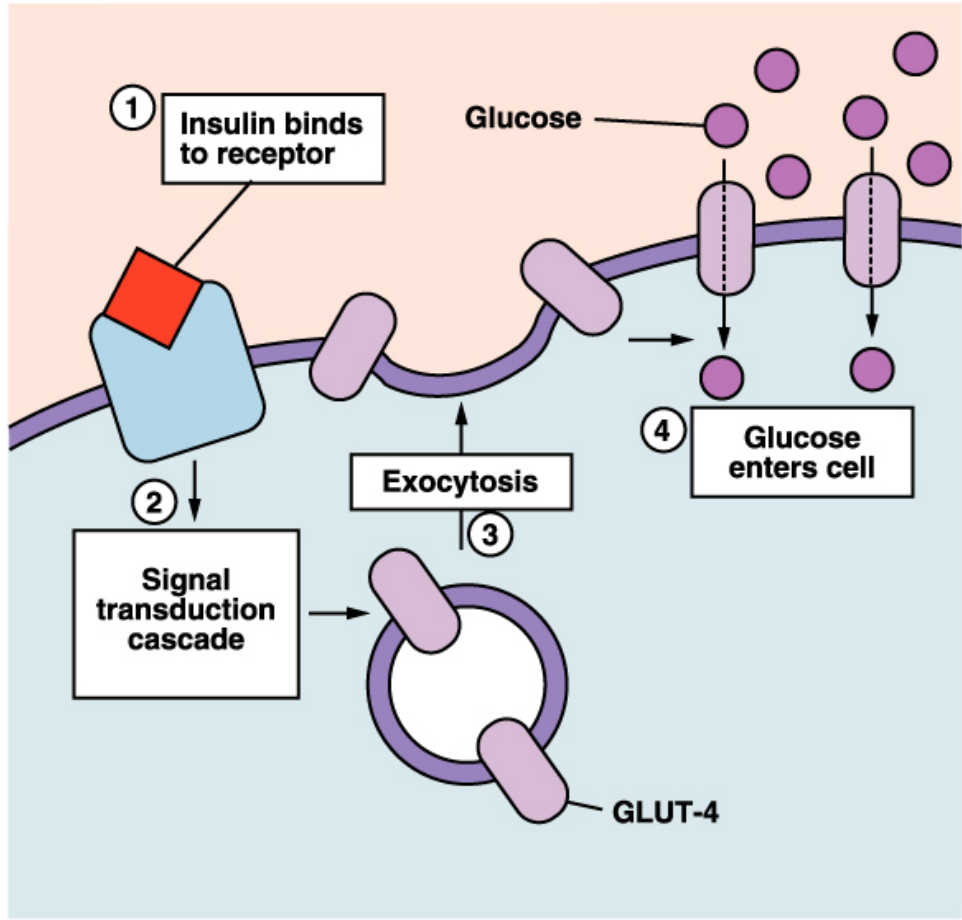
一、Decrease blood glucose level

1. promote glucose transport and utilize
2. inhibit glyconeogenesis
3. promote of glycogen synthesis
4. promote glucose transform to fatty acid

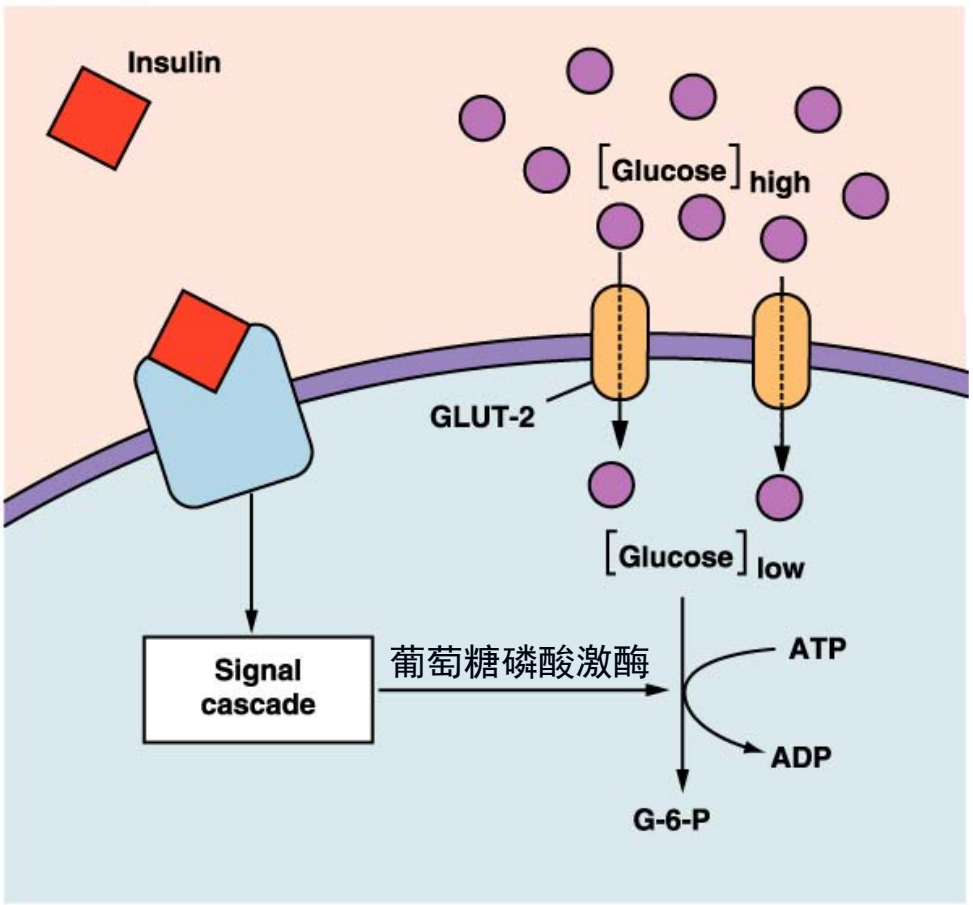
In the absence of insulin, glucose cannot enter the cell

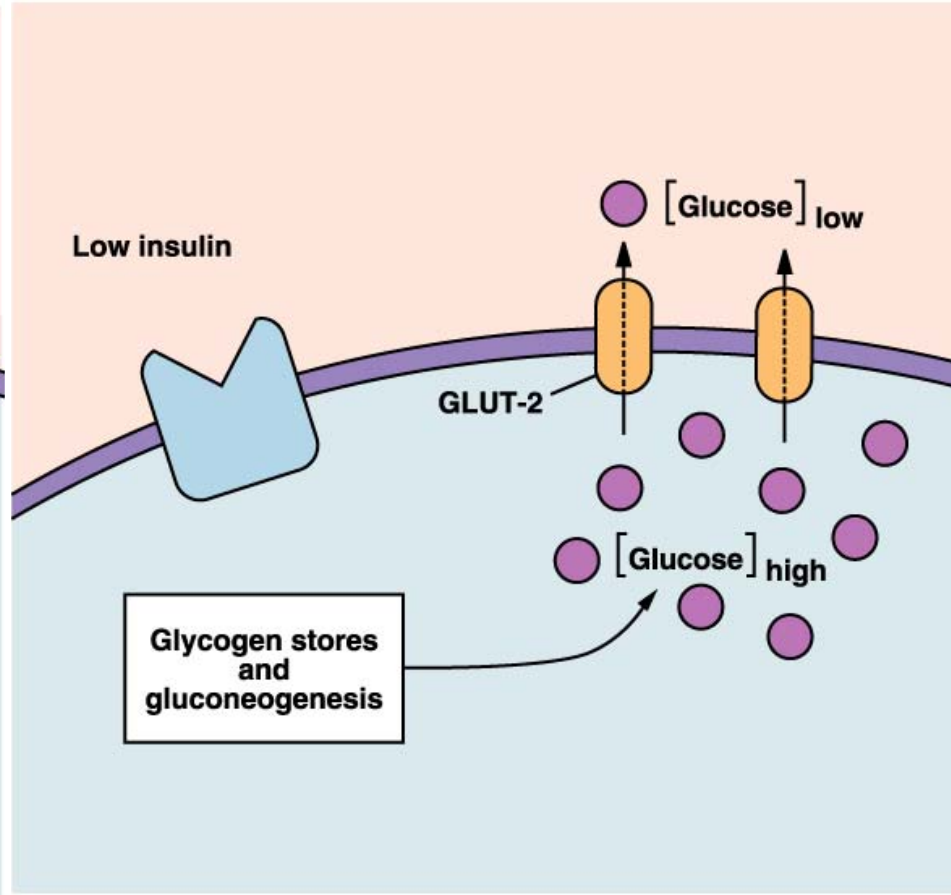


Insulin allows glucose to enter



Hepatocytes





二、 promote adipose synthesis

1. promote fatty acid synthesis in liver and then stored in adipocytes
2. stimulate glucose into adipocytes
3. inhibit lipase activity

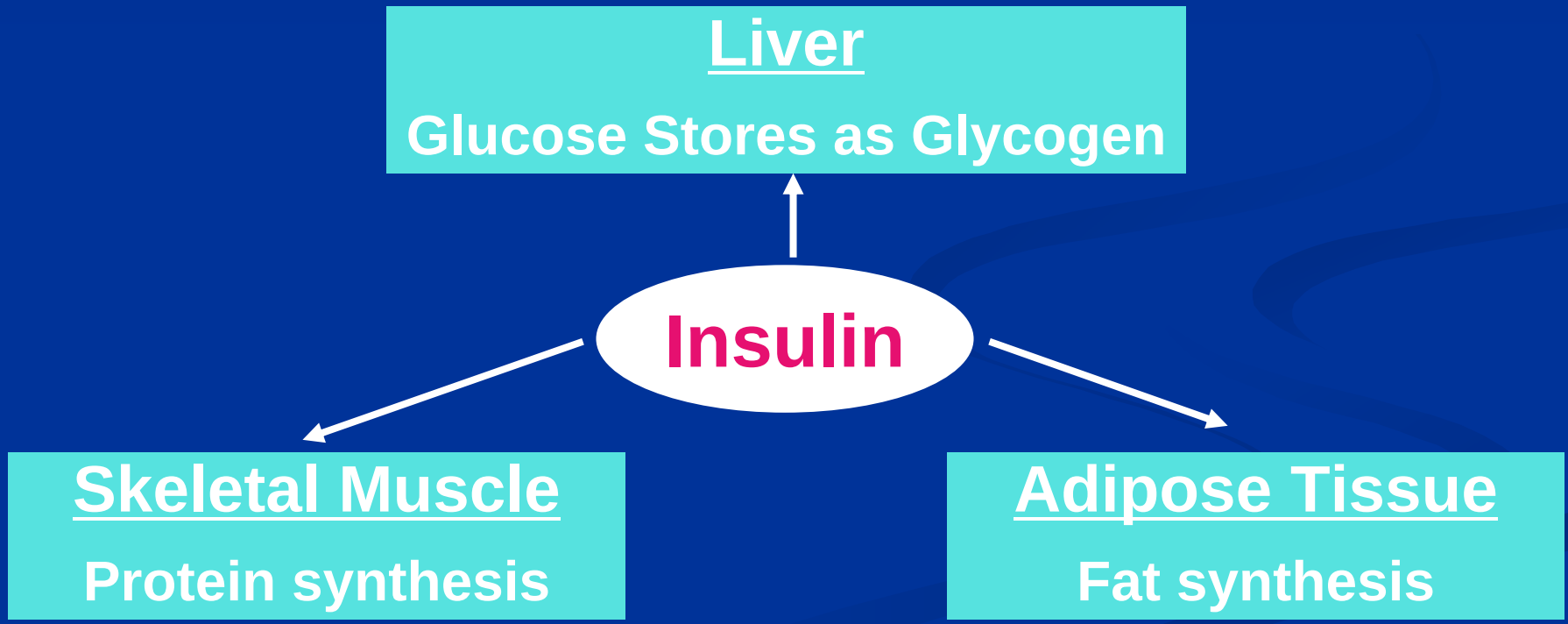
三、promote protein synthesis

1. promote amino acid uptake into tissue
2. promote DNA/RNA synthesis in nucleus
3. Promote protein translation
4. inhibit protein break down

四、Promote growth

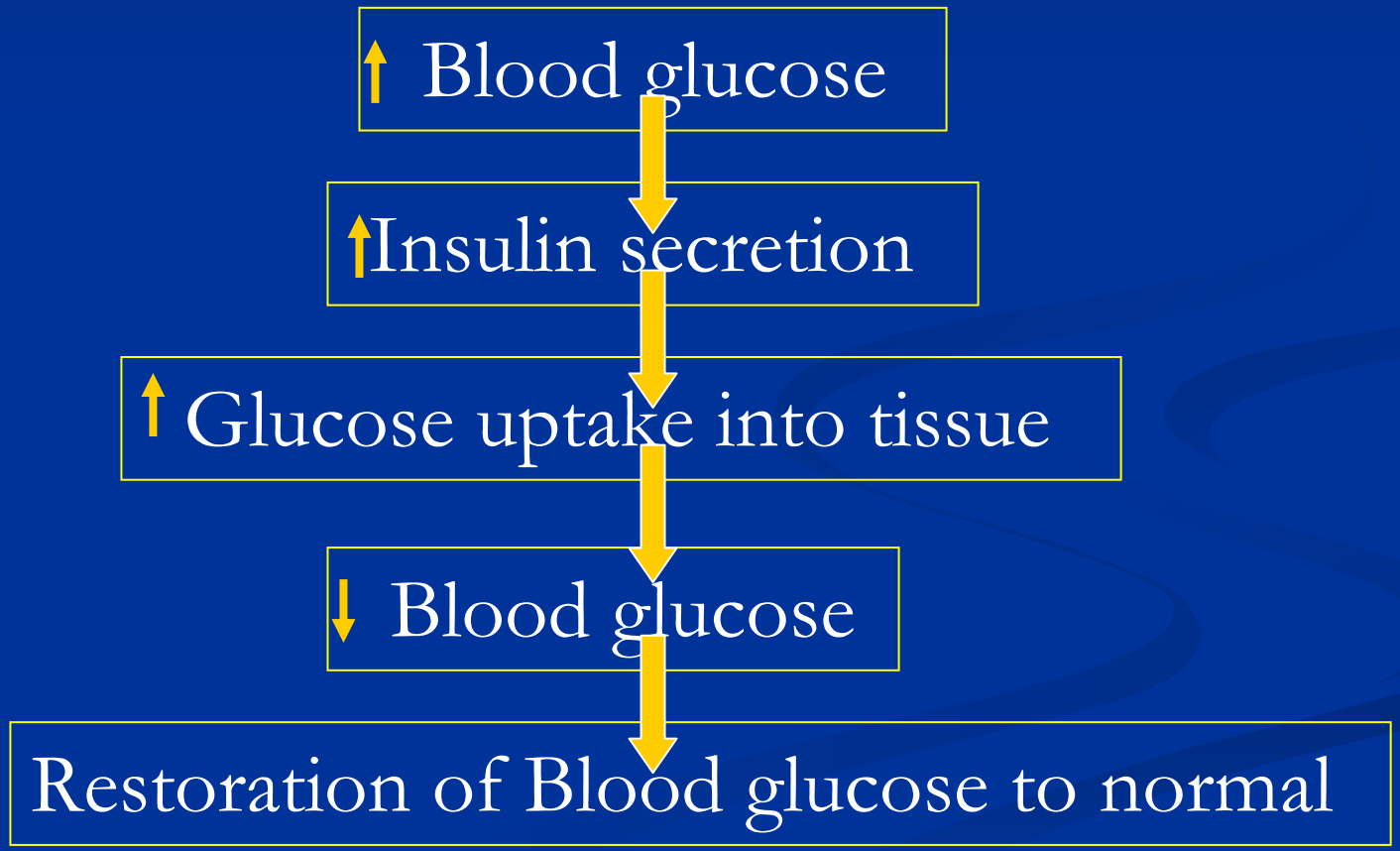
Biological effects of insulin

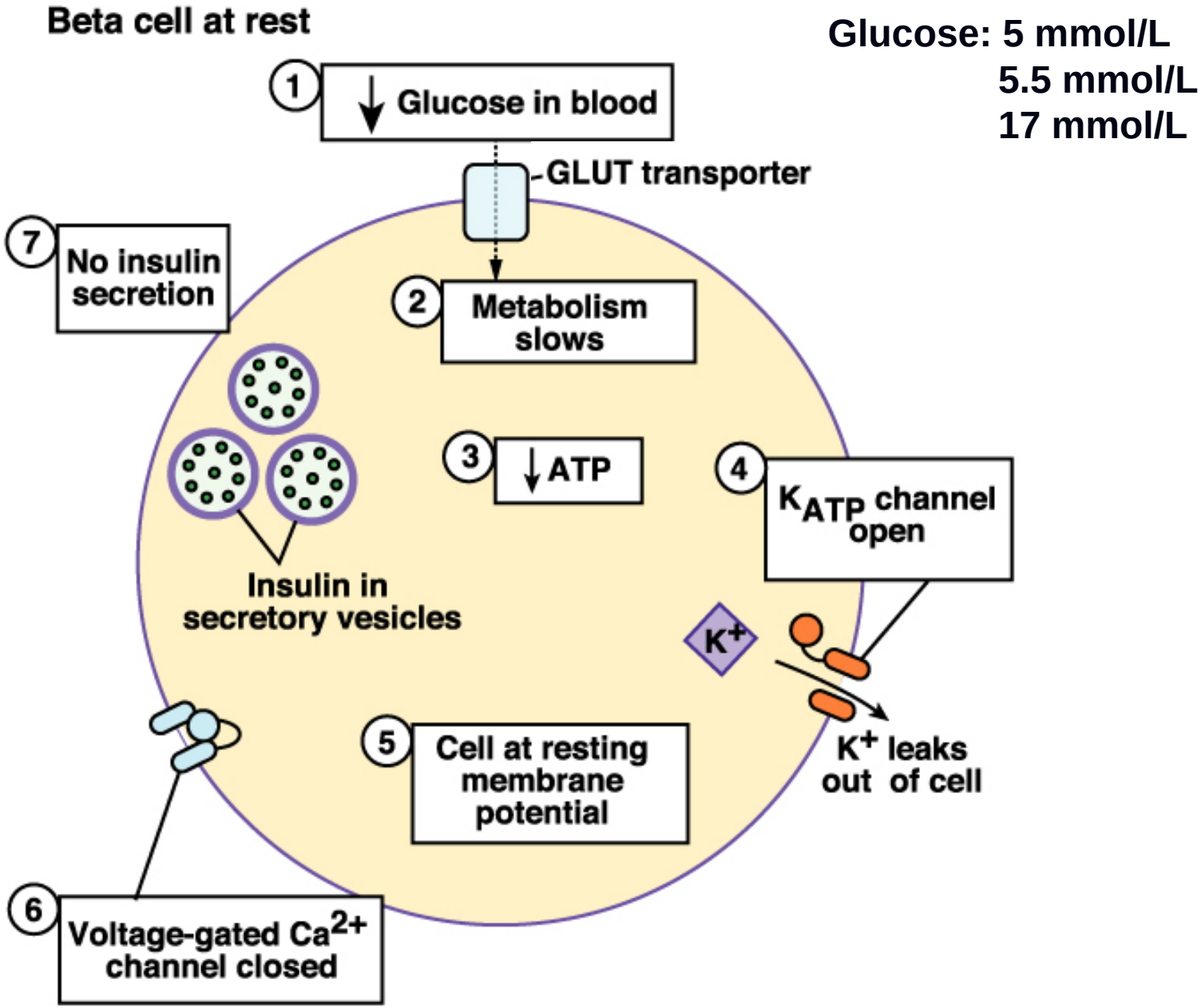
- exert anabolic effects
- maintain blood glucose concentration



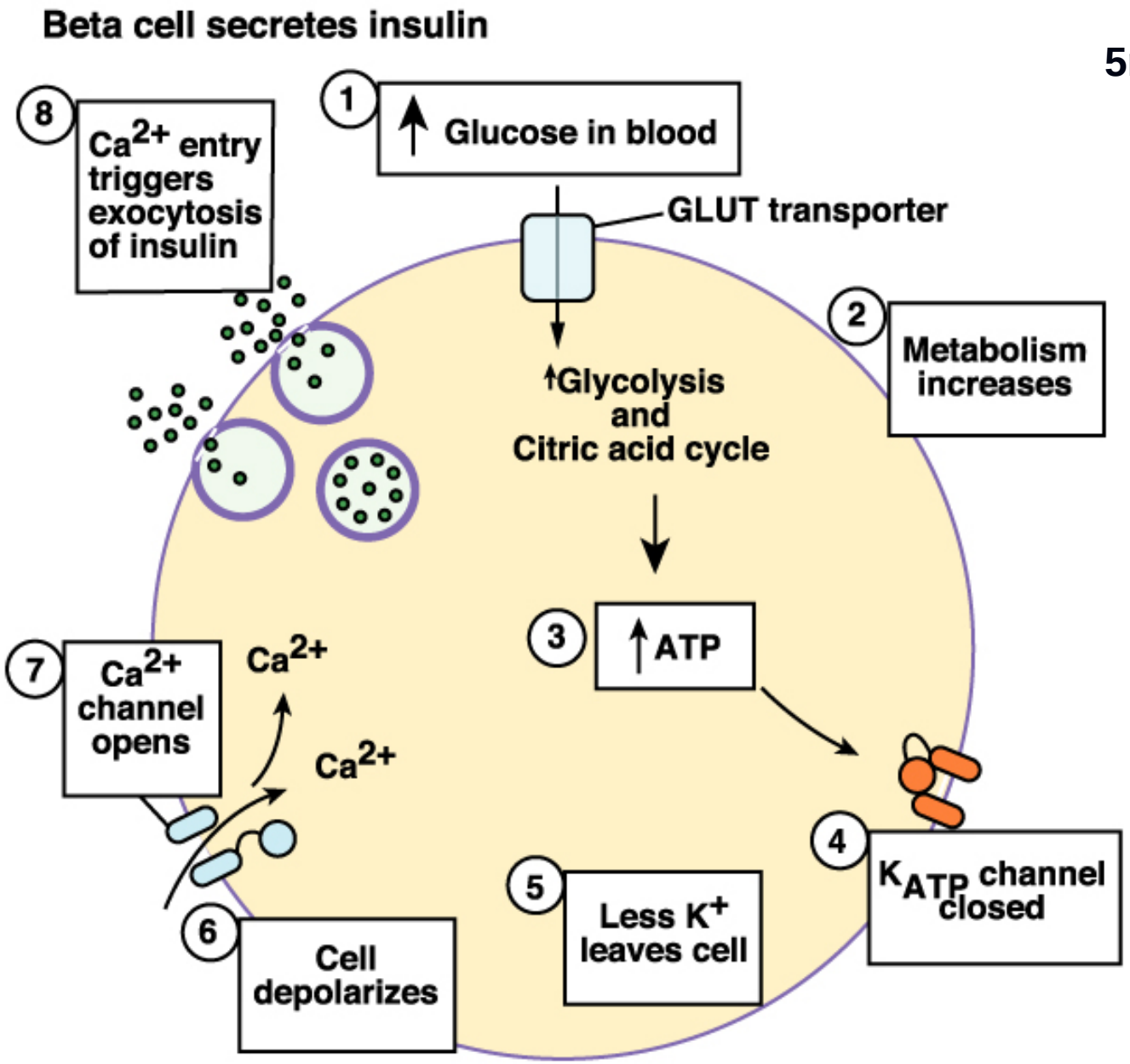
Regulation of insulin secretion

Increased blood glucose




Beta cell at rest
Glucose: 5 mmol/L
5.5 mmol/L
17 mmol/L
1
Glucose in blood
GLUT transporter
7
No insulin secretion
2
Metabolism slows
3
ATP
4
K_{ATP} channel open
Insulin in secretory vesicles
K^+
K^+ leaks out of cell
5
Cell at resting membrane potential
6
Voltage-gated Ca^{2+} channel closed

5min


Beta cell secretes insulin
1
Glucose in blood
GLUT transporter
2
Metabolism increases
Glycolysis and Citric acid cycle
3
ATP
4
K_{ATP} channel closed
5
Less K^+ leaves cell
6
Cell depolarizes
7
Ca^{2+} channel opens
Ca^{2+}
Ca^{2+}
8
Ca^{2+} entry triggers exocytosis of insulin

Regulation of insulin secretion

- fatty acid/amino acid
- Hormones

1. gastrointestinal hormone

   Gastric inhibitory peptide (GIP)

   Gastrin, secretin, CCK

Entero-insular axis: feed-forward regulation

2. paracrine of islets

   glucagon, somatostatin

3. other hormones

   GHRH, GH, TRH, TH, CRH, cortisol

Regulation of insulin secretion

Autonomic nervous system

1. Parasympathetic:

Acetylcholine $\xrightarrow{M}$ ↑ **insulin**

2. sympathetic :

epinephrine $\xrightarrow{\alpha 2}$ ↓ **insulin**

$\xrightarrow{\beta 2}$ ↑

Glucagon

- A cells
- 29 aa
- MW: 3485
- Serum: 50~100ng/L
- Half life: 5~10min

Summary

- **hormone** –is a chemical substance secreted into the internal body fluids by one specialized cell or a group of cells and has a physiological control effect on other cells of the body.
- **Patterns of the hormone action:** Telecrine, Paracrine, Autocrine, Neurocrine
- **Characteristics of hormone action:** Relative specificity Message transmission, Biological amplification, Interaction of hormones
- **Permissive effect.** A hormone is said to have a permissive effect on the action of a second hormone when it **enhances** the responsiveness of a target organ to the second hormone or when it **increases** the activity of the second hormone.

- **Hormones Secreted from the Posterior Pituitary:** vasopressin and oxytocin
- **GH exert much of its effects through intermediate substances called "somatomedins", also called** "insulin-like growth factors" (IGF)
- **What is the physiological functions of growth hormone.**
- **What is the physiological functions of thyroid hormone**
- **Calcium Parathyroid hormone(PTH), calcitonin, and vitamin D are the three hormones of Ca homeostasis.**
- **Distinct biological effects of insulin**