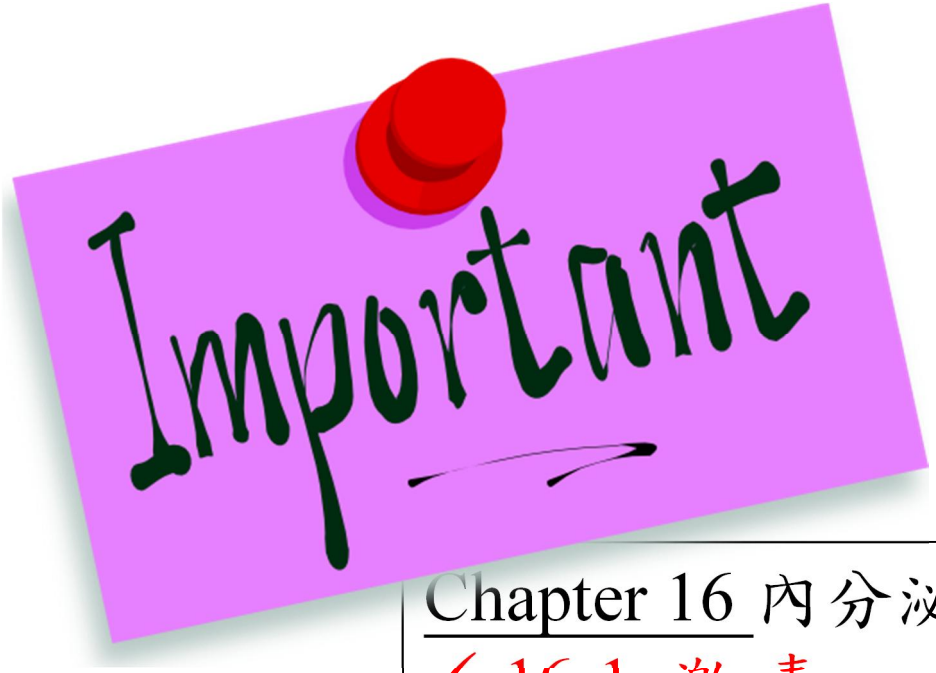


Chapter 16 內分泌系統

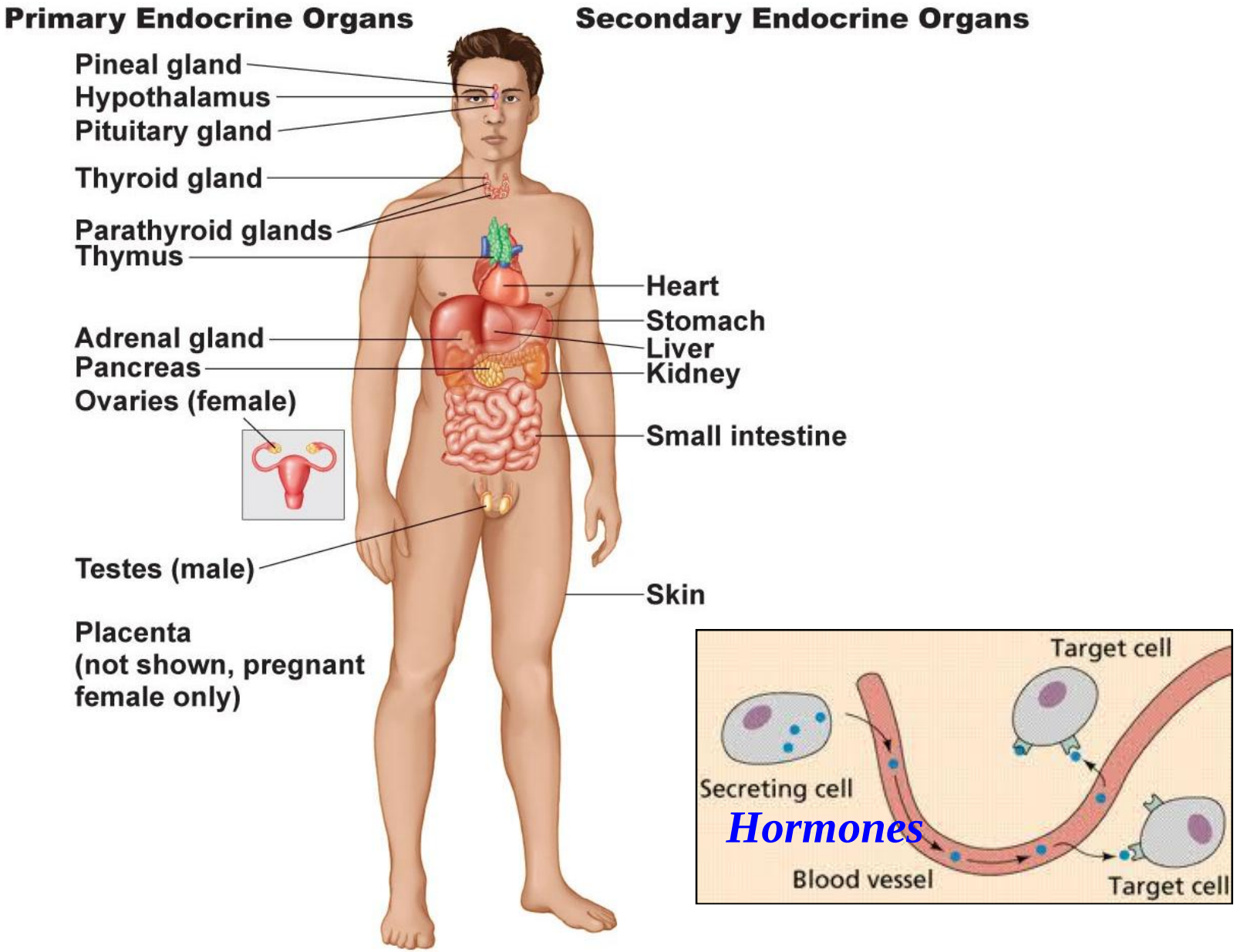
- ✓ 16-1 激 素
- ✓ 16-2 下視丘及腦下腺
- ✓ 16-3 甲狀腺及副甲狀腺
- ✓ 16-4 腎上腺
- ✓ 16-5 其他內分泌腺體及組織

Chapter 17營養及代謝

- ✓ 17-1 能量的轉換及利用
- ✓ 17-2 維生素及礦物質
- ✓ 17-3 基礎代謝率及體溫調節

Endocrine Organs

Endocrine glands are derived from epithelial tissue



Chemical Classification of Hormones

1. Amines

--Derived from **tyrosine** and **tryptophan**

--Examples: hormones from the adrenal medulla, thyroid, and pineal glands

2. Polypeptides and proteins

--Examples: ***antidiuretic hormone, insulin, and growth hormone*** etc.

3. Glycoproteins

--Long polypeptides bound to a carbohydrate

--Examples: ***follicle-stimulating and luteinizing hormones***

4. Steroids

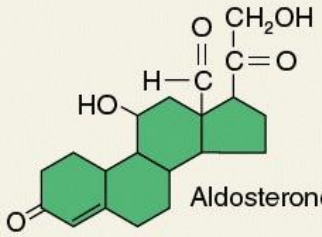
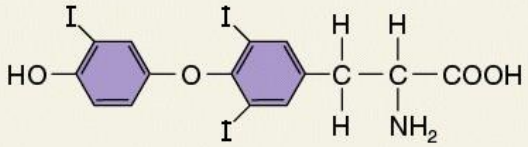
--Lipids derived from **cholesterol**

--Examples: ***testosterone, estradiol, progesterone, cortisol, aldosterone, and 1,25-$(OH)_2D_3$***

--Secreted by adrenal cortex and gonads

Solubility Classification of Hormones

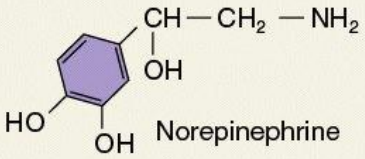
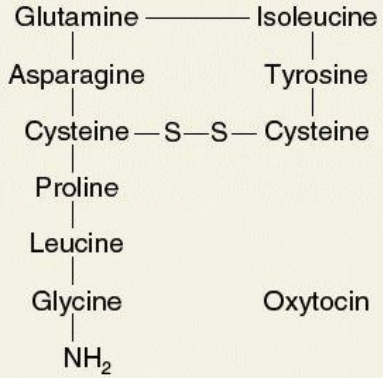
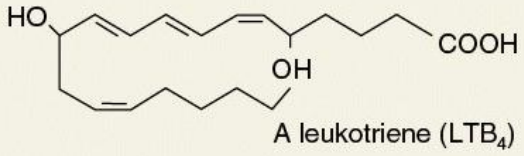
Lipid-soluble Hormones

Chemical Class	Hormones	Site of Secretion
Lipid-soluble		
Steroid hormones	Aldosterone, cortisol, and androgens.	Adrenal cortex.
 Aldosterone	Calcitriol.	Kidneys.
	Testosterone.	Testes.
	Estrogens and progesterone.	Ovaries.
Thyroid hormones	T_3 (triiodothyronine) and T_4 (thyroxine).	Thyroid gland (follicular cells).
 Triiodothyronine (T_3)		
Gas	Nitric oxide (NO).	Endothelial cells lining blood vessels.

- ***Can enter target cells directly***
- ***Can be taken orally in pill form***

Solubility Classification of Hormones

Water-soluble Hormones

Chemical Class	Hormones	Site of Secretion
Water-soluble		
Amines	Epinephrine and norepinephrine (catecholamines).	Adrenal medulla.
 Norepinephrine	Melatonin.	Pineal gland.
	Histamine.	Mast cells in connective tissues.
	Serotonin.	Platelets in blood.
Peptides and proteins	All hypothalamic releasing and inhibiting hormones.	Hypothalamus.
 Oxytocin	Oxytocin, antidiuretic hormone.	Posterior pituitary.
	Human growth hormone, thyroid-stimulating hormone, adrenocorticotropic hormone, follicle-stimulating hormone, luteinizing hormone, prolactin, melanocyte-stimulating hormone.	Anterior pituitary.
	Insulin, glucagon, somatostatin, pancreatic polypeptide.	Pancreas.
	Parathyroid hormone.	Parathyroid glands.
	Calcitonin.	Thyroid gland (parafollicular cells).
	Gastrin, secretin, cholecystokinin, GIP (glucose-dependent insulinotropic peptide).	Stomach and small intestine (enteroendocrine cells).
	Erythropoietin.	Kidneys.
	Leptin.	Adipose tissue.
Eicosanoids	Prostaglandins, leukotrienes.	All cells except red blood cells.
 A leukotriene (LTB_4)		

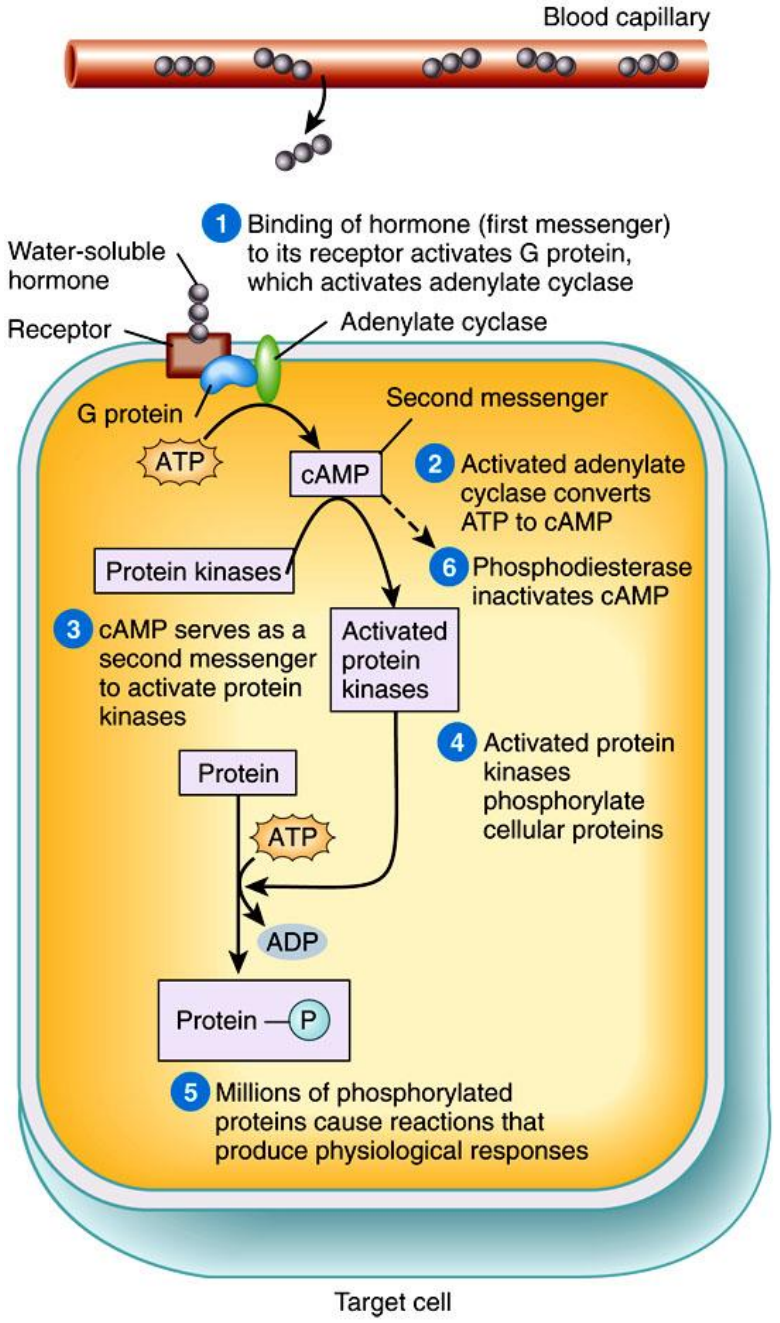
- ***Cannot pass through plasma membranes***
- ***Must be injected if used as a drug***

Mechanisms of Hormone Action

Action of Water-Soluble Hormones

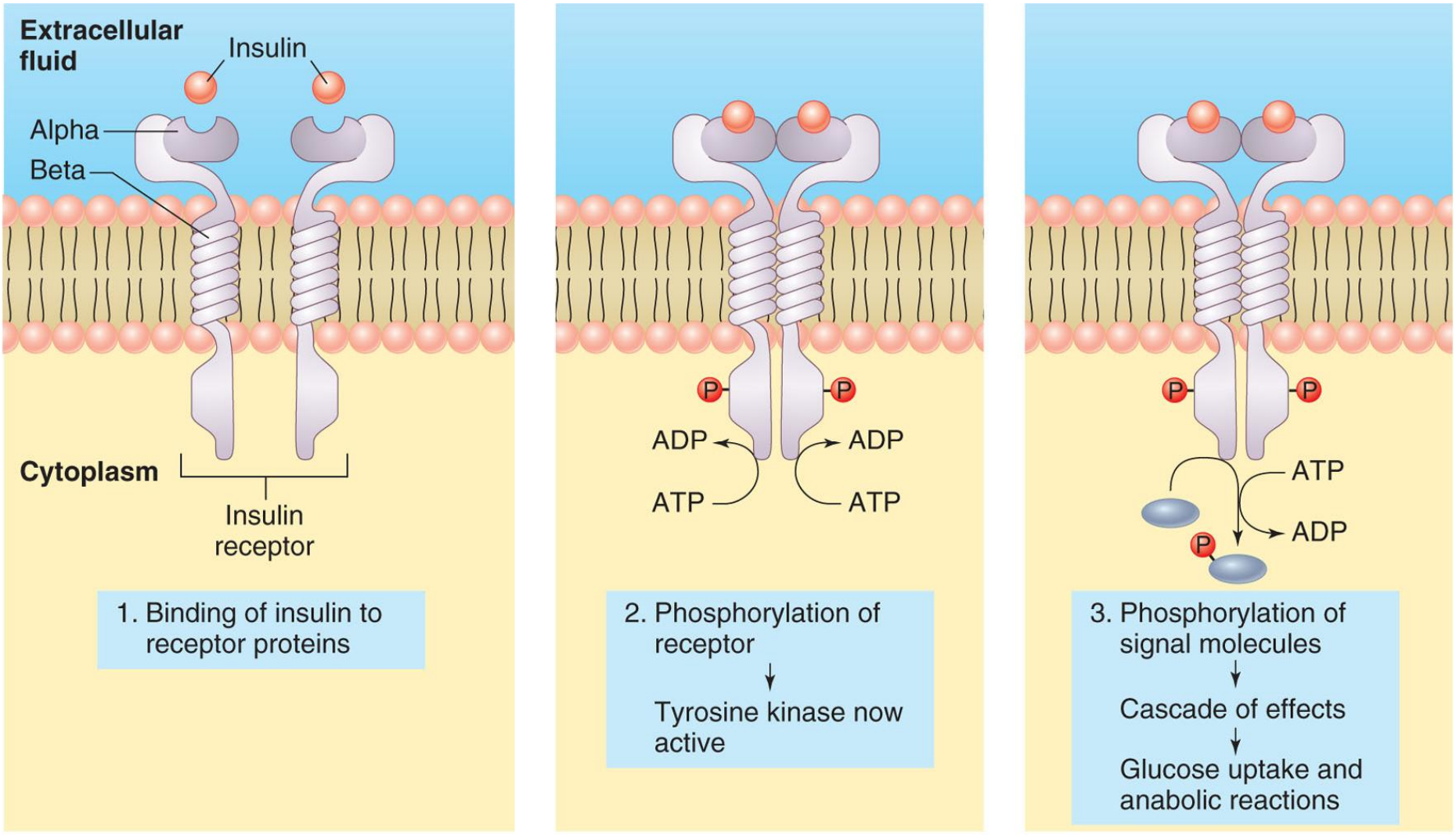
- Activates ***second messenger*** system
  - --Adenylate cyclase ex.Epi, NE (β)
  - --Phospholipase C ex.Epi (α)
  - --Tyrosine kinase ex.insulin
- ***Amplification*** of original small signal

- **Responsiveness of target cell depends on**
  1. ***Hormone's concentration***
  2. ***Abundance of target cell receptors***
  3. ***Influence exerted by other hormones (hormone interactions)***



Mechanisms of Insulin Action

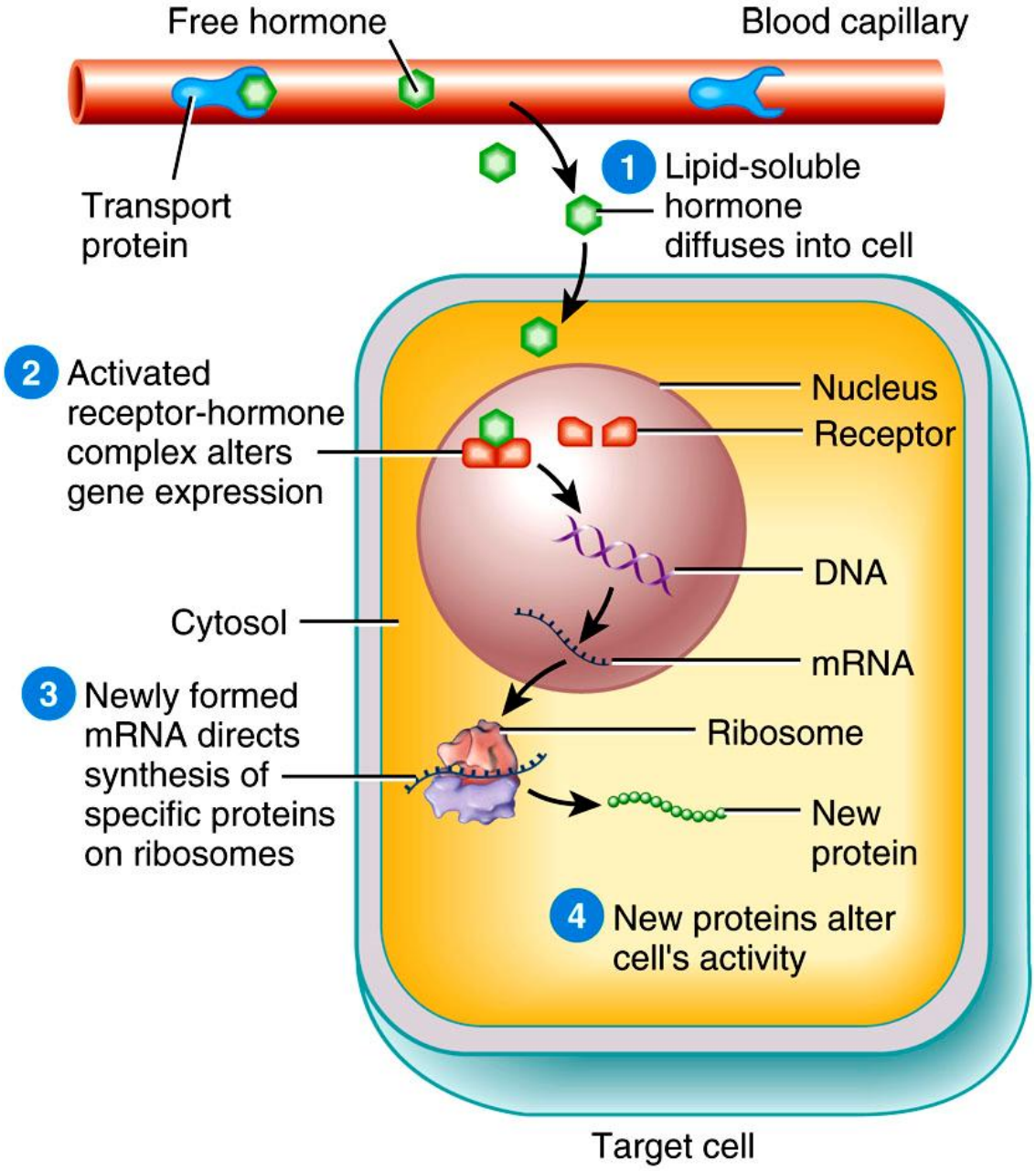
Tyrosine Kinase System



Mechanisms of Hormone Action

Action of Lipid-Soluble Hormones

- **Responsiveness of target cell depends on**
  1. ***Hormone's concentration***
  2. ***Abundance of target cell receptors***
  3. ***Influence exerted by other hormones (hormone interaction)***



Hormone Interactions

- **Antagonistic effect**

  --Effects of hormones oppose each other (1+1<2)

  --Example: **Glucagon vs. insulin; PTH vs. calcitonin**

- **Additive effect**

  --1+1=2

  --Example: **Epinephrine and norepinephrine** each affect the heart in the same way

- **Synergistic effect**

  --1+1>2

  --Example: **Glucagon, cortisol, and epinephrine** on blood glucose

- **Permissive effect**

  --One hormone makes the target cell more responsive to a second hormone

  --Examples: **T3/T4** cause expression of **adrenergic receptors** in bronchiolar smooth muscle; **Estrogen** causes expression of **progesterone receptors** in uterus

Hormone Characteristics

1. **The half-life of hormones circulating in the blood ranges from minutes to hours**
   - --Most hormones are removed from the blood by the **liver**
   - --Thyroid hormone circulates for several days
2. **Tissues only respond when hormone concentrations are at a certain "normal" level**
   - --At higher pharmacological concentrations, effects may be different from normal
   - --High concentrations may result in binding to receptors of related hormones
   - --This can result in **widespread side effects**

Hormone Characteristics

3. **Some target cells respond to a particular hormone by increasing the number of receptors it has for that hormone (upregulation)**

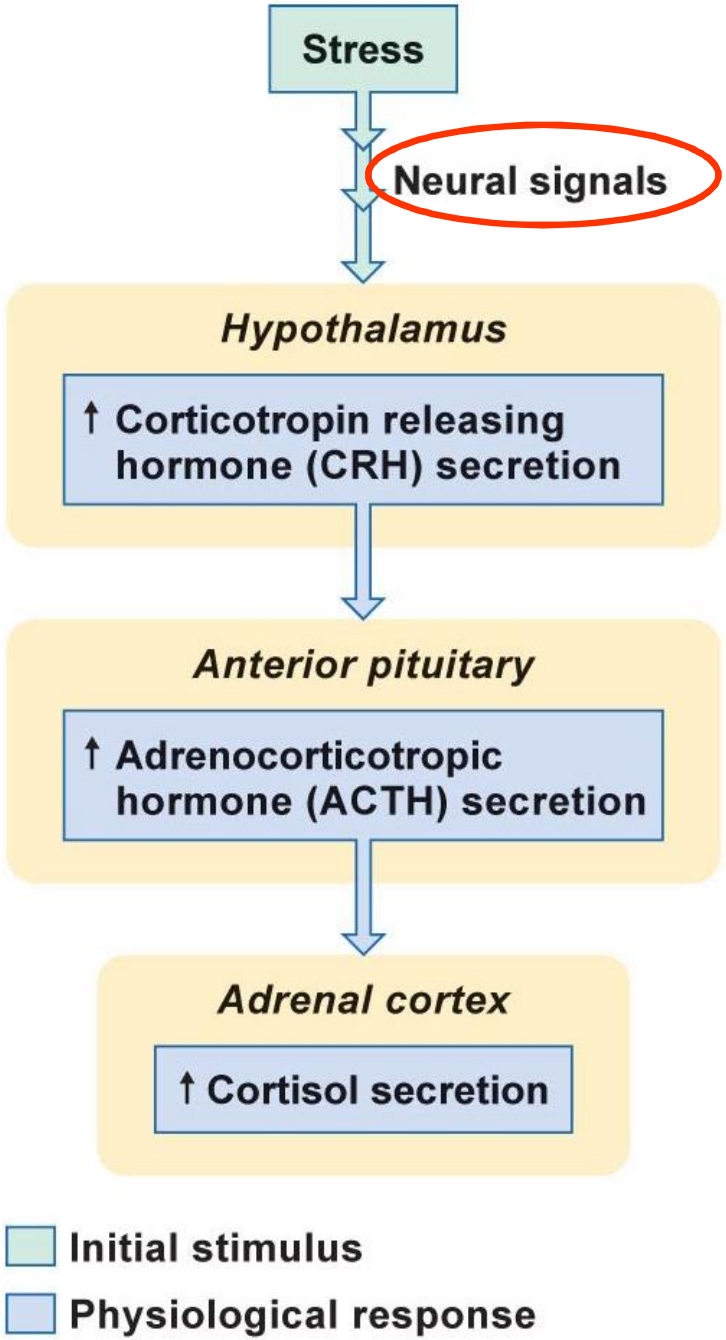
   --This makes it more sensitive to subsequent hormone release

4. **Prolonged exposure to high concentrations of hormone may result in a decreased number of receptors for that hormone (downregulation)**

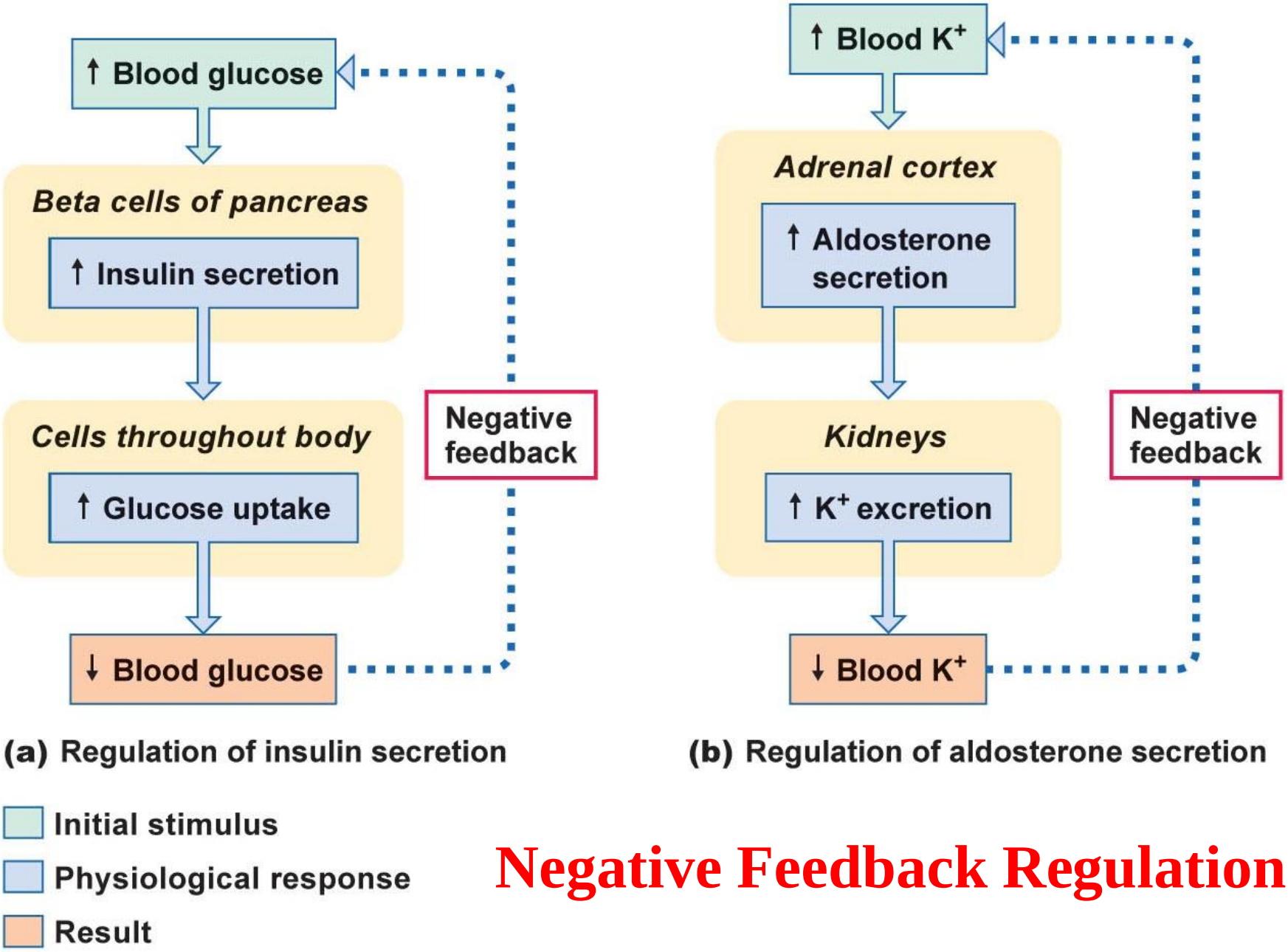
   --Occurs in adipose cells in response to high concentrations of insulin

5. **To avoid desensitization, many hormones are released in spurts, called pulsatile secretion**

Neural Control of Hormone Release



Humoral Control of Hormone Release



Negative Feedback Regulation

Hormonal Control by a Circadian Rhythm

- **Neural control of circadian rhythm**
  --Suprachiasmatic nucleus of the hypothalamus
- **Hormonal control of circadian rhythm**
  --**Melatonin**/Pineal Gland
  --Resets daily cycle based on light stimulus
- **All hypothalamic hormones affected by circadian rhythm from suprachiasmatic nucleus (SCN)**

Transport of Hormones

- **Hydrophilic (Water-Soluble) hormones**
  - --Peptides, catecholamines
  - --Dissolved in plasma
- **Hydrophobic (Lipid-Soluble) hormones**
  - --Steroids, thyroid hormones
  - --Bound to carrier proteins
  - --Only free hormone can bind to receptor
  - --Only free hormone can be metabolized
  - --Longer half-life

Rate of Hormone Metabolism

- **Sites of hormone metabolism**
  - --Target cell
  - --Blood
  - --Liver
- **Lipophilic hormones can be stored in adipose tissue**

Prohormones & Prehormones

- **Prohormones前激素are inactive hormones that must be cut and spliced together to be active**

  --Example: insulin

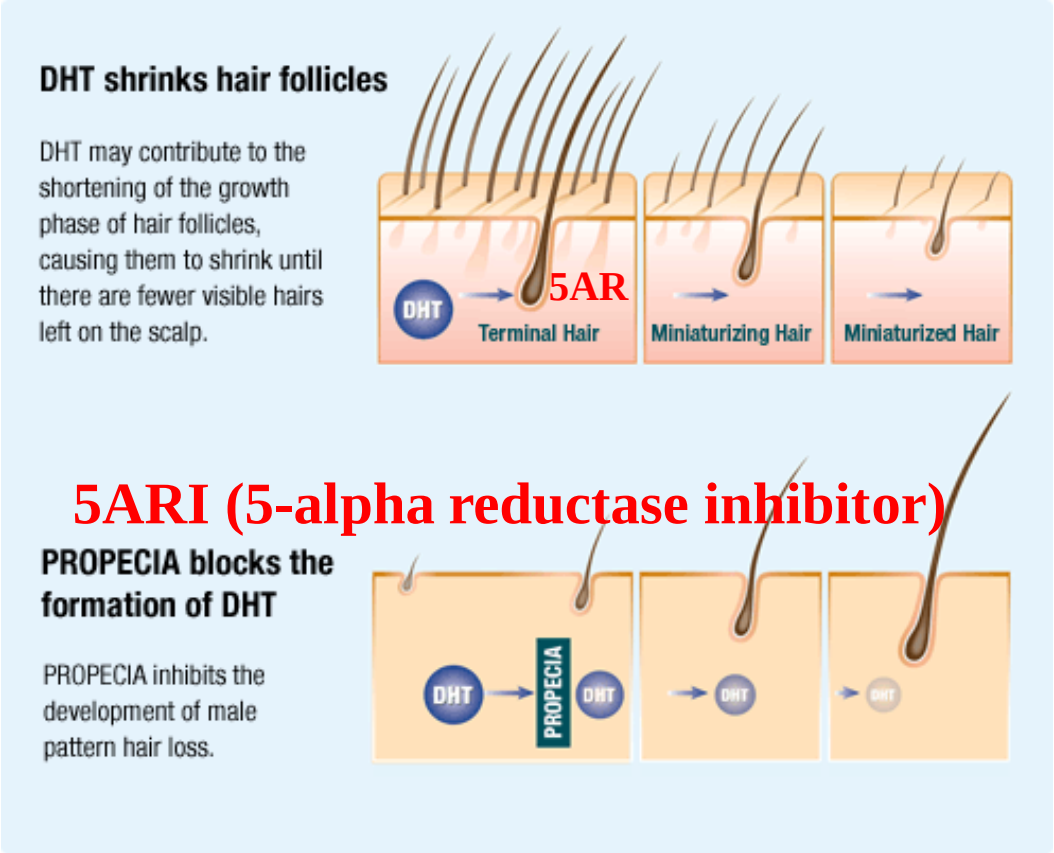
- **Prehormones前原激素are minimal biological activity or inactive hormones that must be modified within their target cells**

內分泌腺體	前原激素	活性產物	註解
皮膚	維生素 D_3(Vitamin D_3)	1,25－二羥維生素 D_3	水解反應發生在肝臟和腎臟
睪丸	睪固酮 —5AR→	二氫睪固酮 (Dihydrotestosterone, DHT)	DHT 和其它的 5α－還原態的雄性素在大多數的雄性素依賴的組織被形成
	睪固酮 —Aromatase→	雌二醇 (Estradiol-17β, E_2)	E_2 在腦中是從睪固酮所形成，它被認為同時影響內分泌的功能和行為睪丸亦可製造少量
5α-Reductase (5AR)			
甲狀腺	甲狀腺素 (T_4)	三碘甲狀腺素 (T_3)	幾乎所有的組織均可將 T_4 轉換成 T_3

➢ ***Aromatase inhibitors (AIs): E2↓ used in the treatment of breast cancer and ovarian cancer in postmenopausal women***

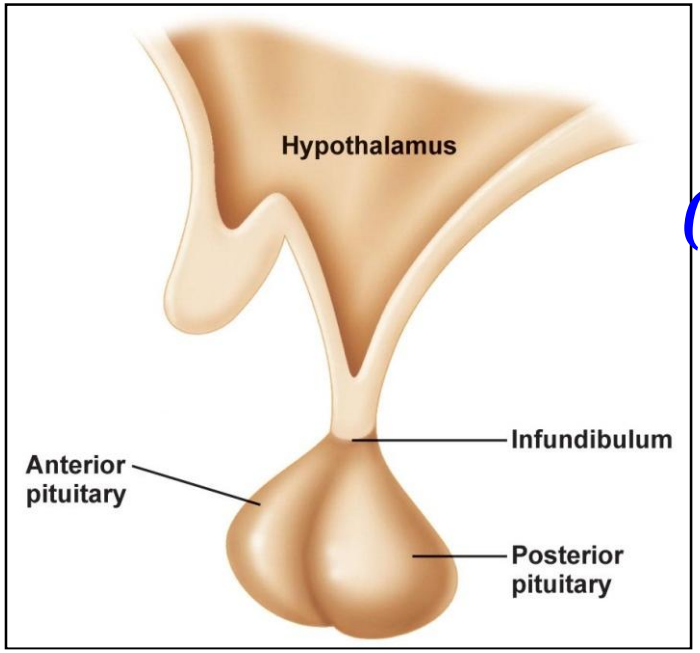
Clinical Application: Propecia

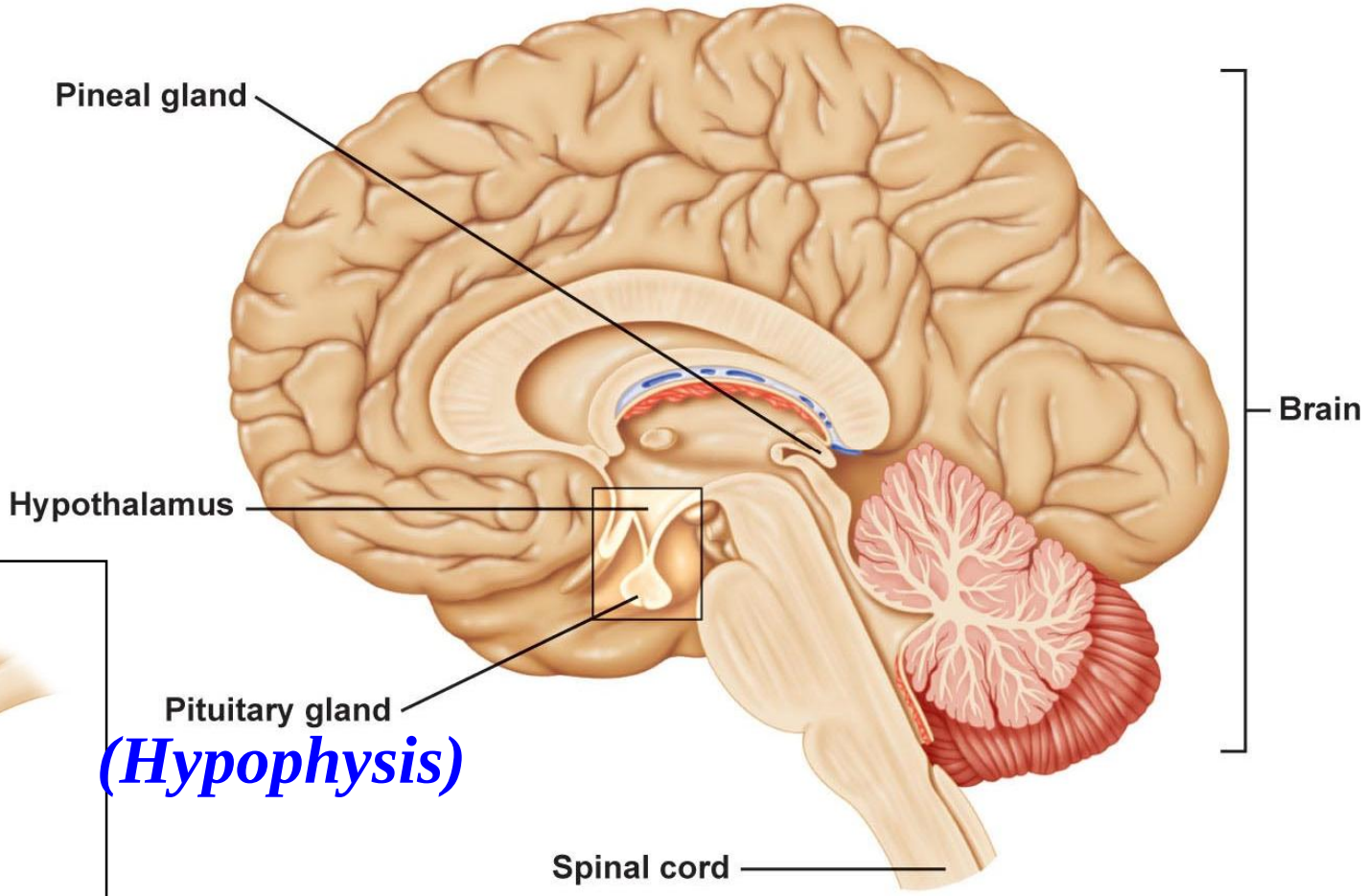
Testosterone —**5α-Reductase (5AR)**→ **DHT**



- **Finasteride (Propecia柔沛): 5ARI**
  - --***Benign prostatic hyperplasia (BPH)***
  - --***Male pattern baldness***

Hypothalamus and Pituitary Gland

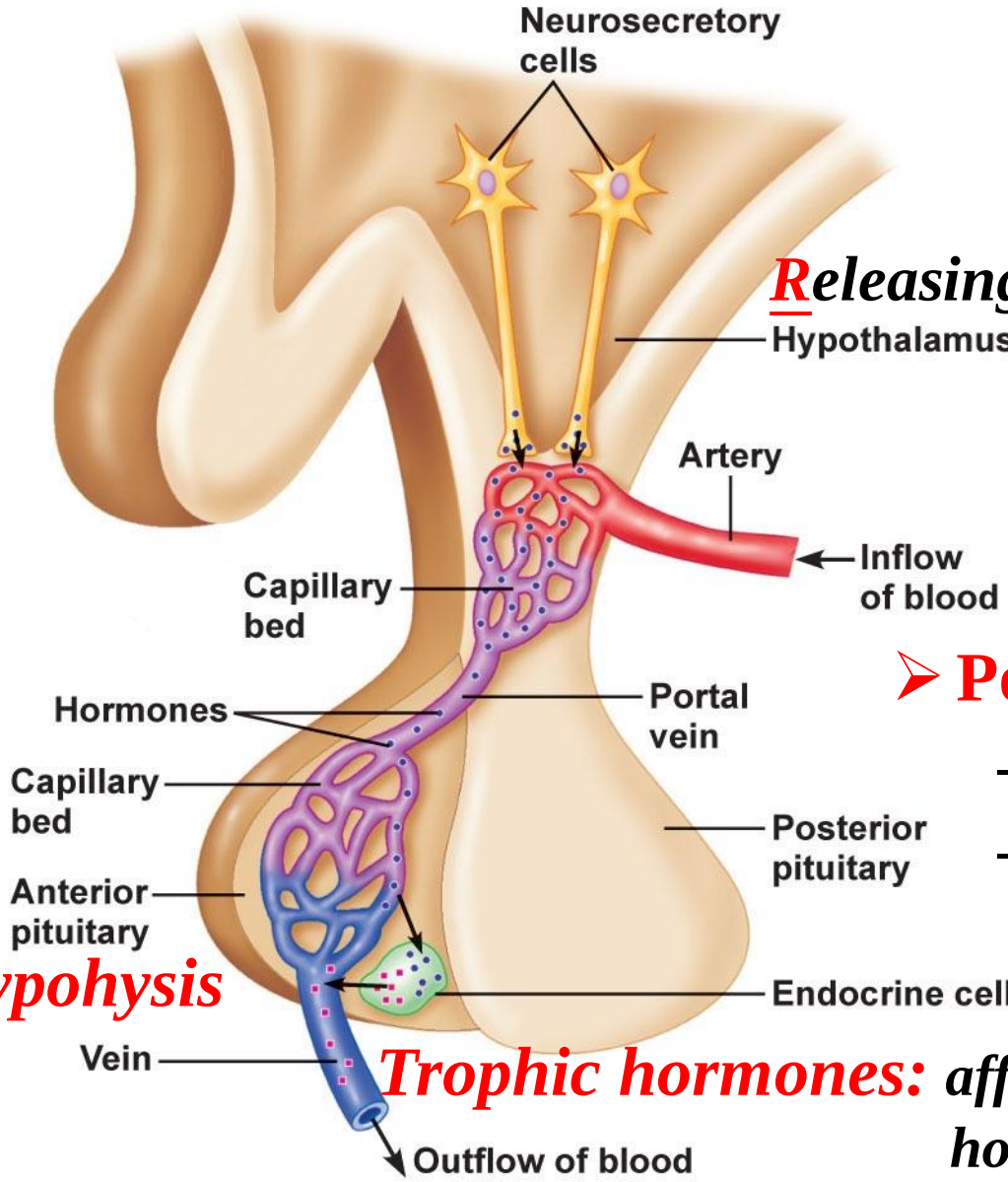




(Hypophysis)

Blood Connection to Anterior Pituitary

Hypothalamic-Hypophyseal Portal System

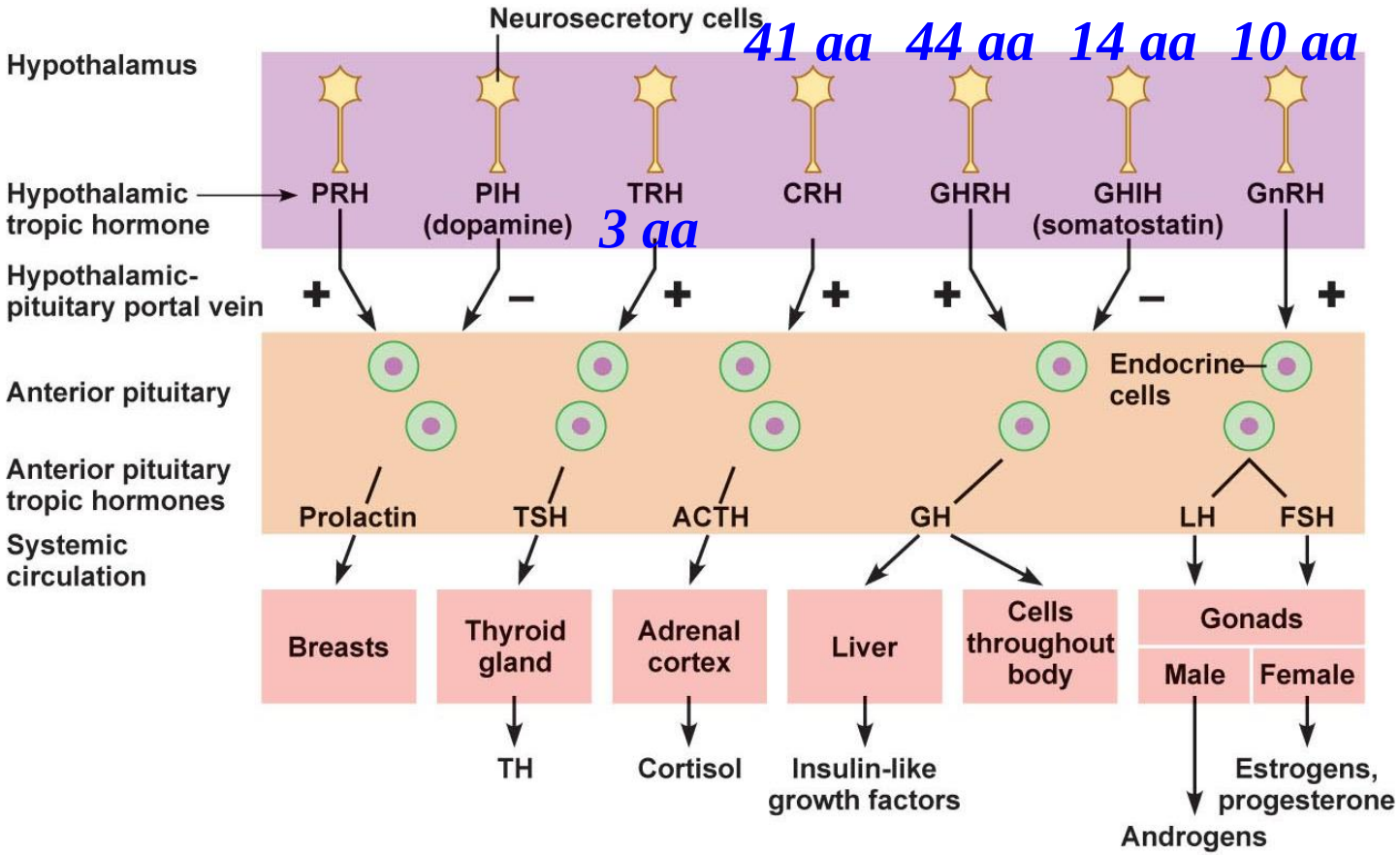


Releasing & Inhibiting hormones

- **Portal system**
  - --Links two capillary beds
  - --Exchange between blood and tissue occurs in capillaries

Adenohypohysis

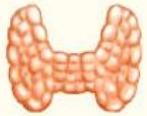
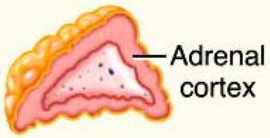
Trophic hormones: ***affect release of another hormone***



Hormones of the Anterior Pituitary

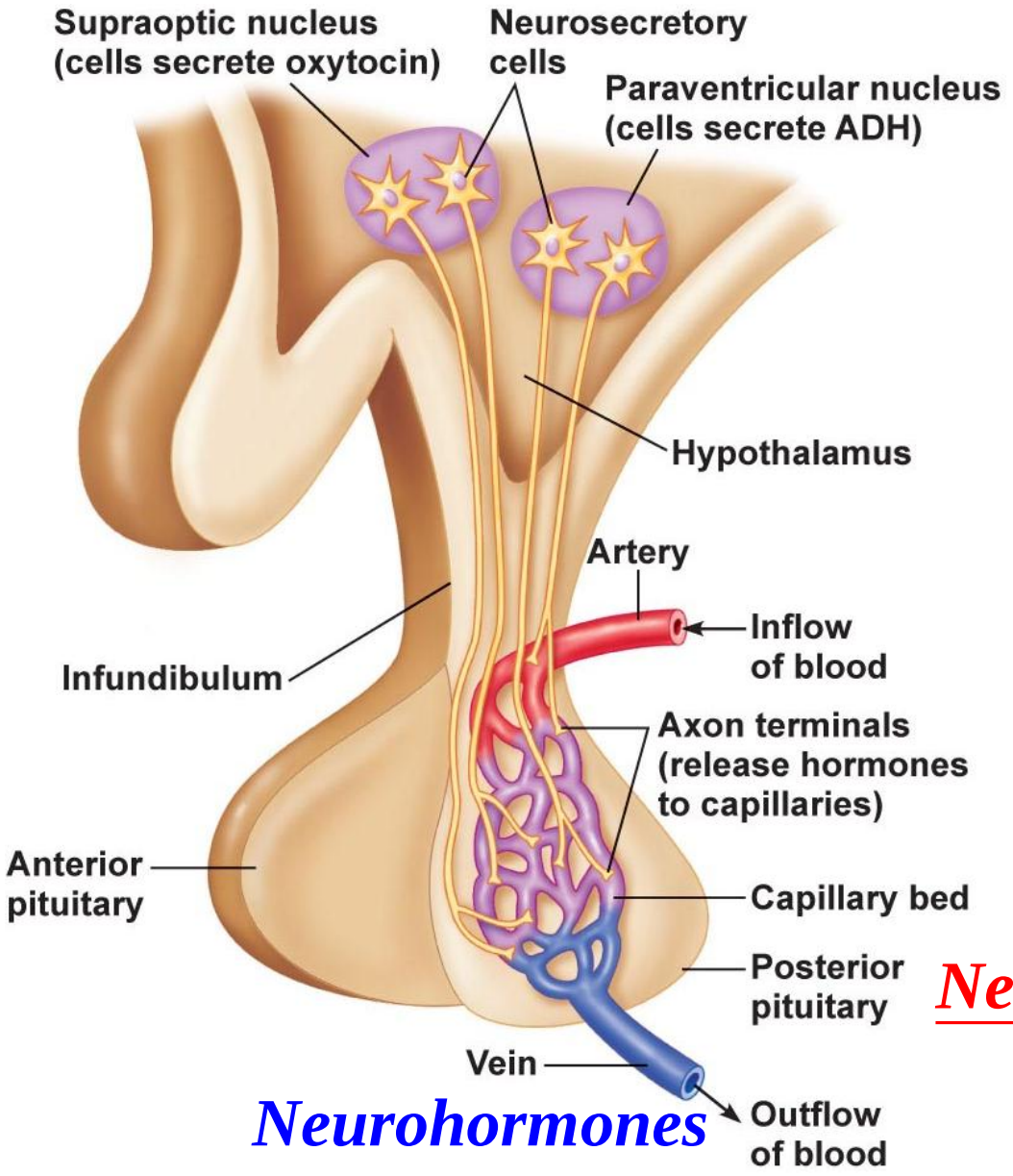
HORMONE	SECRETED BY	RELEASING HORMONE (STIMULATES SECRETION)	INHIBITING HORMONE (SUPPRESSES SECRETION)
Human growth hormone (hGH) or somatotropin	Somatotrophs.	Growth hormone–releasing hormone (GHRH), also known as somatocrinin.	Growth hormone–inhibiting hormone (GHIH), also known as somatostatin.
Thyroid-stimulating hormone (TSH) or thyrotropin	Thyrotrophs.	Thyrotropin-releasing hormone (TRH).	Growth hormone–inhibiting hormone (GHIH).
Follicle-stimulating hormone (FSH)	Gonadotrophs.	Gonadotropin-releasing hormone (GnRH).	—
Luteinizing hormone (LH)	Gonadotrophs.	Gonadotropin-releasing hormone (GnRH).	—
Prolactin (PRL)	Lactotrophs.	Prolactin-releasing hormone (PRH); TRH.	Prolactin-inhibiting hormone (PIH), which is dopamine.
Adrenocorticotropic hormone (ACTH) or corticotropin	Corticotrophs.	Corticotropin-releasing hormone (CRH).	—
Melanocyte-stimulating hormone	Corticotrophs.	Corticotropin-releasing hormone (CRH).	Dopamine.

Summary of the Principal Actions of Anterior Pituitary Hormones

HORMONE AND TARGET TISSUES	PRINCIPAL ACTIONS
Human growth hormone (hGH) or **somatotropin**  Liver	Stimulates liver, muscle, cartilage, bone, and other tissues to synthesize and secrete insulinlike growth factors (IGFs); IGFs promote growth of body cells, protein synthesis, tissue repair, lipolysis, and elevation of blood glucose concentration. ***IGFs=somatomedins***
Thyroid-stimulating hormone (TSH) or **thyrotropin**  Thyroid gland	Stimulates the synthesis and secretion of thyroid hormones by the thyroid gland.
Follicle-stimulating hormone (FSH)  Ovaries  Testes	In females, initiates development of oocytes and induces ovarian secretion of estrogens. In males, stimulates testes to produce sperm.
Luteinizing hormone (LH)  Ovaries  Testes	In females, stimulates secretion of estrogens and progesterone, ovulation, and formation of corpus luteum. In males, stimulates testes to produce testosterone. ***LH=Interstitial cell stimulating hormone (ICSH)***
Prolactin (PRL)  Mammary glands	Together with other hormones, promotes milk secretion by the mammary glands.
Adrenocorticotropic hormone (ACTH) or **corticotropin**  Adrenal cortex	Stimulates secretion of glucocorticoids (mainly cortisol) by the adrenal cortex.
Melanocyte-stimulating hormone (MSH)  Brain	Exact role in humans is unknown but may influence brain activity; when present in excess, can cause darkening of skin.

Neural Connection to Posterior Pituitary

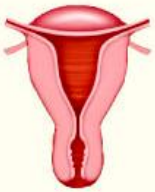
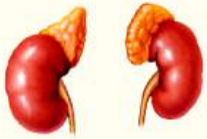
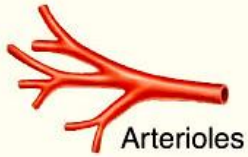
Hypothalamic-Hypophyseal Tract



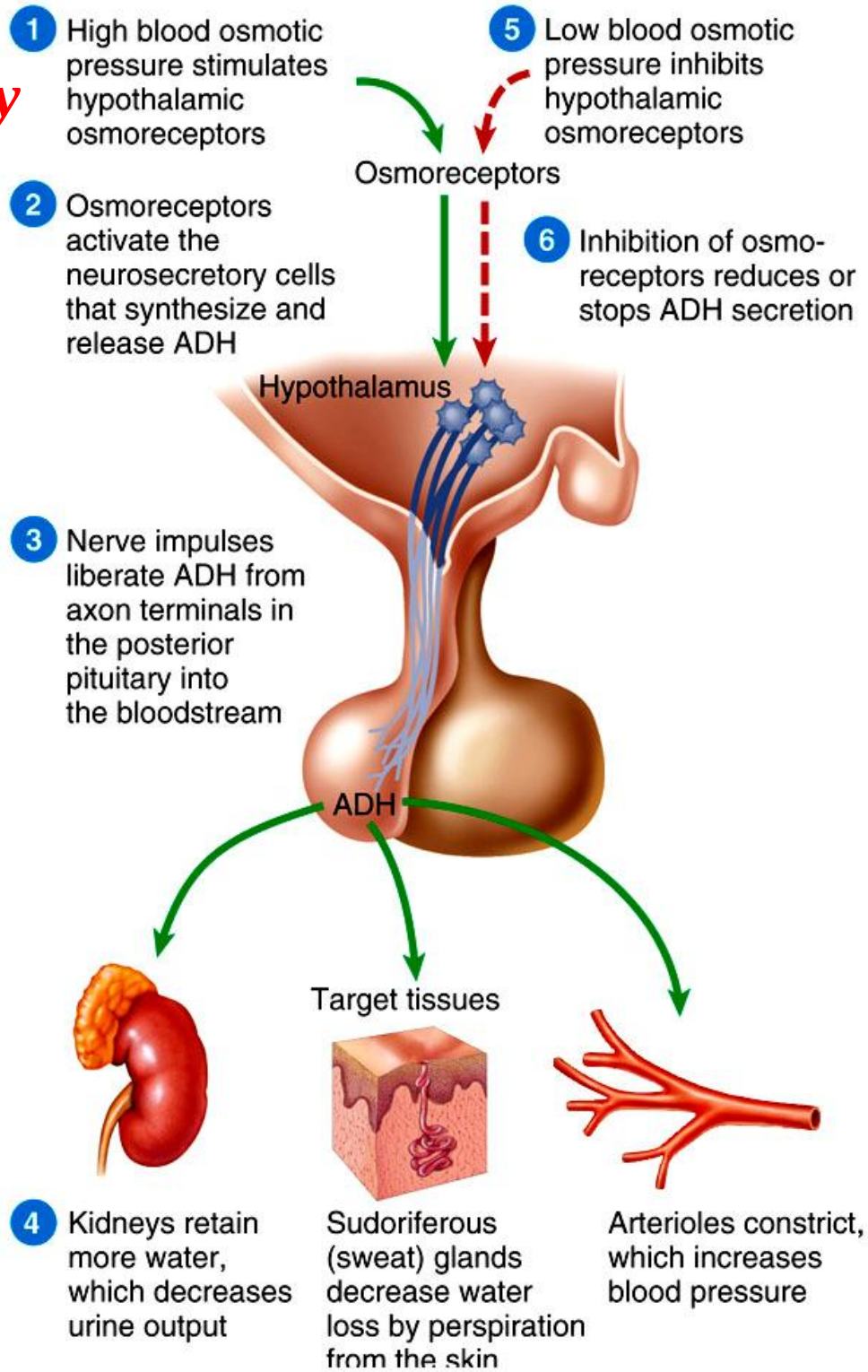
Neurohypophysis

Neurohormones

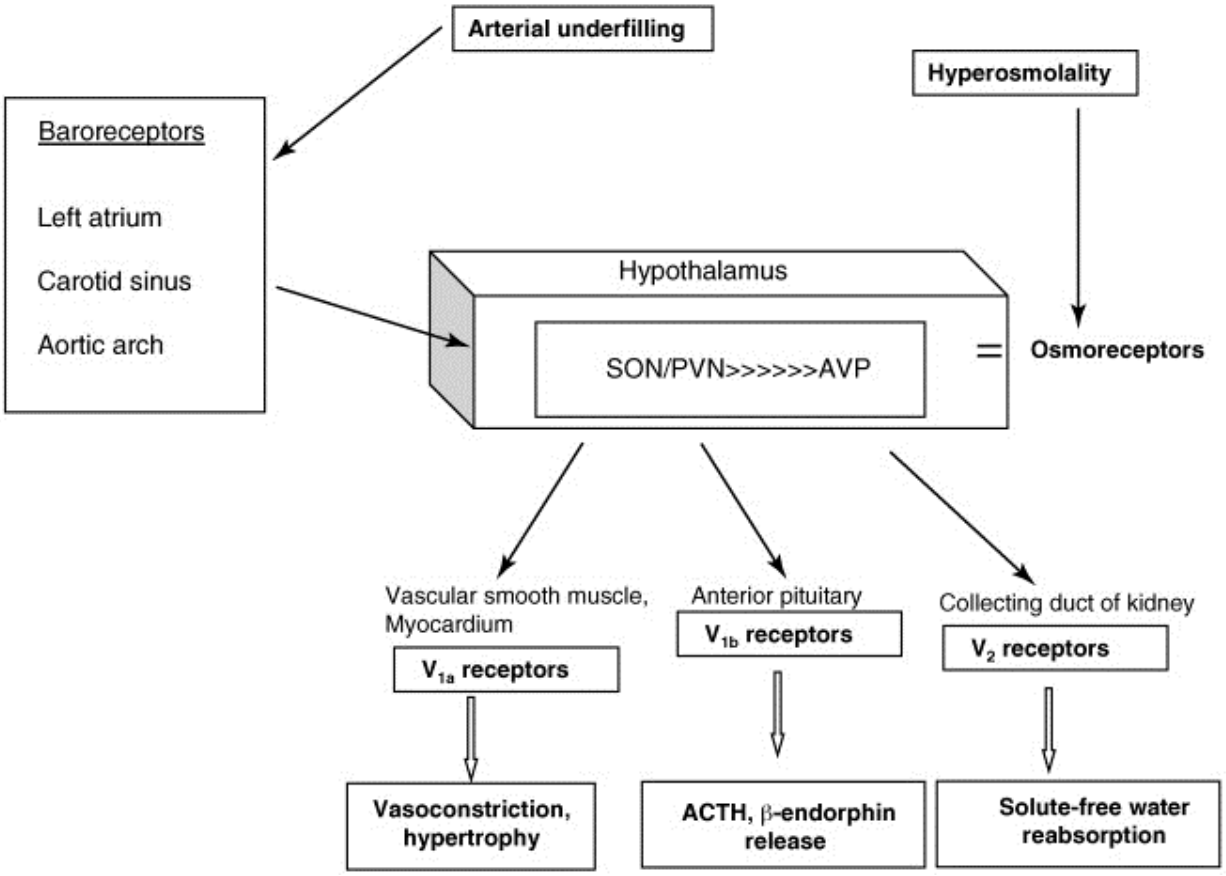
Summary of Posterior Pituitary Hormones

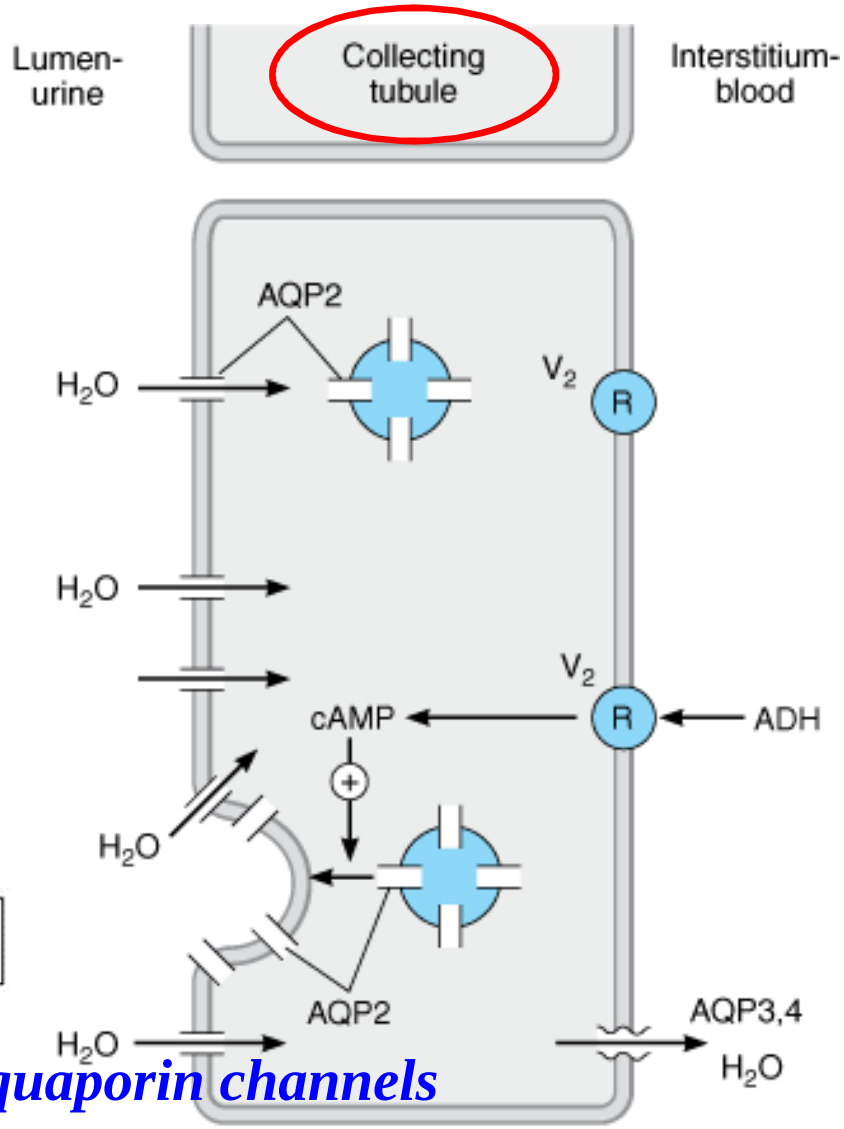
HORMONE AND TARGET TISSUES	CONTROL OF SECRETION	PRINCIPAL ACTIONS
Oxytocin (OT) *8 aa*  Uterus  Mammary glands	Neurosecretory cells of hypothalamus secrete OT in response to uterine distention and stimulation of nipples.	Stimulates contraction of smooth muscle cells of the uterus during childbirth; stimulates contraction of myoepithelial cells in the mammary glands to cause milk ejection.
Antidiuretic hormone (ADH) or vasopressin *8 aa*  Kidneys  Sudoriferous (sweat) glands  Arterioles	Neurosecretory cells of hypothalamus secrete ADH in response to elevated blood osmotic pressure, dehydration, loss of blood volume, pain, or stress; low blood osmotic pressure, high blood volume, and alcohol inhibit ADH secretion.	Conserves body water by decreasing urine volume; decreases water loss through perspiration; raises blood pressure by constricting arterioles.

Action of ADH (AVP)



Action of ADH (AVP)





Aquaporin channels

Endocrine Organs and Hormones

Organ	Hormones	Functions
Primary Endocrine Organs		
Hypothalamus	Releasing and release inhibiting hormones	Regulate secretion of anterior pituitary hormones
Anterior pituitary gland	Growth hormone (GH)	Essential for growth; stimulates bone and soft tissue growth; regulates protein, lipid, and carbohydrate metabolism
	Adrenocorticotropic hormone (ACTH)	Stimulates glucocorticoid secretion by the adrenal cortex
	Thyroid stimulating hormone (TSH)	Stimulates secretion of thyroid hormones by the thyroid gland
	Prolactin	Stimulates development of breasts and milk secretion by the mammary glands
	Follicle stimulating hormone (FSH)	Females: stimulates growth and development of ovarian follicles, estrogen secretion; males: stimulates sperm production by the testis
	Luteinizing hormone (LH)	Females: stimulates ovulation, transformation of ovarian follicle into corpus luteum, and secretion of estrogen and progesterone; males: stimulates testosterone secretion by the testis
Posterior pituitary gland	Antidiuretic hormone (ADH, or vasopressin)	Decreases urine output by the kidneys; promotes constriction of blood vessels (arterioles)
	Oxytocin	Females: stimulates uterine contractions and milk ejection by mammary glands; males: function unknown

Endocrine Organs and Hormones

Organ	Hormones	Functions
Primary Endocrine Organs		
Pineal gland	Melatonin	Regulates biological rhythms according to day-night cycles
Thymus	Thymosin	Stimulates proliferation and function of T lymphocytes
Thyroid gland	Thyroid hormones (triiodothyronine and tetraiodothyronine)	Increase basal metabolic rate; necessary for normal development
	Calcitonin	Promotes calcium deposition in bone; lowers blood calcium levels
Parathyroid glands	Parathyroid hormone (PTH)	Promotes calcium release from bone, calcium absorption by intestine, and calcium reabsorption by kidney tubules; raises blood calcium levels; stimulates vitamin D_3 synthesis
Adrenal cortex	Mineralocorticoids (aldosterone)	Stimulate sodium reabsorption and potassium secretion by kidney tubules
	Glucocorticoids (cortisol, corticosterone)	Promote catabolism of proteins and fats; raise blood glucose levels; adapt the body to stress
	Androgens (dehydroepiandrosterone, androstenedione)	Promote sex drive

Endocrine Organs and Hormones

Organ	Hormones	Functions
Primary Endocrine Organs		
Adrenal medulla	Epinephrine	Stimulates fight-or-flight response
Pancreas	Insulin	Lowers blood glucose levels; stores energy by promoting protein, lipid, and glycogen synthesis
	Glucagon	Raises blood glucose levels; mobilizes energy by promoting glycogenolysis, gluconeogenesis
	Somatostatin	Inhibits secretion of pancreatic hormones; regulates digestion and absorption of nutrients by gastrointestinal system
Gonads		
Testes	Androgens (testosterone, androstenedione)	Necessary for sperm production by testis; promote sex drive and development of secondary sex characteristics (facial hair, deep voice, etc.)
Ovaries	Estrogens (estradiol)	Necessary for follicular development; promote development of secondary sex characteristics (breasts, body fat distribution, etc.)
	Progestins (progesterone)	Promote endometrial growth to prepare uterus for pregnancy
Placenta (during pregnancy)	Chorionic gonadotropin, estrogens, progesterone	Maintain corpus luteum; reinforce actions of hormones secreted by corpus luteum

hCG

Endocrine Organs and Hormones

Organ	Hormones	Functions
Secondary Endocrine Organs		
Heart	Atrial natriuretic peptide (ANP)	Inhibits sodium reabsorption by kidney tubules
Kidneys	Renin	Stimulates aldosterone secretion indirectly via the renin-angiotensin system
	Erythropoietin	Stimulates production of red blood cells in bone marrow
Gastrointestinal tract		
Stomach	Gastrin	Stimulates acid secretion by stomach and intestinal motility
Small intestine	Secretin, cholecystokinin (CCK), glucose-dependent insulinotropic peptide (GIP)	Regulate gastrointestinal motility and secretion; regulate exocrine secretion by liver and pancreas
Liver	Insulin-like growth factors (IGFs)	Promote bone and soft tissue growth
Skin, liver, kidney*	1,25-dihydroxy vitamin D_3	Promotes absorption of calcium by intestine

Calcitriol (active form of Vit D_3)

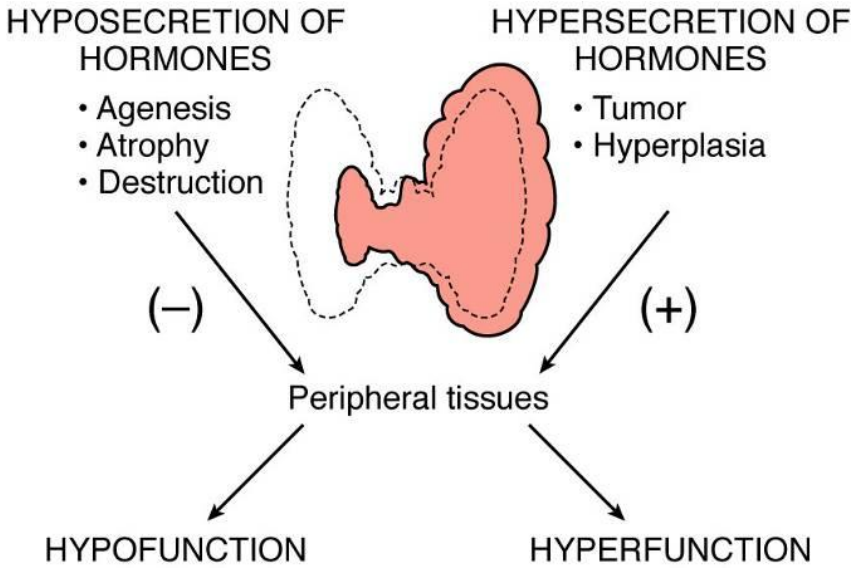
*The skin, liver, and kidney are all necessary for the activation of 1,25-dihydroxy vitamin D_3.

- ***IGFs=somatomedins***
- ***GHRH=somatocrinin***
- ***GHIH=somatostatin***

Endocrine Gland	Major Hormones	Primary Target Organs	Primary Effects
Adipose tissue	Leptin	Hypothalamus	Suppresses appetite
Adrenal cortex	Glucocorticoids Aldosterone	Liver and muscles Kidneys	Glucocorticoids influence glucose metabolism; aldosterone promotes Na^+ retention, K^+ excretion
Adrenal medulla	Epinephrine	Heart, bronchioles, and blood vessels	Causes adrenergic stimulation
Heart	Atrial natriuretic hormone	Kidneys	Promotes excretion of Na^+ in the urine
Hypothalamus	Releasing and inhibiting hormones	Anterior pituitary	Regulates secretion of anterior pituitary hormones
Small intestine	Secretin and cholecystokinin	Stomach, liver, and pancreas	Inhibits gastric motility and stimulates bile and pancreatic juice secretion
Islets of Langerhans (pancreas)	Insulin Glucagon	Many organs Liver and adipose tissue	Insulin promotes cellular uptake of glucose and formation of glycogen and fat; glucagon stimulates hydrolysis of glycogen and fat
Kidneys	Erythropoietin	Bone marrow	Stimulates red blood cell production
Liver	Somatomedins	Cartilage	Stimulates cell division and growth
Ovaries	Estradiol-17β and progesterone	Female reproductive tract and mammary glands	Maintains structure of reproductive tract and promotes secondary sex characteristics
Parathyroid glands	Parathyroid hormone	Bone, small intestine, and kidneys	Increases Ca^{2+} concentration in blood
Pineal gland	Melatonin	Hypothalamus and anterior pituitary	Affects secretion of gonadotrophic hormones
Pituitary, anterior	Trophic hormones	Endocrine glands and other organs	Stimulates growth and development of target organs; stimulates secretion of other hormones
Pituitary, posterior	Antidiuretic hormone Oxytocin	Kidneys and blood vessels Uterus and mammary glands	Antidiuretic hormone promotes water retention and vasoconstriction; oxytocin stimulates contraction of uterus and mammary secretory units
Skin	1,25-Dihydroxyvitamin D_3	Small intestine	Stimulates absorption of Ca^{2+}
Stomach	Gastrin	Stomach	Stimulates acid secretion
Testes	Testosterone	Prostate, seminal vesicles, and other organs	Stimulates secondary sexual development
Thymus	Thymopoietin	Lymph nodes	Stimulates white blood cell production
Thyroid gland	Thyroxine (T_4) and triiodothyronine (T_3); calcitonin	Most organs	Thyroxine and triiodothyronine promote growth and development and stimulate basal rate of cell respiration (basal metabolic rate or BMR); calcitonin may participate in the regulation of blood Ca^{2+} levels

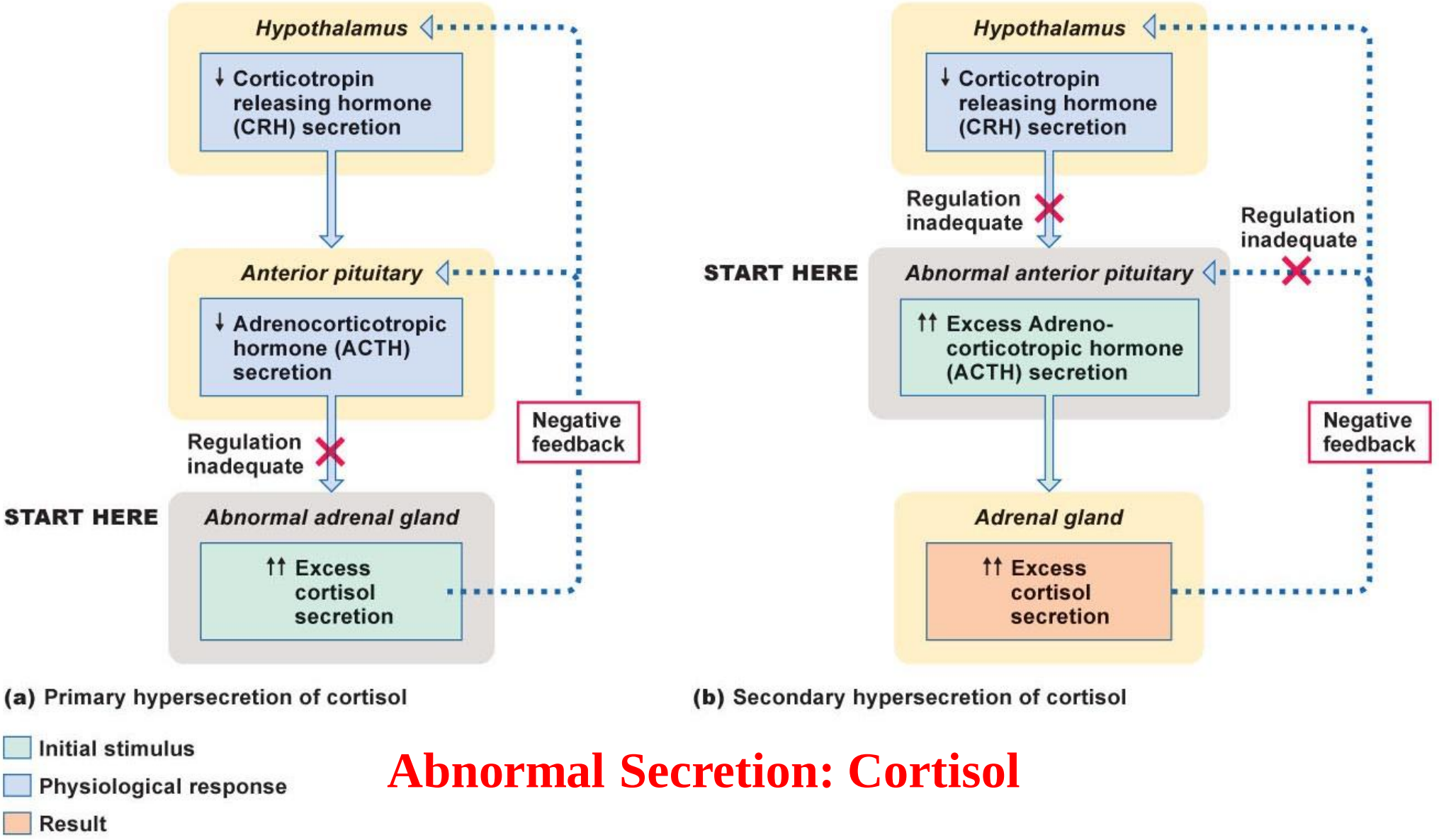
Types of Endocrine Disorders

- **Hormone levels must be kept in balance**
- **Pathologies**
  - ***1. Hyposecretion:*** too little
  - ***2. Hypersecretion:*** too much
  - ***3. Abnormal tissue responsiveness***
    - --Normal hormone levels
    - --Tissue responds inappropriately



- **Primary Secretion Disorders**
  - **--Abnormality in endocrine organ secreting hormone**
- **Secondary Secretion Disorders**
  - **--Abnormality in tropic hormone**
    - Hypothalamic hormone
    - Anterior pituitary tropic hormone

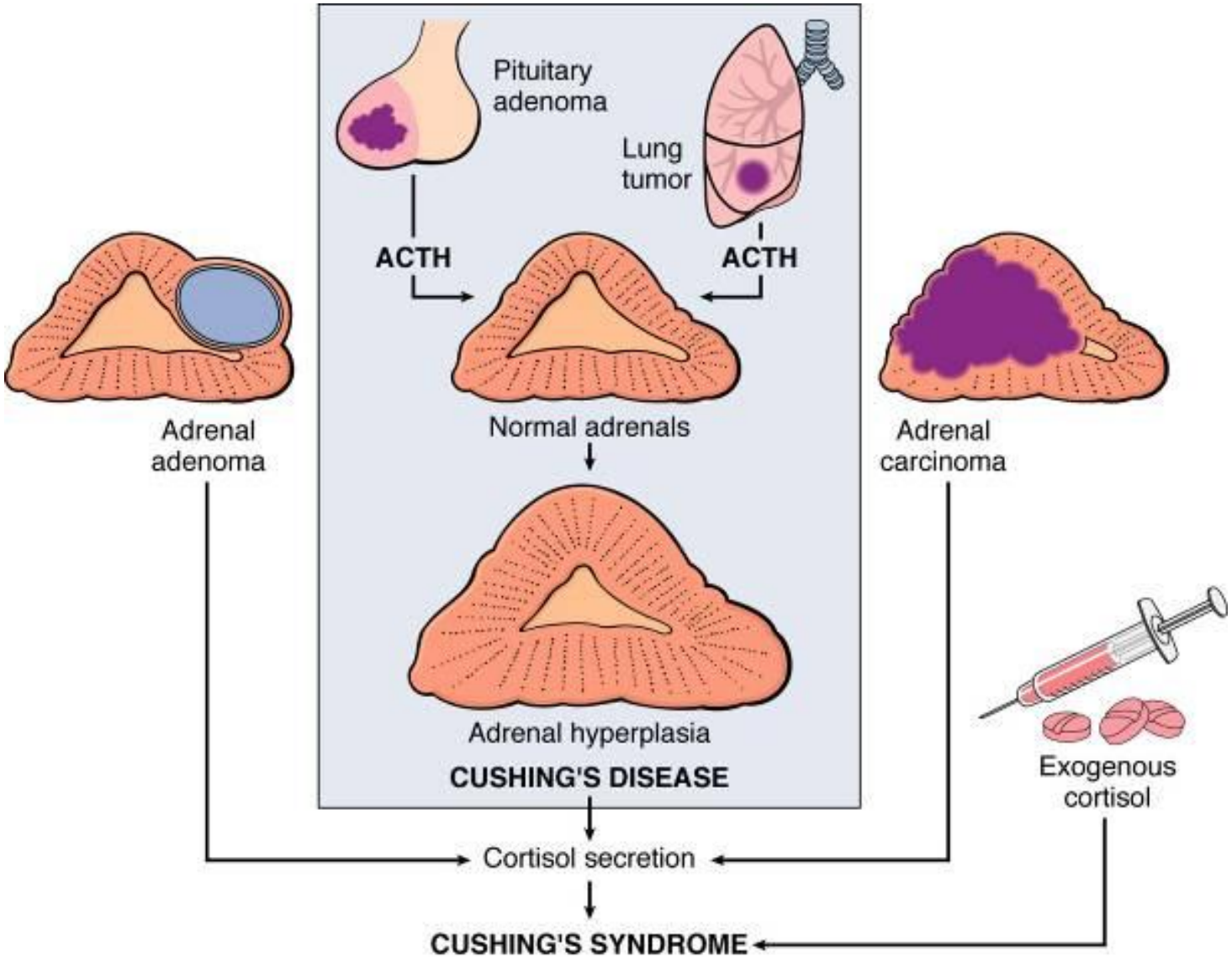
Primary vs. Secondary Secretion Disorders: Cushing's Syndrome



Abnormal Secretion: Cortisol

Causes of Cushing's Syndrome

Abnormal Secretion: Cortisol



hGH Secretion Disorders:

一臨床焦點一

Clinical Focus

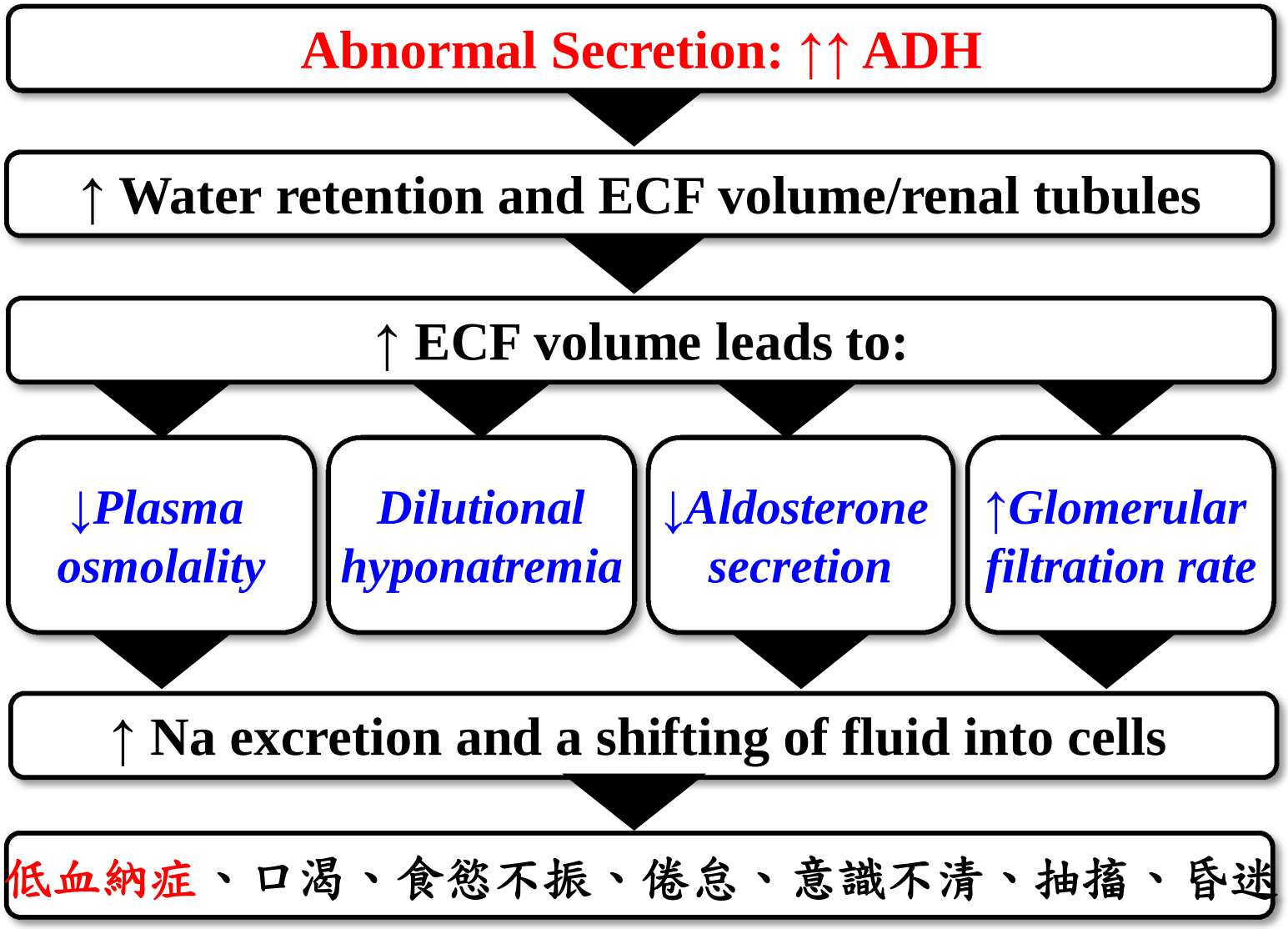
生長激素分泌異常

在幼年時，如果生長激素分泌不足，會導致生長發育遲緩，身體長得特別矮小，造成垂體性侏儒症 (pituitary dwarfism)，又稱為**侏儒症** (dwarfism)；如果生長激素分泌過多，可引起全身各部過度生長，骨骼生長尤為顯著，致使身材異常高大，稱**巨人症** (gigantism)。

在成人時期，生長激素分泌不足會造成垂體性惡病質 (pituitary cachexia)，又稱為 Simmonds 氏症 (Simmonds' disease)，此疾病的特徵之一是由於組織萎縮造成提早老化。成年後，骨骺已融合，長骨不再生長，此時如果生長激素分泌過多，將刺激肢端骨、顏面骨、軟組織等增生，表現為手、足、鼻、下頜、耳、舌以及肝、腎等內臟顯示出不相稱的增大，稱為**肢端肥大症** (acromegaly)。

ADH Secretion Disorders:

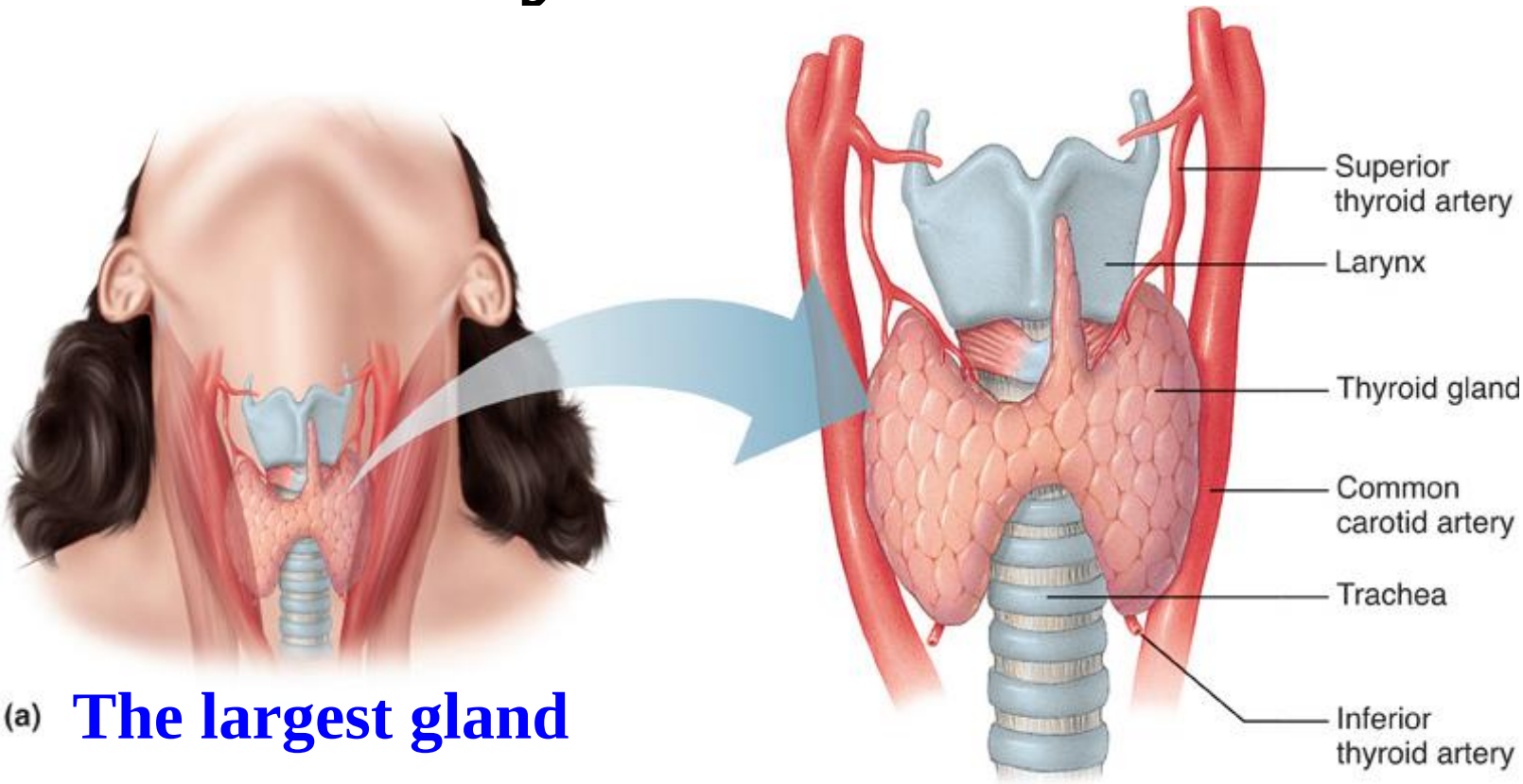
Syndrome of Inappropriate Antidiuretic Hormone (SIADH)



Syndrome of Inappropriate Antidiuretic Hormone (SIADH)

病因	舉例
Cancer	many tumours (most common is **small cell lung cancer**)
Brain disorders	meningitis, cerebral abscess, head injury, tumour
Lung diseases	pneumonia, tuberculosis, lung abscess
Metabolic disorders	porphyria, alcohol withdrawal
Endocrine diseases	hypothyroidism, hypoadrenalism
Drugs	TCA, SSRIs, general anesthetics, thiazide diuretics, oral hypoglycemics (chlorpropamide), narcotic analgesics (opiates), clofibrate, nicotine, carbamezapine, vincristine

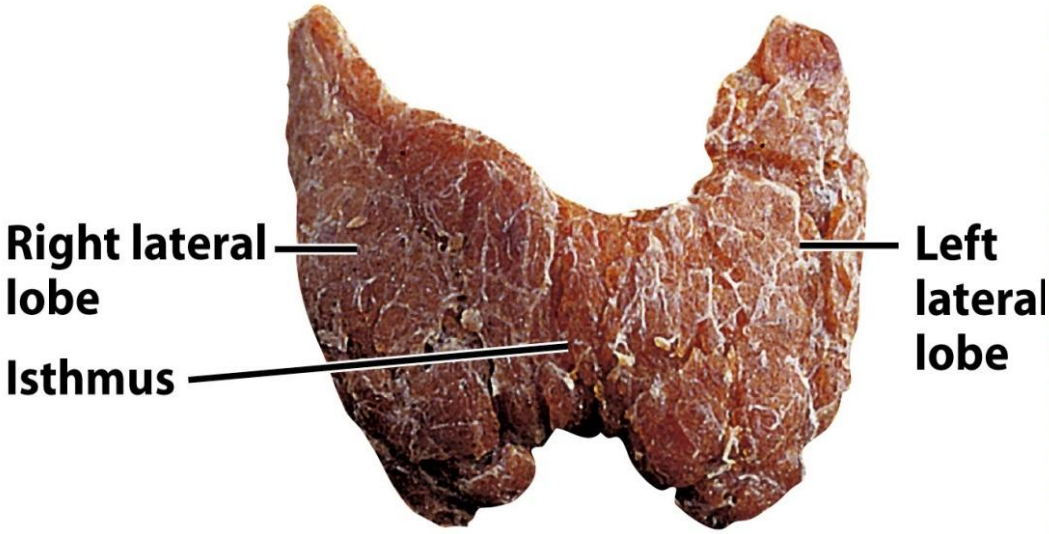
Thyroid Gland



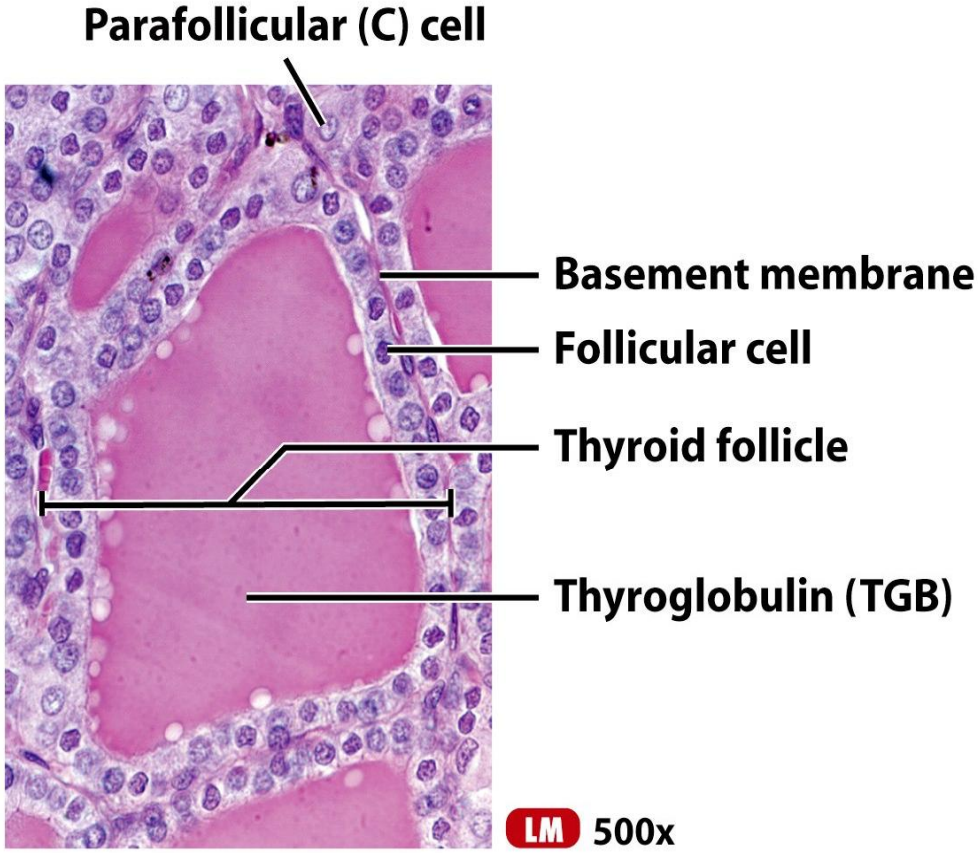
(a) **The largest gland**

- **Located just below the larynx in the neck (15-30 g)**
- **2 lobes connected by isthmus (*2-4 tracheal rings*)**
- **Thyroid follicles produce thyroid hormones**
  1. ***Thyroxine or tetraiodothyronine (T_4)***
  2. ***Triiodothyronine (T_3)***
- **Parafollicular cells or C cells produce *calcitonin***

Histology of Thyroid Gland



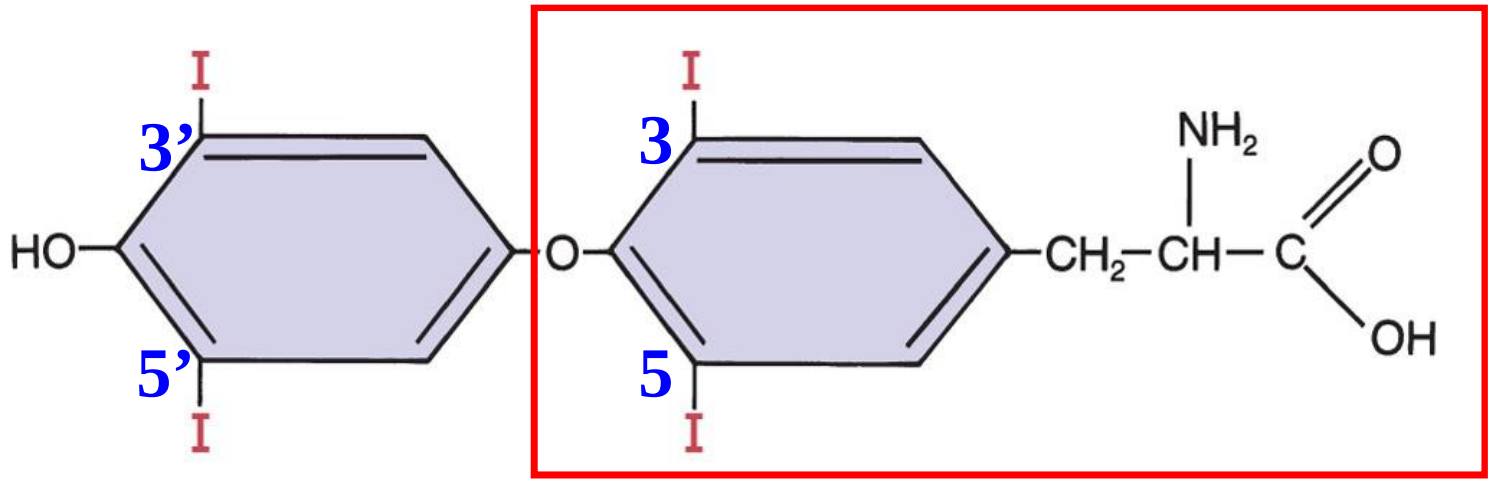
Anterior view of thyroid gland



Thyroid follicles

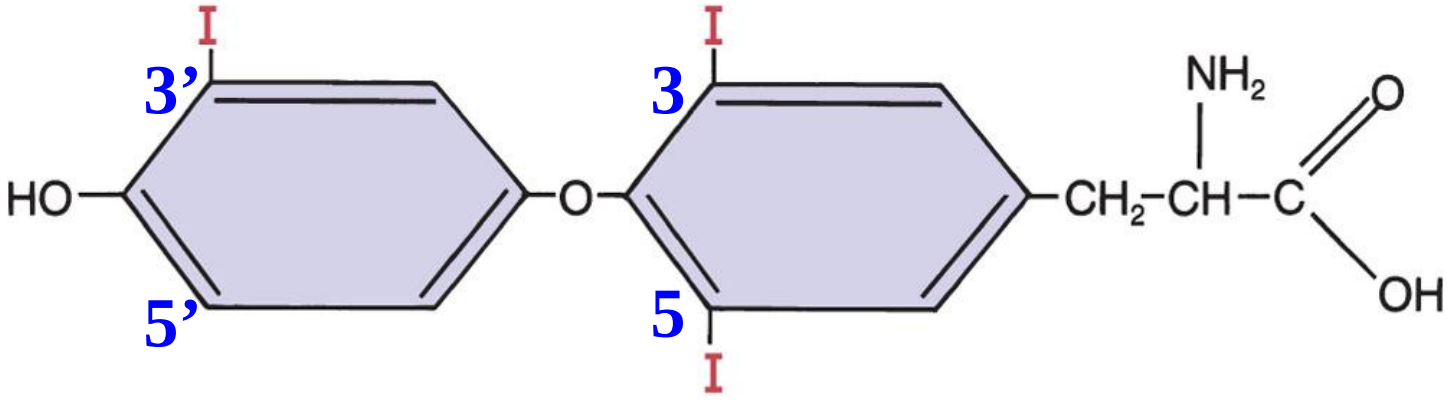
- Thyroid follicle = sac of stored hormone (**colloid**) surrounded by **follicle (follicular) cells** that produced it--**T3 & T4**
- Inactive cells are short
- In between cells called **parafollicular cells** --produce **calcitonin**

Structural Formulas for Thyroid Hormone



Thyroxine, or **tetraiodothyronine (T_4)**

I + Tyrosine residue



Triiodothyronine (T_3)

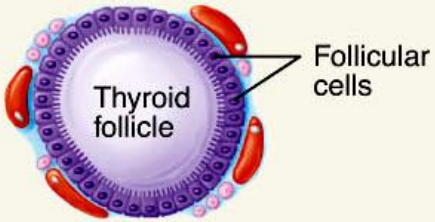
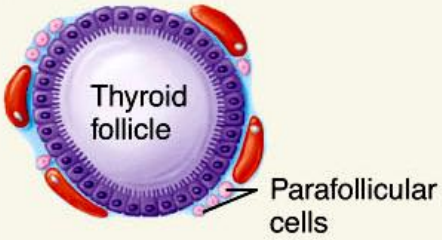
Thyroid Hormone

特性	T4	T3
I 的數目 (位置)	4個 (3，5，3’，5’)	3個 (3，5，3’)
生合成	DIT+DIT	MIT (monoiodide tyrosine; 一個碘的酪胺酸) +DIT(兩個碘的酪胺酸)
生物活性	1倍	4~5倍
Half-life(半衰期)	A week	A day
血中濃度	99.6%	0.35%
Free form	0.1	1
Binding affinity with TBG	10倍	1倍

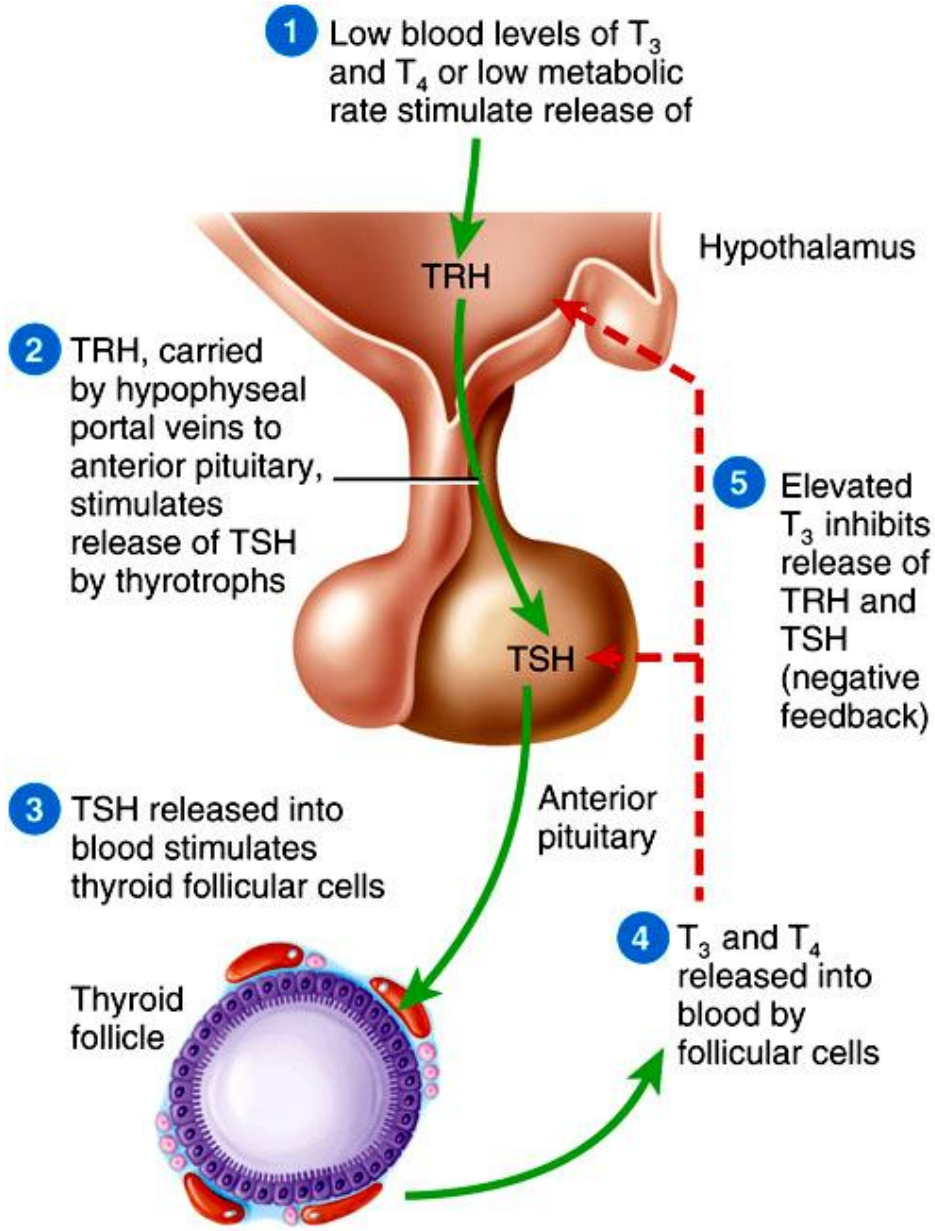
- ***TBG (thyroxine-binding globulin)*** T4 > T3
- TBPA (thyroxine-binding prealbumin) T4 > T3
- Albumin T4 < T3

Thyroid Hormone

Summary of Thyroid Gland Hormones

HORMONE AND SOURCE	CONTROL OF SECRETION	PRINCIPAL ACTIONS
T_3 (triiodothyronine) and **T_4 (thyroxine)** or **thyroid hormones** from follicular cells 	Secretion is increased by thyrotropin-releasing hormone (TRH), which stimulates release of thyroid-stimulating hormone (TSH) in response to low thyroid hormone levels, low metabolic rate, cold, pregnancy, and high altitudes; TRH and TSH secretions are inhibited in response to high thyroid hormone levels; high iodine level suppresses T_3/T_4 secretion.	Increase basal metabolic rate, stimulate synthesis of proteins, increase use of glucose and fatty acids for ATP production, increase lipolysis, enhance cholesterol excretion, accelerate body growth, and contribute to development of the nervous system.
Calcitonin (CT) from parafollicular cells 	High blood Ca^{2+} levels stimulate secretion; low blood Ca^{2+} levels inhibit secretion.	Lowers blood levels of Ca^{2+} and HPO_4^{2-} by inhibiting bone resorption by osteoclasts and by accelerating uptake of calcium and phosphates into bone extracellular matrix.

Control of Thyroid Hormone Secretion



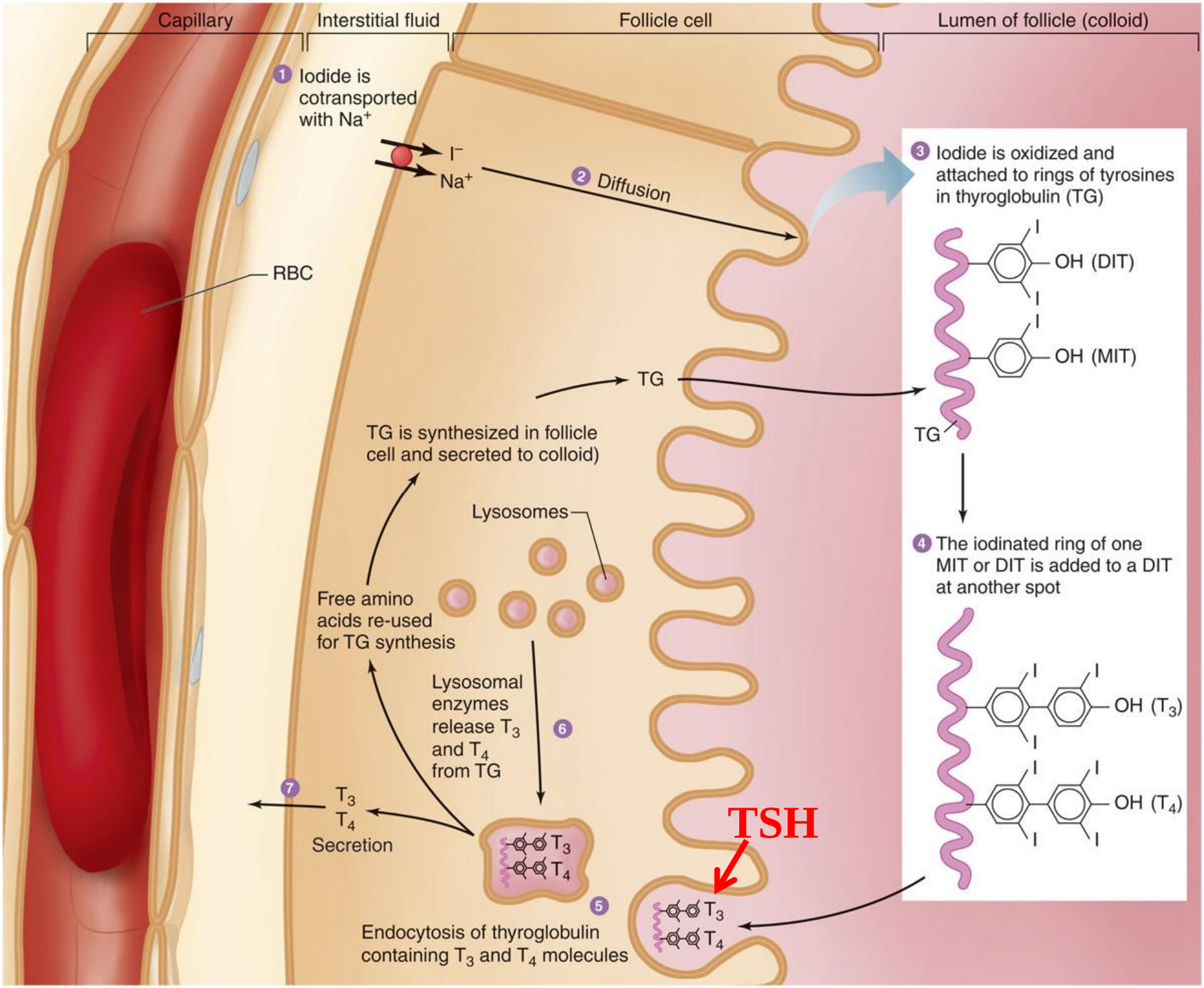
Actions of Thyroid Hormones:

- Increase basal metabolic rate
- Stimulate synthesis of Na^+/K^+ ATPase
- Increase body temperature (calorigenic effect)
- Stimulate protein synthesis
- Increase the use of glucose and fatty acids for ATP production
- Stimulate lipolysis
- Enhance some actions of catecholamines
- Regulate development and growth of nervous tissue and bones

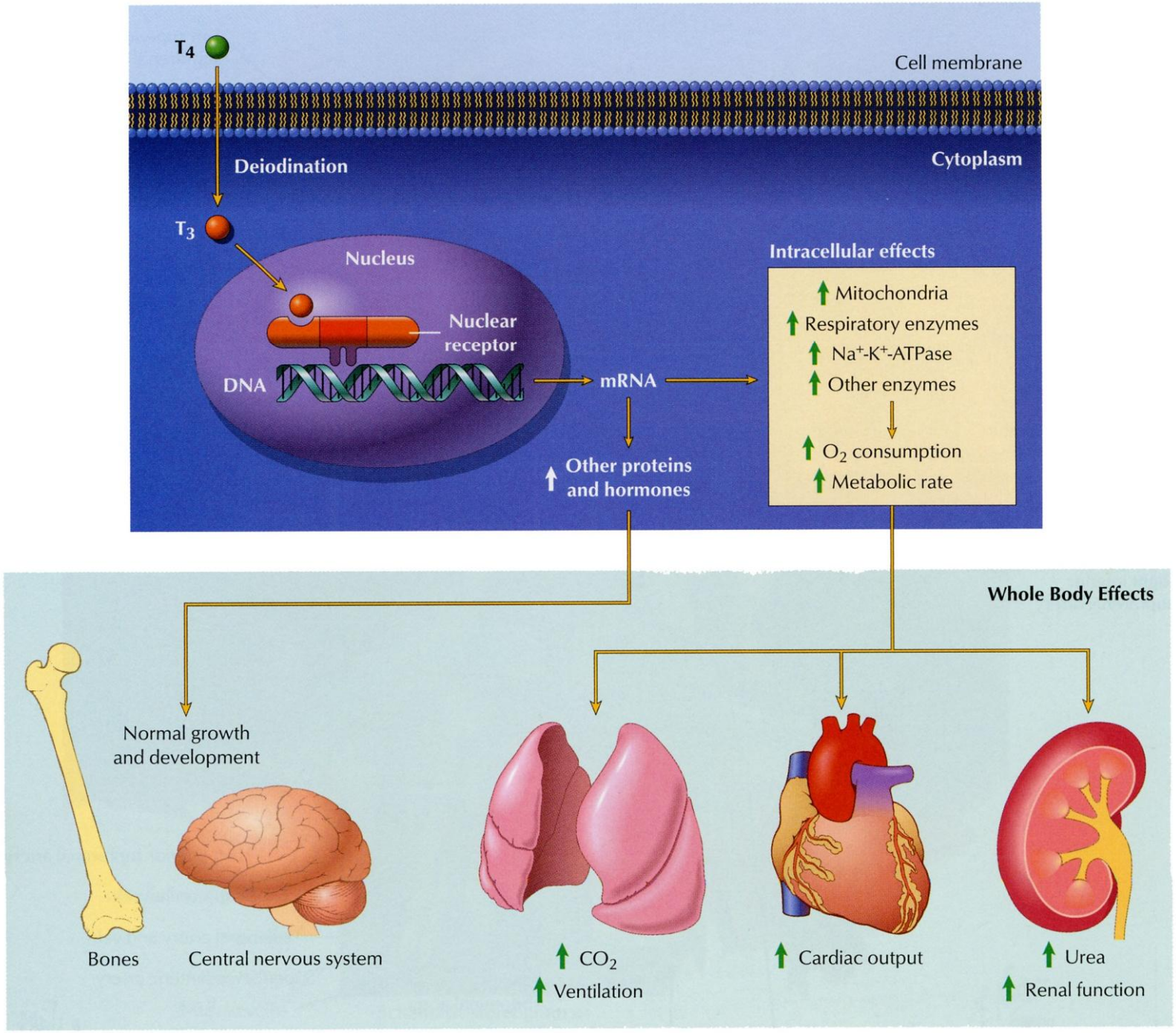
Synthesis of Thyroid Hormone

TGB (tyrosine residue) + Iodide (I^-)

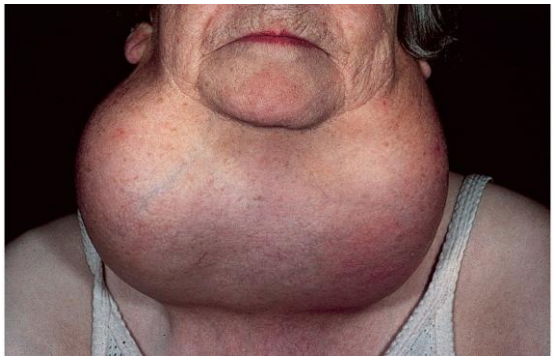
- **Thyroglobulin (TGB or TG)** is made by the follicular cells
- Thyroid follicles actively accumulate **iodine** and secrete it into the colloid
- The iodine is attached to tyrosines within the thyroglobulin molecule
  - --One iodine produces monoiodotyrosine (**MIT**)
  - --Two iodines produce diiodotyrosine (**DIT**)
- Enzymes within the colloid attach MIT and DIT together:
  - --DIT + DIT = **T_4**
  - --DIT + MIT = **T_3**
- These are still bound to thyroglobulin
  - --They dissociate from thyroglobulin when the thyroid gland is stimulated by **TSH**


Capillary
Interstitial fluid
Follicle cell
Lumen of follicle (colloid)
1 Iodide is cotransported with Na+
I−
Na+
2 Diffusion
RBC
3 Iodide is oxidized and attached to rings of tyrosines in thyroglobulin (TG)
OH (DIT)
OH (MIT)
TG
TG
TG is synthesized in follicle cell and secreted to colloid)
Lysosomes
4 The iodinated ring of one MIT or DIT is added to a DIT at another spot
OH (T3)
OH (T4)
Free amino acids re-used for TG synthesis
Lysosomal enzymes release T3 and T4 from TG
6
7
T3
T4
Secretion
T3
T4
TSH
5
T3
T4
Endocytosis of thyroglobulin containing T3 and T4 molecules

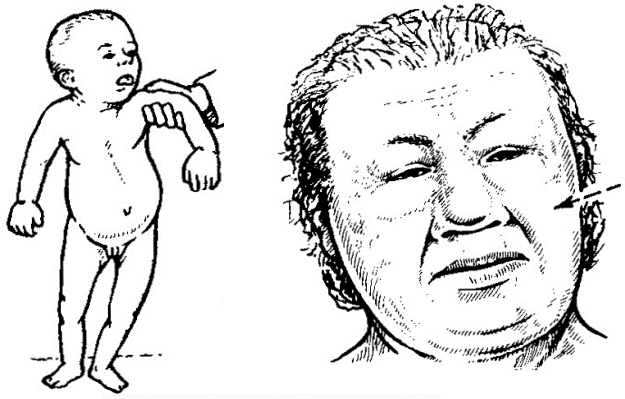
Action of Thyroid Hormone



Thyroid Hormone Secretion Disorders



- ***Endemic Goiter or Simple Goiter***
  - ***--Iodine inadequate***
- ***Hyposecretion: Hypothyroidism***
  - ***--Cretinism in Child***
  - ***--Myxedema in Adult***



- ***Hypersecretion: Hyperthyroidism***
  - ***--Grave's Disease***

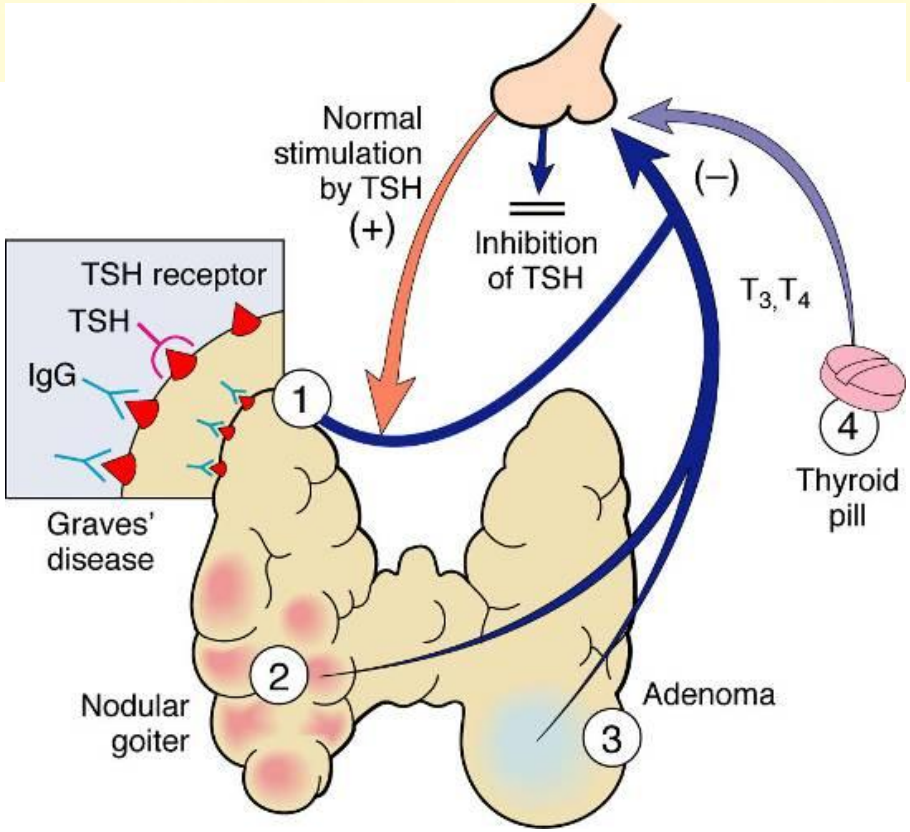
甲狀腺分泌失調

甲狀腺分泌甲狀腺激素不足時，稱為甲狀腺功能低下 (hypothyroidism)，患者會有基礎代謝率過低、體重增加及嗜睡的症狀。甲狀腺素不足亦會導致對於寒冷壓力的適應能力降低。成人的甲狀腺功能低下會造成黏液蛋白及體液堆積於皮下結締組織中，稱為黏液水腫 (myxedema)，其症狀包括手、臉、足及眼部周圍組織浮腫。

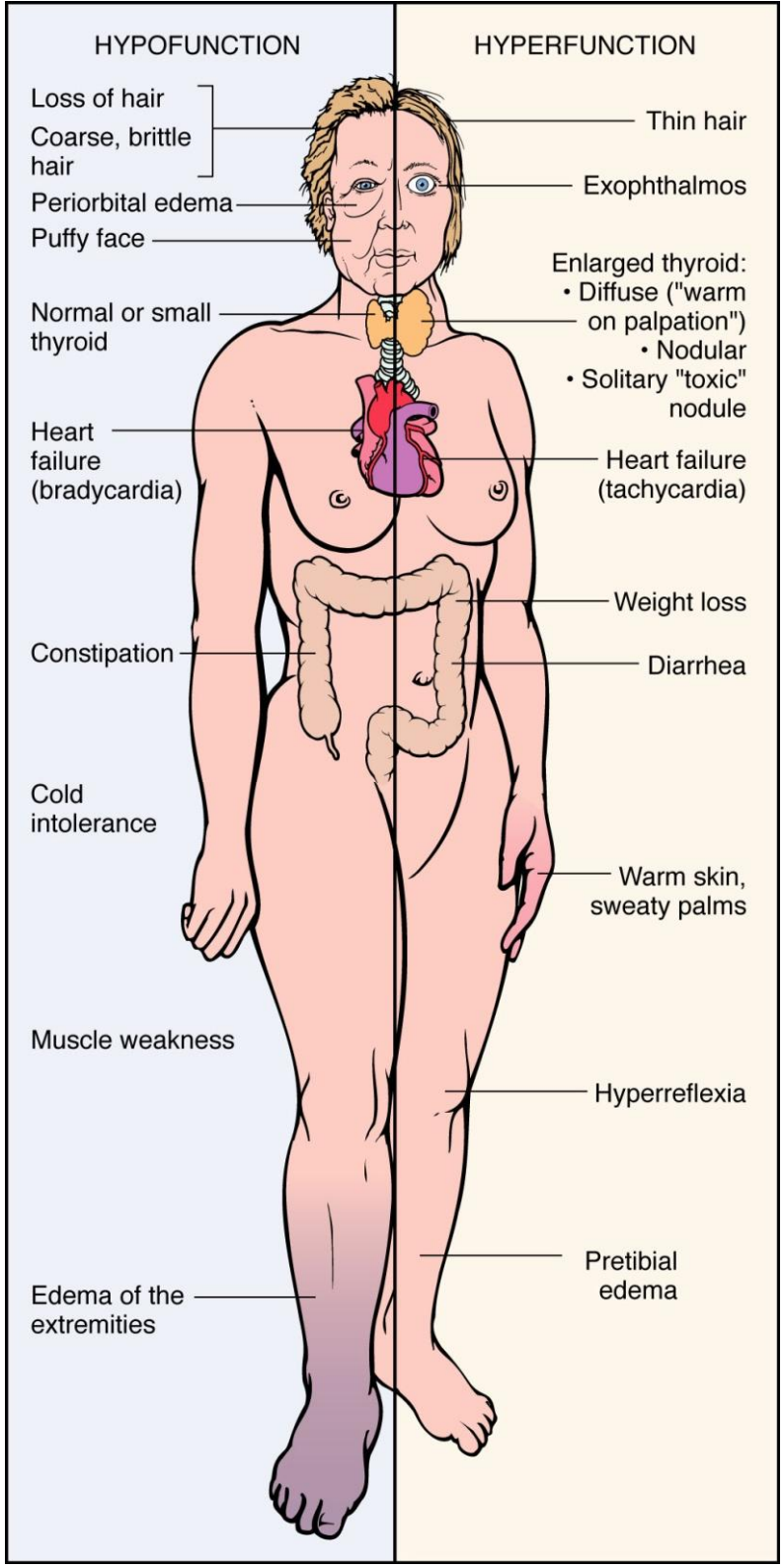
甲狀腺激素可刺激蛋白質合成，是孩童個體成長和中樞神經系統發育所必需。尤其在妊娠 3 個月到出生後 6 個月之間，對甲狀腺素的需求量最多。此時若發生甲狀腺功能低下，則會影響神經系統發育，造成身材矮小、智能發育遲緩，稱為呆小症 (cretinism)。

另一方面，甲狀腺激素分泌過多會導致甲狀腺功能亢進 (hyperthroidism)。主要臨床表現為多食、體重減輕、體溫升高、怕熱、多汗、心跳加快、容易激動等高代謝症候群，神經和血管興奮增強，以及不同程度的甲狀腺腫大 (goiter) 和突眼 (exophthalmos) 等的特徵。

Causes of Hyperthyroidism



Hypothyroidism

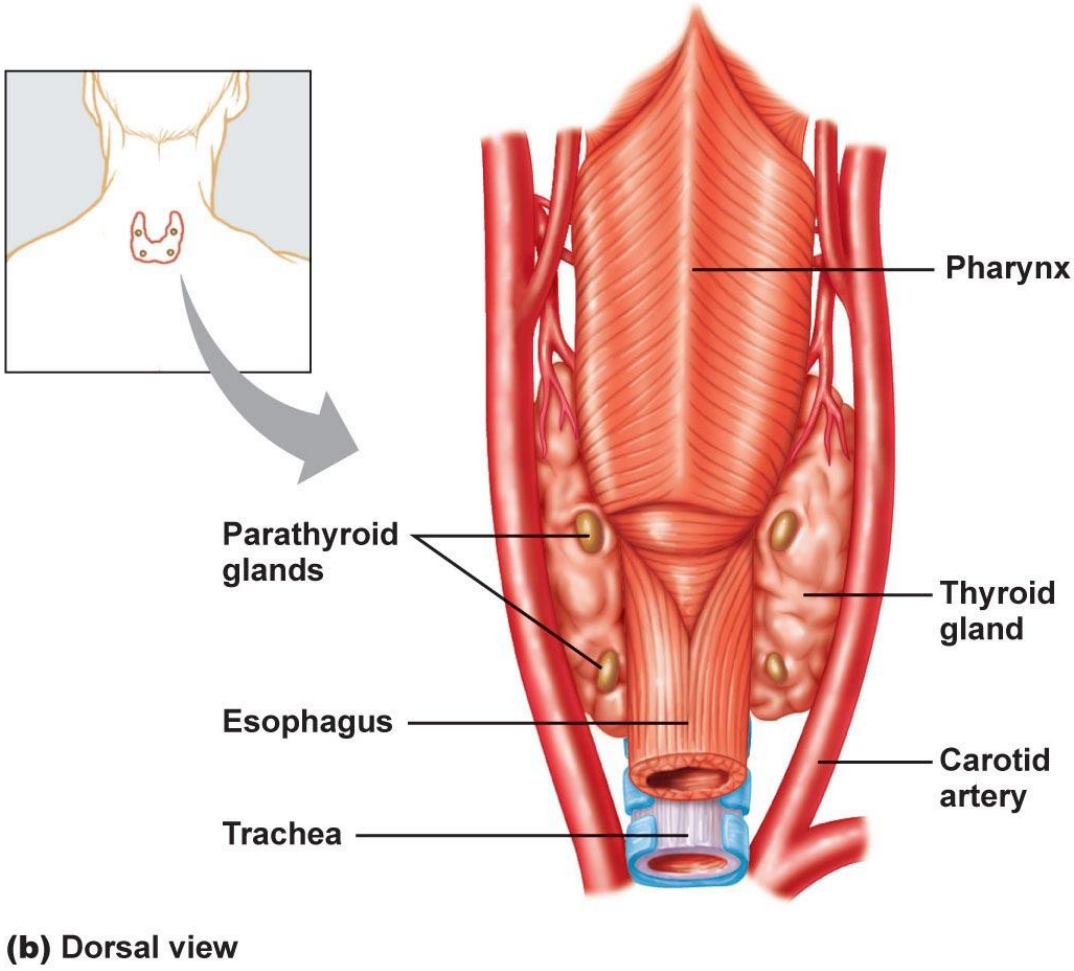


Hyperthyroidism

Hypothyroidism vs. Hyperthyroidism

Feature	Hypothyroid	Hyperthyroid
Growth and development	Impaired growth	Accelerated growth
Activity and sleep	Lethargy; increased sleep	Increased activity; decreased sleep
Temperature tolerance	Intolerance to cold	Intolerance to heat
Skin characteristics	Coarse, dry skin	Normal skin
Perspiration	Absent	Excessive
Pulse	Slow	Rapid
Gastrointestinal symptoms	Constipation; decreased appetite; increased weight	Frequent bowel movements; increased appetite; decreased weight
Reflexes	Slow	Rapid
Psychological aspects	Depression and apathy	Nervous,“emotional” state
Plasma T_4 levels	Decreased	Increased

Parathyroid Gland



(b) Dorsal view

➢ ***Located on the dorsal surface of the thyroid gland***

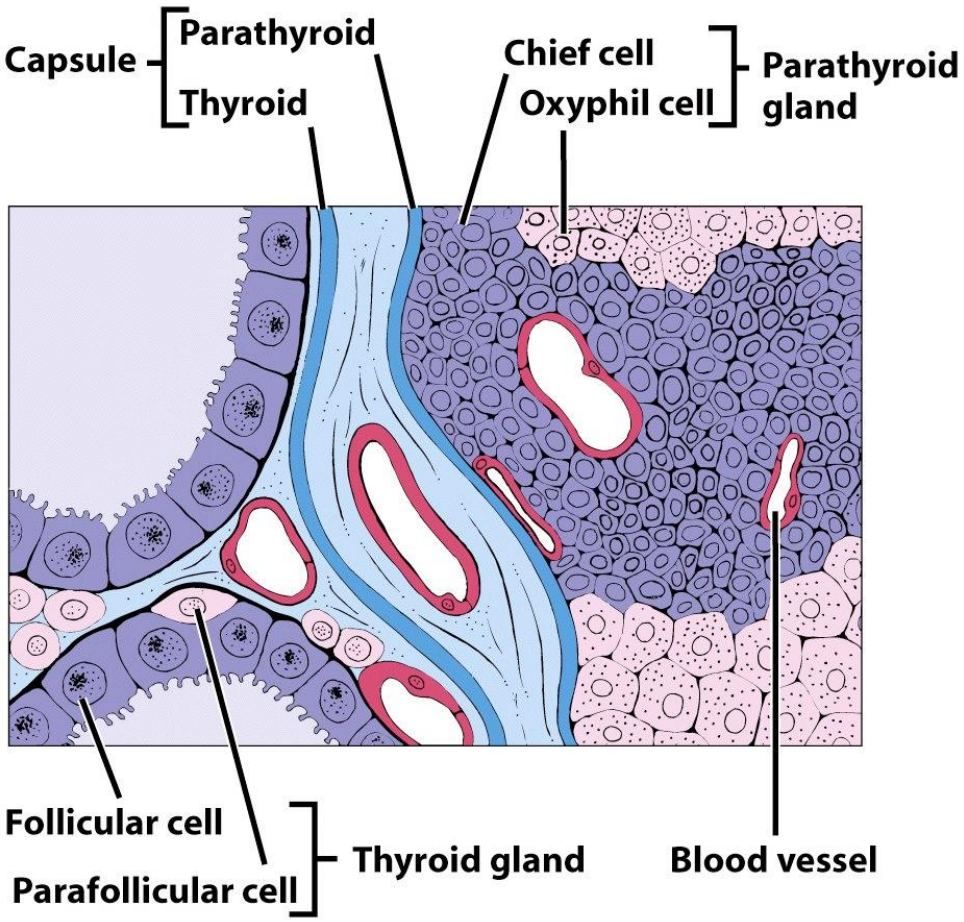
- **Four parathyroid glands**
- **Parathyroid hormone (PTH) or parathormone**

  --Major regulator of calcium, magnesium, and phosphate ions in the blood

  --Increases number and activity of osteoclasts (bone resorption)

- **Blood calcium level directly controls secretion of both calcitonin and PTH via negative feedback**

Histology of Parathyroid Gland



Portion of the thyroid gland (left) and parathyroid gland (right)

- The ***parathyroid glands*** are embedded on the posterior surfaces of the lateral lobes of the thyroid
  - --***Chief cells*** produce **PTH**
  - --***Oxyphil cells***: function is unknown
- ***PTH*** regulates the homeostasis of **calcium** and **phosphate**
  - --***Increase blood Ca^{2+} level***
  - --***Increase blood Mg^{2+} level***
  - --***Decrease blood $HPO4^{2-}$ level***

Parathyroid Hormone

Summary of Parathyroid Gland Hormone

HORMONE AND SOURCE	CONTROL OF SECRETION	PRINCIPAL ACTIONS
Parathyroid hormone (PTH) from chief cells	Low blood Ca^{2+} levels stimulate secretion. High blood Ca^{2+} levels inhibit secretion.	Increases blood Ca^{2+} and Mg^{2+} levels and decreases blood HPO_4^{2-} level; increases bone resorption by osteoclasts; increases Ca^{2+} reabsorption and HPO_4^{2-} excretion by kidneys; and promotes formation of calcitriol (active form of vitamin D), which increases rate of dietary Ca^{2+} and Mg^{2+} absorption.

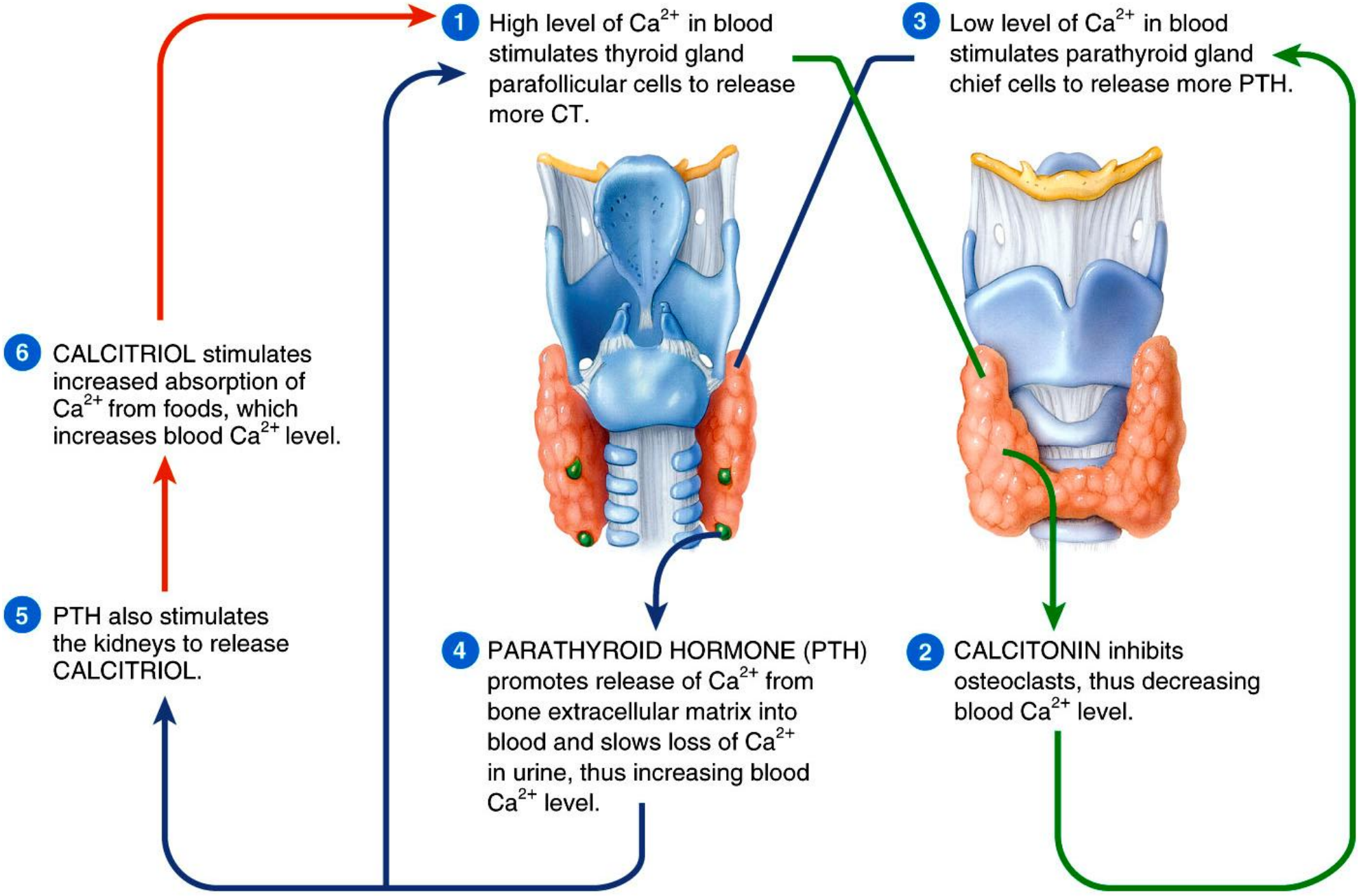
Chief cell

- ***Hormone promotes a rise in blood calcium by acting on bones, kidneys, and intestine***

- ***Active form of Vit D_3:***

  Calcitriol =1,25-dihydroxy Vit D_3 =1,25-$(OH)_2$Vit D_3 =1,25-dihydroxycholecalciferol =1,25-DHCC

Control of PTH Secretion



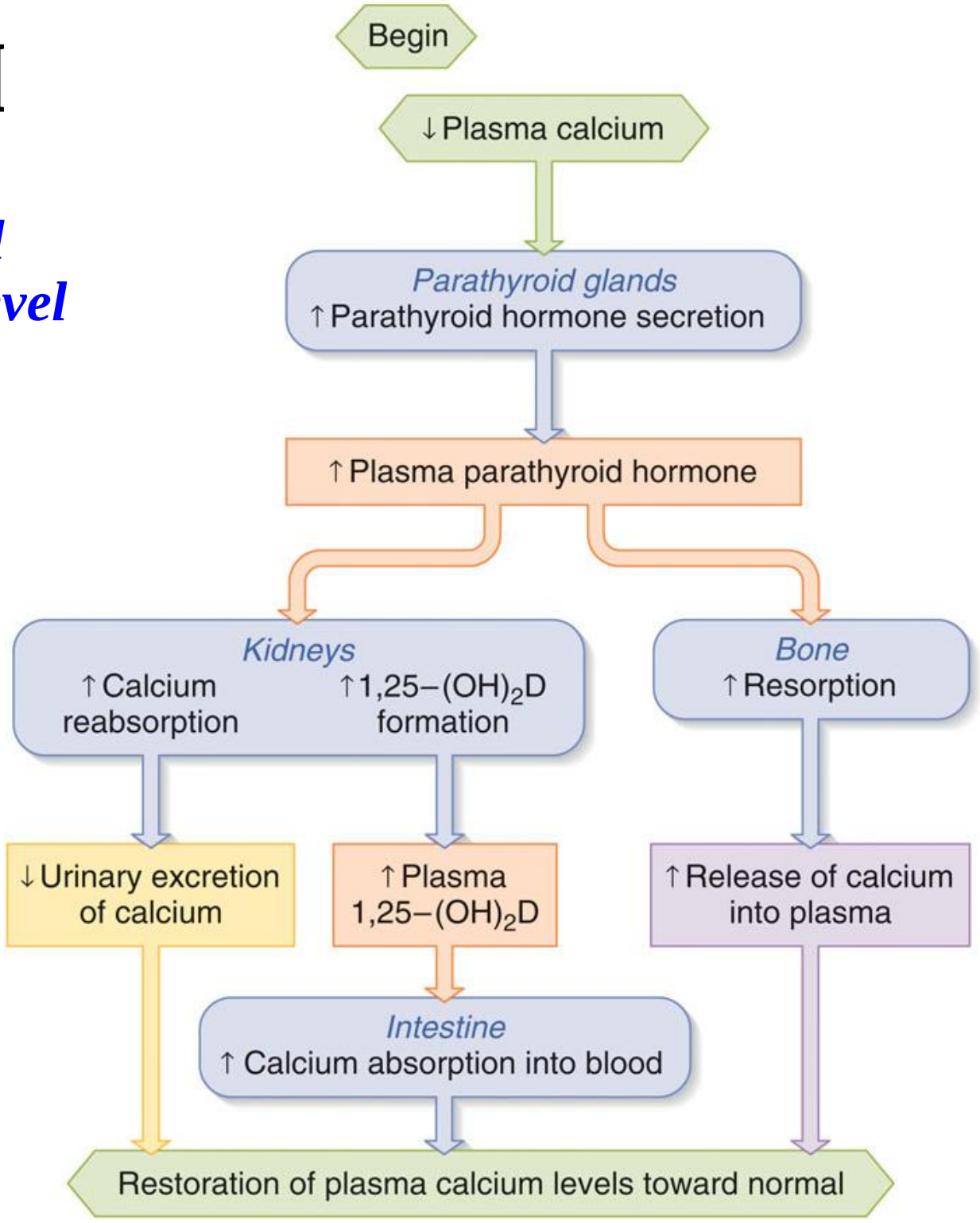
Action of PTH

--Increase blood Ca^{2+} level

--Increase blood Mg^{2+} level

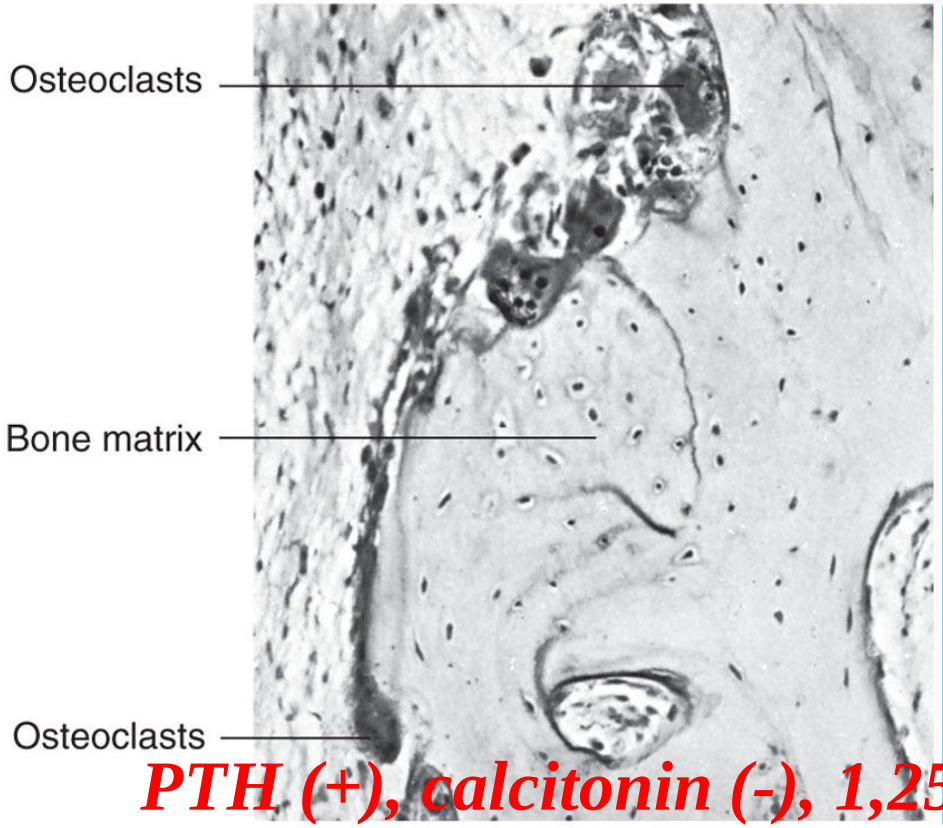
--Decrease blood $HPO4^{2-}$ level

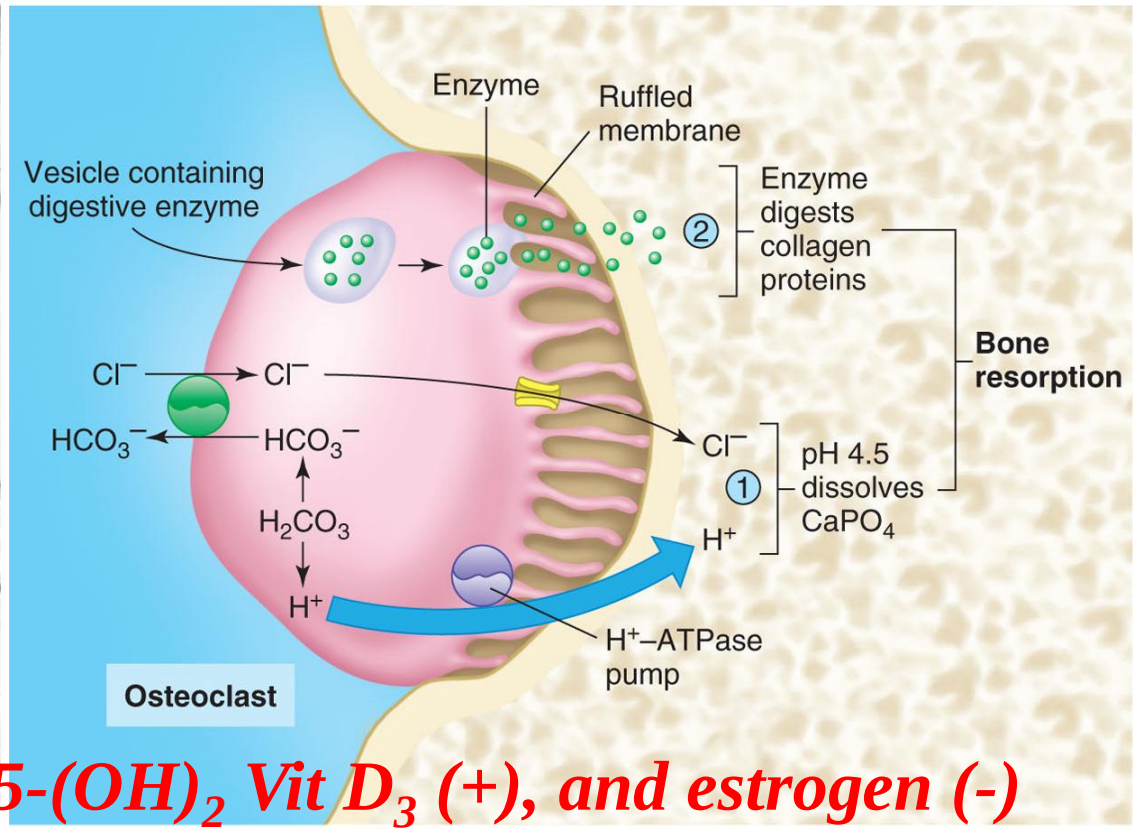
- **Bone:**
  --Increases the number and activity of osteoclasts
- **Kidneys:**
  --Increases the rate of Ca^{+2} and Mg^{+2} from reabsorption from urine
  --Inhibits the reabsorption of $HPO4^{-2}$ so more is secreted in the urine
- **Intestine:**
  --Promotes formation of **calcitriol**, which increases the absorption of Ca^{+2}, Mg^{+2},and $HPO4^{-2}$ from the GI tract



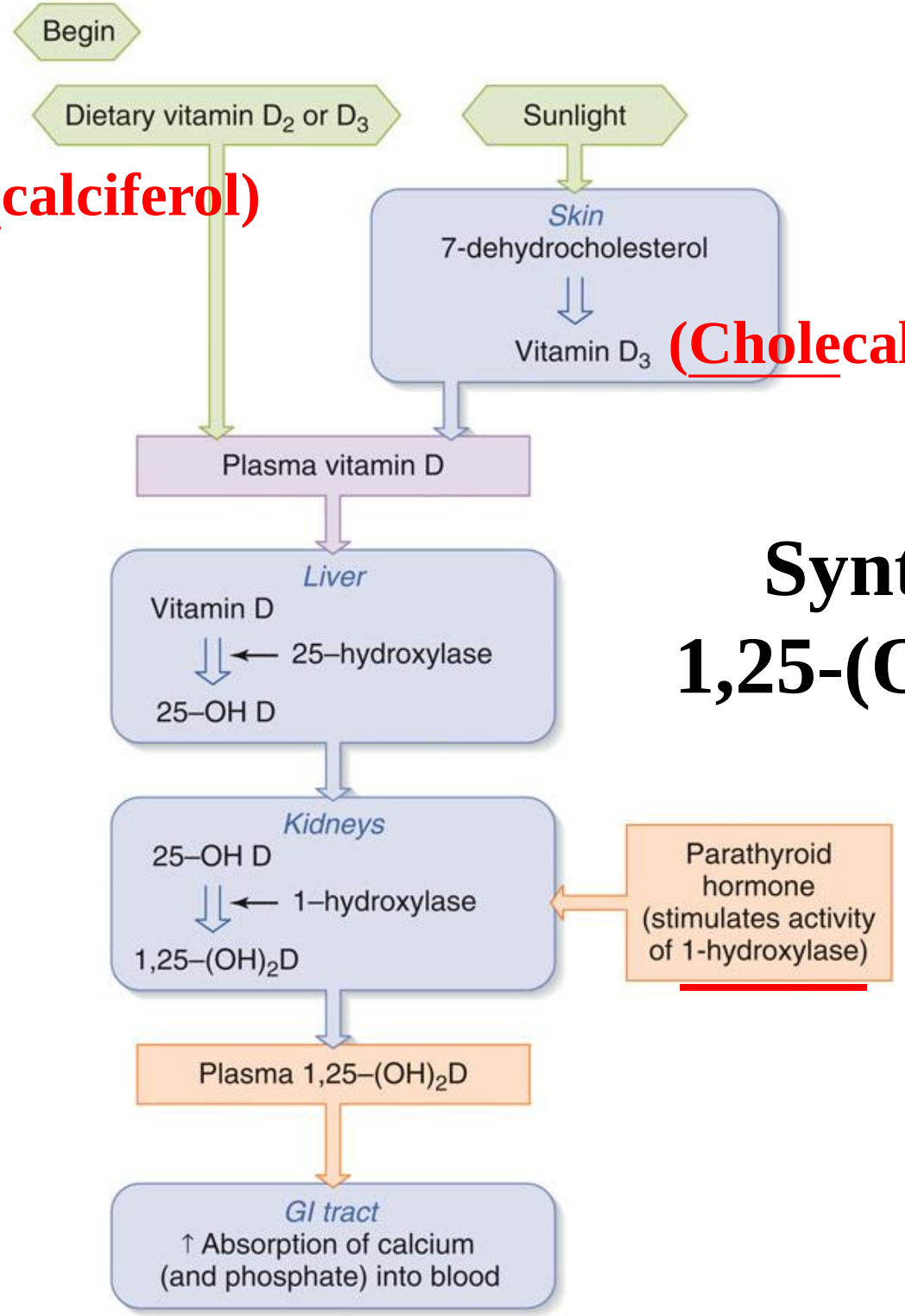
Bone Resorption

- ***Osteoclasts secrete acid and enzymes***
- ***Acid dissolves calcium phosphate crystals***
- ***Enzymes degrade bone matrix***
- ***Calcium and phosphate released into blood***





PTH (+), calcitonin (-), 1,25-$(OH)_2$ Vit D_3 (+), and estrogen (-)

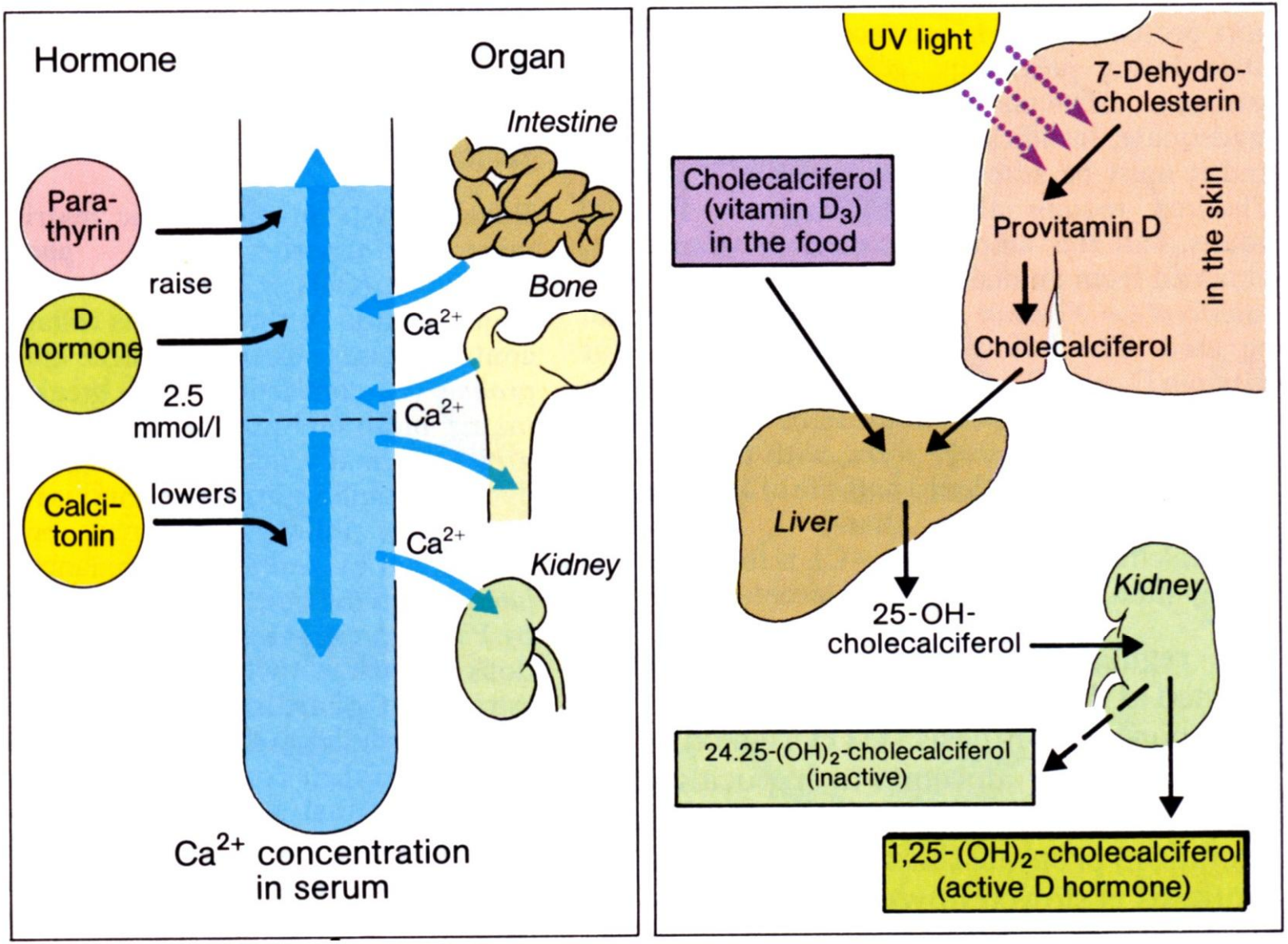


(Ergocalciferol)

(Cholecalciferol)

Synthesis of $1,25-(OH)_2$Vit D_3

Endocrine Regulation of Calcium Balance



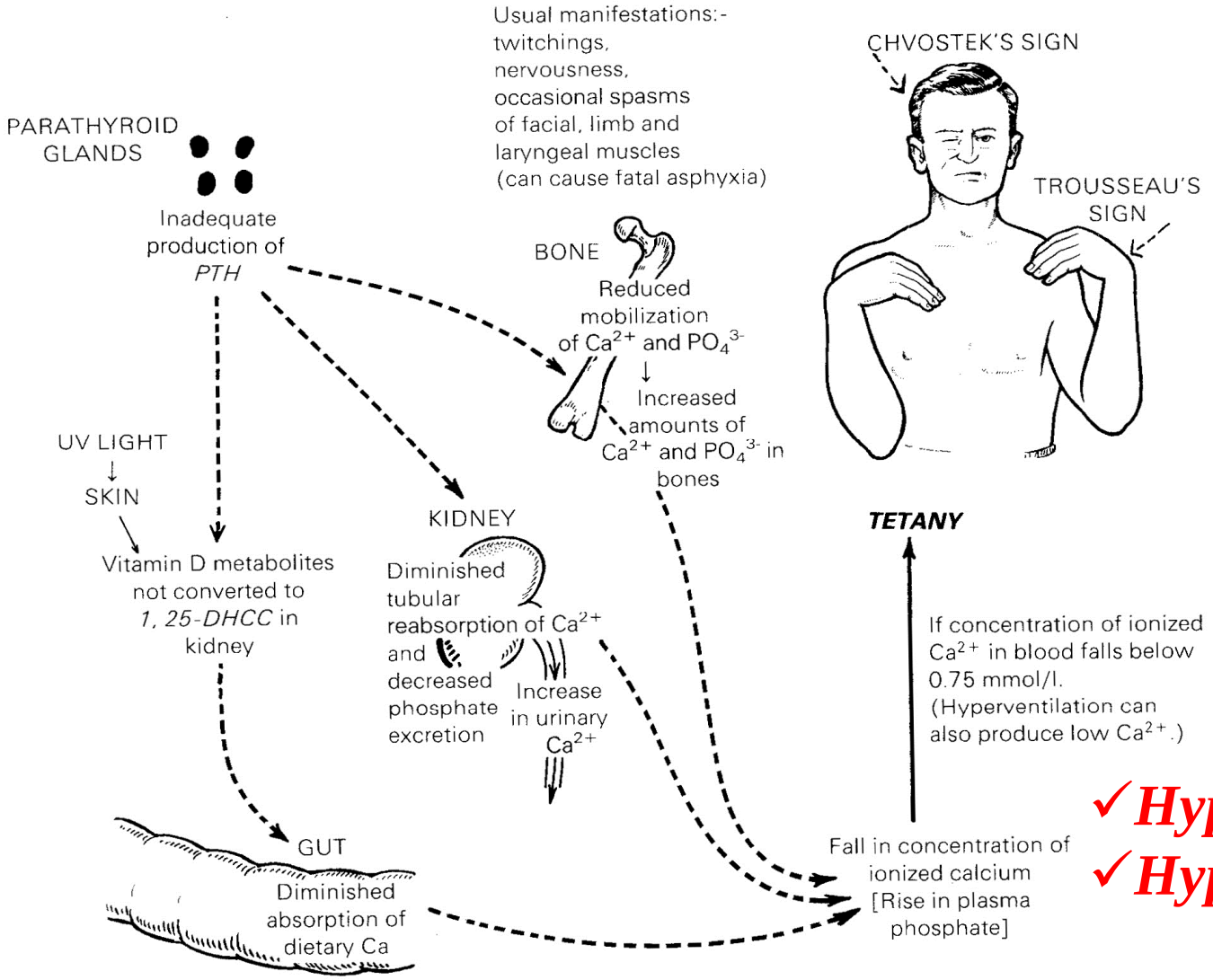
Endocrine Regulation of Ca^{2+} and PO_4^{3-} Balance

Hormone	Effect on Intestine	Effect on Kidneys	Effect on Bone	Associated Diseases
Parathyroid hormone (PTH)	No direct effect	Stimulates Ca^{2+} reabsorption; inhibits PO_4^{3-} reabsorption	Stimulates resorption	Osteitis fibrosa cystica with hypercalcemia due to excess PTH
1,25-dihydroxyvitamin D_3	Stimulates absorption of Ca^{2+} and PO_4^{3-}	Stimulates reabsorption of Ca^{2+} and PO_4^{3-}	Stimulates resorption	Osteomalacia (adults) and rickets (children) due to deficiency of 1,25-dihydroxyvitamin D_3
Calcitonin	None	Inhibits resorption of Ca^{2+} and PO_4^{3-}	Stimulates deposition	None

PTH Secretion Disorders

Hyposecretion: Hypoparathyroidism

Atrophy or removal of parathyroid tissue causes a fall in **blood calcium** level and increased excitability of neuromuscular tissue. This leads to severe convulsive disorder – **tetany**.

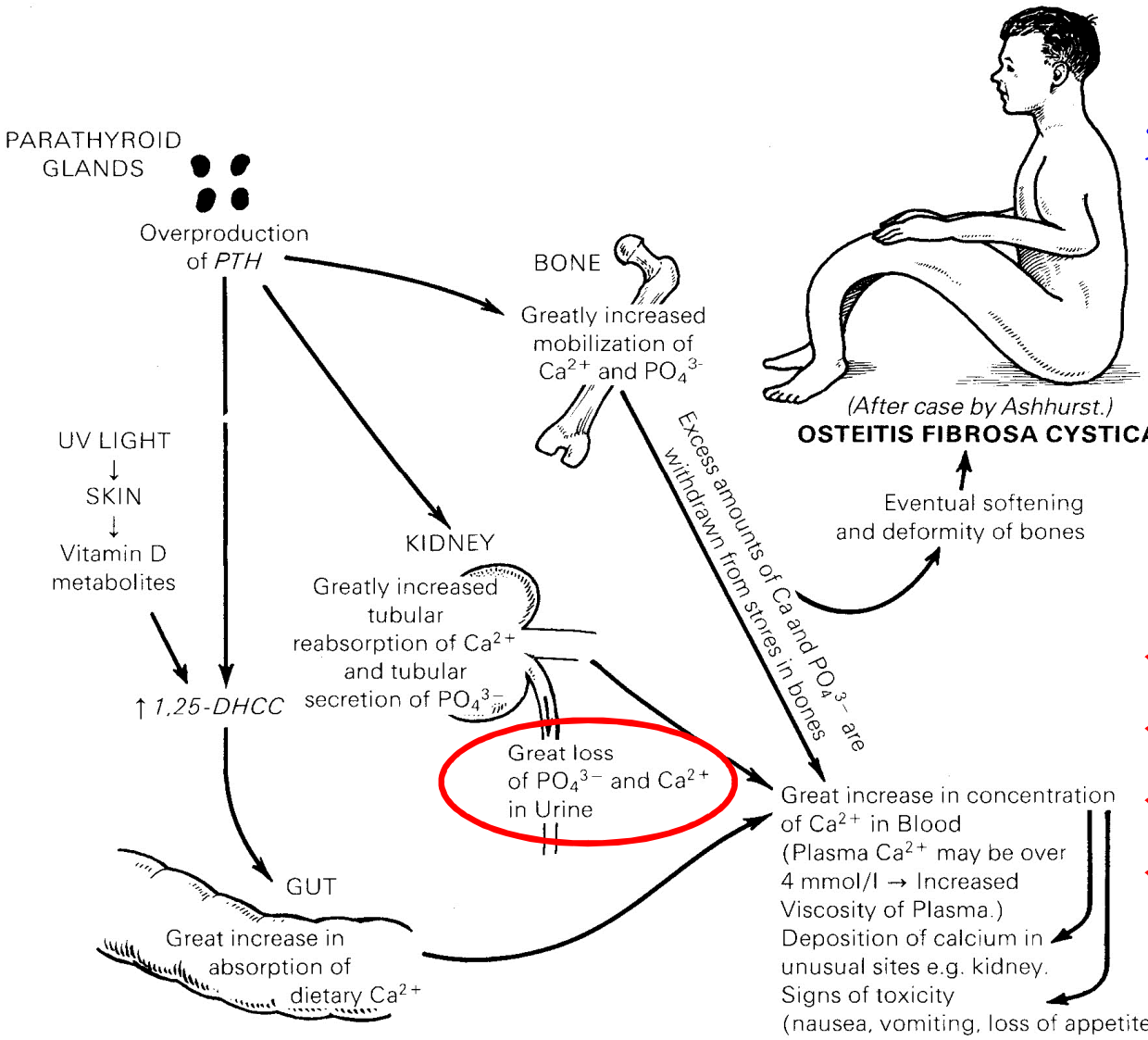


- ✓ *Hypocalcemia*
- ✓ *Hyperphosphatemia*

PTH Secretion Disorders

Hypersecretion: *Hyperparathyroidism*

Overactivity of the parathyroids (due often to tumour) leads to rise in **blood calcium** level and eventually to **osteitis fibrosa cystica**.



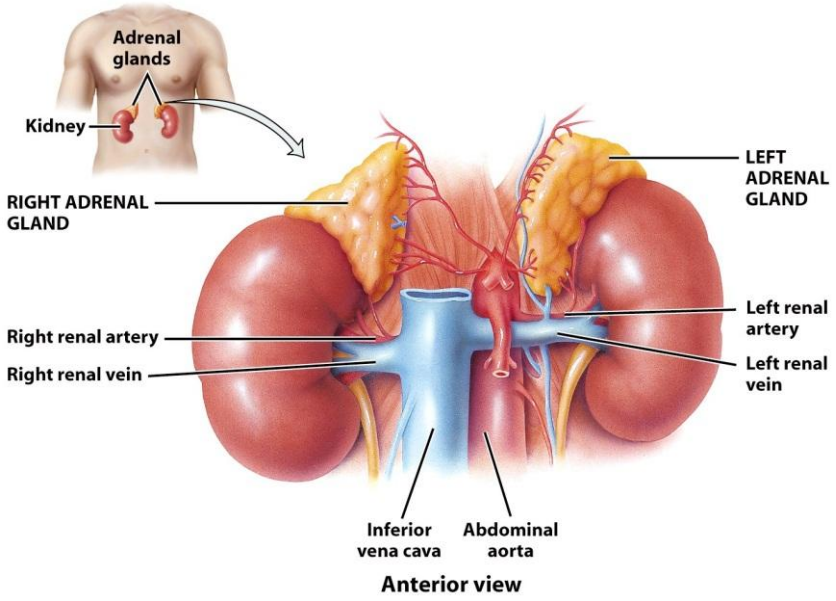
(After case by Ashhurst.)

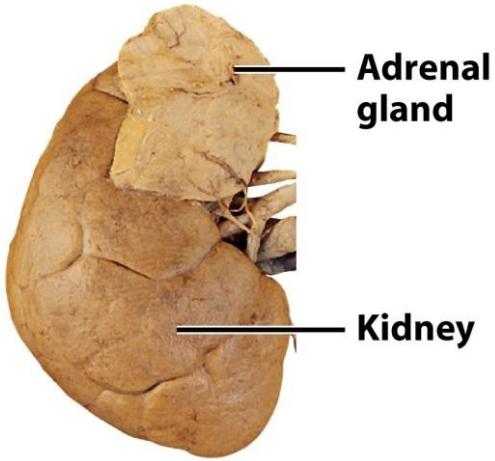
OSTEITIS FIBROSA CYSTICA

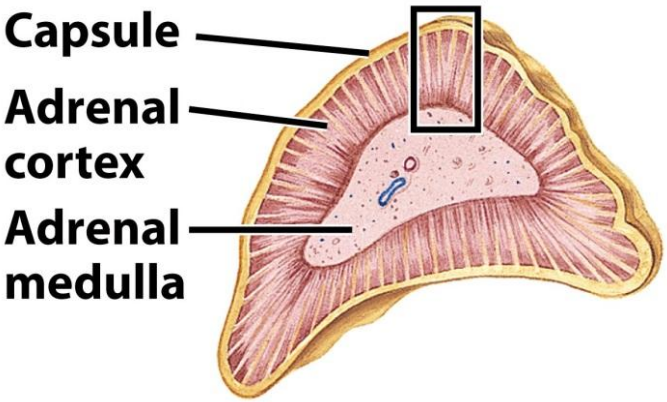
囊狀纖維性骨炎

- ✓*Osteoporosis*
- ✓*Bone fracture*

- ✓*Hypercalcemia*
- ✓*Hypophosphatemia*
- ✓*Polyuria*
- ✓*Thirst*



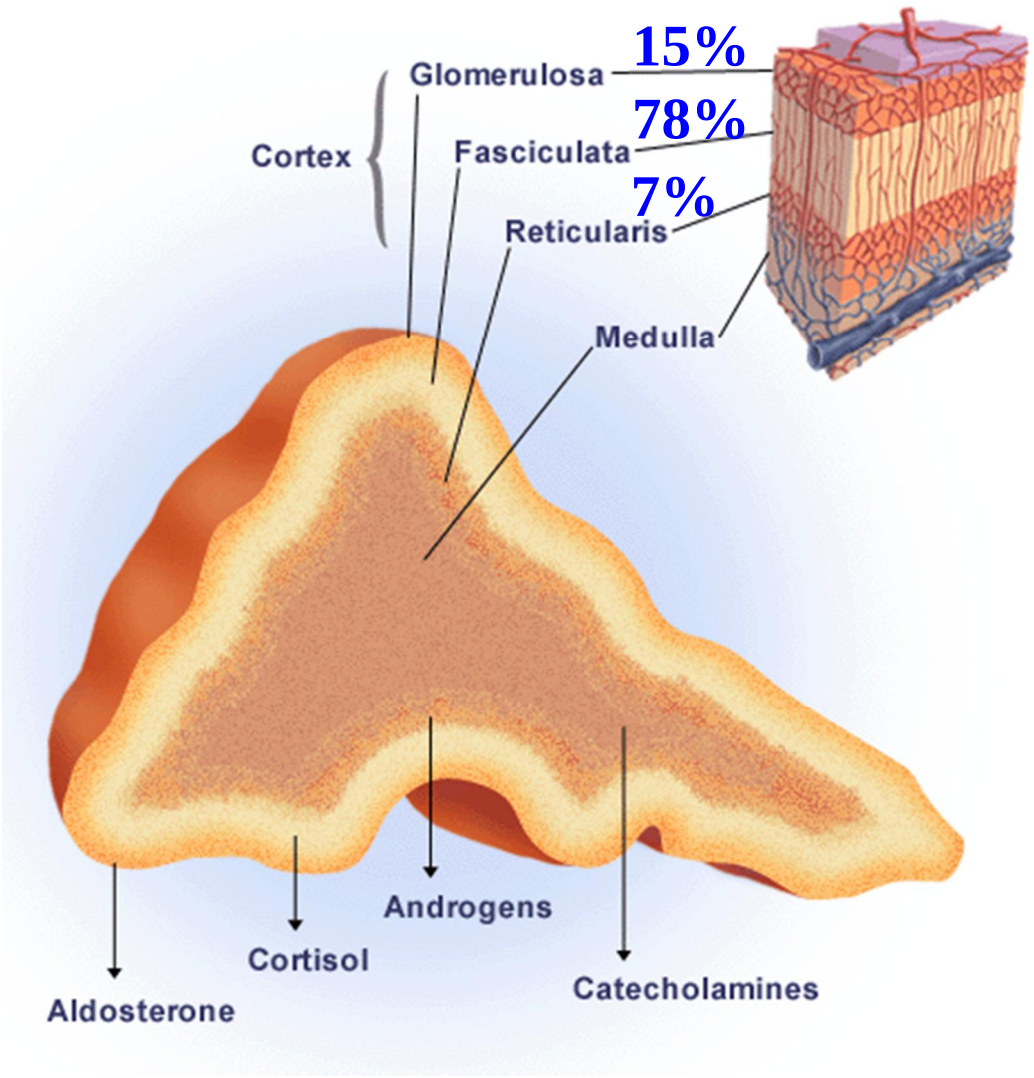


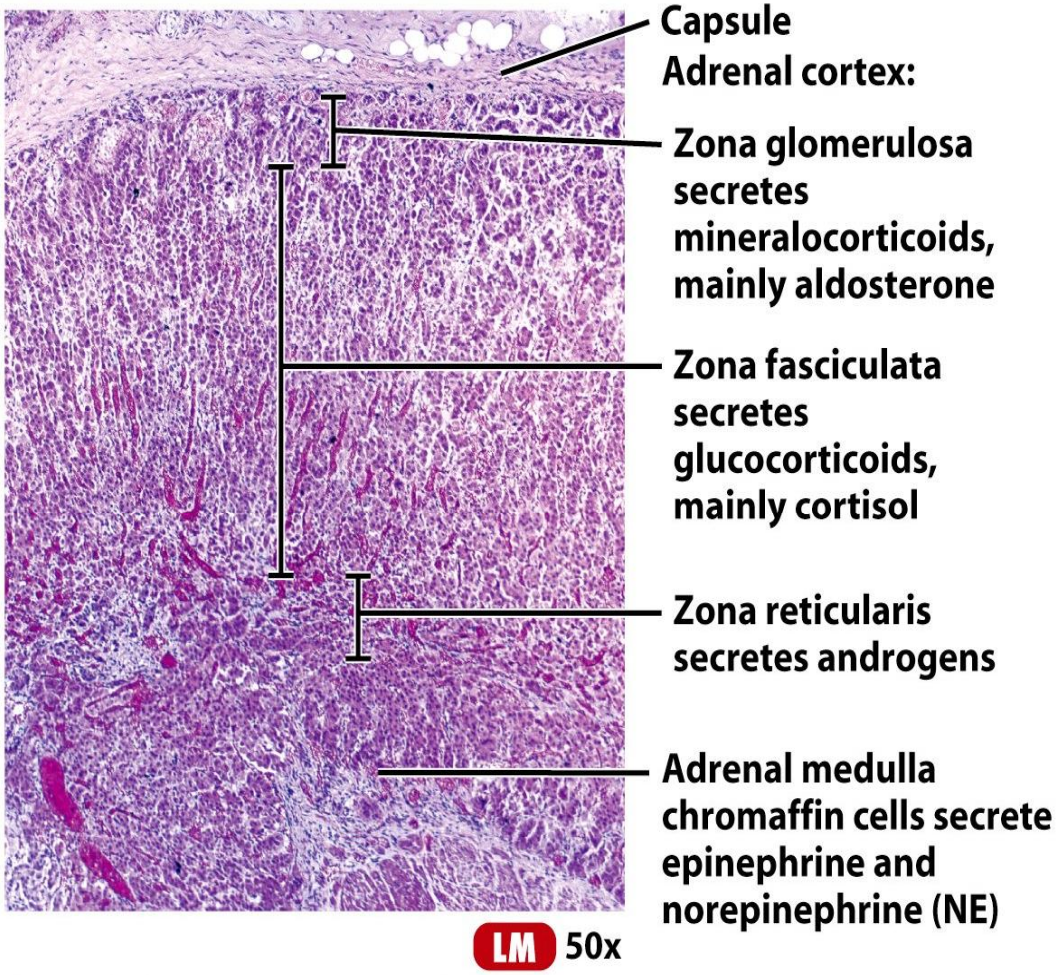


Adrenal Gland

- The ***adrenal glands*** are located superior to the kidneys
- **3 x 3 x 1 cm** in size and weighs **5 grams**
- Consists of an outer **cortex** and an inner **medulla**
  - --**Cortex** produces 3 different types of hormones from 3 zones of cortex
  - --**Medulla** produces epinephrine & norepinephrine

Adrenal Gland





Subdivisions of the adrenal gland

Adrenal Gland Hormones

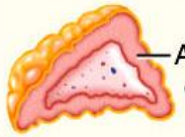
Adrenocorticoids

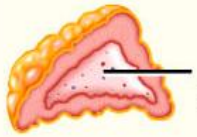
名稱	特性
腎上腺皮質 (adrenal cortex)	1.分泌 **corticosteroid** (皮質類固醇)，來自胚胎的**中胚層**，佔 adrenal gland 的 80~90% 。 2.分為三層： ❶**絲（球）狀帶（zona glomerulosa）：Aldosterone** 分泌 **mineralcorticoids** (礦物質皮質類固醇) 。 ❷**束狀帶（zona fasciculata）：Cortisol** 分泌 **glucocorticoids** (糖質皮質類固醇) 。 ❸**網狀帶（zona reticularis）：Androgens & estrogens** 分泌性類固醇 (**sex steroids**) 。
腎上腺髓質 (adrenal medulla)	分泌 **catecholamines**， **Epi：NE**分泌比例 4：1 ，來自胚胎的**外胚層** ，佔 adrenal gland 的 10~20% 。

Adrenal Gland Hormones

Summary of Adrenal Gland Hormones

HORMONES AND SOURCE	CONTROL OF SECRETION	PRINCIPAL ACTIONS
ADRENAL CORTEX HORMONES		
Mineralocorticoids (mainly aldosterone) from zona glomerulosa cells	Increased blood K^+ level and angiotensin II stimulate secretion. *(RAA system)*	Increase blood levels of Na^+ and water and decrease blood level of K^+ **and H^+**
Glucocorticoids (mainly cortisol) from zona fasciculata cells	ACTH stimulates release; corticotropin-releasing hormone (CRH) promotes ACTH secretion in response to stress and low blood levels of glucocorticoids.	Increase protein breakdown (except in liver), stimulate gluconeogenesis and lipolysis, provide resistance to stress, dampen inflammation, and depress immune responses.
Androgens (mainly dehydroepiandrosterone or **DHEA)** from zona reticularis cells	ACTH stimulates secretion.	Assist in early growth of axillary and pubic hair in both sexes; in females, contribute to libido and are source of estrogens after menopause.
ADRENAL MEDULLA HORMONES		
Epinephrine and **norepinephrine** from chromaffin cells (嗜鉻細胞)	Sympathetic preganglionic neurons release acetylcholine, which stimulates secretion.	Produce effects that enhance those of the sympathetic division of the autonomic nervous system (ANS) during stress.



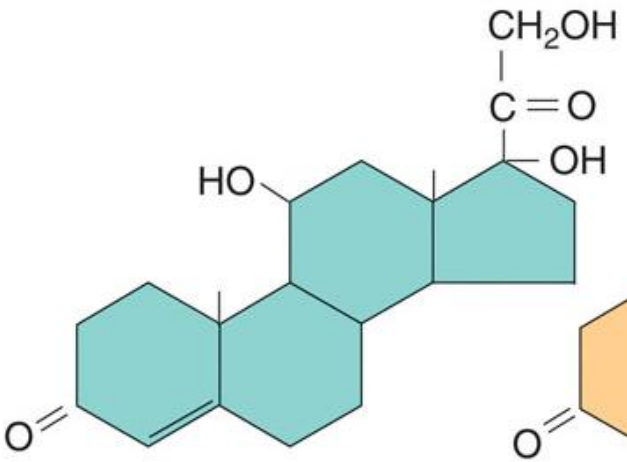


➢ ***DHEA only important in females***

RAA system = Renin-Angiotensin-Aldosterone system)

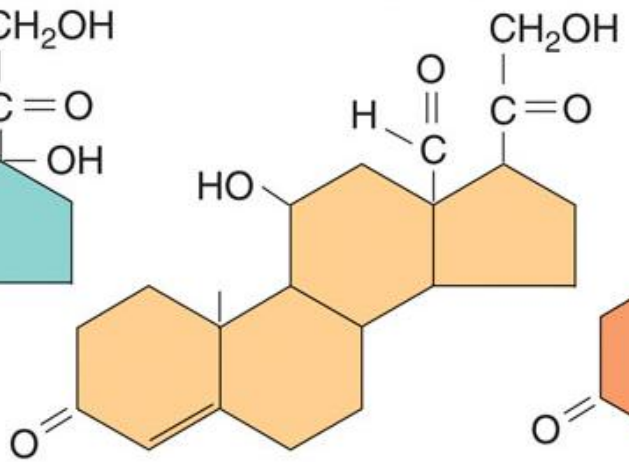
Adrenal Cortex Hormones

Steroid Hormones = Lipid-Soluble Hormones



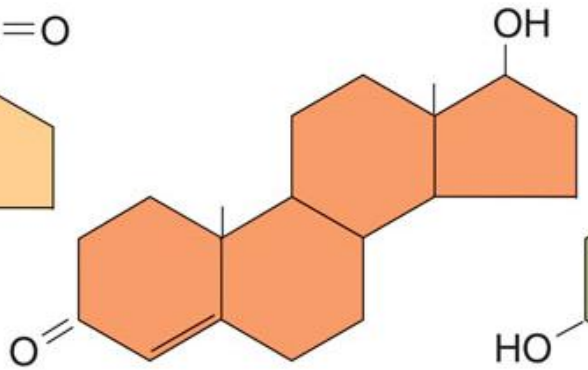
Cortisol

Glucocorticoids

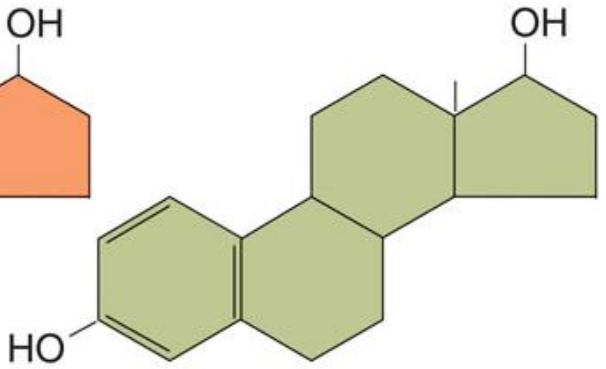


Aldosterone

Mineralcorticoids

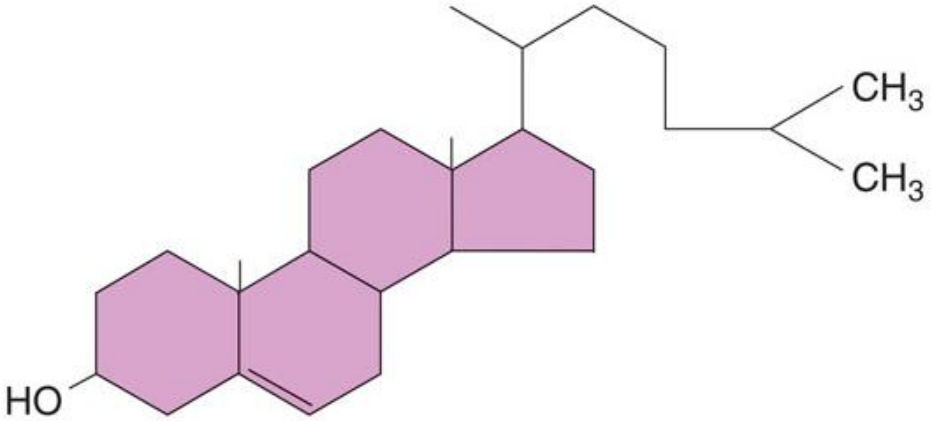


Testosterone



Estradiol

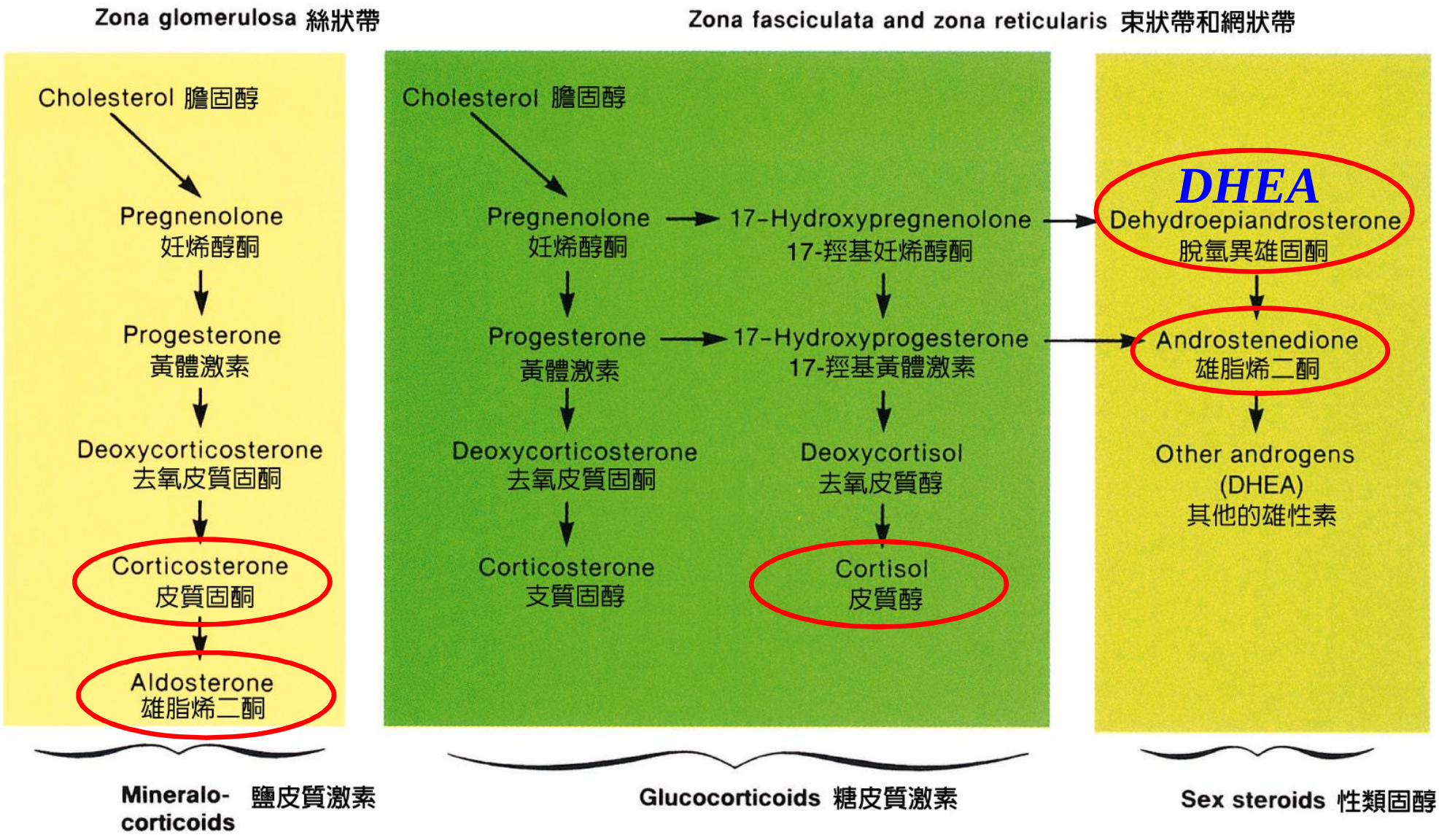
Sex Steroids



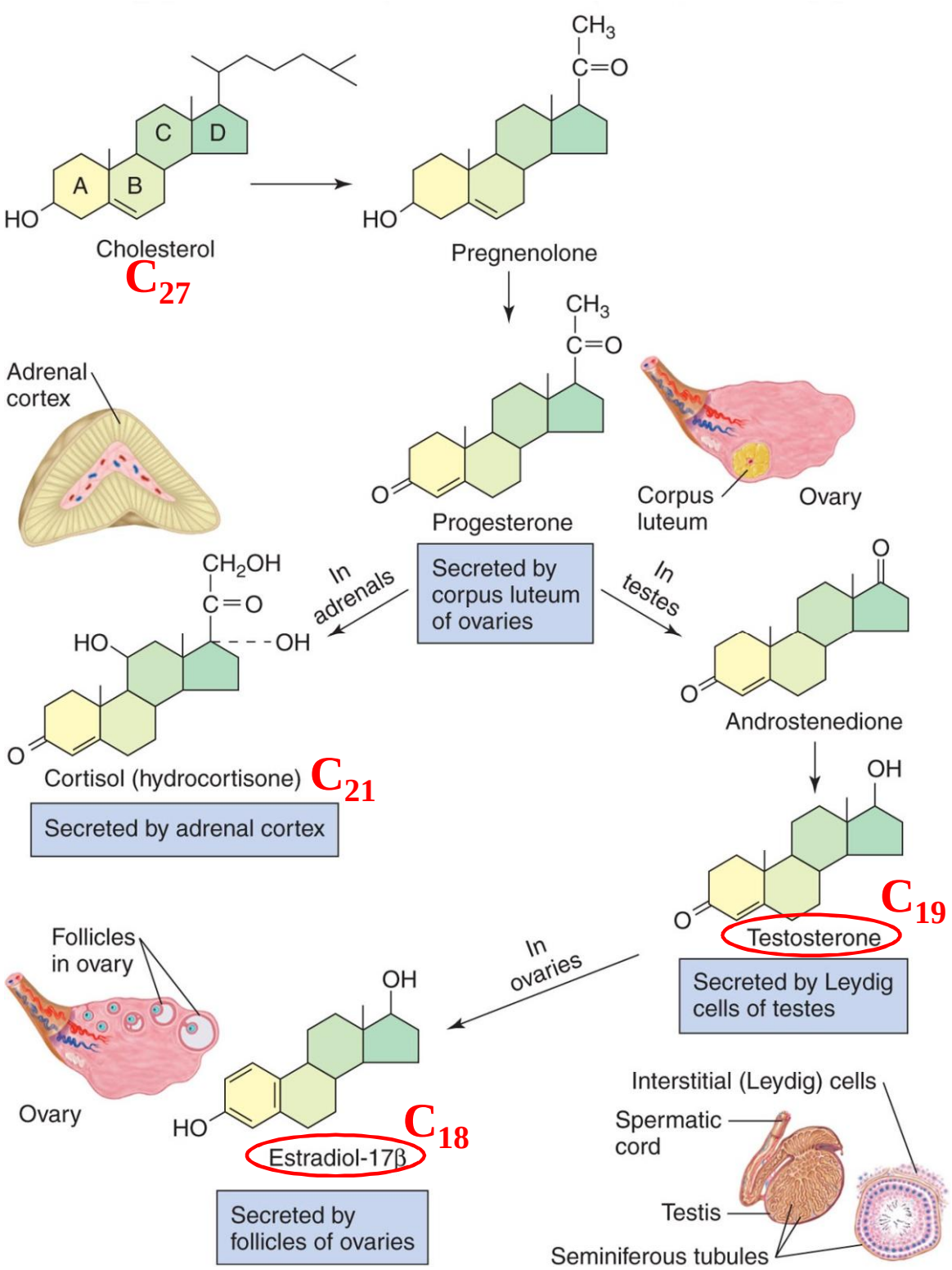
Cholesterol

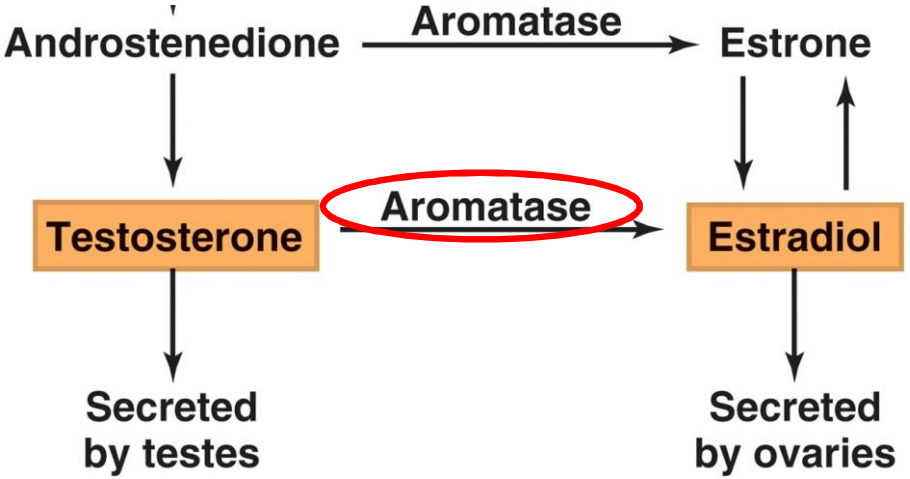
Synthesis of Adrenal Cortex Hormones

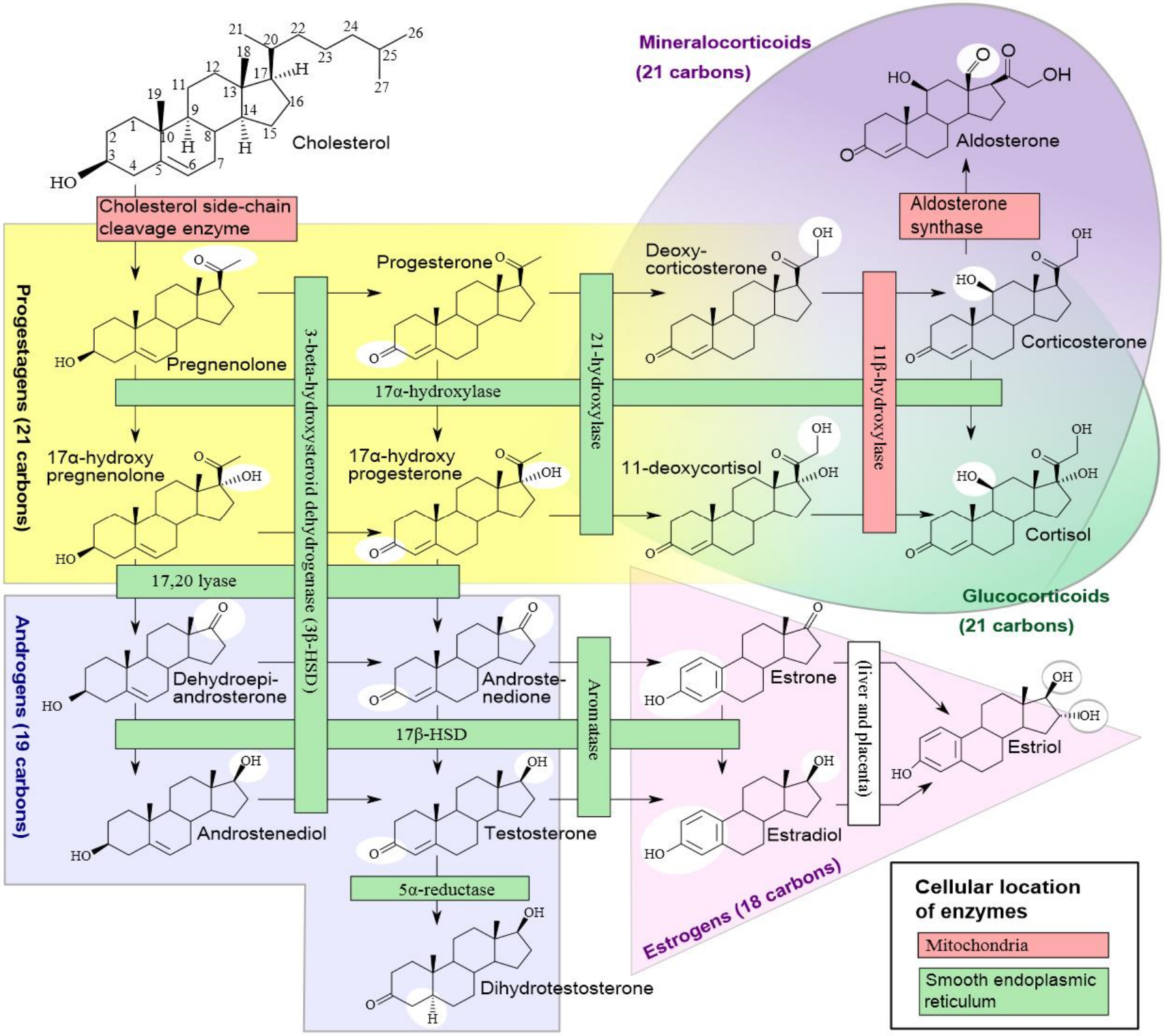
Corticosteroids



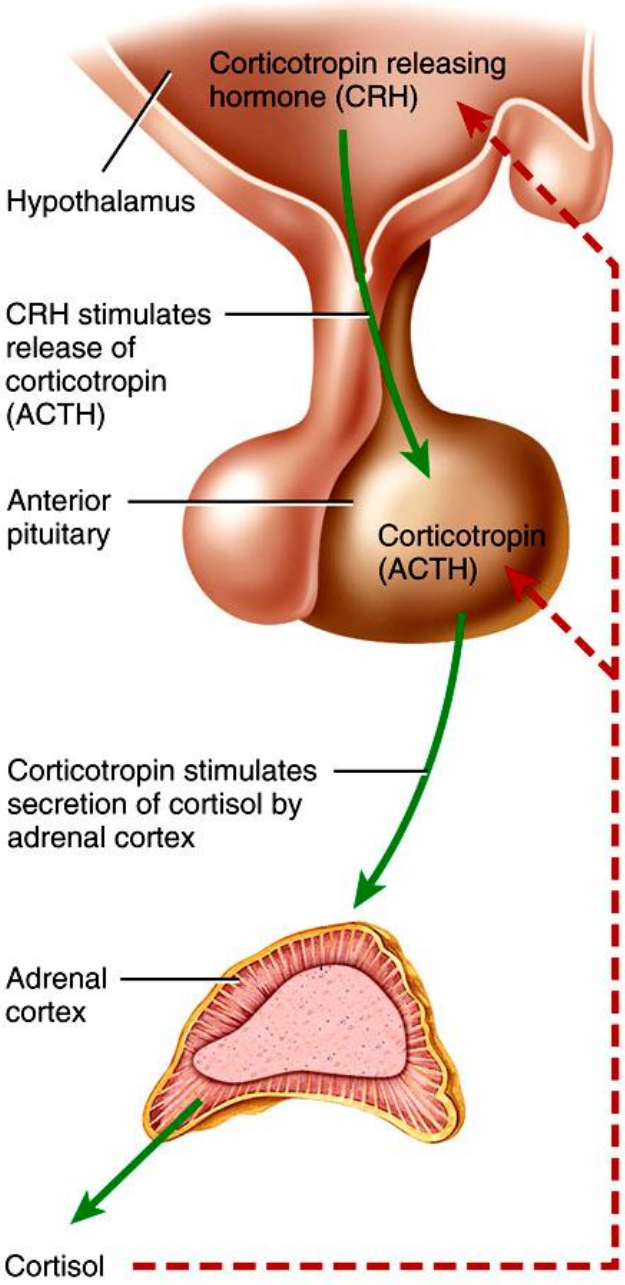
Synthesis of Gonadal Steroid Hormones





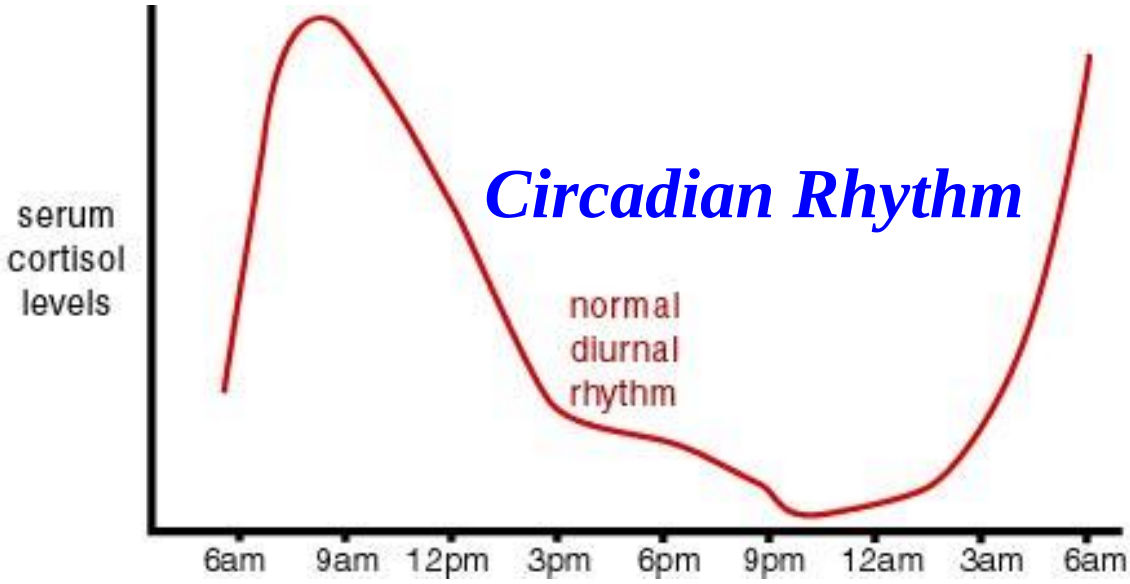

Mineralocorticoids
(21 carbons)
Cholesterol
Cholesterol side-chain cleavage enzyme
Progestagens (21 carbons)
Pregnenolone
Progesterone
17α-hydroxy pregnenolone
17α-hydroxy progesterone
3-beta-hydroxysteroid dehydrogenase (3β-HSD)
17α-hydroxylase
17,20 lyase
21-hydroxylase
Deoxy-corticosterone
11-deoxycortisol
11β-hydroxylase
Aldosterone synthase
Aldosterone
Corticosterone
Cortisol
Glucocorticoids
(21 carbons)
Androgens (19 carbons)
Dehydroepi-androsterone
Androste-nedione
17β-HSD
Androstenediol
Testosterone
5α-reductase
Dihydrotestosterone
Aromatase
Estrone
Estradiol
(liver and placenta)
Estriol
Estrogens (18 carbons)
Cellular location of enzymes
Mitochondria
Smooth endoplasmic reticulum

Control of Cortisol Secretions



Elevated cortisol inhibits release of CRH by hypothalamic neurosecretory cells

Elevated cortisol inhibits release of corticotropin by anterior pituitary corticotrophs



Circadian Rhythm

Negative Feedback Regulation

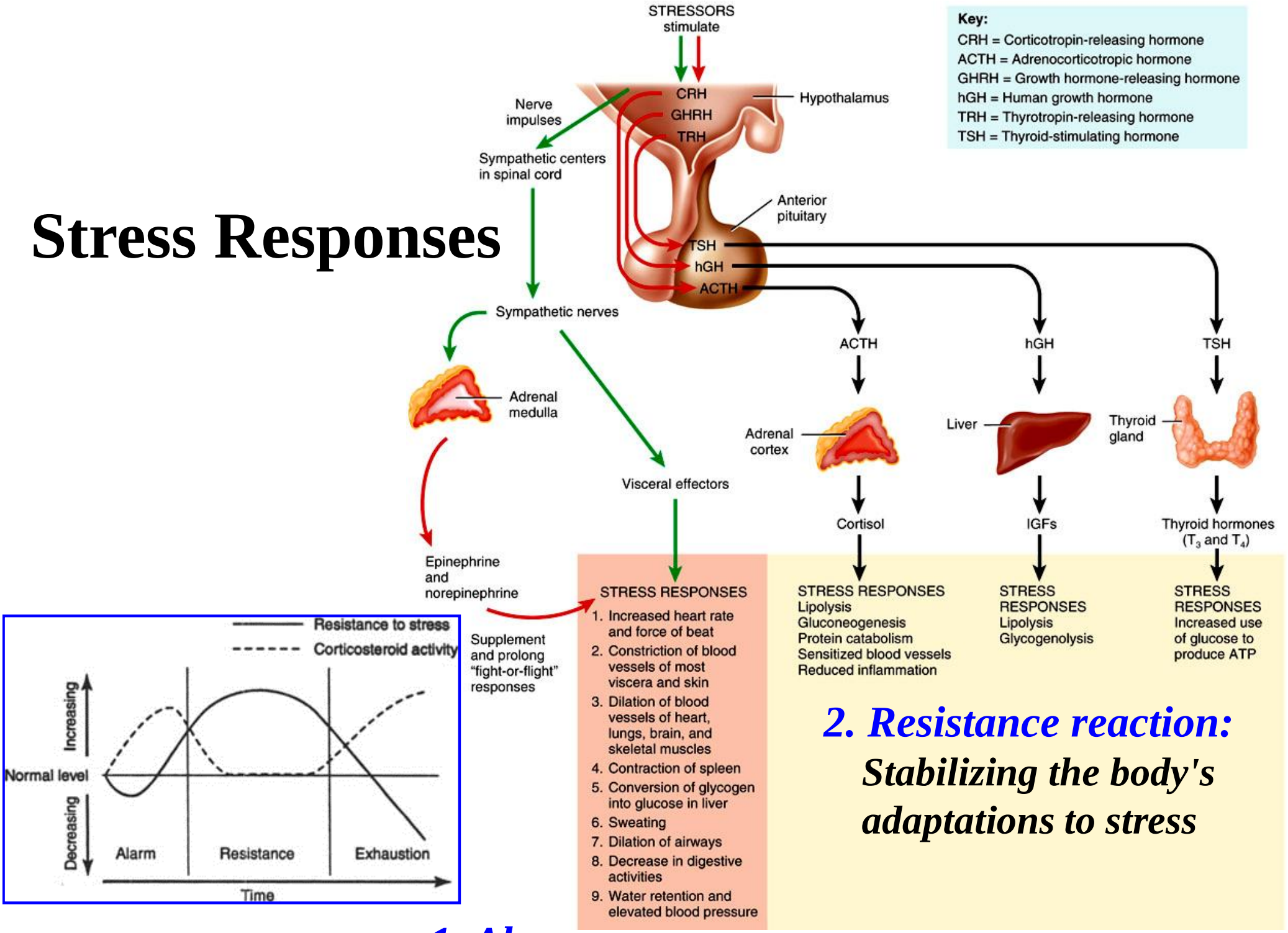
Stress Responses & Cortisol

- **Eustress** in helpful stress/**Distress** is harmful
- Body's homeostatic mechanisms attempt to counteract stress (**resistance to stress**)
- Stressful conditions can result in **stress response** or **general adaptation syndrome (GAS)**

  --3 stages: initial flight-or-fight (alarm) , **slower resistance reaction**, **eventually exhaustion**

  --Prolonged exposure to **cortisol** can result in wasting of muscles, suppression of immune system, ulceration of GI tract, and failure of pancreatic beta cells

Stress Responses



2. Resistance reaction:

Stabilizing the body's adaptations to stress

1. Alarm responses

壓力反應：一般適應症候群 (General Adaptation Syndrome)

當代第一位研究持續的嚴重壓力 (stress) 對於人體影響的研究者是 Hans Selye，他是一位加拿大的內分泌學者。1930 年代末，Selye 報告了實驗動物對傷害性事件的一系列複雜反應，這些事件包括細菌感染、中毒、外傷、強制性束縛、炎熱、寒冷等。根據 Selye 的壓力理論，許多種壓力都會引發相同的反應或一般性的身體反應。所有這些壓力源 (stressor) 需要「適應」，即一個生物體必須尋回其平衡或穩定，從而維持或恢復其完整和安寧。

Selye 將個體面對壓力的整個適應過程的生理反應稱為「一般適應症候群」(general adaptation syndrome, GAS)，包括三個階段：警戒反應期 (stage of alarm response)、抵抗期 (stage of resistance) 和耗竭期 (stage of exhaustion)。警戒反應期是一個短暫的生理喚醒期，當個體感受到壓力時所產生的反應，如交感神經活化、腎上腺皮質激素增加等，使身體做好準備應對壓力。如果壓力源持續存在，則會進入抵抗期。在抵抗期內，警戒反應消退，個體嘗試適應壓力源，調整對環境刺激的反應程度。然而，如果壓力源持續的時間過長或強度過大，身體的資源將會耗盡，個體將會進入耗竭期，難以再應付壓力，可導致疾病的產生。

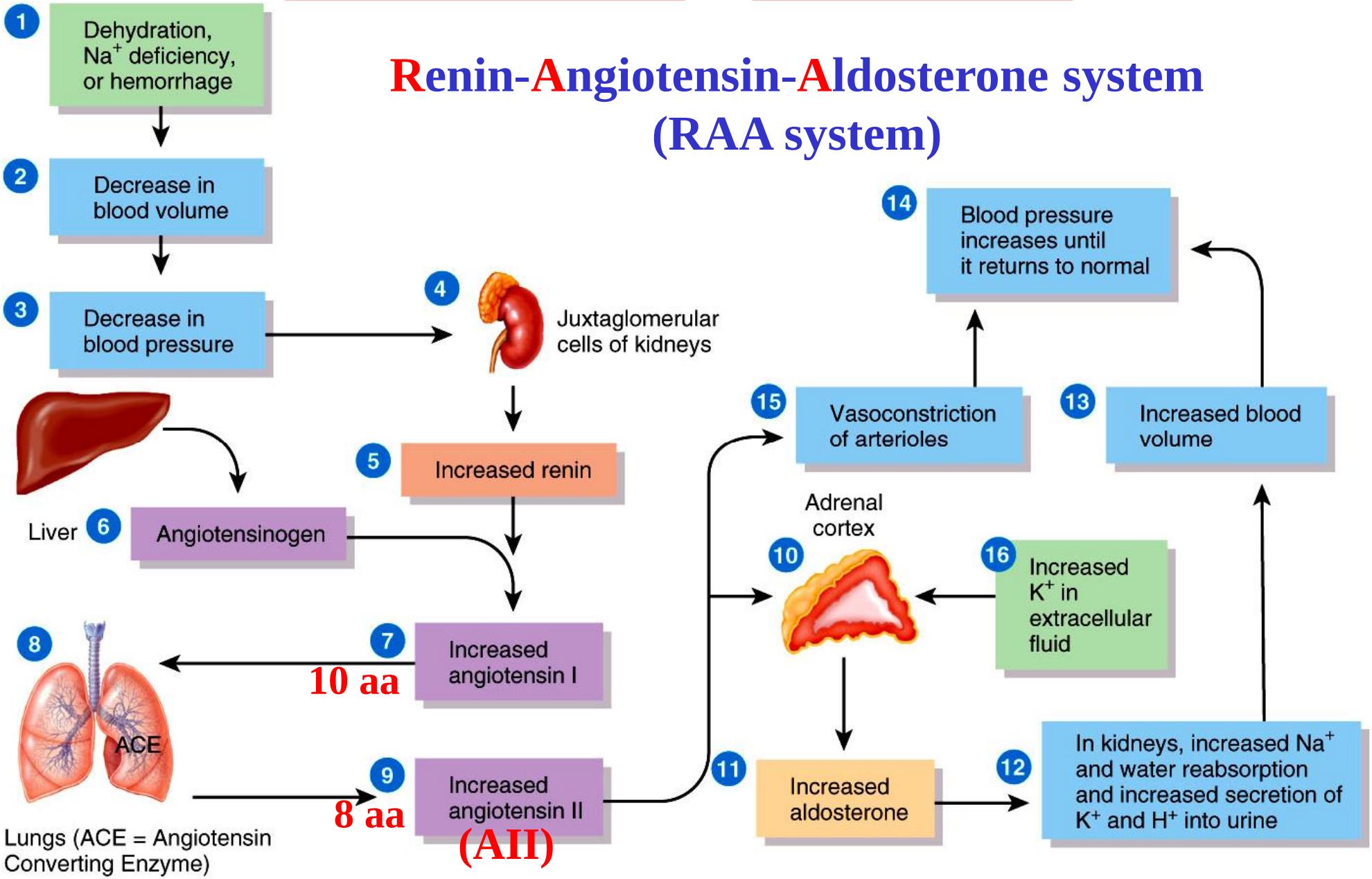
長期的壓力會導致某些嚴重的健康問題，例如：引起高血壓和動脈硬化；影響免疫功能，增加引發感冒、感染、風濕性關節炎、癌症、疱疹、愛滋病的機會；肌肉疼痛或僵硬（特別是頸部、肩膀和下背部）；緊張或偏頭痛等。

Stress Responses vs. Relaxation Responses

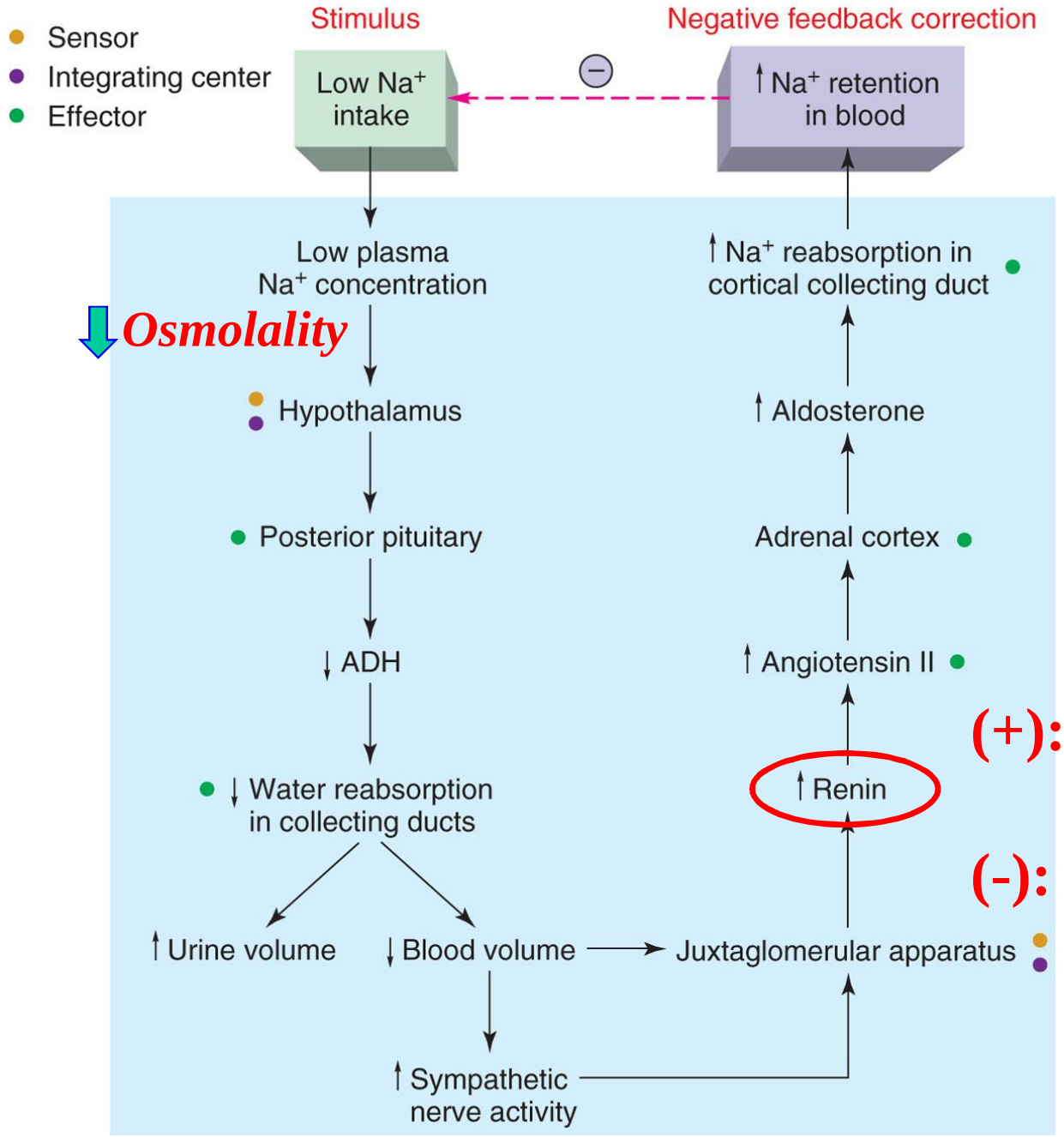
Are You Happy?

Control of Aldosterone Secretions

Blood K^+ level & RAA system



Control of Plasma Na Balance



(+): ***Sym. sti. (β1) NE, Epi, PG***

(-): ***AII, ADH PG inhibitors (NSAIDs) Salt loading***

Corticosteroid Secretion Disorders

Hyposecretion: *Primary Adrenal Insufficiency*

Atrophy of adrenal cortex (occasionally occurs with destructive disease of the gland, e.g. tuberculosis, cancer.)

gives
inadequate production of all *corticoids*:-

↓ 'MINERALOCORTICOID' EFFECT:

ADDISON'S DISEASE

Inadequate reabsorption of sodium and water and **Reduced tubular secretion** of potassium and hydrogen

Blood sodium level falls (hyponatraemia) → **body fluid** volume decreases (dehydration) → Blood volume falls → **blood pressure falls** (hypotension) → ↑ risk of **circulatory failure**

Hydrogen retention → **metabolic acidosis**

Potassium retention → Potassium **intoxication** (hyperkalaemia) → Muscular weakness and wasting

(Increase in blood urea eventually)

Excessive loss of sodium and water in urine (polyuria)

Potassium level falls in Urine

↓ 'ADRENAL ANDROGEN' EFFECT: Females show loss of pubic and axillary hair.

↓ 'GLUCOCORTICOID' EFFECT:

GLUCOSE formation from **PROTEIN** is depressed → Fasting blood sugar level low (hypoglycaemia) .... may be fatal. Reduced mobilization of proteins and fat causes lack of energy for metabolism.

Patients show:

Great muscular weakness and **wasting**, **great loss** of **weight**, **loss** of **appetite**
hypotension,
vomiting and **abdominal pain.**
anaemia (↓ RBC formation)
pigmentation of exposed and pressure areas of **skin** (due to rise in *ACTH* which has melanophore-stimulating properties).
↓ resistance to **stress** and **infections**.
Increased eosinophils and lymphocytes in blood.

If untreated, eventually fatal.

Corticosteroid Secretion Disorders

Hypersecretion: Primary Adrenal Hyperplasia

Overactivity or tumour of adrenal cortex may give **overproduction of any or all of the corticoids:**

Conn's syndrome=

e.g. **ALDOSTERONE** → **PRIMARY ALDOSTERONISM**

↑ **TUBULAR SECRETION** of K^+ and H^+ (lost with water) → Signs of **potassium depletion** predominate

ALKALOSIS

MUSCLE WEAKNESS → Occasional periods of muscular paralysis due to nerve blocks

Excessive reabsorption of Sodium and Water → ↑ Blood sodium → Expanded ECF volume **HYPERTENSION** ↑ BP

↓ loss of Na^+ ↑ of K^+ and H^+ in urine

Overproduction of **CORTISOL** *and/or* **CORTICOSTERONE** → **CUSHING'S SYNDROME**

↑ RBC → polycythaemia → florid complexion

↑ viscosity of blood → ↑ BP

Excess **glucose** formation from **protein** → ↓ Tissue protein ↓ Connective tissue

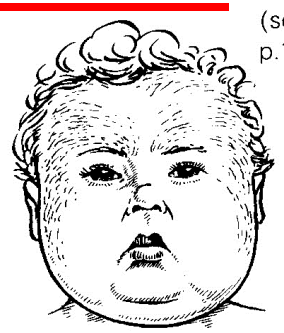
Purple striae in skin, muscular wasting

Altered resistance to stress

High blood sugar → Obesity especially of face and trunk

Lipolysis ↑ → ↑ Free fatty acids in blood

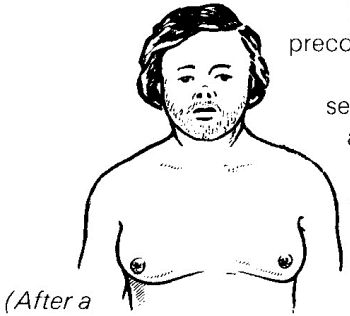
Glucose in urine



(see also p.182)

Overproduction of **ADRENAL ANDROGENS** → **ADRENOGENITAL SYNDROME**

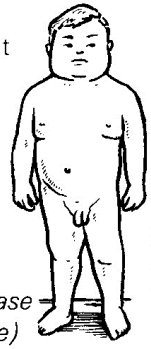
(Frequently excess production of *androgens*)



In CHILDREN precocious development of secondary sex characteristics and secondary sex organs

Virilism in 9-year-old girl

(After a case by Kepler et al.)

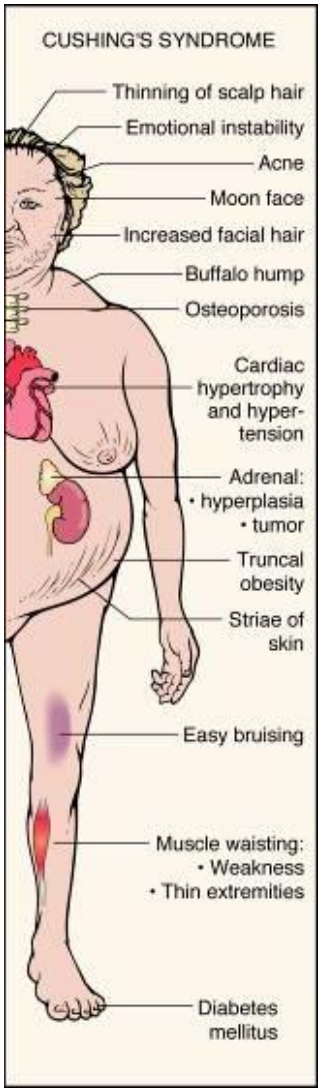


(After a case by Guthrie)

Muscular hypertrophy in 6-year-old boy 'Pocket Hercules'

Virilism in ADULT woman

Secondary: --AII or renin



Adrenal Medulla Secretion Disorders

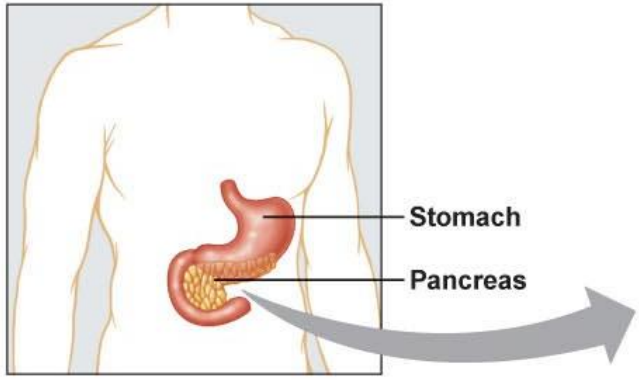
Hypersecretion: Pheochromocytoma

Epidemiology	Adults; both sexes; all ages, especially 30–50 years
Biologic behavior	90% benign; 10% malignant
Secretion	High levels of catecholamines; most secrete norepinephrine
Clinical presentation	Episodic or sustained hypertension, sweating, palpitations, hyperglycemia, glycosuria
Macroscopic features	Mass, often hemorrhagic; 10% bilateral; 10% extra-adrenal

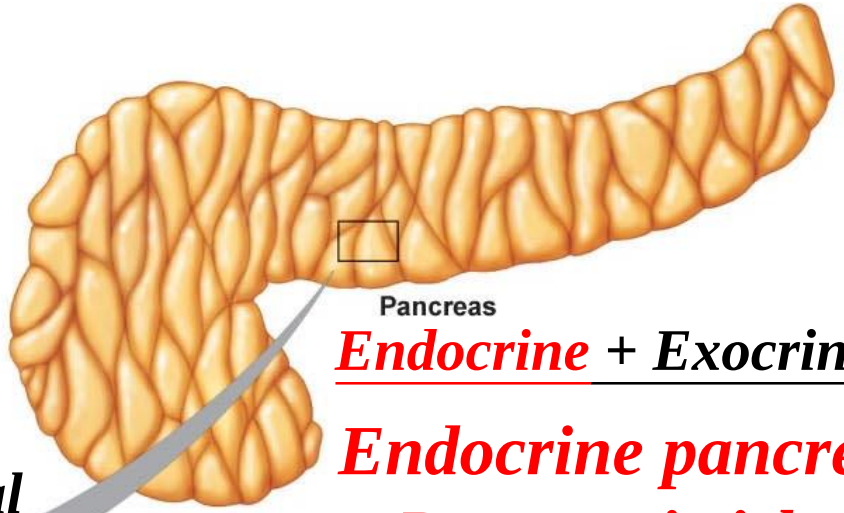
嗜鉻性細胞瘤

- Neuroendocrine tumor of the **adrenal medulla (chromaffin cells)**
- Extra-adrenal chromaffin tissue secretes excessive amounts of **catecholamines (Epi and NE)**
- Signs and symptoms are those of **sympathetic nervous system hyperactivity**

Anatomy of the Pancreas

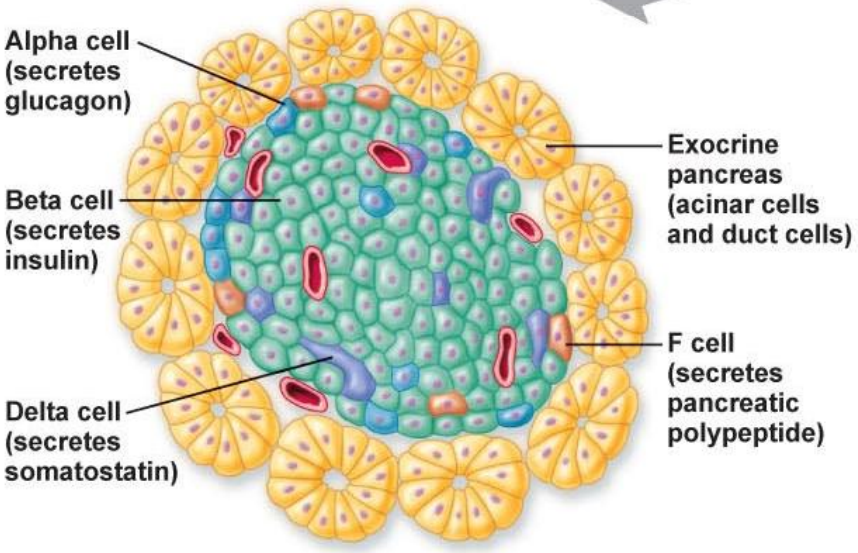


(a) *Located in the abdominal cavity below the stomach*

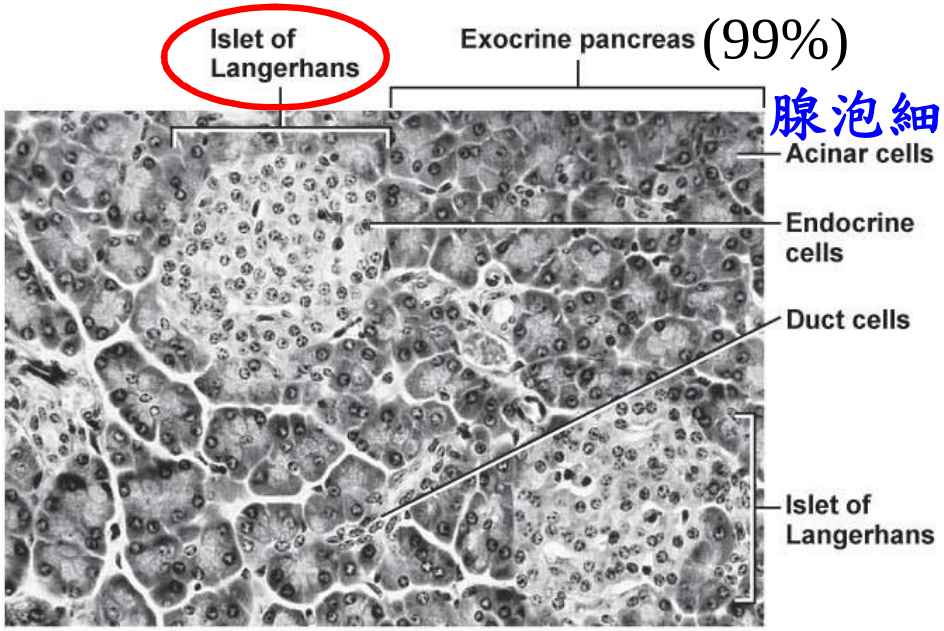


Endocrine* + *Exocrine gland

Endocrine pancreas = Pancreatic islets

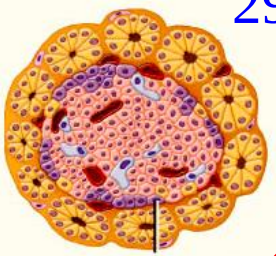
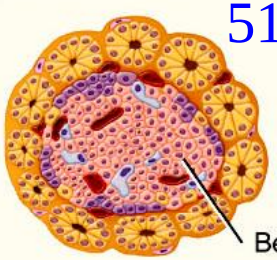
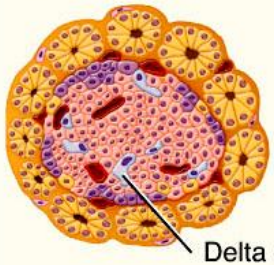
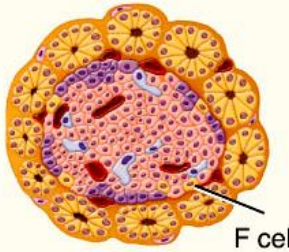


(b)

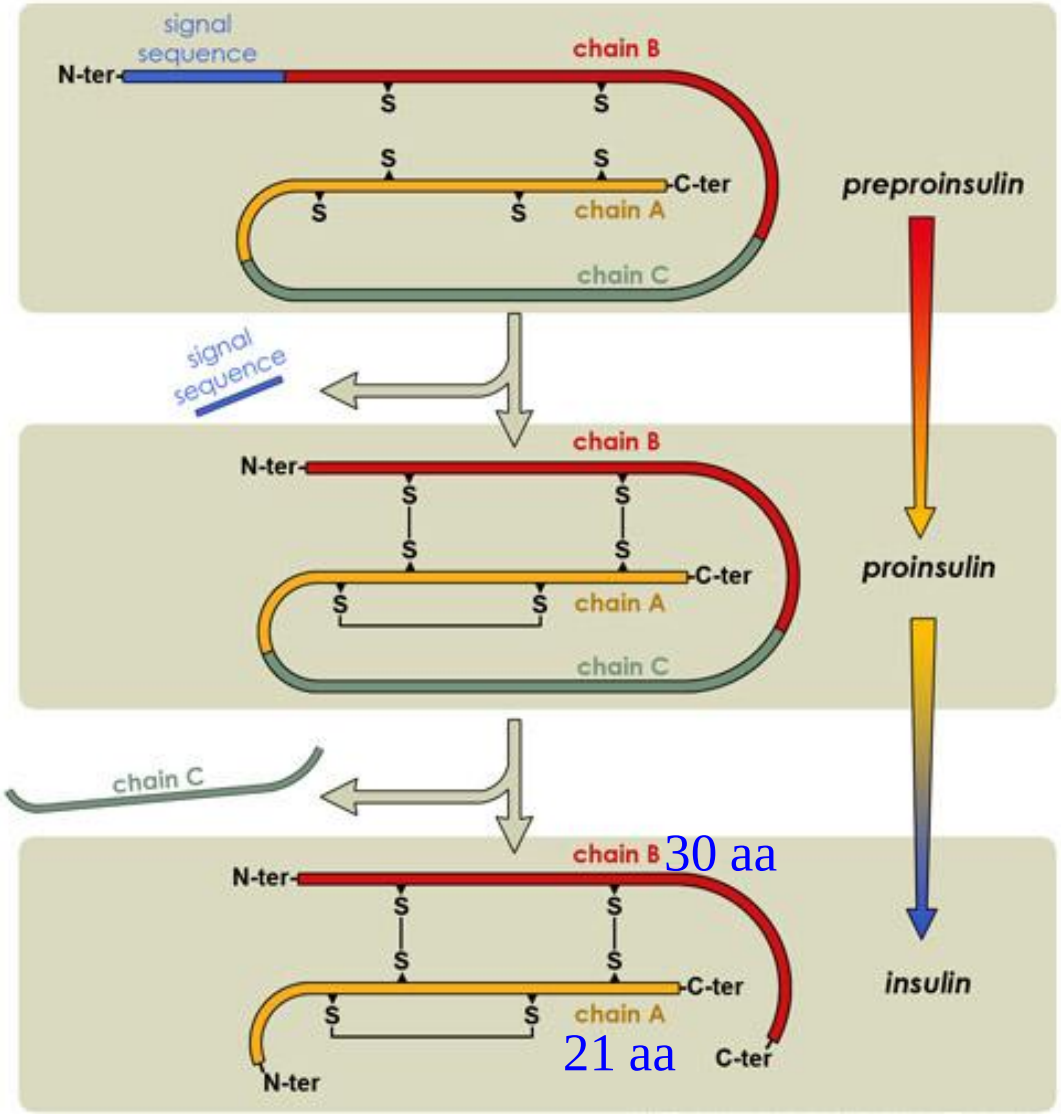


(c)

Summary of Pancreatic Islet Hormones

HORMONE AND SOURCE	CONTROL OF SECRETION	PRINCIPAL ACTIONS
Glucagon from alpha cells of pancreatic islets 29 aa  (20%)	Decreased blood level of glucose, exercise, and mainly protein meals stimulate secretion; somatostatin and insulin inhibit secretion.	Raises blood glucose level by accelerating breakdown of glycogen into glucose in liver (glycogenolysis), converting other nutrients into glucose in liver (gluconeogenesis), and releasing glucose into the blood.
Insulin from beta cells of pancreatic islets 51 aa  (60~70%)	Increased blood level of glucose, acetylcholine (released by parasympathetic vagus nerve fibers), arginine and leucine (two amino acids), glucagon, GIP, hGH, and ACTH stimulate secretion; somatostatin inhibits secretion.	Lowers blood glucose level by accelerating transport of glucose into cells, converting glucose into glycogen (glycogenesis), and decreasing glycogenolysis and gluconeogenesis; also increases lipogenesis and stimulates protein synthesis.
Somatostatin from delta cells of pancreatic islets  (10%)	Pancreatic polypeptide inhibits secretion.	Inhibits secretion of insulin and glucagon and slows absorption of nutrients from the gastrointestinal tract.
Pancreatic polypeptide from F cells of pancreatic islets 	Meals containing protein, fasting, exercise, and acute hypoglycemia stimulate secretion; somatostatin and elevated blood glucose level inhibit secretion.	Inhibits somatostatin secretion, gallbladder contraction, and secretion of pancreatic digestive enzymes.

Insulin

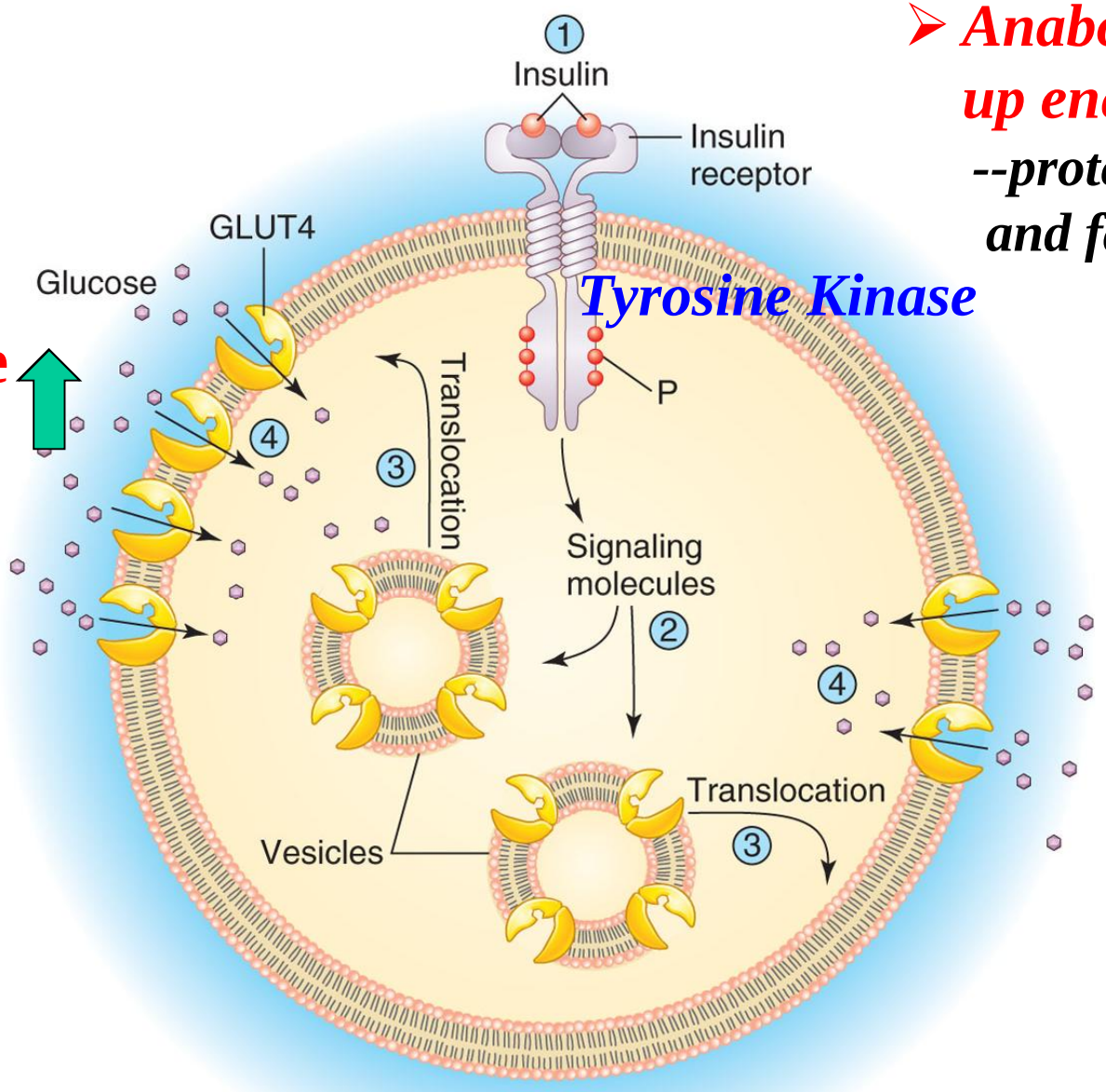


- The name comes from the Latin ***insula*** for "**island**“
- A **peptide hormone** composed of **51** amino acids (the B- and A-chains, are bound together by **disulfide bonds**)
- Secreted from **beta (B) cells** of the islets of Langerhans of the pancreas
- Its purpose is to **lower blood glucose levels** to the “normal” range
  - --Promotes synthesis of energy storage molecules (**anabolic reactions**)
  - --Promotes **glucose uptake** by body cells

Action of Insulin

Insulin is an anabolic hormone

- ***Anabolism to build up energy stores***
  --protein, glycogen and fat storage

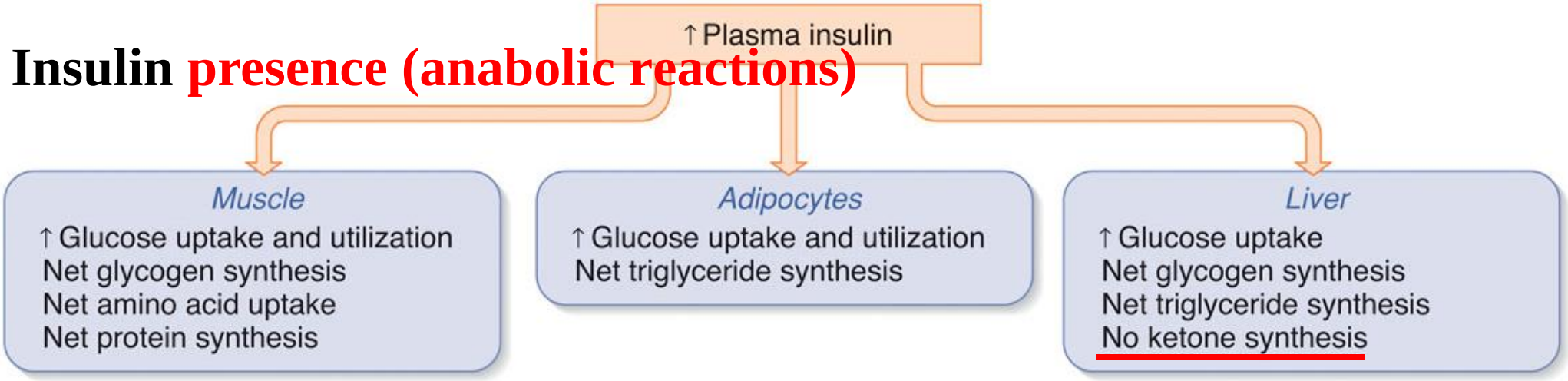


Glucose uptake & utilization

Skeletal muscle, Adipose tissue and Liver

Taget-cell Responses of Insulin

Insulin presence (anabolic reactions)



1. Anabolism to build up energy stores

--Glycogen synthesis

--Triglyceride synthesis

--Protein synthesis

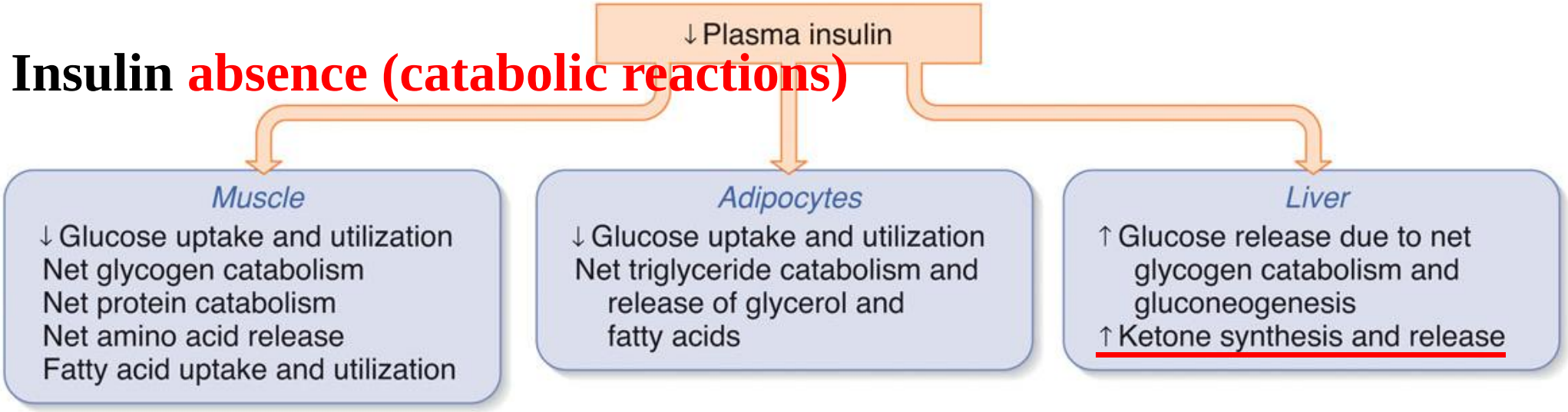
2. Promote glucose use for energy

--Increase glucose uptake by cells

3. Decrease catabolism

Taget-cell Responses of Insulin

Insulin absence (catabolic reactions)



酮体 (ketone body)：Acetone，Acetoacetate，β-hydroxybutyrate

1. Increase catabolism

--Glycogen catabolism (glucose release)

--Triglyceride catabolism (fatty acid and glycerol release)

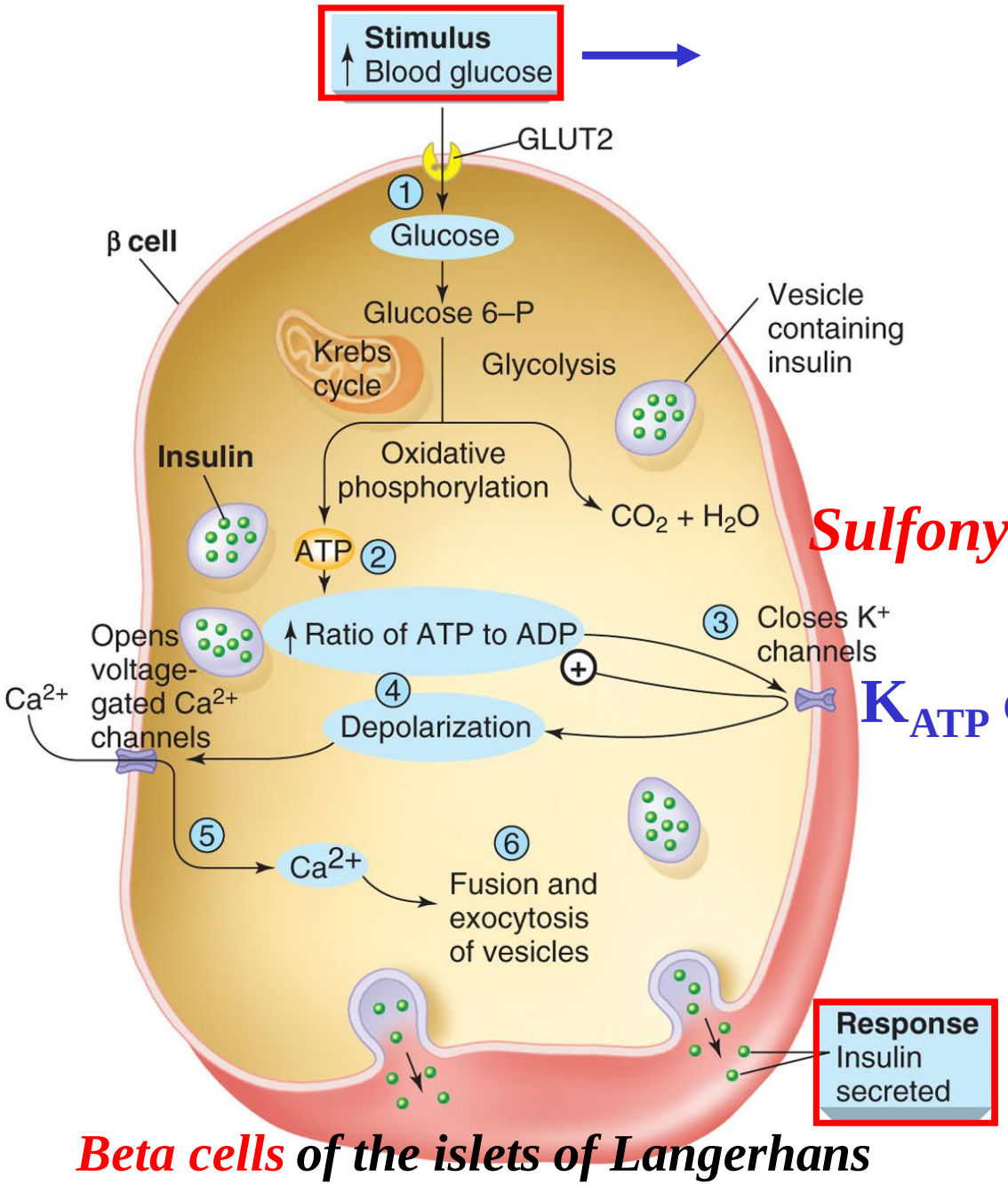
--Protein catabolism (amino acid release)

2. Decrease glucose use for energy

--Decrease glucose uptake by cells

3. Decrease anabolism

Regulation of Insulin Secretion

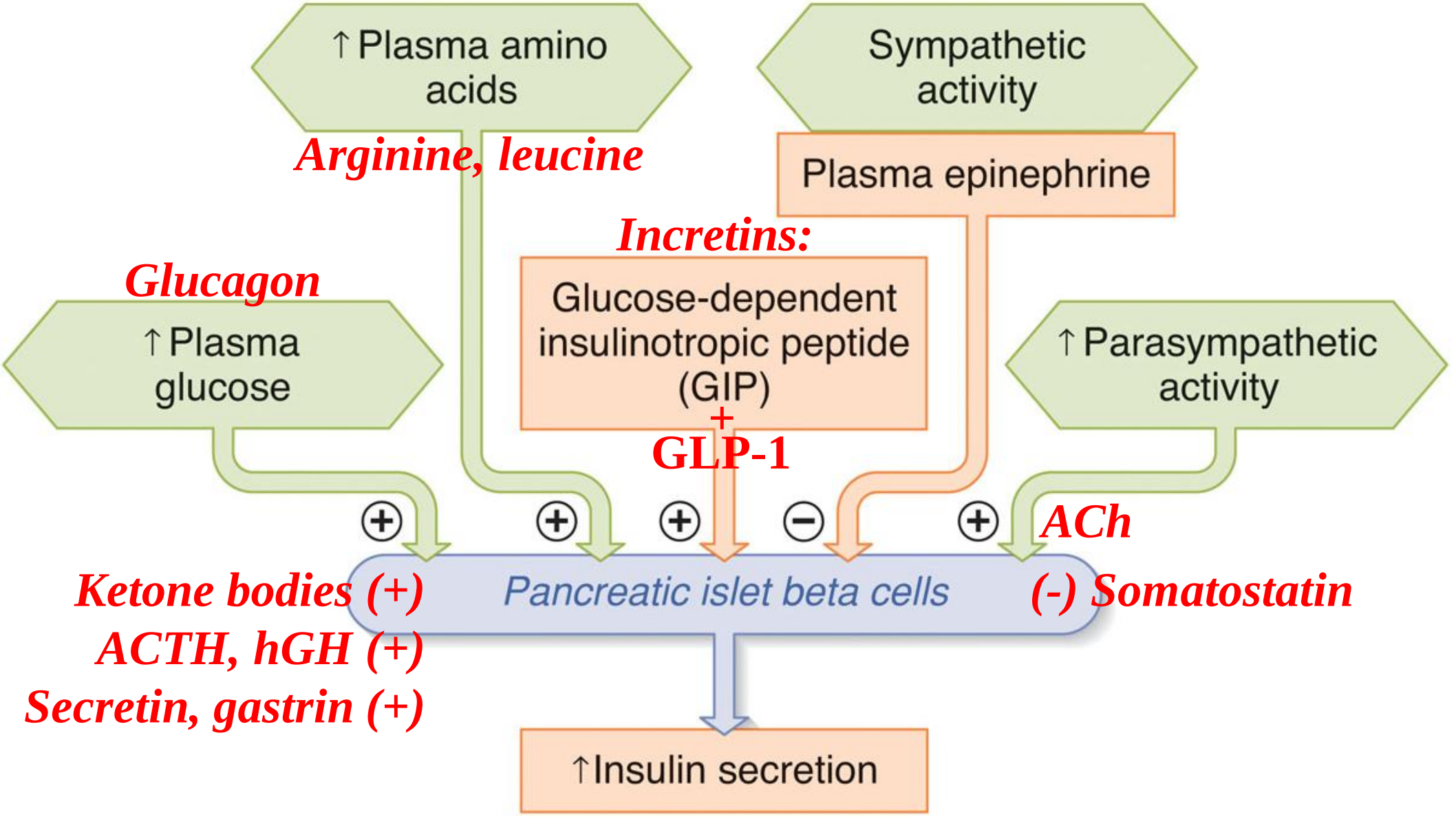


Sulfonylurea therapy

K_{ATP} channel

***Beta cells* of the islets of Langerhans**

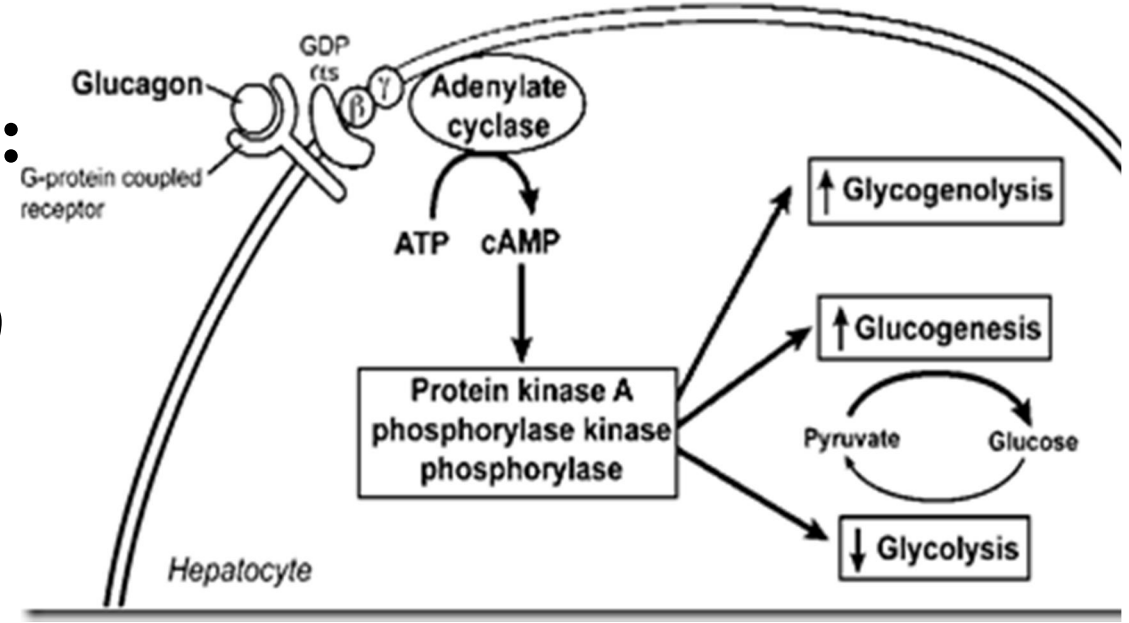
Regulation of Insulin Secretion



GLP-1:Glucagon-like peptide-1

Glucagon

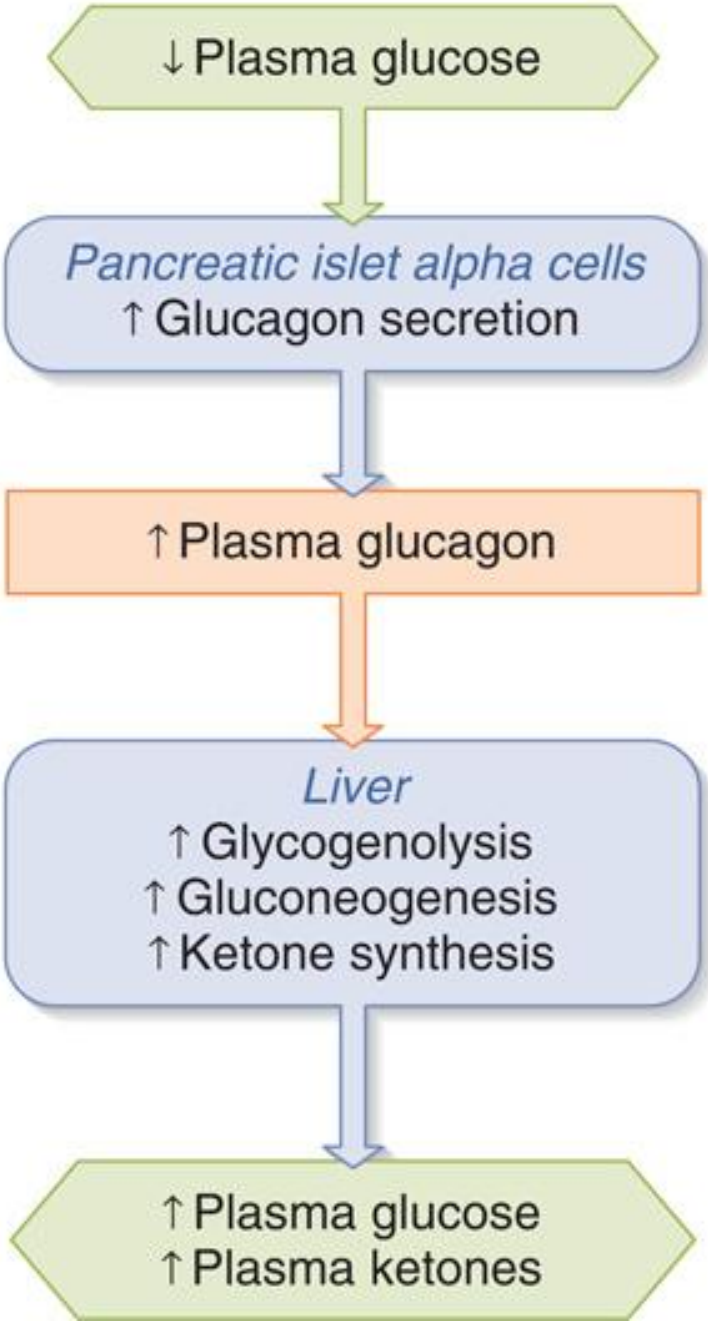
- **Antagonistic** to insulin
- **Peptide** hormone (**29 aa**) secreted by **alpha cells** when blood glucose levels are low
- Promotes breakdown of energy storage molecules (**catabolic reactions**)
- **Action of mechanism:**
  activates cAMP system (adenylate cyclase)
- Purpose is to raise blood glucose levels to a "normal" range



Taget-cell Responses of Glucagon

Catabolic Reactions

1. Stimulates liver to hydrolyze glucagon into glucose and release it into the blood (**glycogenolysis**)
2. Stimulates **gluconeogenesis**, conversion of noncarbohydrates (aa or fa) into glucose
3. Stimulates **lipolysis** in adipose tissue so fat is released and used as a fuel source instead of glucose in liver (**ketogenesis**)



Regulation of Glucagon Secretion

Stimulated by:

- ✓*Hypoglycemia*
- ✓*Sym. activity stimulation*
- ✓*Parasym. activity stimulation*
- ✓*Epinephrine*
- ✓*Plasma amino acid ex.arginine*
- ✓*Acetylcholine*
- ✓*Cholecystokinin*
- ✓*Exercise*
- ✓*Trauma*
- ✓*Infection*

Inhibited by:

- ✓*Hyperglycemia*
- ✓*Somatostatin*
- ✓*Insulin*
- ✓*Incretin*
- ✓*Free fatty acids*
- ✓*Free keto acids*
- ✓*Urea production*

Incretin腸泌素: GIP and GLP-1

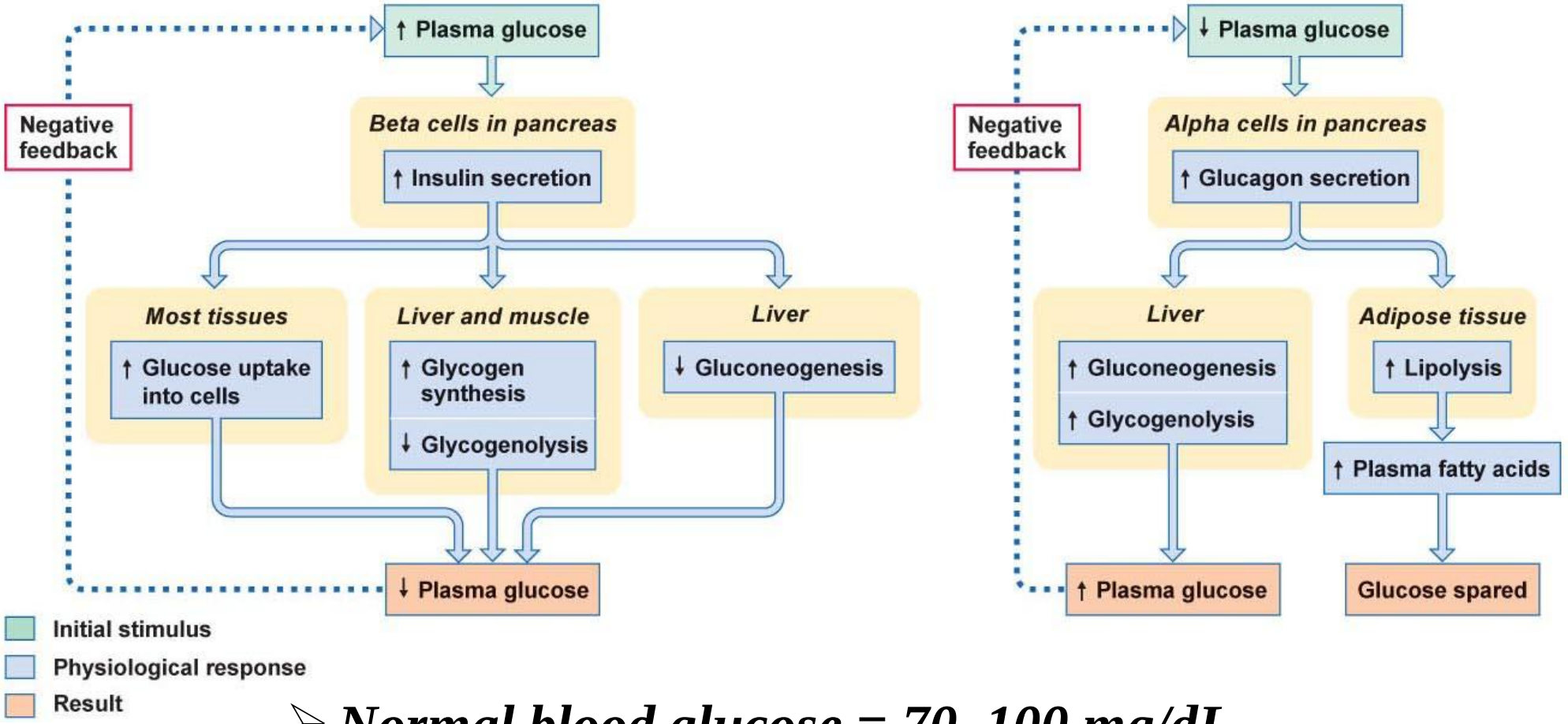
＋ insulin release

－ glucagon release

Factors Affecting Insulin and Glucagon Release

Factor	Effect on insulin secretion	Effect on glucagon secretion
↑ Plasma [glucose]	Increase	Decrease
↑ Plasma [amino acids]	Increase	Increase
↑ Plasma [GIP]	Increase	Increase
↑ Parasympathetic activity	Increase	Increase
↑ Sympathetic activity	Decrease	Increase
↑ Plasma [epinephrine]	Decrease	Increase

Regulation of Plasma Glucose Concentration

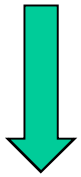


- ***Normal blood glucose = 70–100 mg/dL***
- ***Hyperglycemia = glucose > 140 mg/dL***
- ***Hypoglycemia = glucose < 60 mg/dL***
- ***Blood glucose levels maintained primarily by actions of insulin and glucagon***

Clinical Application:

Diabetes Mellitus (DM)

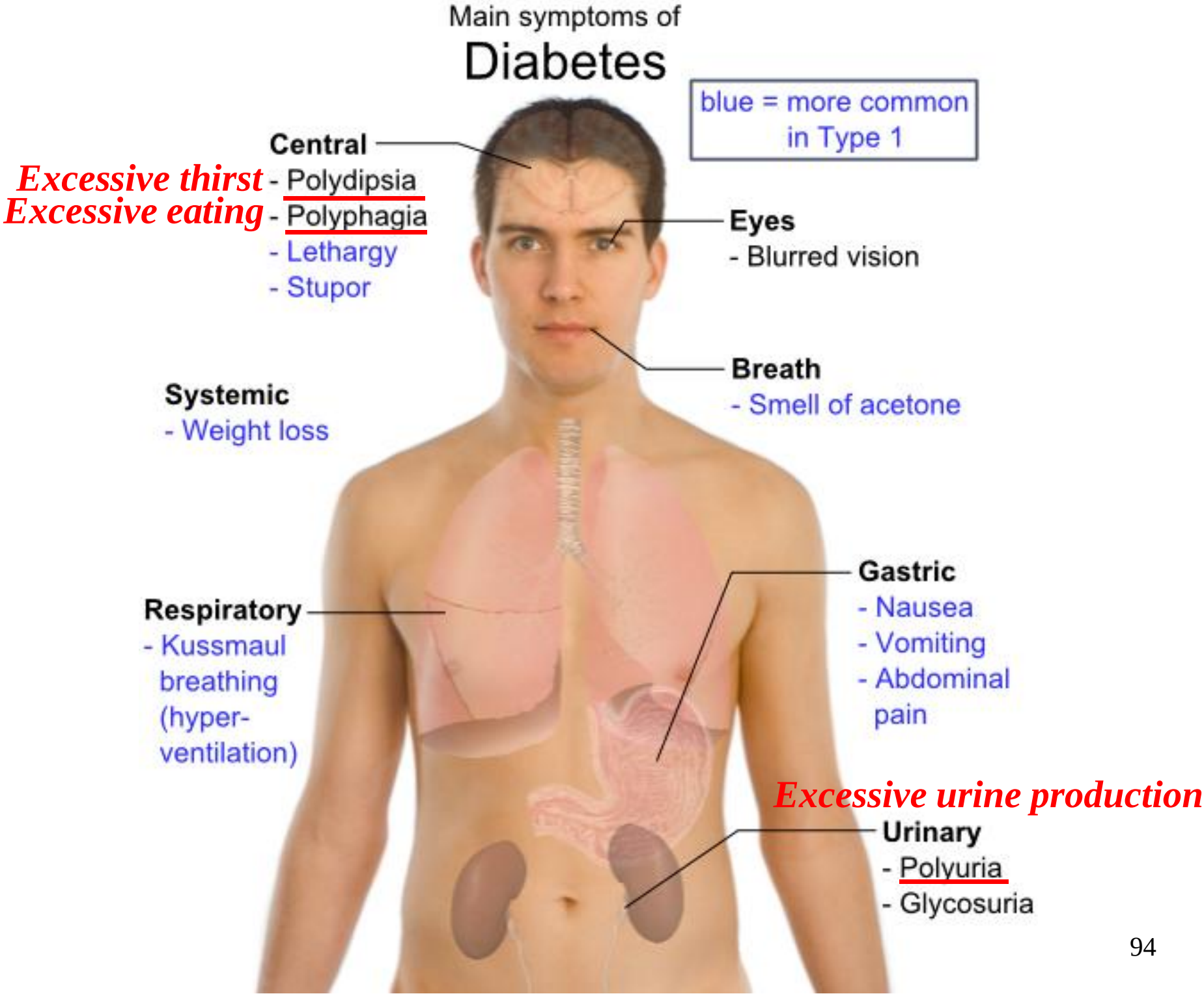
Inadequate secretion Or action of insulin



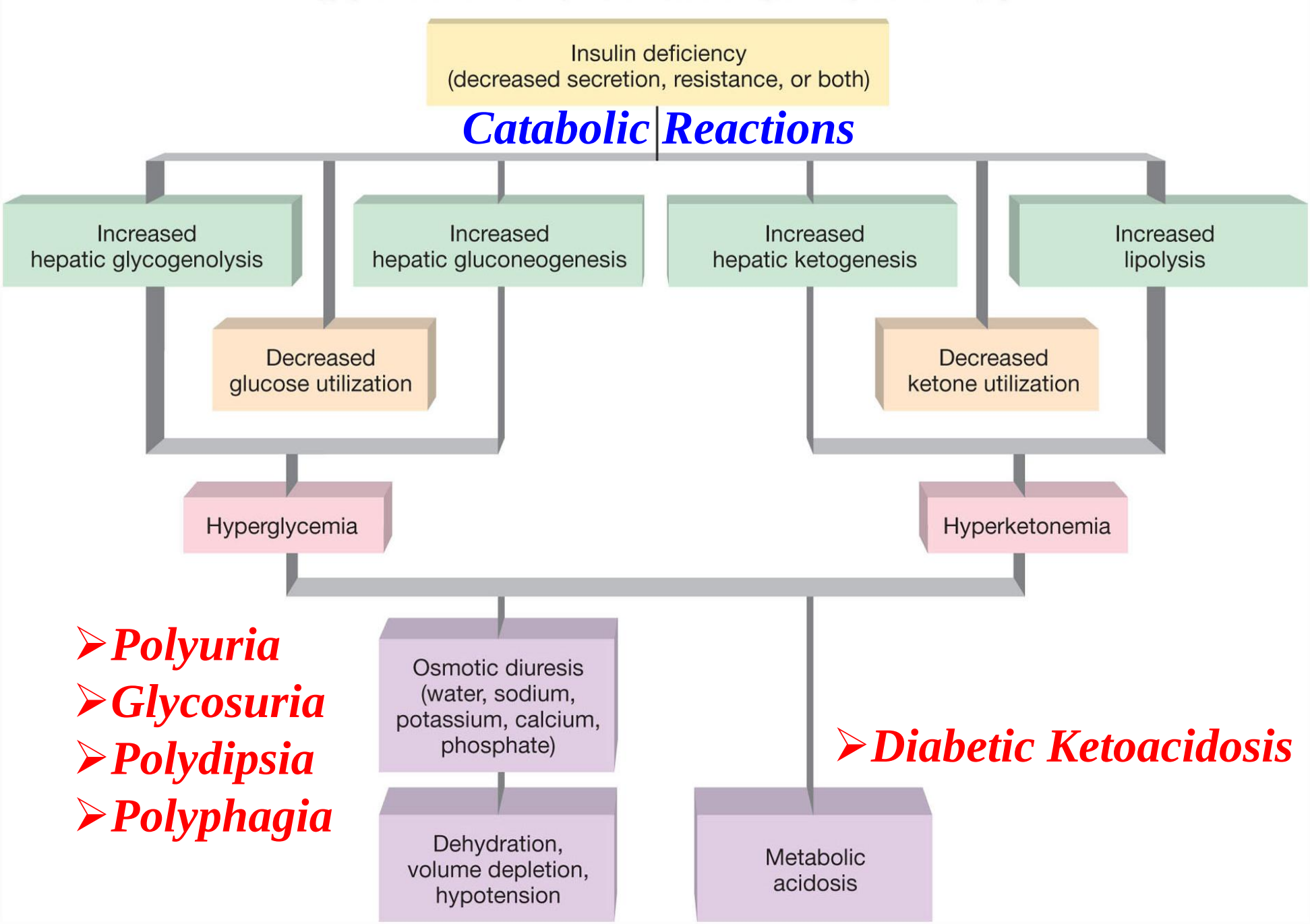
Chronic hyperglycemia

- **Type I (IDDM): Insulin-dependent diabetes or juvenile-onset diabetes**
- **Type II (NIDDM): Insulin-independent diabetes**

Feature	Type 1	Type 2
Usual age at onset	Under 20 years	Over 40 years
Development of symptoms	Rapid	Slow
Percentage of diabetic population	About 5%	About 95%
Development of ketoacidosis	Common	Rare
Association with obesity	Rare	Common
Beta cells of islets (at onset of disease)	Destroyed	Not destroyed
Insulin secretion	Decreased	Normal or increased
Autoantibodies to islet cells	Present	Absent
Associated with particular MHC antigens*	Yes	Unclear
Treatment	Insulin injections	Diet and exercise; oral stimulators of insulin sensitivity


Main symptoms of
Diabetes
blue = more common in Type 1
Central
- Polydipsia
- Polyphagia
- Lethargy
- Stupor
Excessive thirst
Excessive eating
Eyes
- Blurred vision
Breath
- Smell of acetone
Systemic
- Weight loss
Respiratory
- Kussmaul breathing (hyper-ventilation)
Gastric
- Nausea
- Vomiting
- Abdominal pain
Excessive urine production
Urinary
- Polyuria
- Glycosuria

Pathophysiology of Type I Diabetes

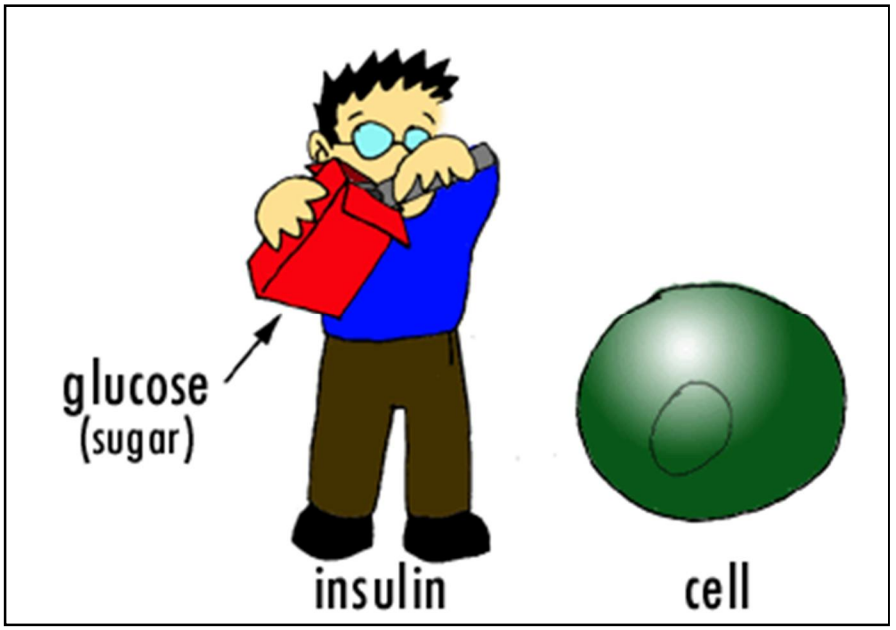


- ***Polyuria***
- ***Glycosuria***
- ***Polydipsia***
- ***Polyphagia***

- ***Diabetic Ketoacidosis***

Insulin Sensitivity

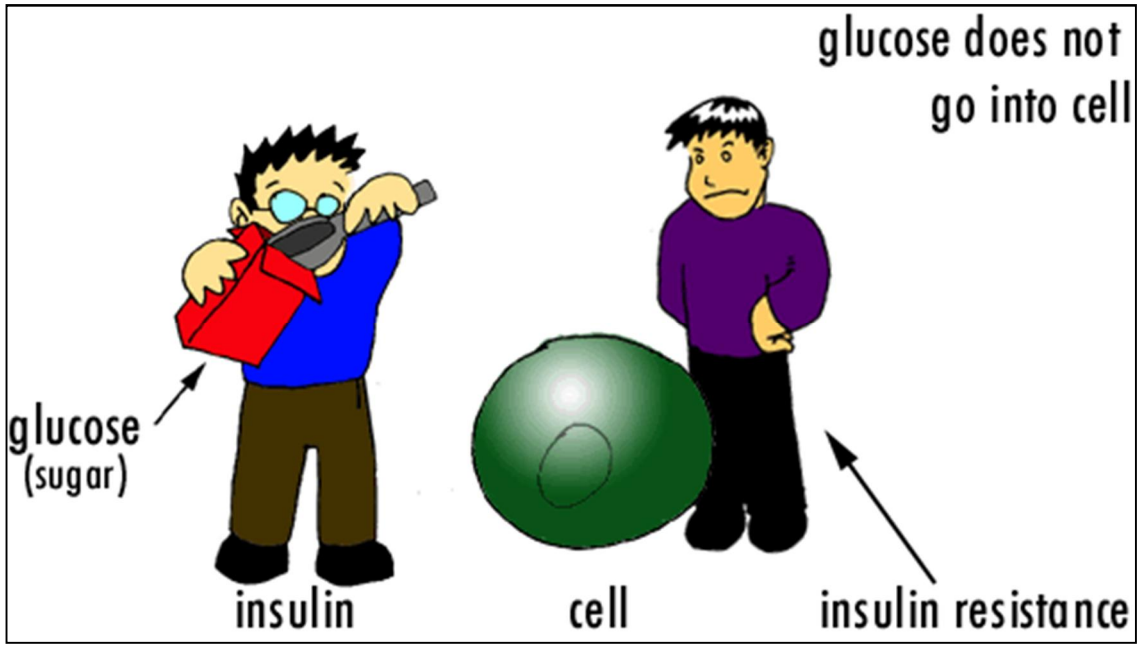
- **A medical term used to describe people who require relatively normal or low levels of insulin to process glucose**
- **Varies from person to person and from situation to situation**
  - --**Exercise** makes skeletal muscle cells more sensitive to insulin
    Increasing production of GLUT4 and caloric expenditure (lose fat cells)
  - --**Obesity** makes all insulin target cells less sensitive to insulin
    An obese person must secrete more insulin to get the same effects as an average-weight person
  - --Can lead to **impaired glucose tolerance** or **type II diabetes**



Type II Diabetes

Insulin Resistance

Very low insulin sensitivity in target cell



- **Type II diabetes (NIDDM) is most likely to occur in obese people**
  - --A person with a **BMI > 30** is five times as likely to develop diabetes as someone with a **BMI < 25**
  - --Research shows that type II diabetics can reduce the severity of the disease by **losing weight**
  - **--Weight reduction** can also **prevent** the disease from developing

Hypoglycemic Agents for Type II Diabetes

- **Initial therapy**

  --***Lifestyle*** ***to decrease weight and to increase activity***

  --***Biguanides (BGs)*** ***(-formin): Metformin (inh. hepatic gluconeogenesis)***

- **Additional therapy**

  --***Sulfonylurea (SU)*** ***(-amide) : Tolbutamide, Glibenclamide (sti. liver insulin release)***

  --***Thiazolidinediones (TZDs)*** ***(-glitazone): Troglitazone, Pioglitazone, Rosigitazone (Insulin sensitizers--PPARγ activator: sti. GLUT4 activity)***

  - **PPARγ: peroxisome proliferator-activated receptors**
    --Nuclear receptor proteins that function as transcription factors regulating the expression of genes

Hypoglycemic Agents for Type II Diabetes

- **Other new therapy**

  --***Incretins (GI hormones: GLP-1 + GIP) Therapy***

  1. ***Incretin mimetics (GLP-1 agonist) (-tide):***
     Exenatide, Liraglutide (injection form)

  2. ***Incretin enhancer (DPP-4 inhibitors) (-agliptin):***
     Vildagliptin (Galvus), Sitagliptin (Januvia) oral form

  --***α-Glucosidase inhibitor (AGIs) (-bose, -ol):***
  Acarbose, Miglitol

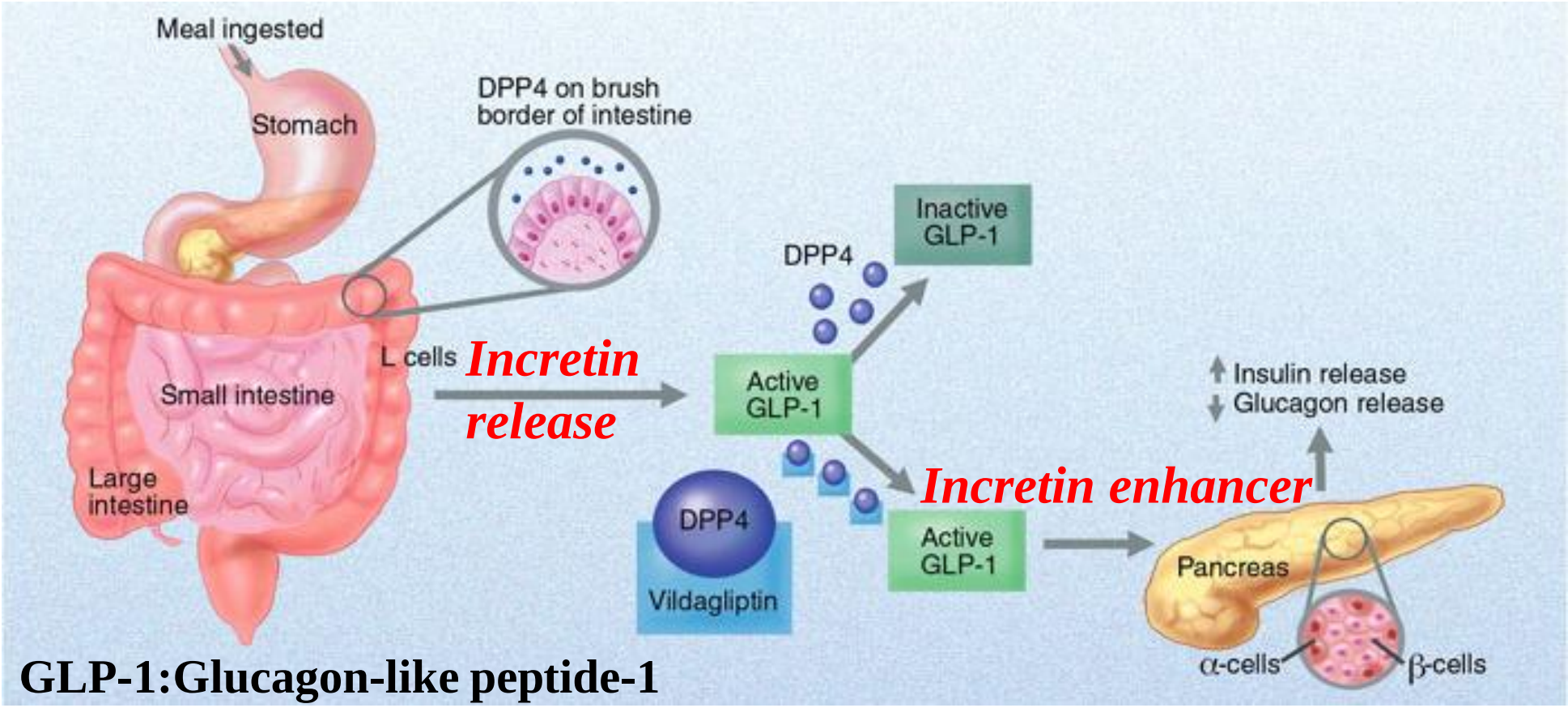
  - **GLP-1:Glucagon-like peptide-1**
  - **DPP-4 : Dipeptidyl peptidase IV (degradation of incretins)**

Clinical Application:

Vildagliptin (Galvus) and Sitagliptin (Januvia)

DPP-4 Inhibitors

Improved Glycemic Control in Type II Diabetes



GLP-1:Glucagon-like peptide-1

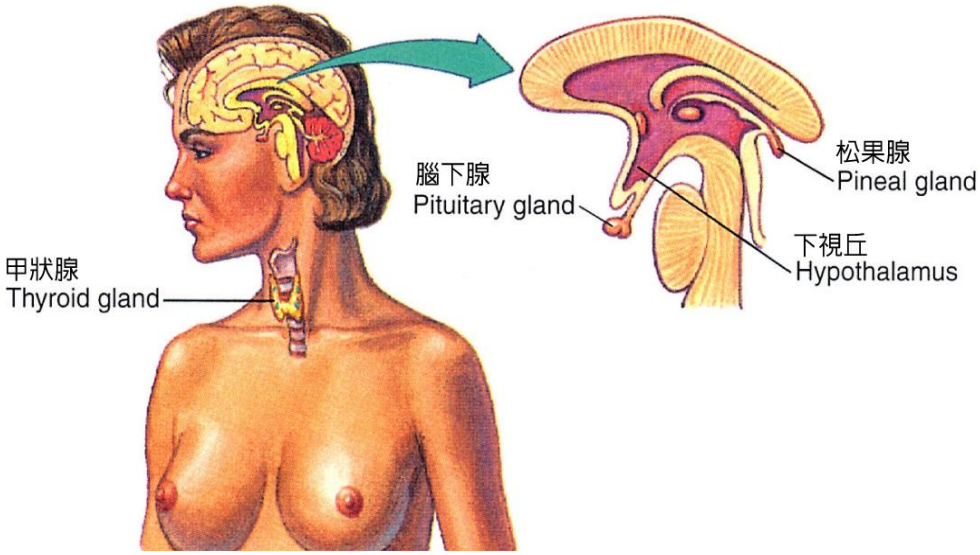
DPP-4 : Dipeptidyl peptidase IV (degradation of incretins)

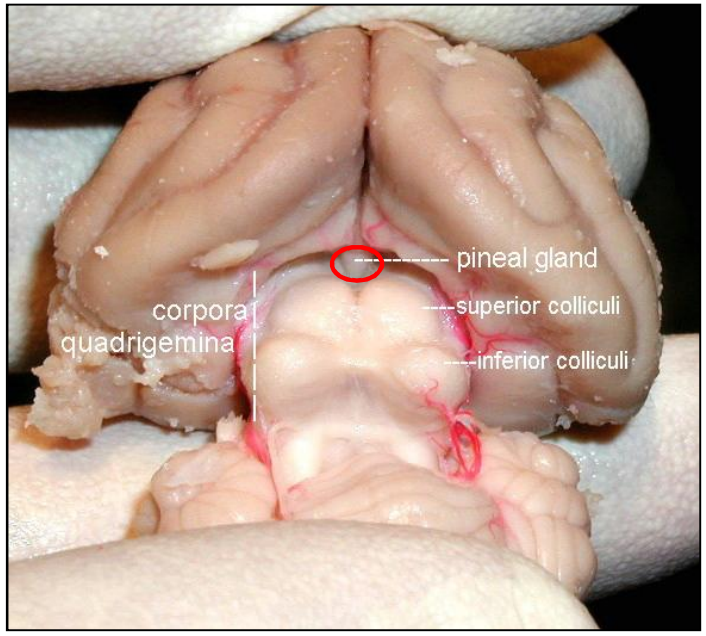
知識小補帖 Knowledge Supplements

低血糖症 (hypoglycemia) 是指因血糖過低，導致患者出現神智不清、視力模糊、感覺異常、頭暈、噁心、出冷汗、心悸、肌肉震顫等症狀，嚴重時可導致昏迷。低血糖症可因蘭氏小島細胞增生或腫瘤、服用降血糖藥物或注射胰島素等原因，導致體內胰島素過多而引起。進食醣類之後，蘭氏小島 β 細胞若對於血糖上升反應過度，分泌過量胰島素，常造成輕微低血糖症狀，稱為**反應性低血糖症** (reactive hypoglycemia)。此外，對胰島素過度敏感、肝臟疾病、藥物中毒、攝取醣類不足等，亦可造成低血糖症。

- ***Severe Hypoglycemia*** ***can occur in response to insulin injections***
- ***Insulin shock*** ***is a severe case of hypoglycemia leading to coma***

Pineal Gland

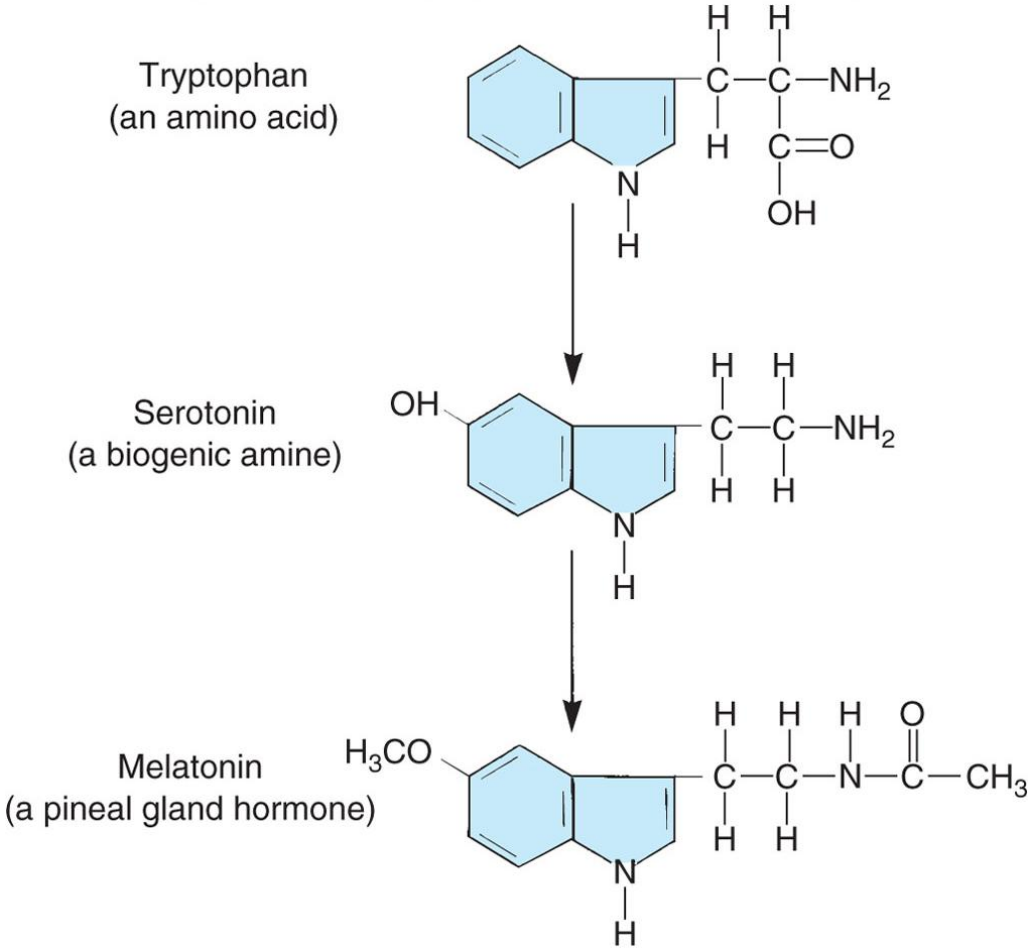




- Small gland located on **roof of 3rd ventricle** of brain
- Consists of **pinealocytes** & neuroglia
- **Melatonin** (**amine** hormone) responsible for setting of **biological clock**
- Melatonin regulated by the **suprachiasmatic nucleus (SCN)** of the hypothalamus
- Melatonin have **antigonadal function**

Melatonin

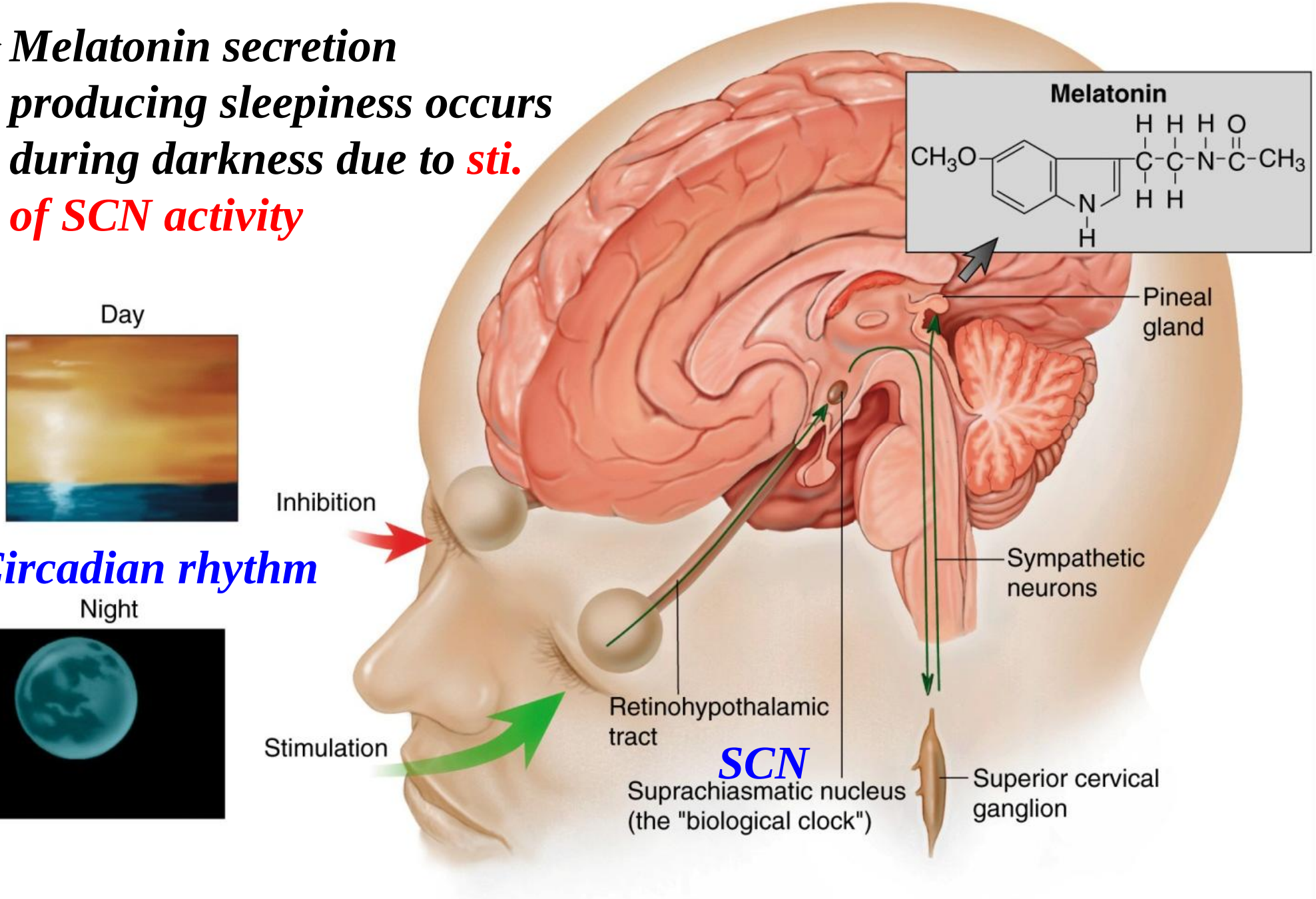
- **Potential treatments:**
  - ✓ ***Cancer***
  - ✓ ***Immune disorders***
  - ✓ ***Cardiovascular diseases***
  - ✓ ***Depression***
  - ✓ ***Seasonal affective disorder (SAD)***
  - ✓ ***Circadian rhythm sleep disorders (Jet lag)***
  - ✓ ***Sexual dysfunction***



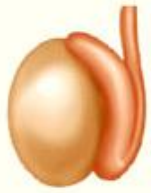
Amine hormone derived from serotonin

Effect of Day-Night Cycle on Pineal Gland

- ***Melatonin secretion producing sleepiness occurs during darkness due to sti. of SCN activity***



Summary of Hormones of the Ovaries and Testes

HORMONE	PRINCIPAL ACTIONS
OVARIAN HORMONES	
Estrogens and progesterone	Together with gonadotropic hormones of the anterior pituitary, regulate the female reproductive cycle, regulate oogenesis, maintain pregnancy, prepare the mammary glands for lactation, and promote development and maintenance of female secondary sex characteristics.
 Ovaries	
Relaxin	Increases flexibility of pubic symphysis during pregnancy and helps dilate uterine cervix during labor and delivery.
Inhibin	Inhibits secretion of FSH from anterior pituitary.
TESTICULAR HORMONES	
Testosterone	Stimulates descent of the testes before birth, regulates spermatogenesis, and promotes development and maintenance of male secondary sex characteristics.
 Testes	
Inhibin	Inhibits secretion of FSH from the anterior pituitary.

Secondary Endocrine Organs

- **Adipose tissue:** ***Leptin, Adiponectin***
- **Heart:** ***Atrial natriuretic peptide (ANP)***
- **Kidneys:** ***Erythropoietin (EPO), Renin***
- **Skin and kidneys:** ***Calcitriol (1,25-DHCC)***
- **Liver:** ***Insulin-like growth factors (IGFs) (somatomedins)***
- **Placenta:** ***Human chorionic gonadotropin (hCG), Human placental lactogen (hPL), Estrogen (estriol) and Progesterone***
- **GI tract:** ***Gastrin, Cholecystokinin (CCK), Secretin*** **and** ***Incretin (GLP-1 and GIP)***

The Endocrine System: Regulation of Energy Metabolism and Growth

Nutrients

Nutrients are chemical substances in food that body cells use for growth, maintenance, and repair

	Form absorbed across GI tract	Form circulating in blood	Form stored	Storage site	Percentage of total energy stored
Carbohydrates	Glucose	Glucose	Glycogen	Liver, skeletal muscle	1%
Proteins	Amino acids, some small peptides	Amino acids	Proteins	Skeletal muscle*	22%
Lipids	Monoglycerides and fatty acids (in chylomicrons)	Free fatty acids, lipoproteins	Triglycerides	Adipose tissue	77%

*Even though proteins are found in all cells of the body, most of the proteins mobilized for energy come from skeletal muscle cells.

- ***6 main types***
  - ***--Water: needed in largest amount***
  - ***--Carbohydrates, Proteins and Lipids***
  - ***--Minerals***
  - ***--Vitamins***

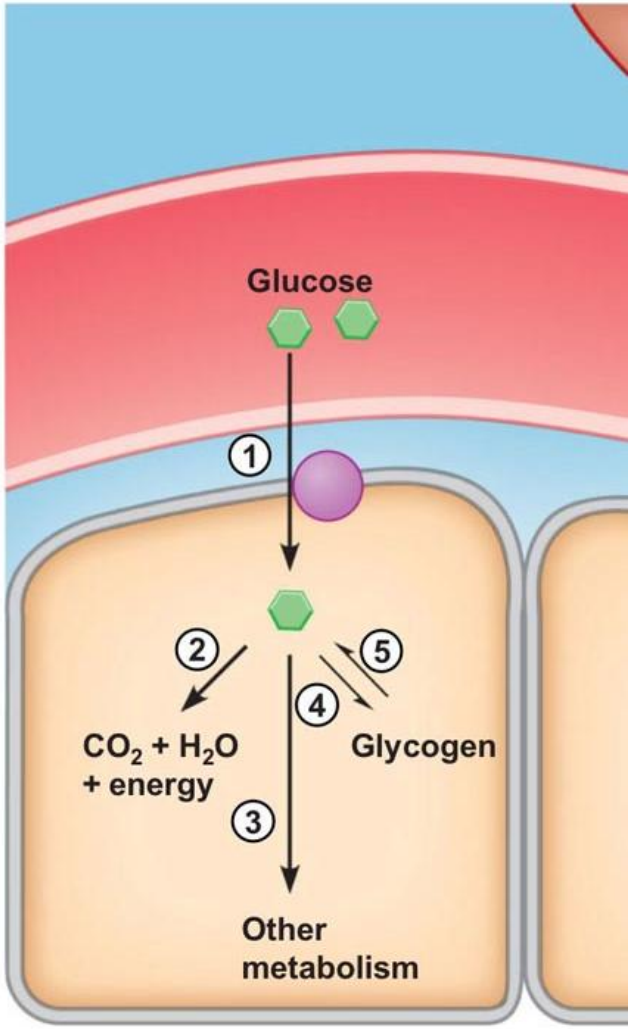
- ***<u>Essential nutrients</u> must be obtained from the diet***

Major Vitamins

維生素	來源	作用	缺乏造成的症狀
A	黃色蔬菜及水果	視覺色素的構成物；加強上皮膜的結構	夜盲症、皮膚乾燥
B_1 (硫胺)	肝、未精製的穀類	催化脫羧基酵素的輔因子	腳氣病 (beriberi)、神經炎
B_2 (核黃素)	肝、牛奶	黃素蛋白的一部分 (如 FAD)	舌炎、口角炎
B_6 (吡哆醇)	肝、玉米、麥、酵母	脫羧基酵素及轉胺酶的輔酶	痙攣
B_{12} (氰鈷胺)	肝、肉、蛋、牛奶	胺基酸代謝的輔酶；紅血球生成所需	惡性貧血
生物素 (biotin)	蛋黃、肝、番茄	脂肪酸合成所需	皮膚炎、腸炎
C	柑橘類、綠色葉菜	結締組織形成膠原所需	壞血病 (scurvy)
D	魚肝	小腸吸收鈣和磷所需	佝僂症 (rickets)、軟骨症 (osteomalacia)
E	牛奶、蛋、肉、葉菜	抗氧化劑	肌肉萎縮 (非遺傳性)
葉酸 (folate)	綠色葉菜	傳遞碳原子反應所必需	口炎性腹瀉 (sprue)、貧血
K	綠色葉菜	促進凝血因子功能	出血；無法形成血凝塊
菸鹼酸 (niacin)	肝、肉、酵母	NAD 及 NADP 的部分	癩皮病 (pellagra)
泛酸 (pantothenic acid)	肝、蛋、酵母	輔酶 A 的部分	皮膚炎、腸炎、腎上腺機能不全

Energy Intake, Utilization, and Storage

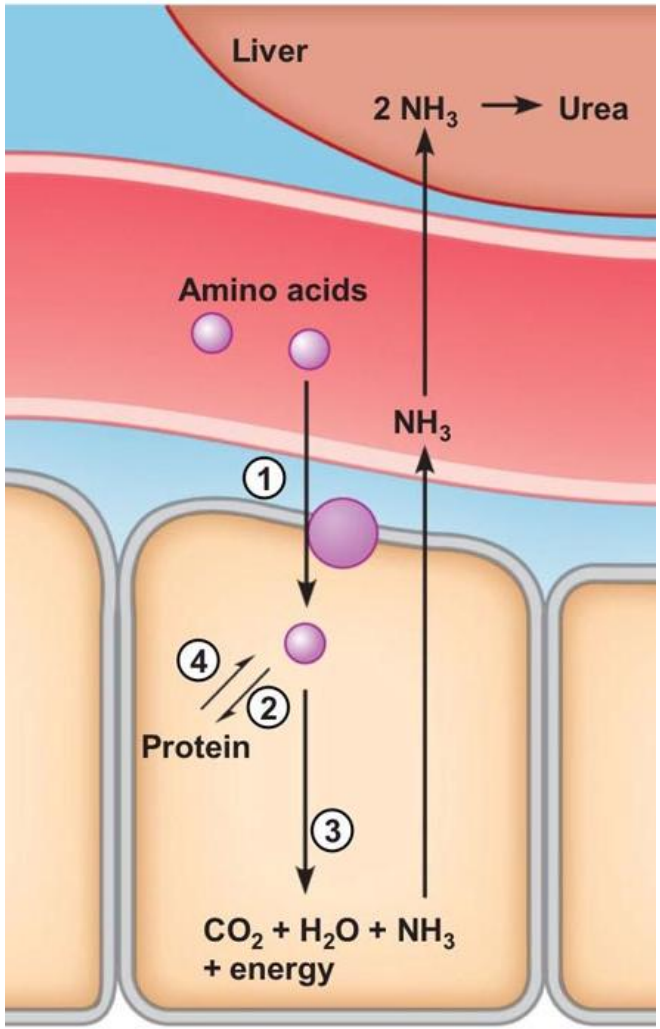
- **Carbohydrates**
  - ***Absorbed forms***
    --Monosaccharides
  - ***Circulating in blood***
    --Glucose
  - ***Usable forms***
    --Glucose → energy
    --Glycogen → stores energy
    --Polysaccharides → membranes



(a) Carbohydrates

Energy Intake, Utilization, and Storage

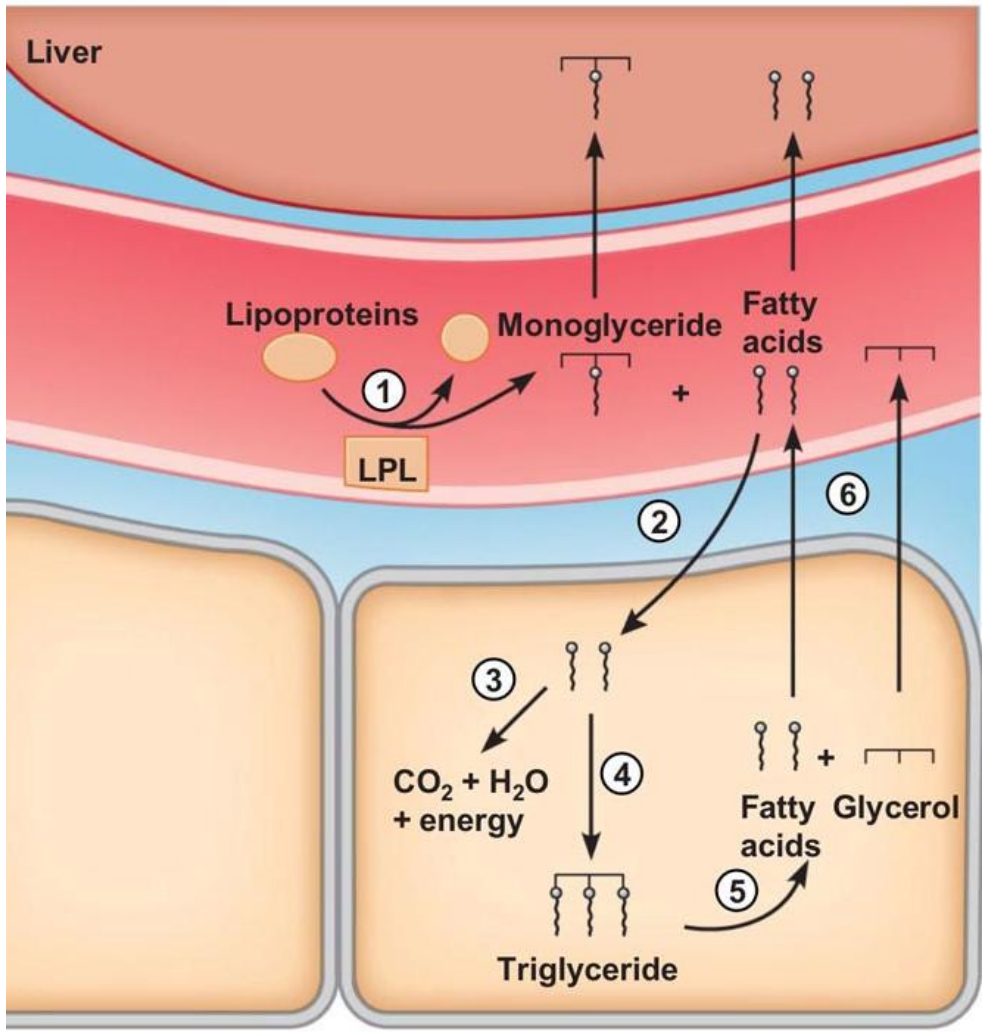
- **Protein**
  - ***Absorbed forms***
    - --Tripeptides
    - --Dipeptides
    - --Amino acids
  - ***Circulating in blood***
    - --Amino acids
  - ***Usable form***
    - --Amino acids → proteins
    - --Amino acids → energy



(b) Proteins

Energy Intake, Utilization, and Storage

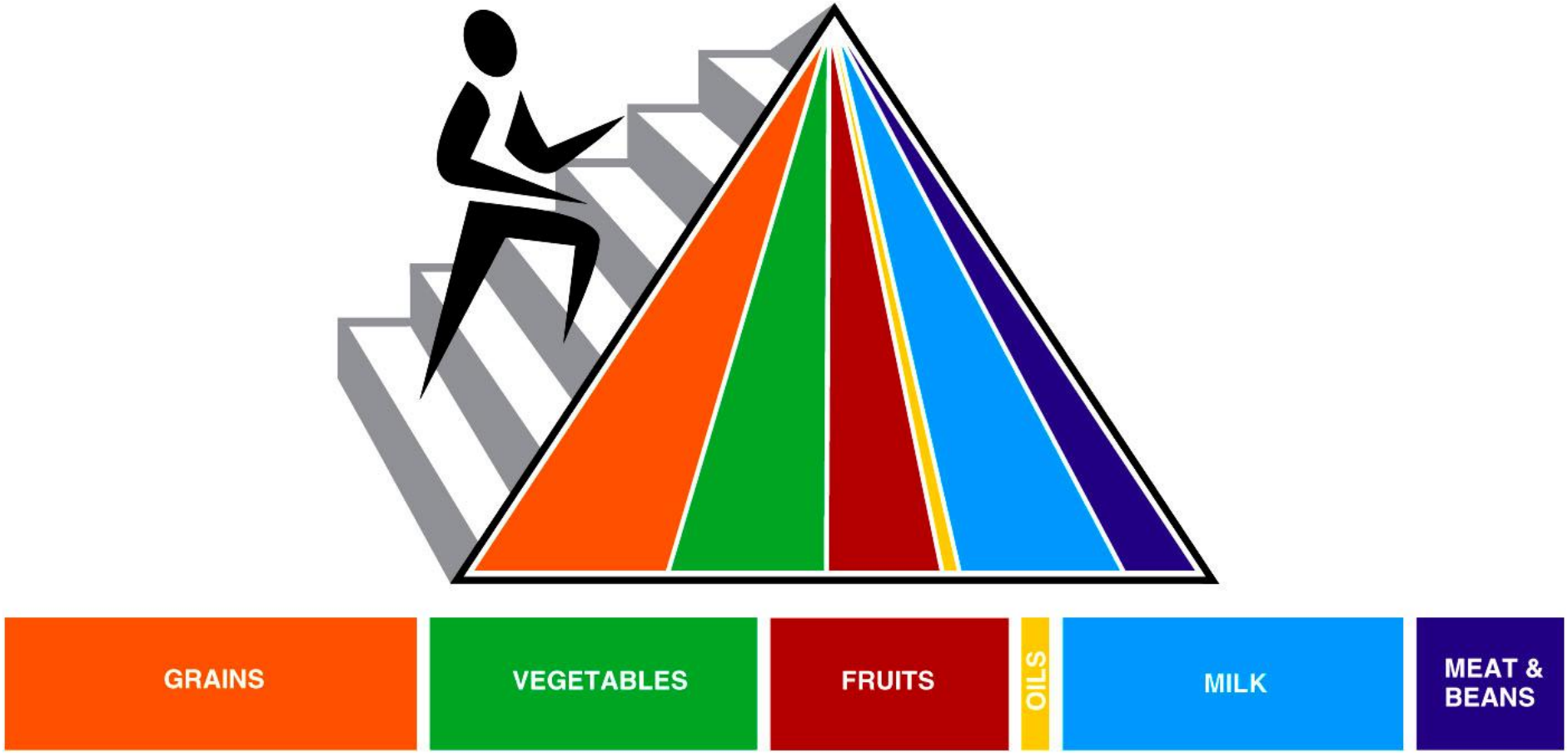
- **Lipids**
  - ➢ ***Absorbed forms***
    - --Triglycerides
  - ➢ ***Circulating in blood in lipoproteins***
    - --Fatty acids
    - --Monoglycerides
  - ➢ ***Usable forms***
    - --Fatty acids → energy
    - --Triglycerides (white fat) → store energy
    - --Steroids and phospholipids



(c) Lipids

MyPyramid

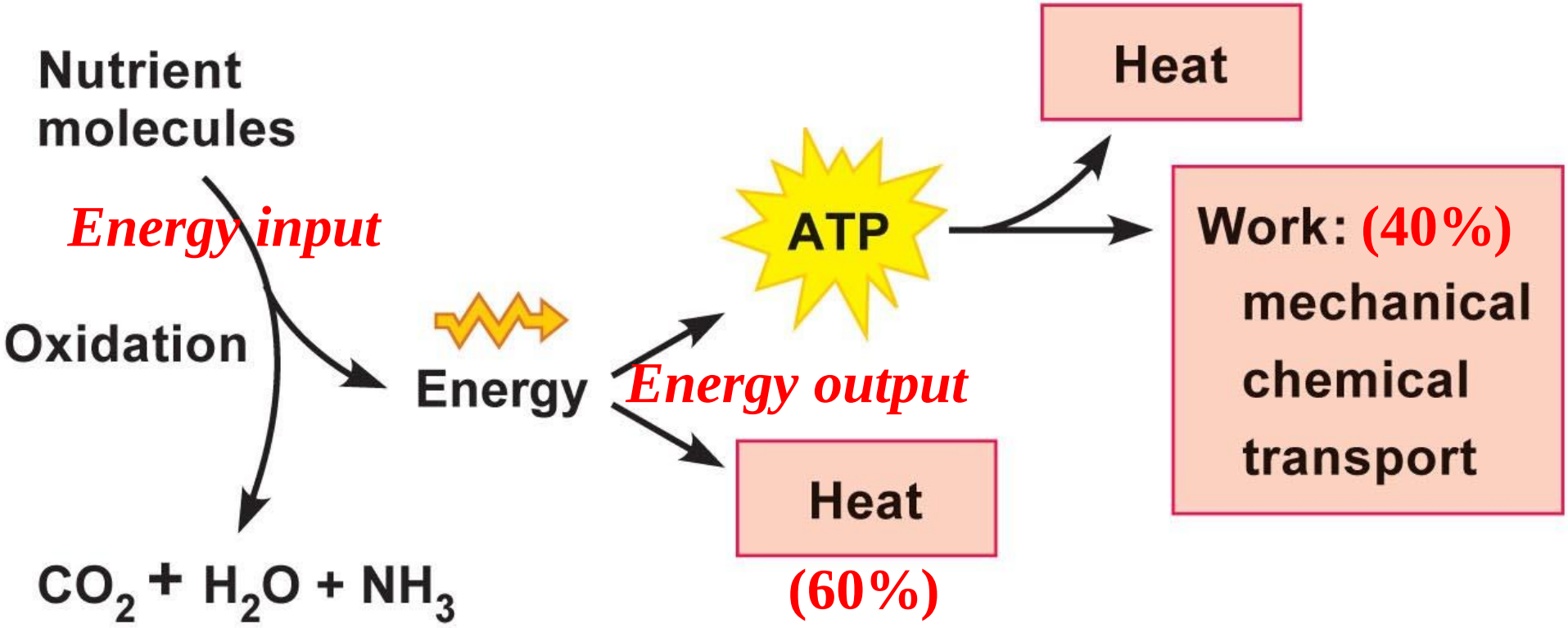
- ***Basic guidelines***
  1. *Eat a variety of foods*
  2. *Maintain a healthy weight*
  3. *Choose foods low in fat, saturated fat and cholesterol*
  4. *Eat plenty of vegetables, fruits and grain products*
  5. *Use sugars in moderation only*



Energy Balance

Energy input (intake) = Energy output (expenditure)

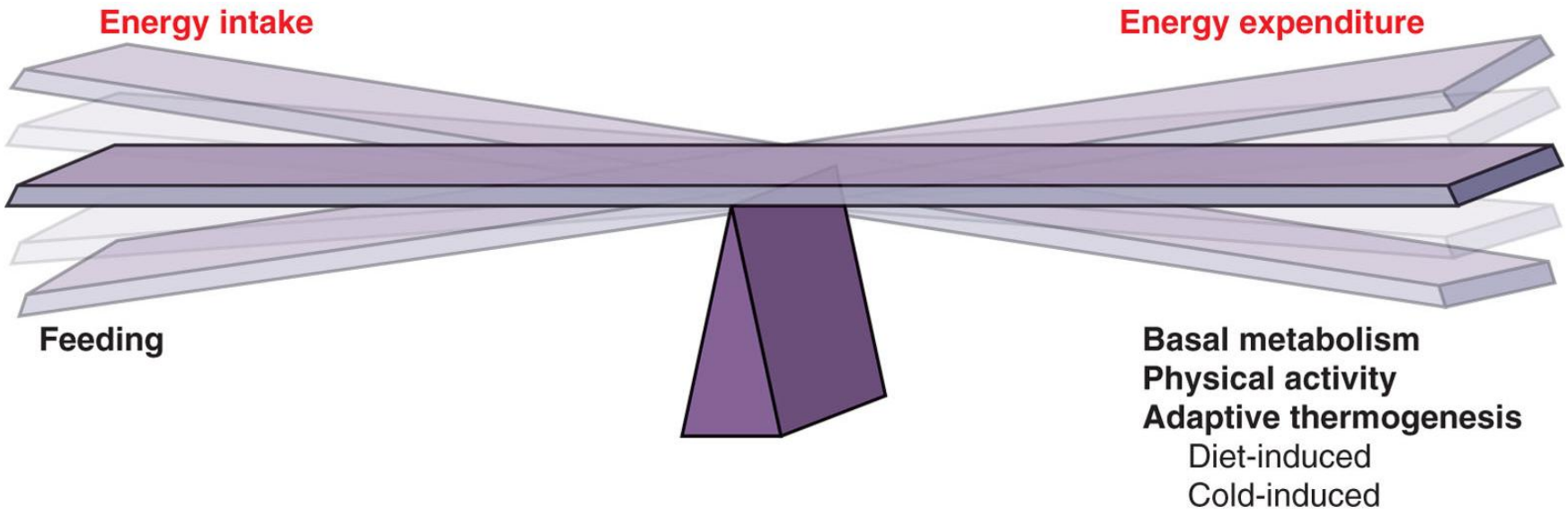
Regulated by Endocrine System



Energy input > Energy output (obesity)

Energy input < Energy output (thin)

Energy Balance



- **Energy expenditure three components:**

  --**Basal metabolic rate (BMR):** rate of energy expenditure of a person awake, resting, lying down, and fasted for 12 hours; **60%** caloric expenditure

  --**Adaptive thermogenesis:** energy expended to adapt to changes in ambient temperature (cold-induced) and digestion/absorption of food (diet-induced); **~10%** caloric expenditure

  --**Physical activity:** highly variable depending on activity levels

Factors Affecting the BMR

Sleep (↓ during sleep)

Age (↓ with ↑ age)

Gender (women less than men at any given size)

Fasting (BMR decreases, which conserves energy stores)

Height, weight, and body surface area
Growth
Pregnancy, menstruation, lactation
Infection or other disease
Body temperature
Recent ingestion of food
Muscular activity
Emotional stress
Environmental temperature
Circulating levels of various hormones, especially epinephrine, thyroid hormone, and leptin

} (The presence of, or an increase in any of these factors causes an increase in metabolic rate.)

Adaptive Thermogenesis

- **Cold promotes cutaneous vasoconstriction and shivering (shivering requires a lot of energy)**

  --**Nonshivering thermogenesis:** Brown adipose tissue has mitochondria that produce heat instead of ATP

  --**Thermic effect of food:** Feeding increases metabolism 25–40%

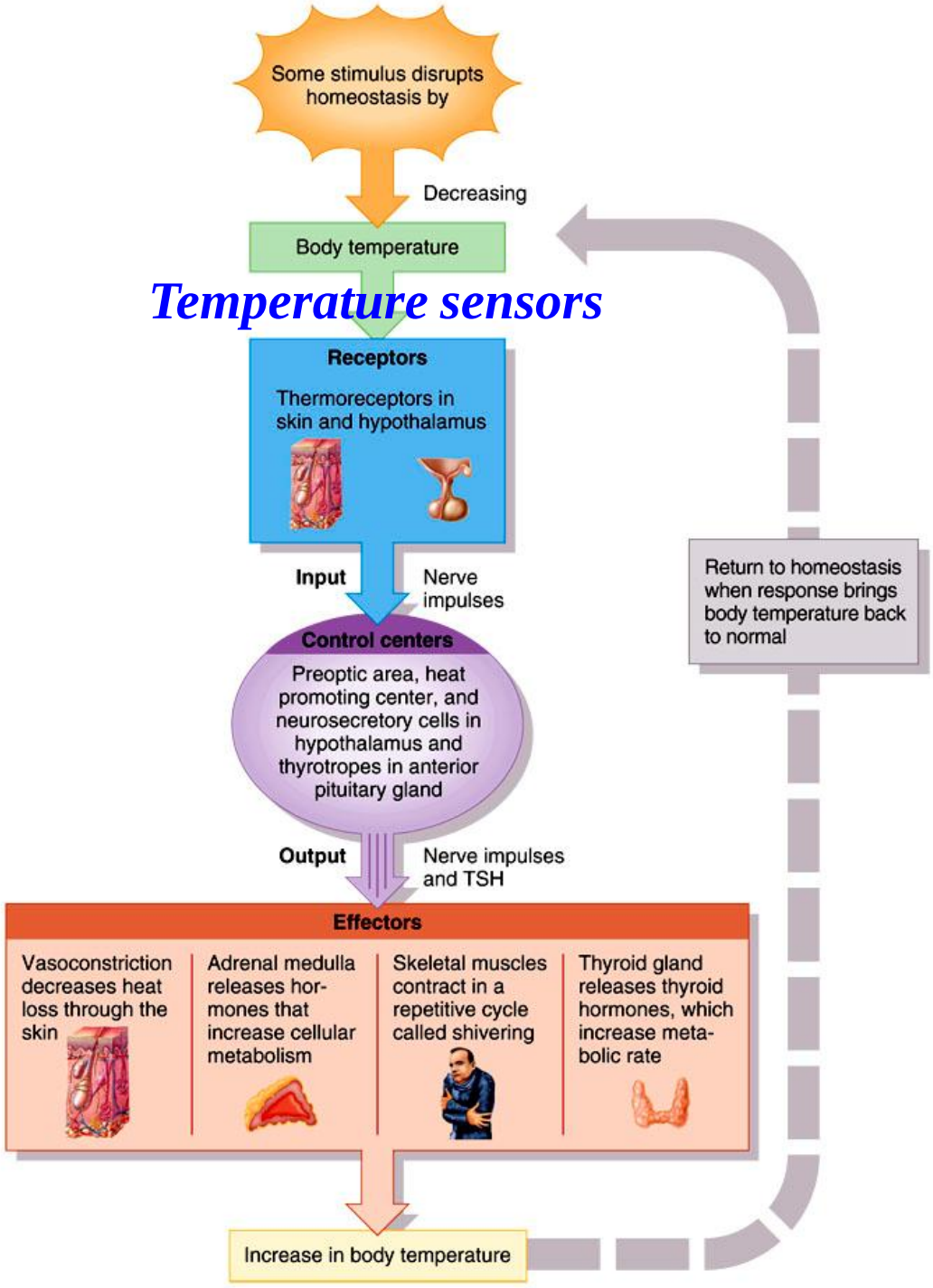
- **Regulated by the brain via:**

  --**Sympathoadrenal stimulation** of skeletal muscles and brown fat

  --**TRH → TSH → thyroxine:** falls in starvation in response to decreased leptin production

Thermoregulation

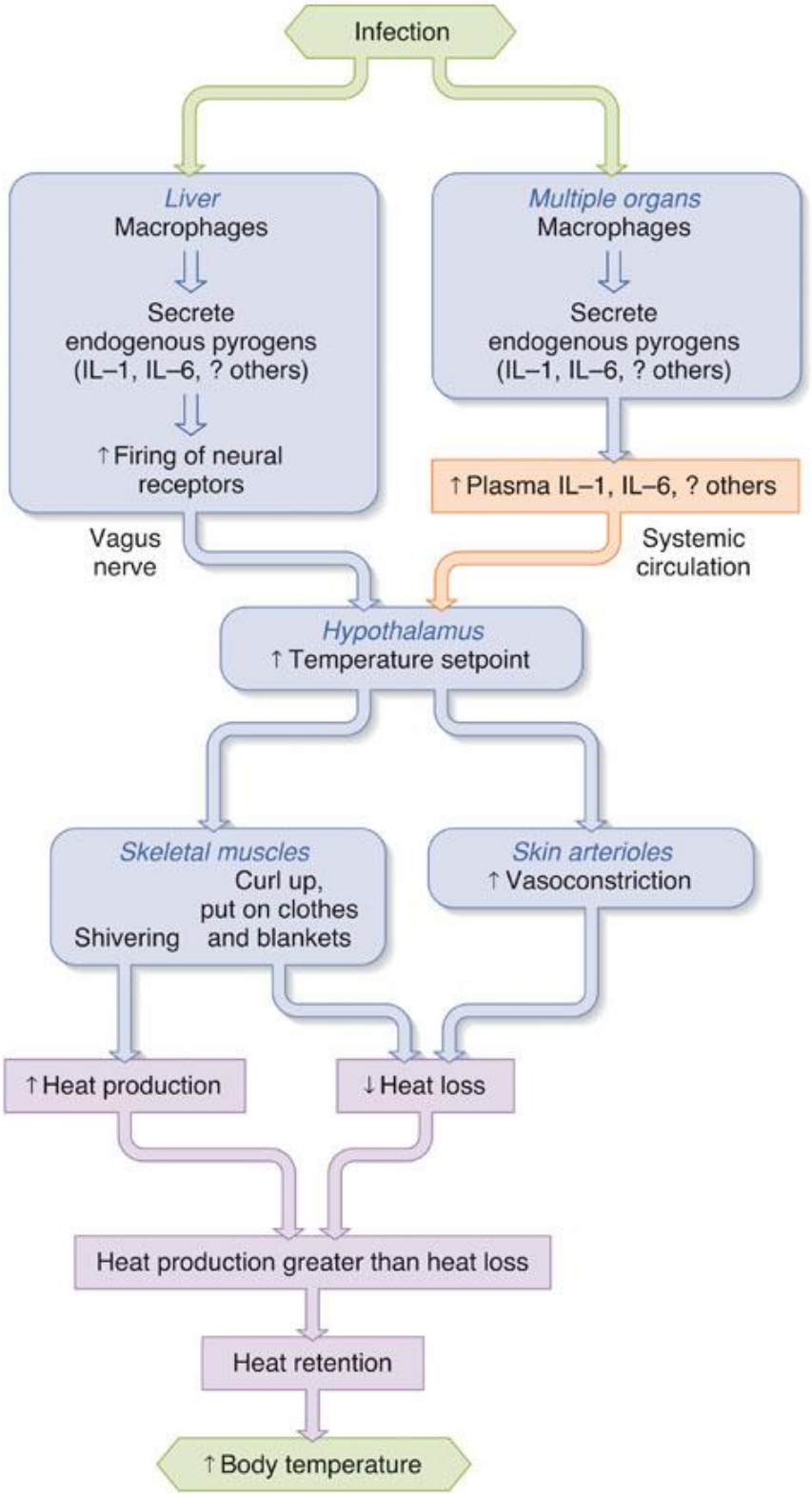
- **If core temperature declines**
  - --Skin blood vessels constrict
  - --Release of thyroid hormones, epinephrine and norepinephrine increases cellular metabolism
  - --Shivering
- **If core body temperature too high**
  - --Dilation of skin blood vessels
  - --Decrease metabolic rate
  - --Stimulate sweat glands



- **Heat can be lost through**
  1. **Conduction** to solid materials in contact with body
  2. **Convection** – transfer of heat by movement of a gas or liquid
  3. **Radiation** – transfer of heat in form of infrared rays
  4. **Evaporation** exhaled air and skin surface (insensible water loss)
- **Hypothalamic thermostat in preoptic area**
  --Heat-losing center and heat-promoting center

Clinical Application: Fever

A common medical sign characterized by an elevation of body temperature above the normal range of 36.5–37.5 ℃ due to an increase in the temperature regulatory set-point

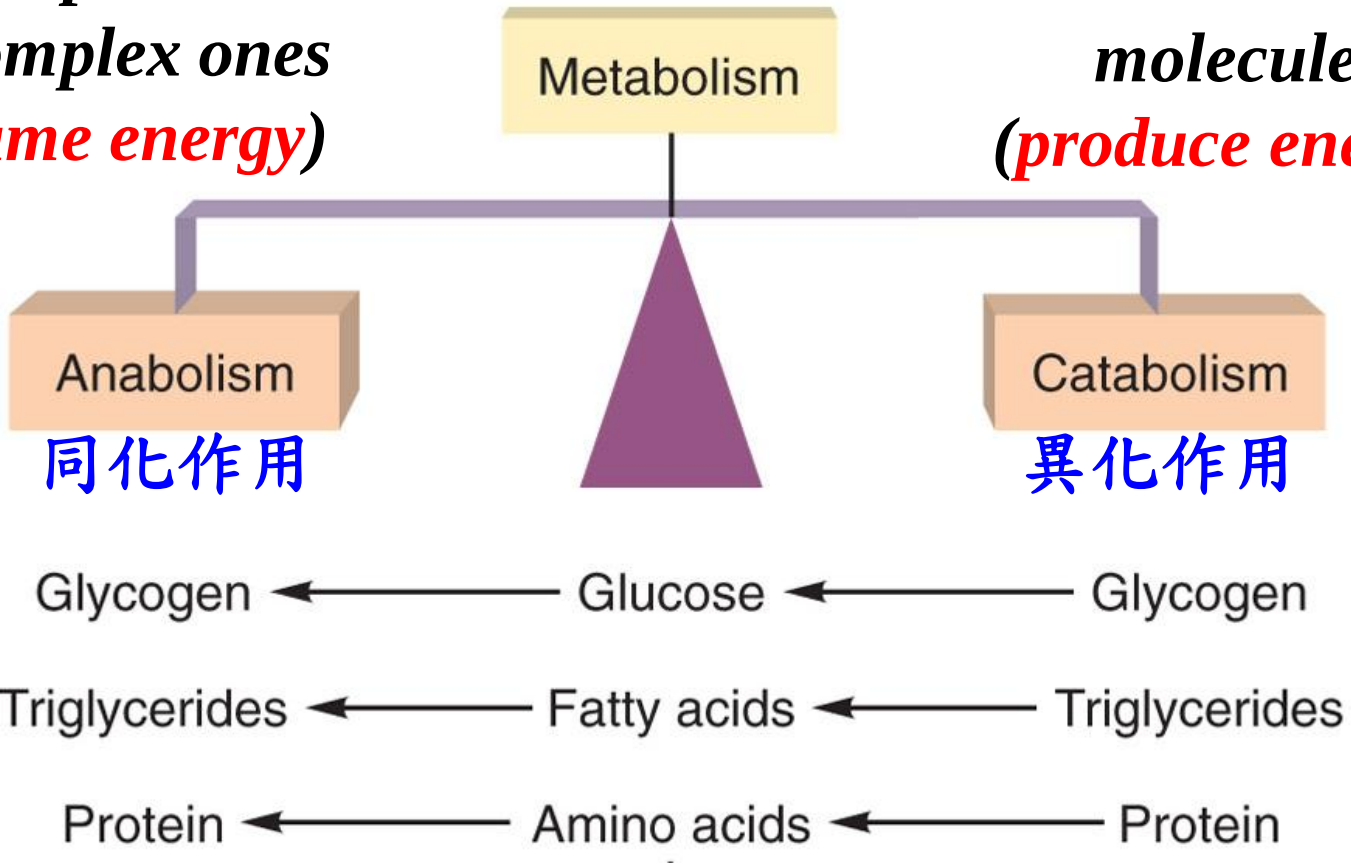


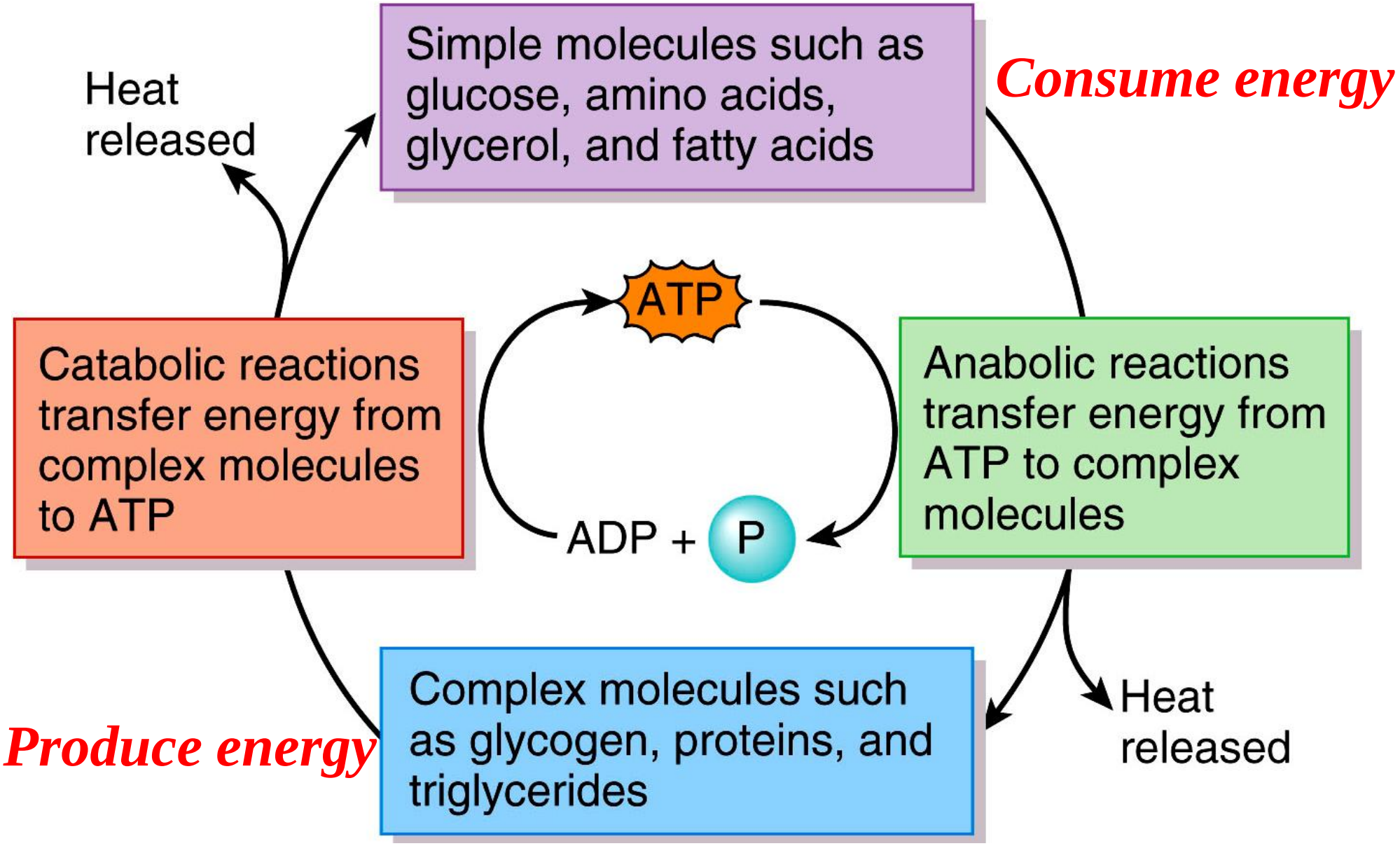
Metabolism

營養素在體內經過一系列化學反應，合成體內所需要的大分子物質，同時有能量轉換現象

Combine simple molecules into complex ones (consume energy)

Break down complex molecules (produce energy)

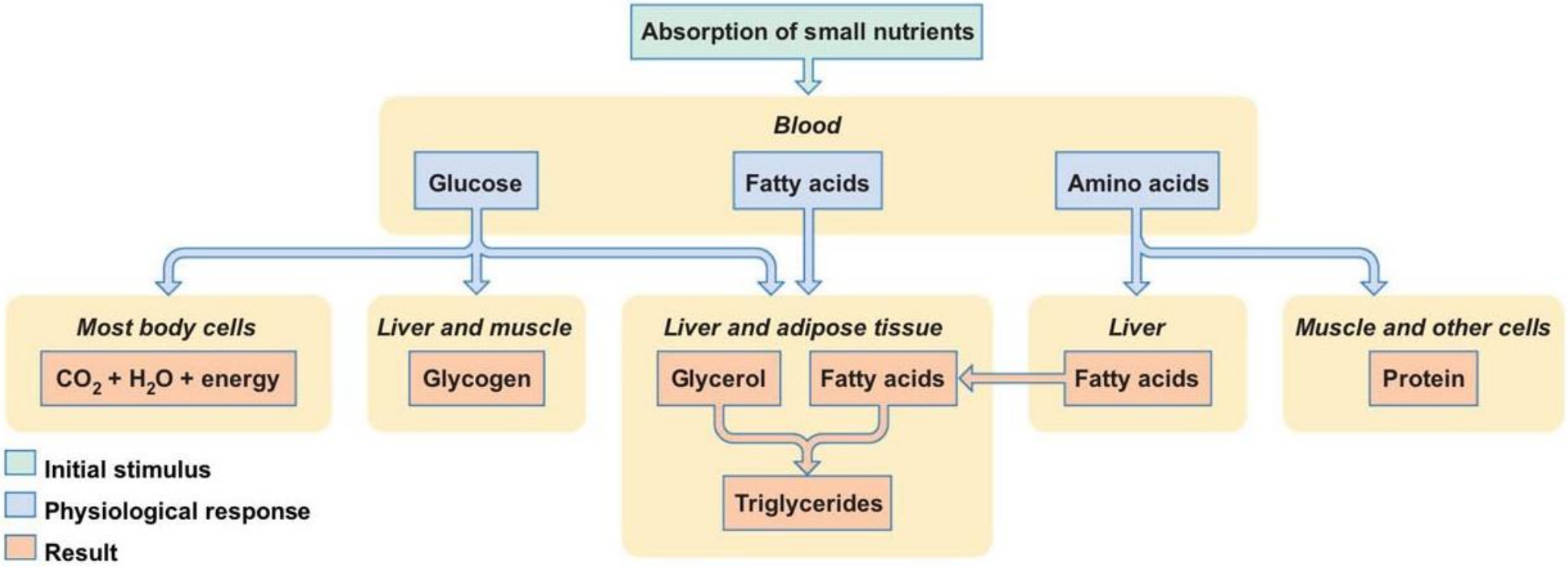



Simple molecules such as glucose, amino acids, glycerol, and fatty acids
Consume energy
Heat released
ATP
Catabolic reactions transfer energy from complex molecules to ATP
Anabolic reactions transfer energy from ATP to complex molecules
ADP +
P
Complex molecules such as glycogen, proteins, and triglycerides
Heat released
Produce energy

Metabolism During Absorptive State

- **Soon after a meal nutrients enter blood**
- **Energy input > output as nutrients absorbed**
- **2 metabolic hallmarks**
  - **--Oxidation of glucose** for ATP production in all body cells
  - **--Storage of excess fuel molecules** in hepatocytes, adipocytes, and skeletal muscle cells
- **Pancreatic beta cells release insulin**
  - --Promotes entry of glucose and amino acids into cells

Absorptive State Reactions



- ***Energy input > output as nutrients absorbed***
- ***Glucose = primary energy source for cell***
- ***Excess nutrients taken up will be stored***
  - ***--Liver and muscle store glycogen***
  - ***--Adipose tissue stores triglycerides***

Metabolism During

Postabsorptive State

- About **4 hours** after the last meal absorption in small intestine nearly complete (**Between meals**)
- **Energy input < output** (Stored nutrients broken down and mobilized)
- Blood glucose levels start to fall
- Main metabolic challenge to **maintain normal blood glucose levels**

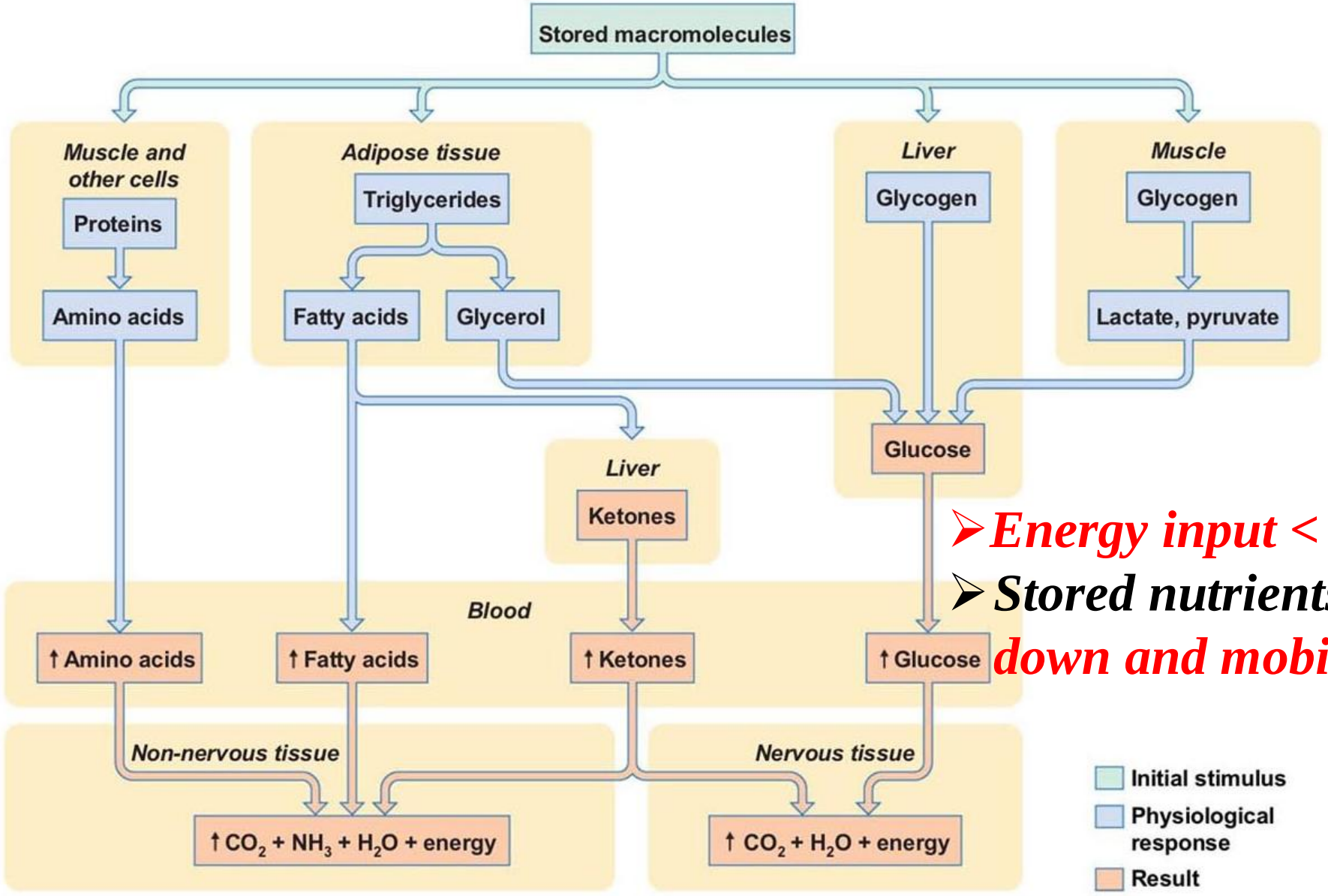
1. Glucose production

Breakdown of liver glycogen, lipolysis, gluconeogenesis using lactic acid and/or amino acids

2. Glucose conservation

Oxidation of fatty acids, lactic acid, amino acids, ketone bodies and breakdown of muscle glycogen

Postabsorptive State Reactions



- ***Energy input < output***
- ***Stored nutrients broken down and mobilized***

Endocrine Regulation of Metabolism

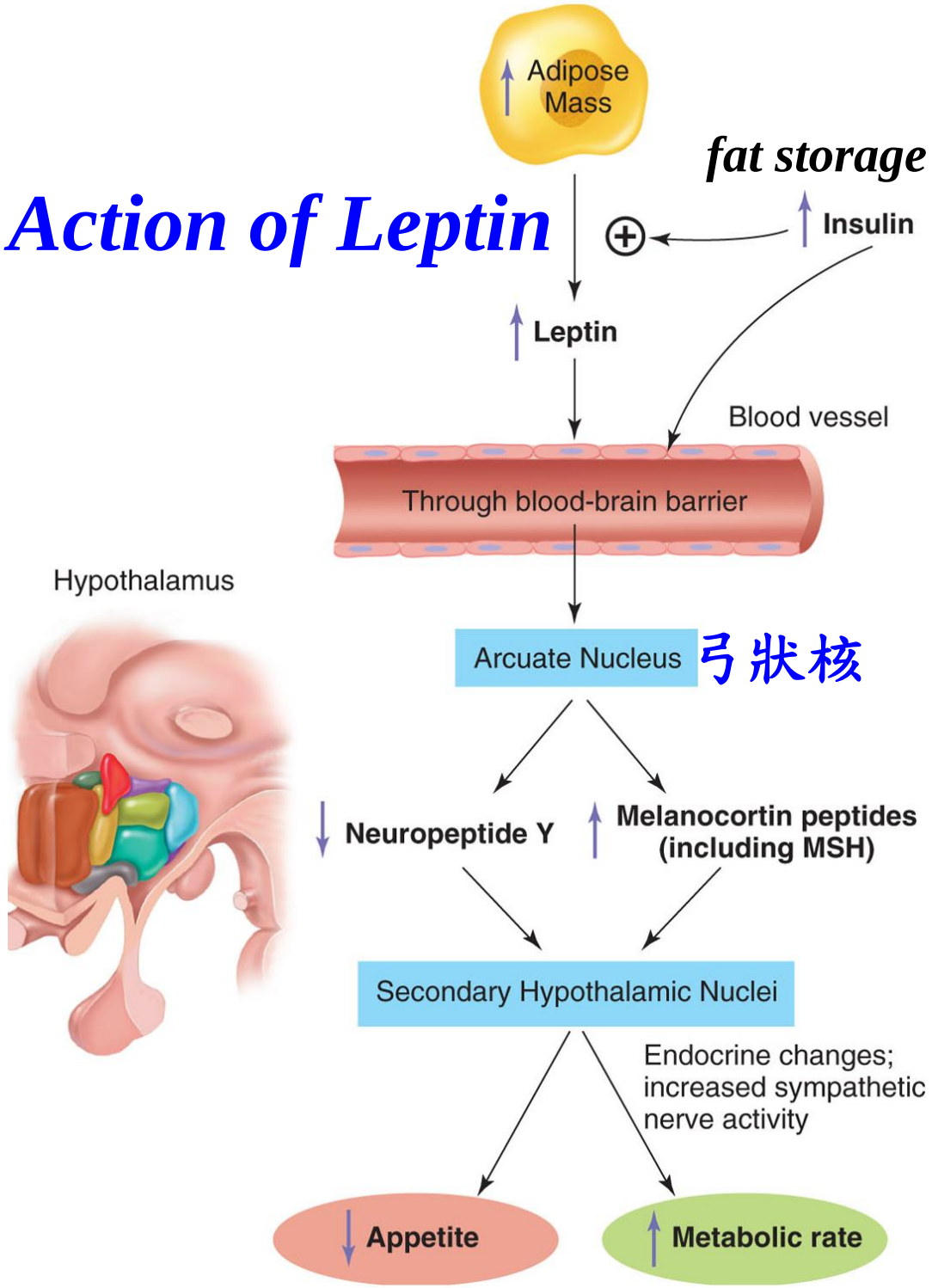
Hormone	Blood Glucose	Carbohydrate Metabolism	Protein Metabolism	Lipid Metabolism
Insulin	Decreased	↑ Glycogen formation ↓ Glycogenolysis ↓ Gluconeogenesis	↑ Protein synthesis	↑ Lipogenesis ↓ Lipolysis ↓ Ketogenesis
Glucagon	Increased	↓ Glycogen formation ↑ Glycogenolysis ↑ Gluconeogenesis	No direct effect	↑ Lipolysis ↑ Ketogenesis
Growth hormone	Increased	↑ Glycogenolysis ↑ Gluconeogenesis ↓ Glucose utilization	↑ Protein synthesis	↓ Lipogenesis ↑ Lipolysis ↑ Ketogenesis
Glucocorticoids (hydrocortisone)	Increased	↑ Glycogen formation ↑ Gluconeogenesis	↓ Protein synthesis	↓ Lipogenesis ↑ Lipolysis ↑ Ketogenesis
Epinephrine	Increased	↓ Glycogen formation ↑ Glycogenolysis ↑ Gluconeogenesis	No direct effect	↑ Lipolysis ↑ Ketogenesis
Thyroid hormones	No effect	↑ Glucose utilization	↑ Protein synthesis	No direct effect

Endocrine Regulation of Metabolism

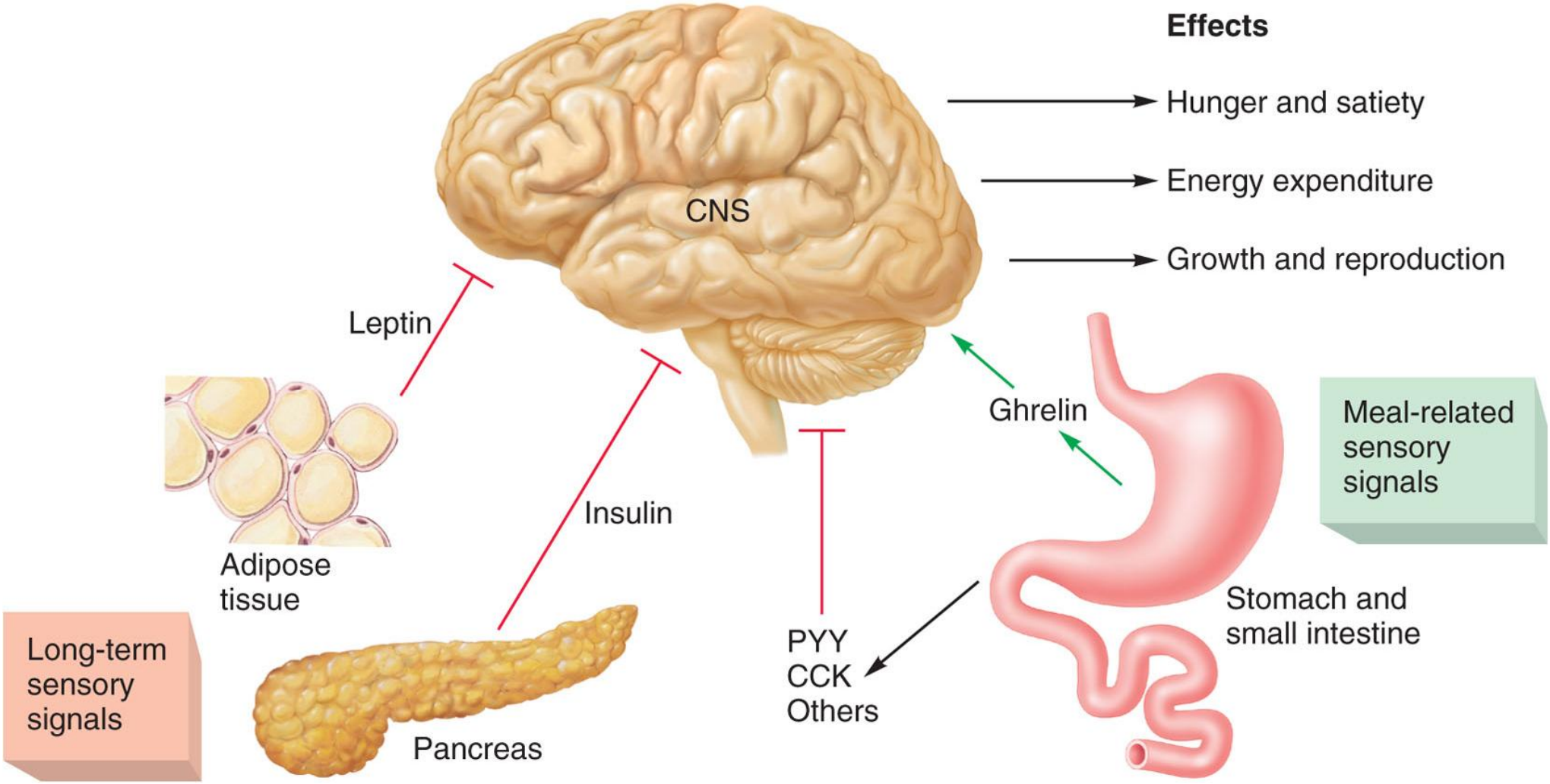
	Site of secretion	Primary stimuli for secretion (indirect stimuli in parentheses)	Net effect on carbohydrate metabolism	Effect on plasma glucose	Net effect on lipid metabolism	Net effect on protein metabolism
Insulin	Beta cells of islets of Langerhans in pancreas	↑ Plasma glucose ↑ Plasma amino acids	↑ Glucose uptake into cells ↑ Glycogen stores	↓ Plasma glucose	↑ Triglyceride stores	↑Amino acid uptake into cells ↑ Protein synthesis
Glucagon	Alpha cells of islets of Langerhans in pancreas	↓ Plasma glucose ↑ Plasma amino acids	↑ Glycogenolysis ↑ Gluconeogenesis	↑ Plasma glucose	↑ Lipolysis	↑ Proteolysis
Epinephrine	Adrenal medulla	Sympathetic nerve activity (stress, exercise)	↑ Glycogenolysis	↑ Plasma glucose	↑ Lipolysis	None
Growth hormone	Anterior pituitary	GHRH from hypothalamus (↓plasma glucose, ↑plasma amino acids, ↓fatty acids, sleep, stress, exercise)	↓ Glucose uptake into cells	↑ Plasma glucose	↑ Lipolysis	↑ Amino acid uptake into cells ↑ Protein synthesis
Thyroid hormones (T_3 and T_4)	Thyroid gland	TSH from anterior pituitary (TRH from hypothalamus, cold temperatures in infants)	↑ Glycolysis	None	↑ Lipolysis	↑ Protein synthesis
Cortisol	Adrenal cortex	ACTH from anterior pituitary (CRH from hypothalamus, stress)	↓ Glucose uptake into cells ↑ Gluconeogenesis	↑ Plasma glucose	↑ Lipolysis	↓ Amino acid uptake into cells ↑ Proteolysis

Regulation of Hunger

- Hormones regulate fat storage and breakdown
- Adipose cells (**leptin**) and GI (**ghrelin**) secrete hormones that regulate hunger and metabolism
- **Arcuate nucleus** of hypothalamus: produces hormones involved in hunger (**NPY increase appetite; MSH decreases appetite**)
- **Ghrelin**: secreted by the stomach when it is empty
  - --Acts on the arcuate nucleus to stimulate hunger
  - --Stimulates the release of NPY



Regulation of Hunger



Clinical Application: Metabolic Syndrome

Syndrome X= Insulin Resistance Syndrome= Reaven's syndrome

- **A combination of medical disorders** for a group of risk factors that occur together and increase the risk for coronary artery disease, stroke, and type 2 diabetes
- **The two most important risk factors:**

  --**Central obesity** "apple-shaped"

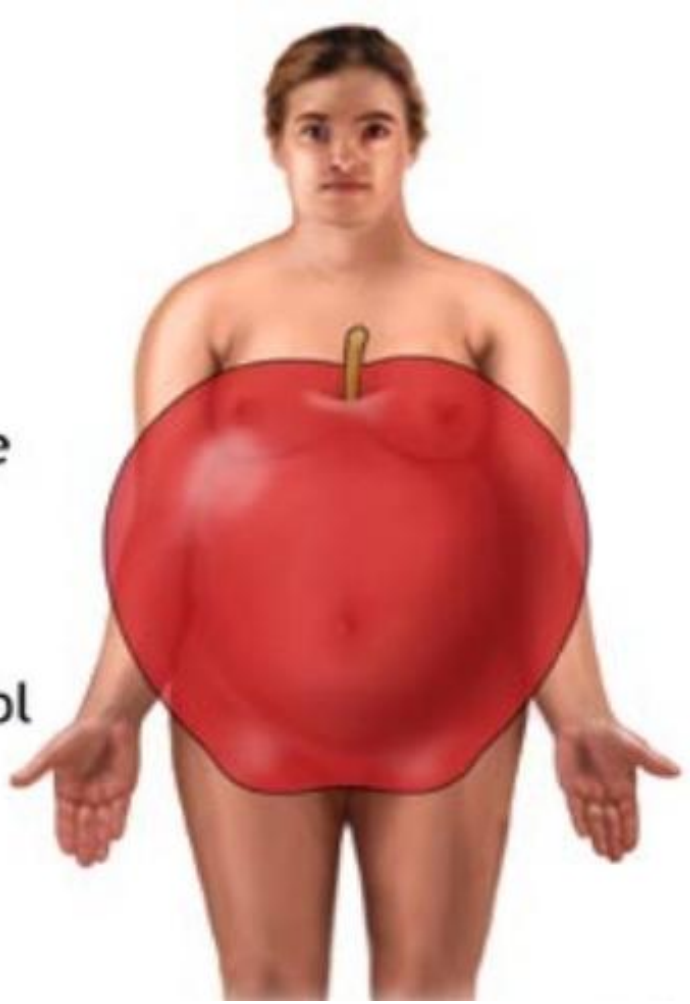
  --**Insulin resistance** (body cannot use insulin effectively → blood sugar and fat levels rise)
- **Other risk factors include:**

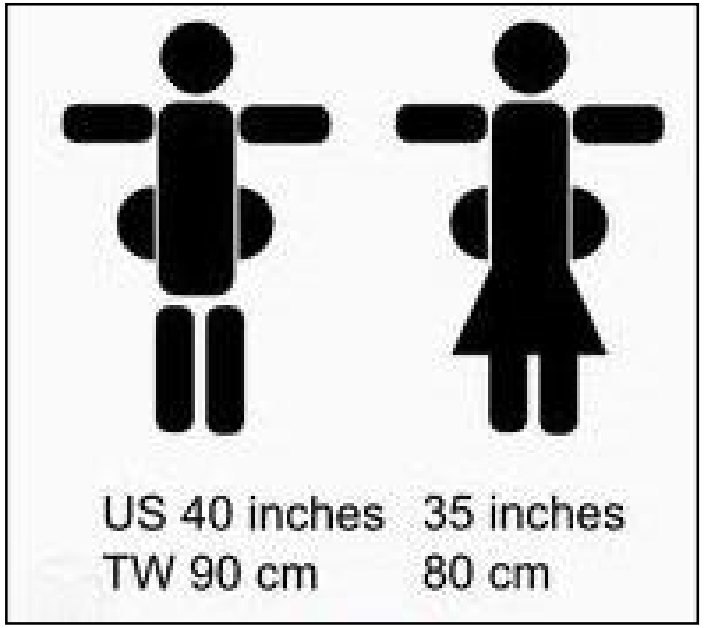
  --Aging, Genes, Hormone changes, and Lack of exercise

Metabolic Syndrome

Metabolic syndrome
(Syndrome X)

- Central obesity
- High blood pressure
- High triglycerides
- Low HDL-cholesterol
- Insulin resistance





Metabolic Syndrome

生活可以很多角度

有位老師進了教室，在白板上點了一個黑點。
他問班上的學生說「這是什麼？」
大家都異口同聲說「一個黑點。」

老師故作驚訝的說

「只有一個黑點嗎？這麼大的白板大家都沒有看見？」

試想
你看到的是什麼？每個人身上都有一些缺點，
但是你看到的是那些呢？
是否只有看到別人身上的"黑點"
卻忽略了他擁有了一大片的白板(優點)？
其實每個人必定都有許多的優點，
換一個角度去看吧!!你會有更多新的發現。