

ENDOCRINE SYSTEM

The Regulation of Pituitary , adrenal, and gonad hormones

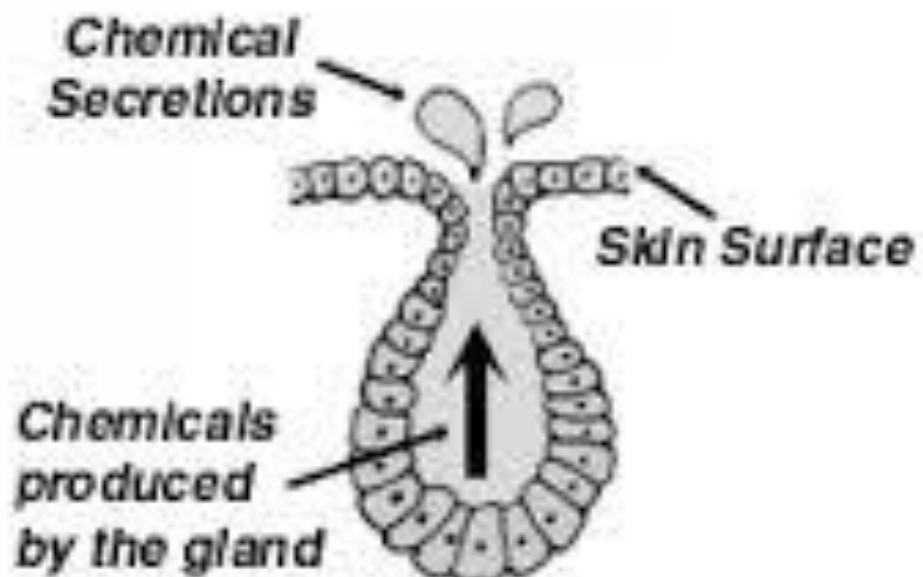
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Learning Objective

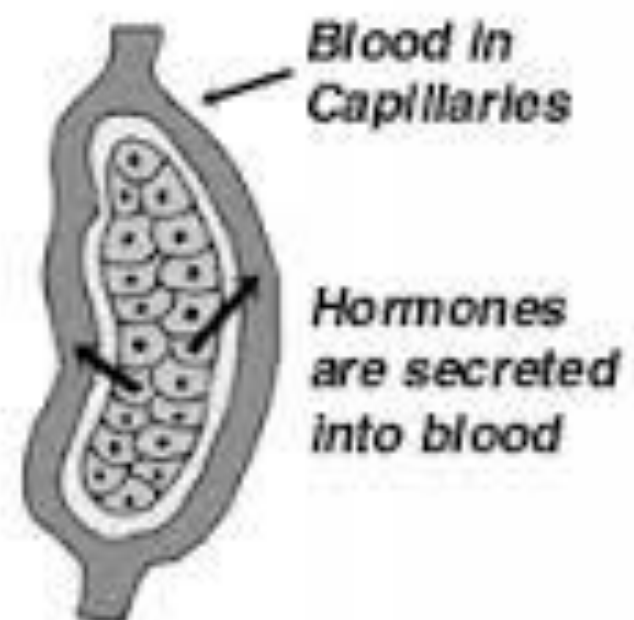
- Understand the regulation of pituitary hormones, adrenal (cortex and medulla) hormones, and gonad
- Understand the normal synthesise of adrenal cortex hormones

Endocrine vs Exocrine gland

- Endocrine gland : secretes hormones directly into the bloodstream; a ductless gland
- Exocrine gland : a gland that secretes substances into ducts which then leave the body (i.e. sweat/sebaceous gland) or into an internal space or lumen (i.e. digestive glands)
- Exocrine gland is not part of endocrine system!



Exocrine Gland



Endocrine Gland

What is endocrine system?

- A system that controls numerous of body process, like :
 - Growth and development
 - Metabolism
 - Reproduction
 - Homeostasis
- **Work in conjunction with nervous system**

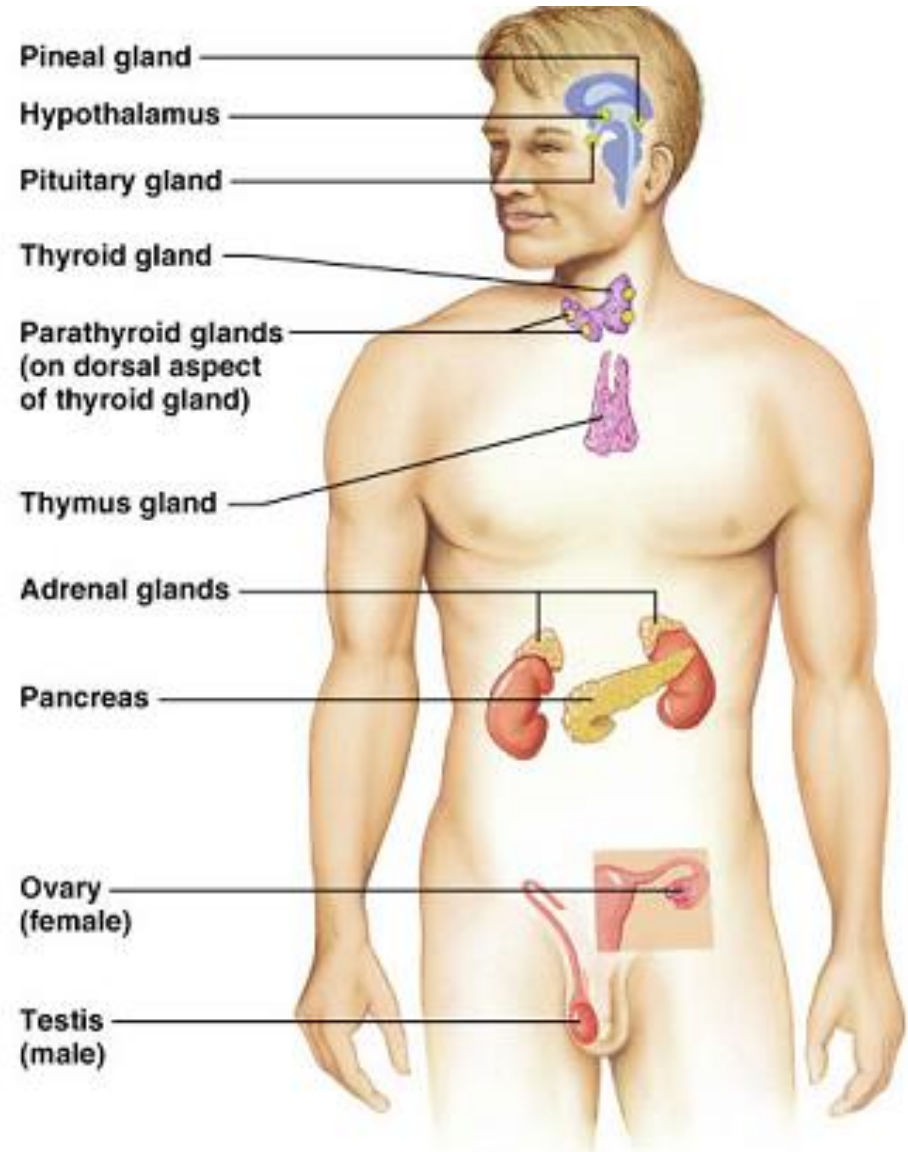
Endocrine Vs Nervous control

- Both share role in coordination and control throughout the body
- Can not be separated :
 - Some endocrine gland respond to nervous stimuli
 - Endocrine system maintain nervous system

Comparison of Control by the Nervous and Endocrine Systems

CHARACTERISTIC	NERVOUS SYSTEM	ENDOCRINE SYSTEM
Mediator molecules	Neurotransmitters released locally in response to nerve impulses.	Hormones delivered to tissues throughout body by blood.
Site of mediator action	Close to site of release, at synapse; binds to receptors in postsynaptic membrane.	Far from site of release (usually); binds to receptors on or in target cells.
Types of target cells	Muscle (smooth, cardiac, and skeletal) cells, gland cells, other neurons.	Cells throughout body.
Time to onset of action	Typically within milliseconds (thousandths of a second).	Seconds to hours or days.
Duration of action	Generally briefer (milliseconds).	Generally longer (seconds to days).

Major Endocrine Organ



What is hormones?

- Chemical substances secreted by cells into the extracellular fluids
 - Regulate the metabolic function of other cells
 - Have lag times ranging from seconds to hours
 - Tend to have prolonged effects

*“A hormone is a chemical secreted by a cell or group of cells into the blood for transport to a distant target, where it exerts its effect at **very low concentration**”*

Classification of Hormone

- Based on its action
 - Endocrine action, paracrine action, autocrine action, and neuroendocrine action
- Based on structure
 - Steroid hormone, polypeptide hormone, and amine hormone
- Based on the receptor
 - Intracellular and cell surface receptor
- Based on solubility
 - Lipophilic and hydrophilic (water soluble)

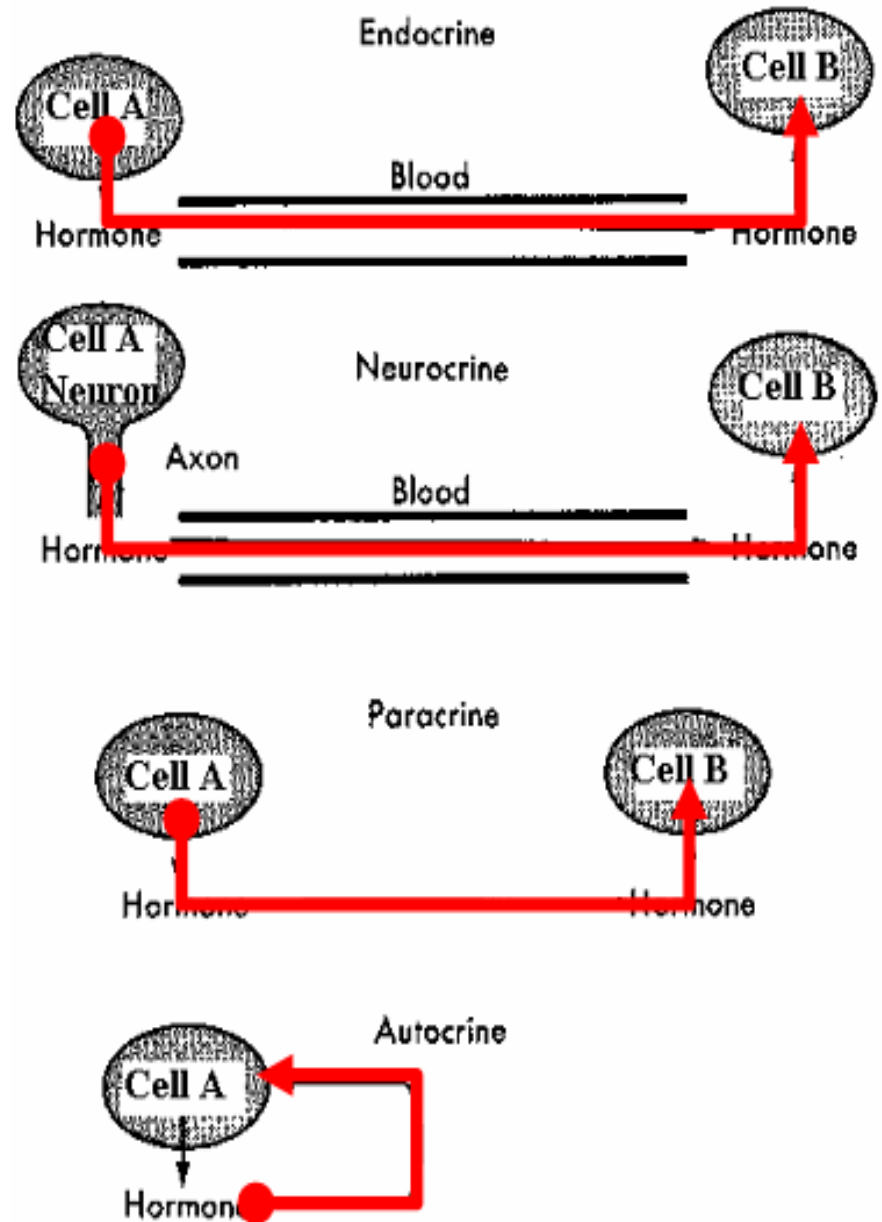
Endocrine vs Autocrine vs Paracrine

- Endocrine – a chemical that exerts their effect in a long distance target cell
- Autocrine – chemicals that exert their effect on the same cells that secrete them
- Paracrine – locally acting chemical that affects adjacent cells in the same tissue.

- Hormones can have
 - Endocrine action (circulating hormone)
 - Neuroendocrine action

-Paracrine action
-Autocrine action

Local hormone



Hormones based on structure

- Polypeptide hormone – most hormones belong to this class
- Steroid – gonadal and adrenocortical hormones
- Amine hormone

Peptide	Amine	Steroid
<ul style="list-style-type: none"> •Most abundant •Cell surface receptor •Water soluble •Stored in vesicles •Fast acting •Short half life <p>Ex: most hormone include in this class, glucagon, insulin, etc</p>	<ul style="list-style-type: none"> •Derivatives of single amino acid tyrosin •Can behave either like peptides or steroids •Receptor : surface , Intracellular •Liphophilic •Require carrier molecules •Fast and slow acting <p>Ex: thyroid hormone, epinefrine and norepinefrine</p>	<ul style="list-style-type: none"> •Intracellular receptor •From cholesterol based, lipophilic (not stored), enter target cell, mostly in nuclear receptors or cytoplasmic •Activate DNA for protein synthesis •Slower acting – genomic actions •Longer half-life •Has a specific protein carrier molecules <p>Ex : cortisol, estrogen, testosterone.</p>

Steroid hormone

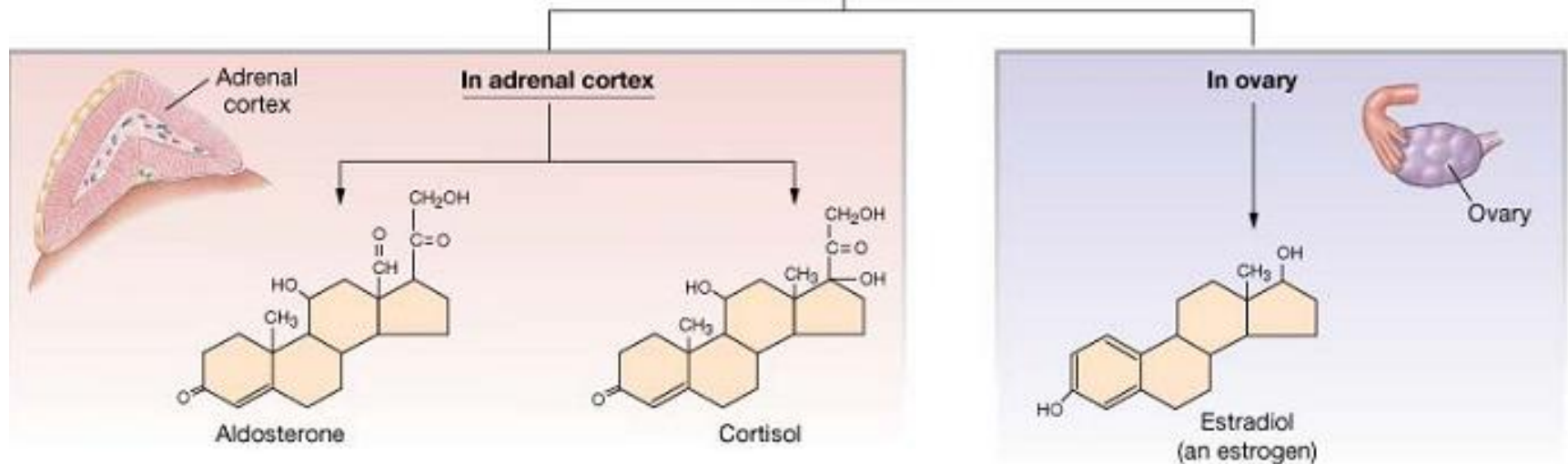
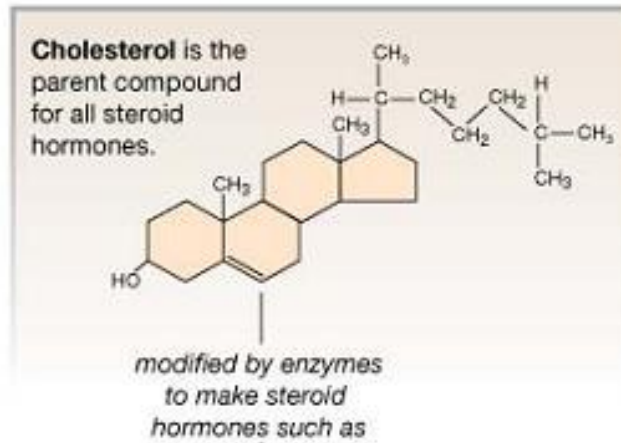
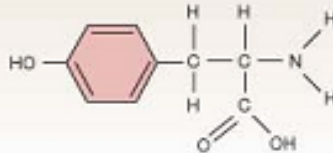


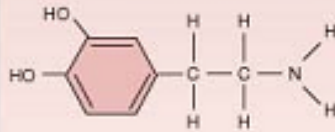
Figure 7-6: Steroid hormones are derived from cholesterol

Amine hormone

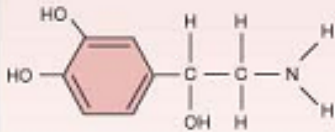
Tyrosine
is the parent amino acid for
catecholamines and thyroid hormones.



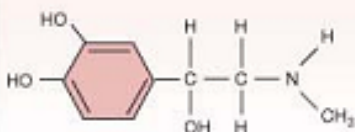
Catecholamines
are made by modifying the
side groups of tyrosine.



Dopamine

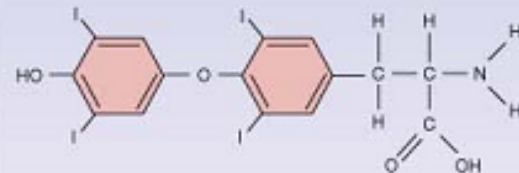


Norepinephrine

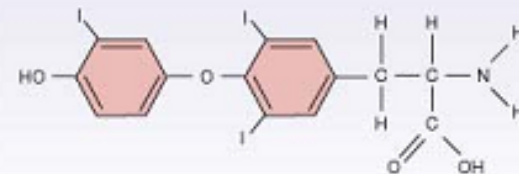


Epinephrine

Thyroid hormones
are synthesized from two tyrosines
and iodine (I) atoms.



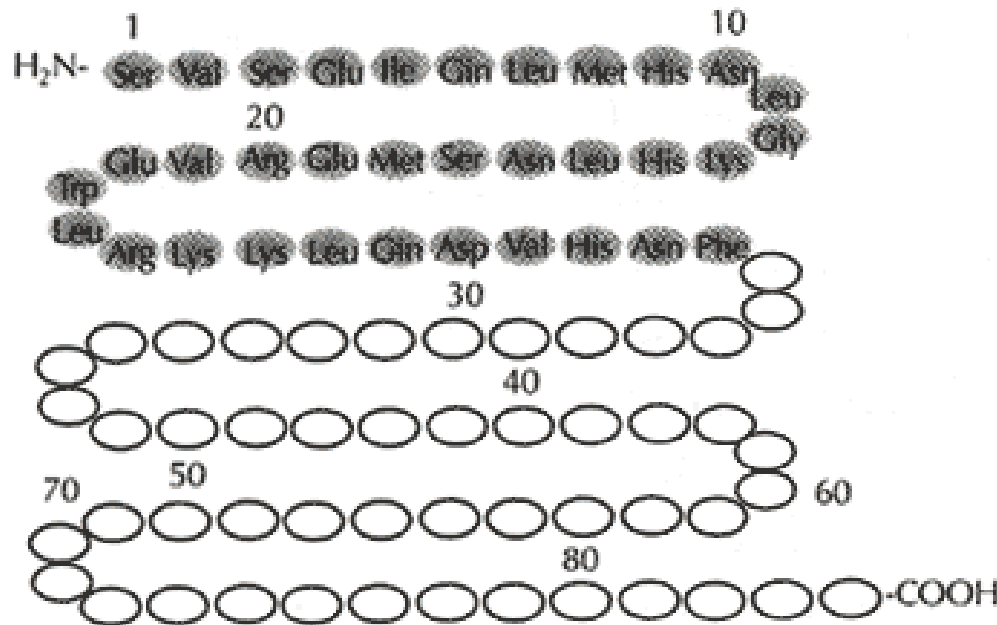
Thyroxine (Tetraiodothyronine, T₄)



Triiodothyronine (T₃)

Polypeptide hormone

Human parathyroid hormone
1-34



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Based on Receptor

- Intracellular
 - Located inside target cell, in **cytoplasm or nucleus**, and function as ligand-dependent transcription factors.
 - Steroid and thyroid hormones act on these receptors.
- Cell surface Receptor
 - Located on plasma membrane of target cells
 - Binding of hormone to receptor initiate a series of event which leads to generate of **2nd messengers** within the cells.

Second Messenger System

- Water soluble hormones act through binding to cell surface receptors and activation of one of the second messenger system.
- The small signal generated by hormone binding to its receptor **is amplified within the cell into a cascade of actions** that changes the cell's physiologic state.
- Ex : c-AMP, protein kinase activity, c-GMP, Ca, and so on.

Based on Solubility

LIPOPHILIC	HYDROPHILIC/LIPOPHOBIC
<ul style="list-style-type: none">•Transported in plasma by special proteins•Long half life•Prolonged action•Receptor is in cytoplasm or nucleus•Their action is by altering function of portion of DNA <p>Ex: Steroid hormones of adrenal cortex, testes and ovary</p>	<ul style="list-style-type: none">•Half life is very short•Very short time action•Receptor is on cell membrane•Further action is mediated through 2nd messenger•The hormone itself is 1st messenger <p>Ex: most peptide hormones like insulin, glucagon, hormone of pituitary gland</p>

Hormone Action

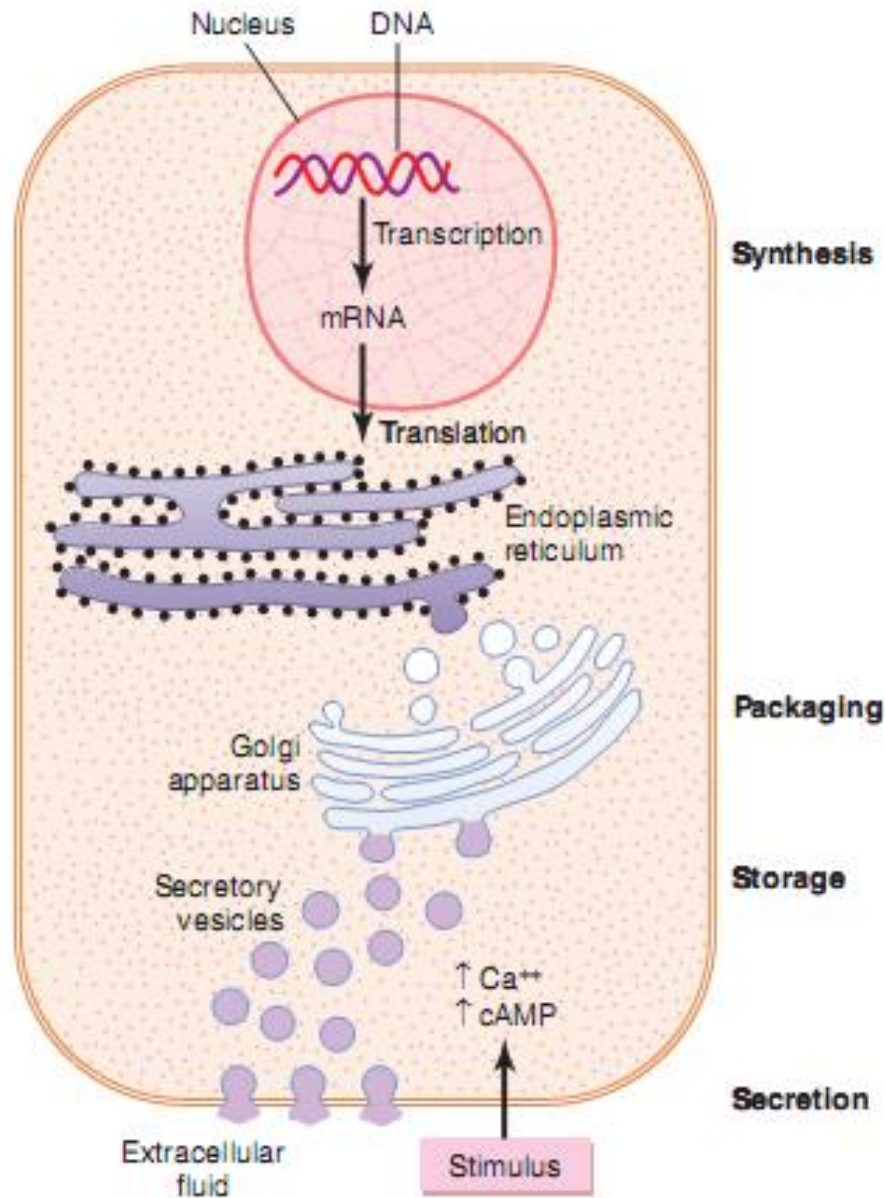
- Hormones alter target cell activity by one of two mechanisms:
 - Second messengers involving polypeptide based hormones
 - Direct gene activation involving steroid hormones
- Each of the different hormones has its own characteristic onset and duration of action—each tailored to perform its specific control function. Ex: epinefrin vs GH

Hormone receptor

- Hormon hanya berikatan dengan reseptor di target organnya. Misal, TSH berikatan dengan reseptor sel klj.thyroid, tapi tidak berikatan dengan sel ovarium
- Receptors, like other cellular proteins, are constantly being synthesized and broken down.
- Hormone \uparrow \rightarrow the number of target-cell receptors may decrease \rightarrow **down-regulation**. For example, testes are exposed to a high concentration of LH \rightarrow reseptor LH decreases. Down-regulation makes a target cell less sensitive to a hormone.
- Hormone \downarrow \rightarrow jumlah receptors increase \rightarrow **up-regulation** \rightarrow makes a target cell more sensitive to a hormone

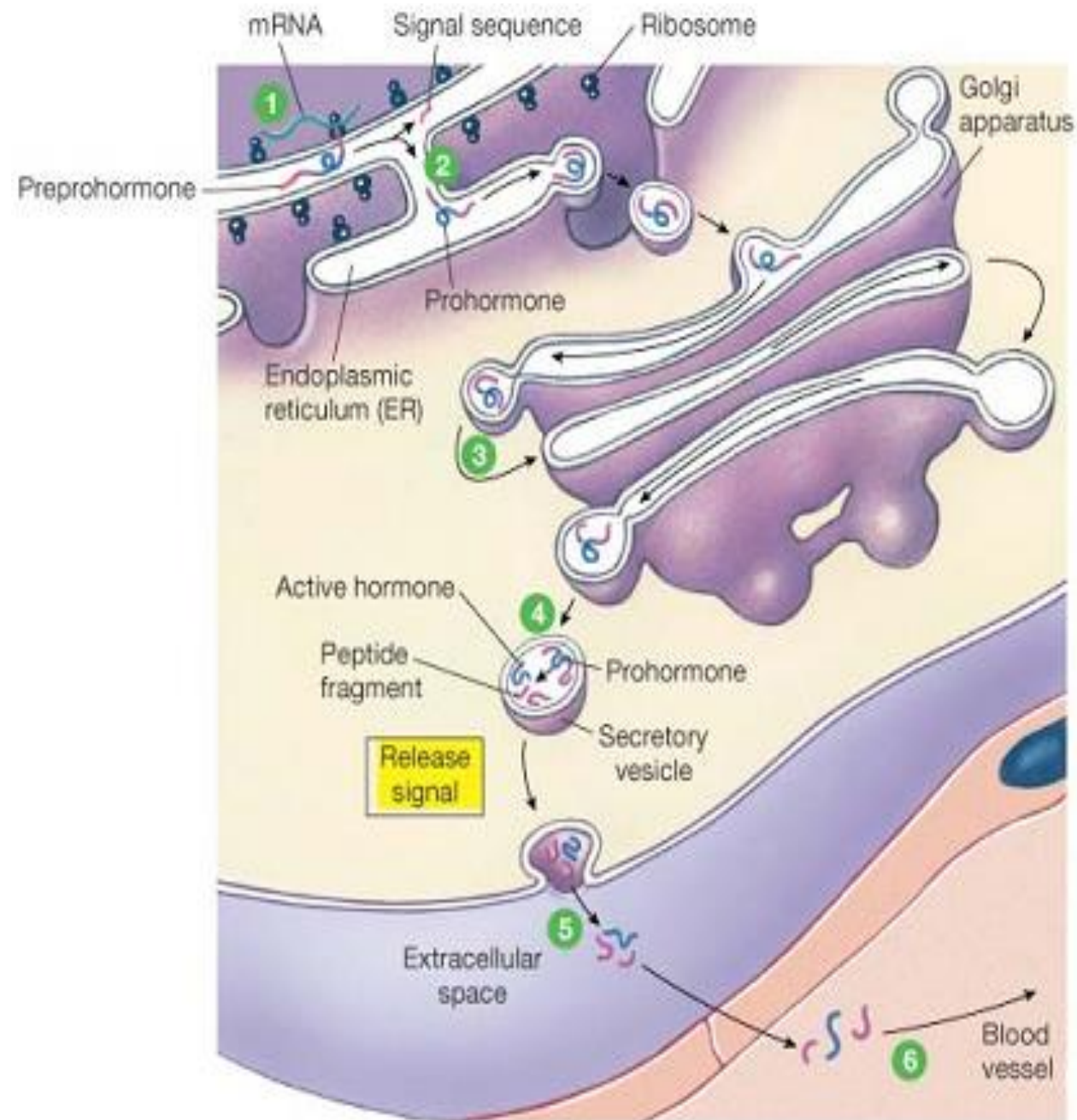
Synthesis and release:

Protein and polypeptide hormones



Polypeptide and Protein Hormones Are Stored in Secretory Vesicles (within cytoplasm) Until Needed.

The stimulus for hormone **secretion** often involves changes in intracellular **calcium** or changes in cyclic adenosine monophosphate (**cAMP**) in the cell. Subsequently activation of **protein kinases that initiate secretion of the hormone**.



1 Messenger RNA on the ribosomes of the ER binds amino acids into a peptide chain called a **preprohormone**. The chain is directed into the ER lumen by a **signal sequence** of amino acids.

2 Enzymes in the ER chop off the signal sequence, creating an inactive **prohormone**.

3 The prohormone passes from the ER through the Golgi apparatus.

4 Secretory vesicles containing enzymes and prohormone bud off the Golgi. The enzymes chop the prohormone into one or more active peptides plus additional peptide fragments.

5 The secretory vesicle releases its contents by exocytosis into the extracellular space.

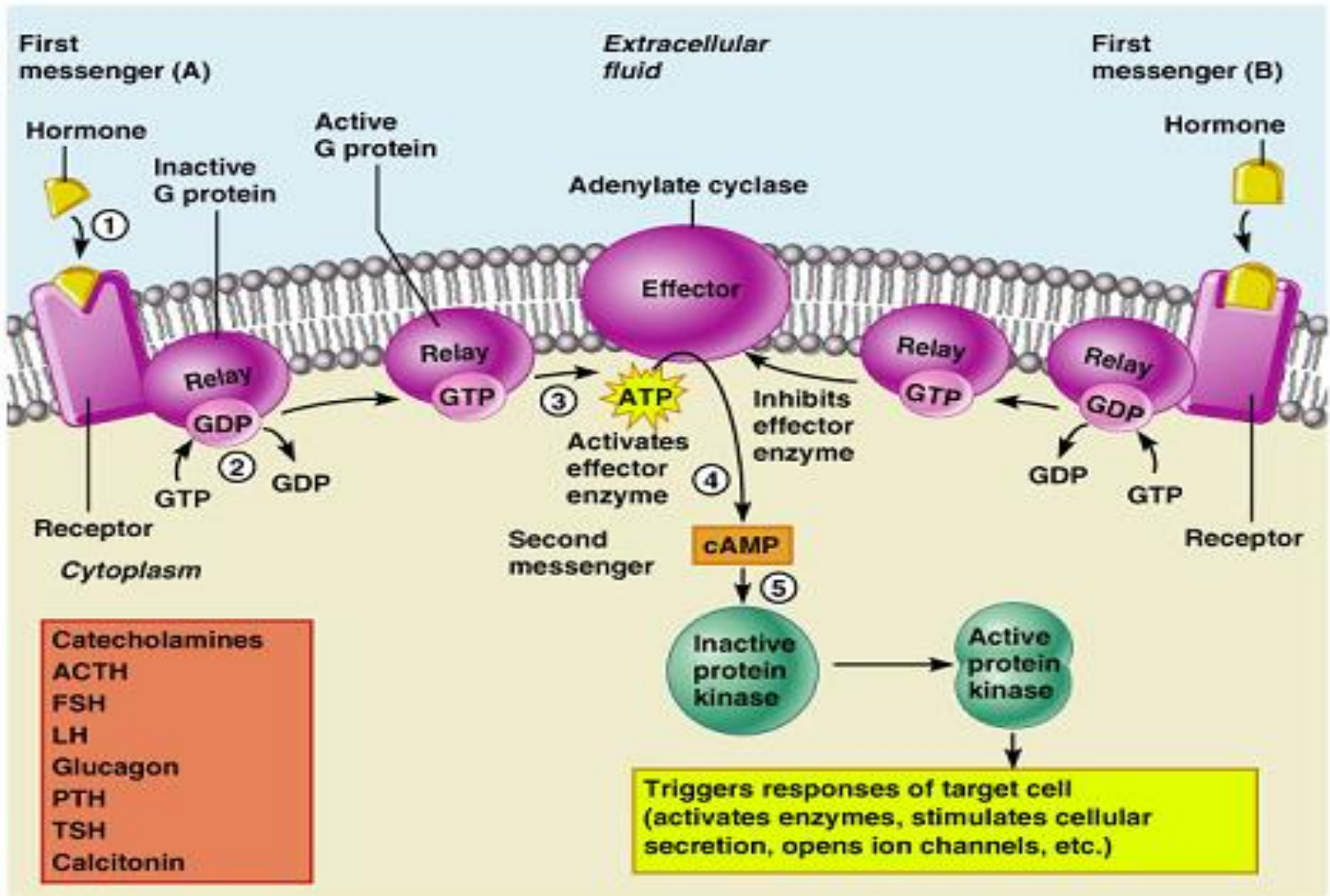
6 The hormone moves into the circulation for transport to its target.

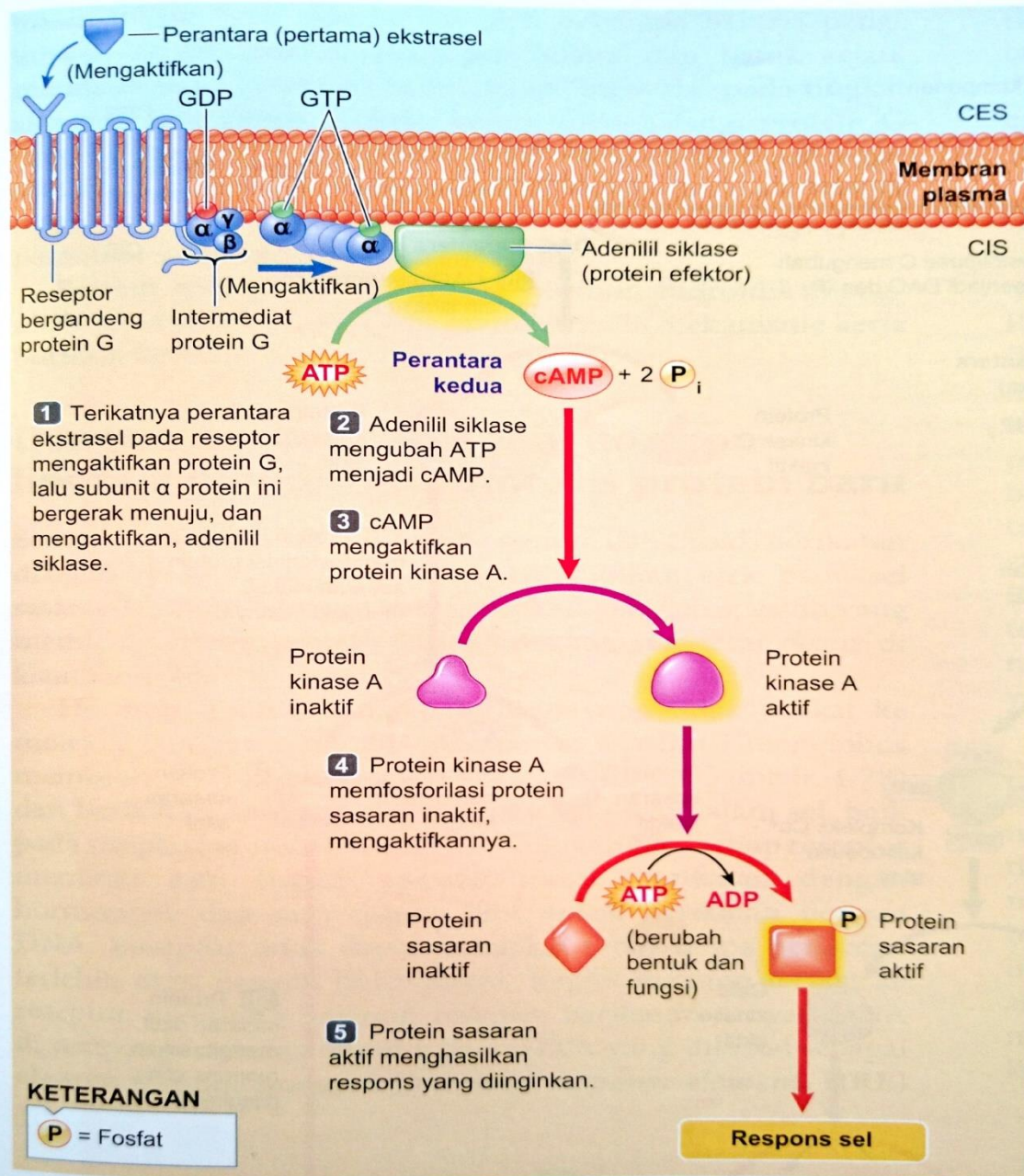
Figure 7-3: Peptide hormone synthesis, packaging, and release

Synthesis and Release : Steroid Hormones

- Usually Synthesized From Cholesterol and Are Not Stored.
- The chemical structure of steroid hormones is similar to that of cholesterol and in most instances hormones are synthesized from cholesterol.
- Although there is usually **very little hormone storage** in steroid producing endocrine cells, large stores of cholesterol esters in **cytoplasm vacuoles** can be rapidly mobilized for steroid synthesis after a stimulus.
- Much of the cholesterol in steroid producing cells comes from the **blood plasma**, but there is also **de novo synthesis** of cholesterol in steroid producing cells.
- Because the steroids are **highly lipid soluble**, once they are synthesized, they can simply diffuse across the cell membrane and enter the interstitial fluid and then the blood.

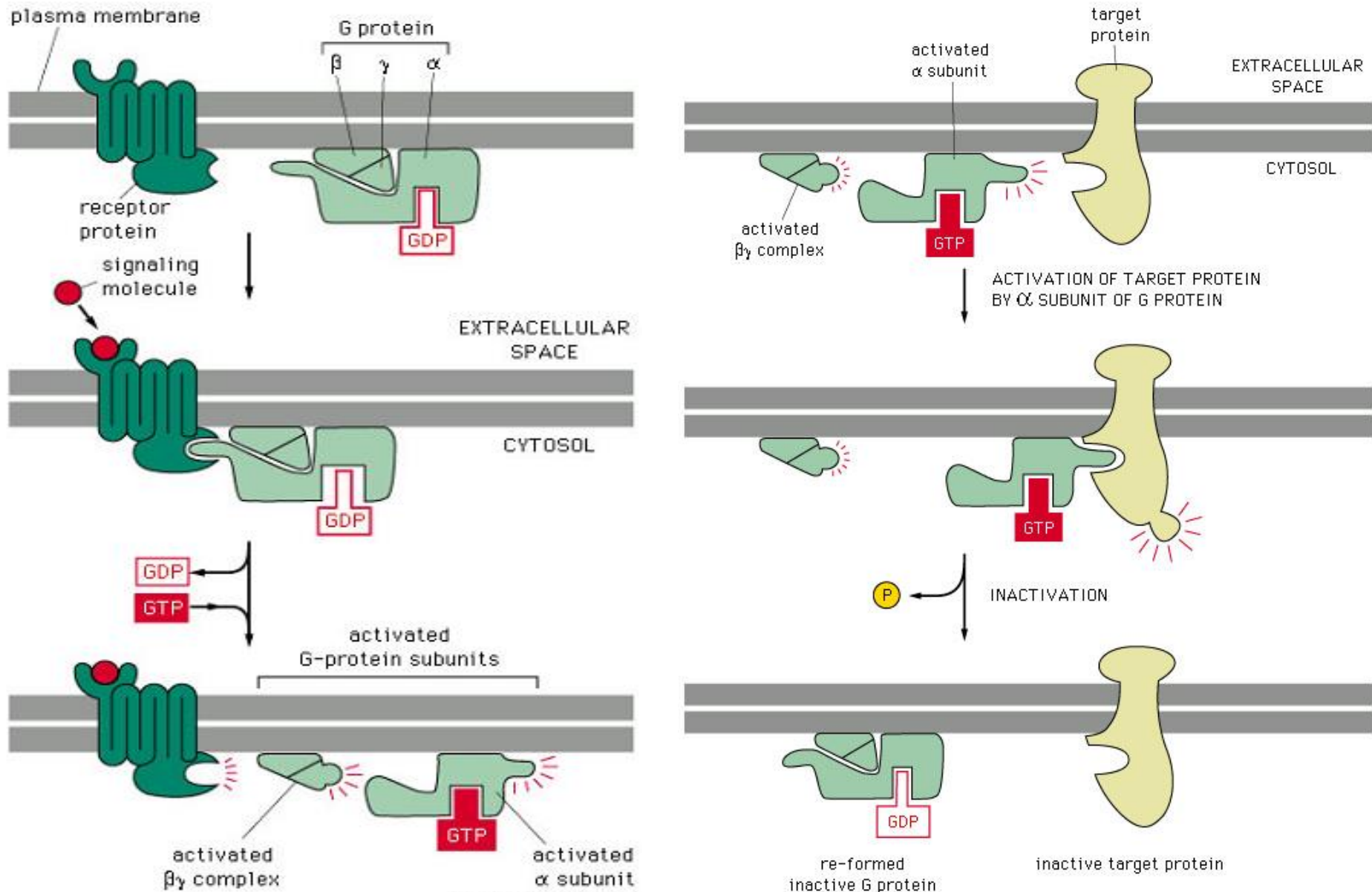
HORMONE ACTION : Protein & polypeptide hormone → cAMP Second messenger





Gambar 4-25 Mekanisme kerja hormon hidrofilik melalui aktivasi jaras perantara-kedua AMP siklik.

G protein coupled receptor

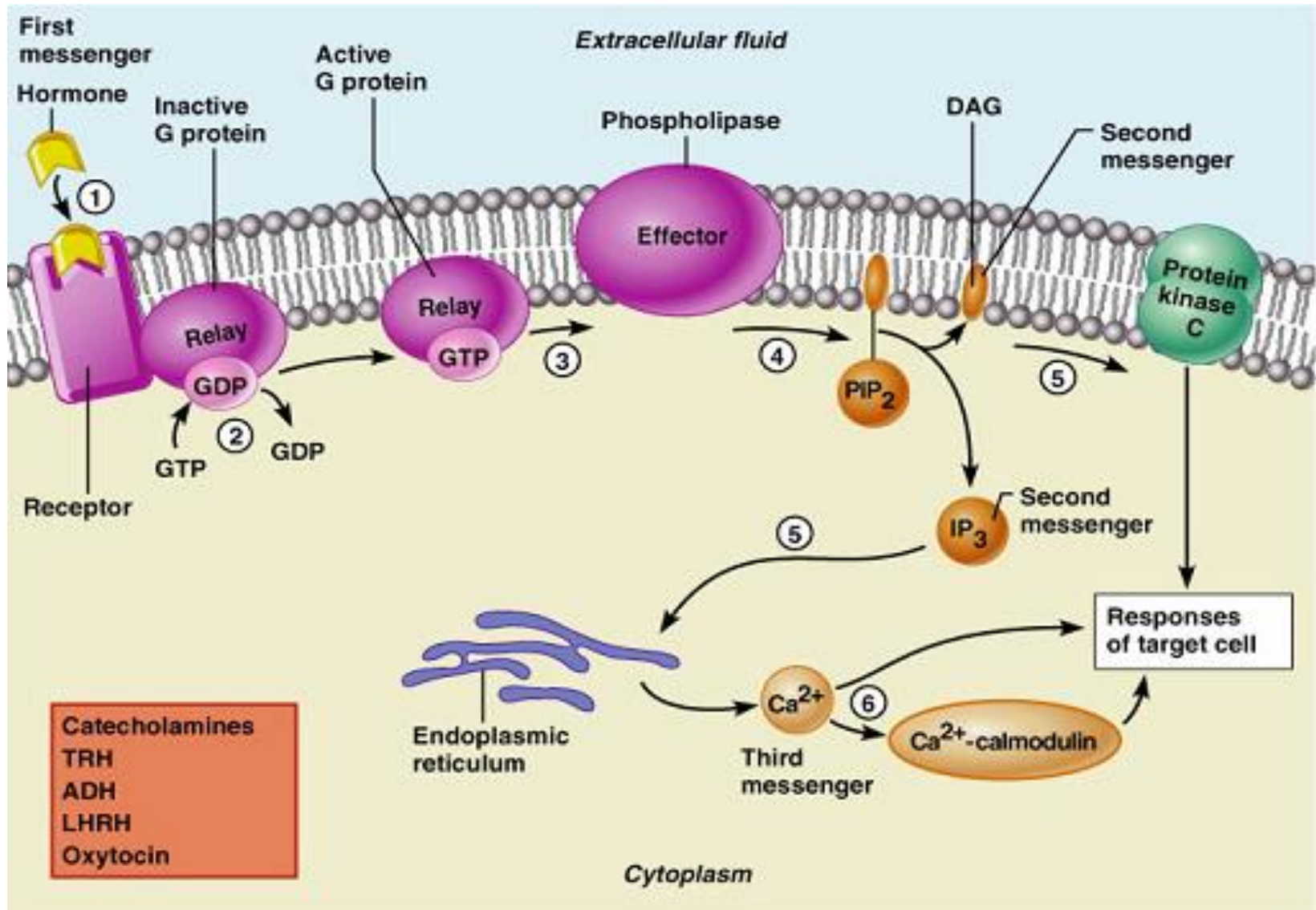


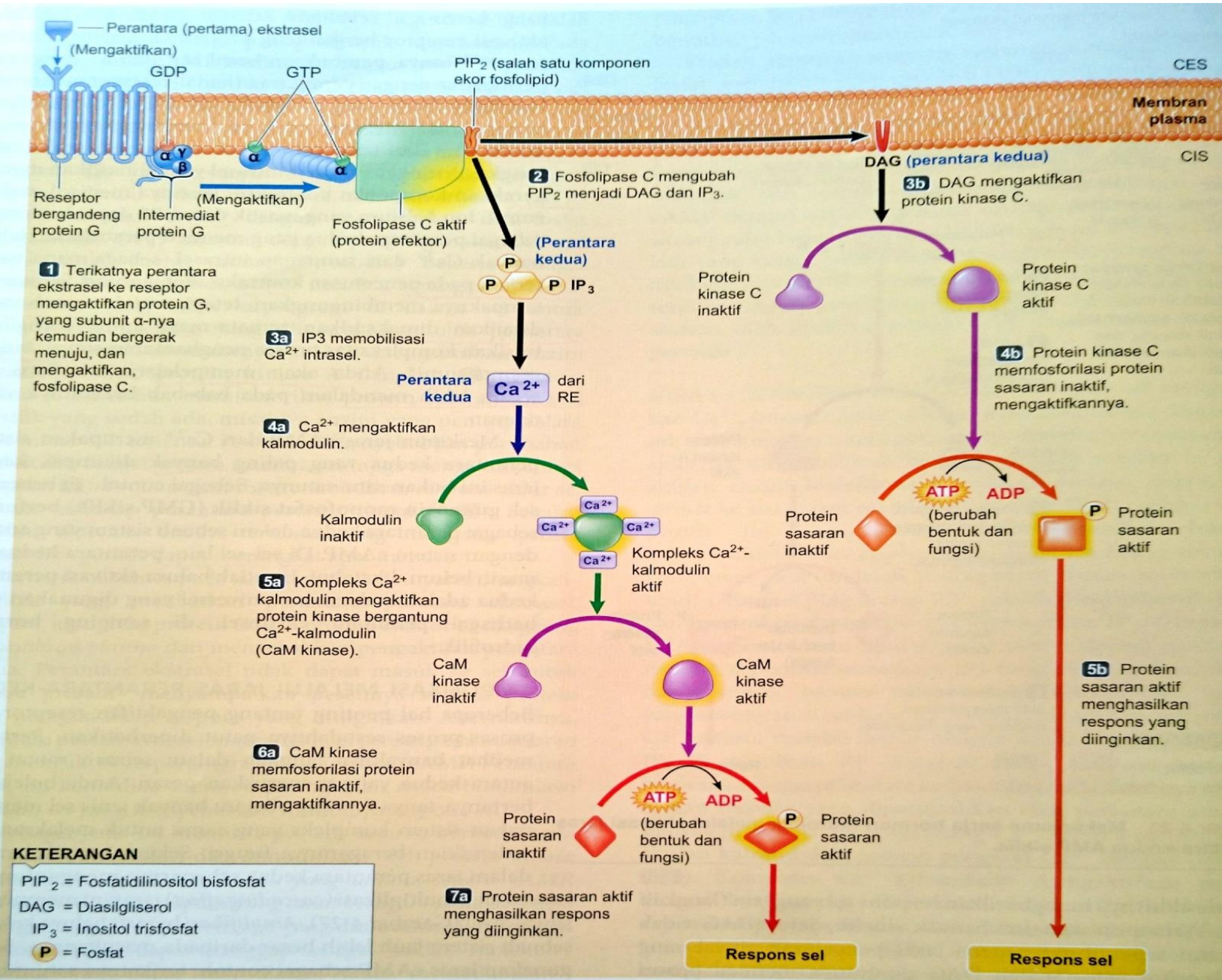
Aksi hormon polipeptida: Second messenger cAMP

- Hormon (1st messenger) berikatan dg reseptor kemudian berikatan dg protein G
- Protein G teraktivasi dg menyingkirkan GDP dan mengikat GTP
- Protein G yang teraktivasi → aktifkan enzim efektor adenilat siklase
- Adenilat siklase memacu cAMP (2nd messenger) dari ATP
- cAMP mengaktifkan protein kinase → efek seluler

Hormone Action : Protein & polypeptide

→ PIP-Calsium Second messenger



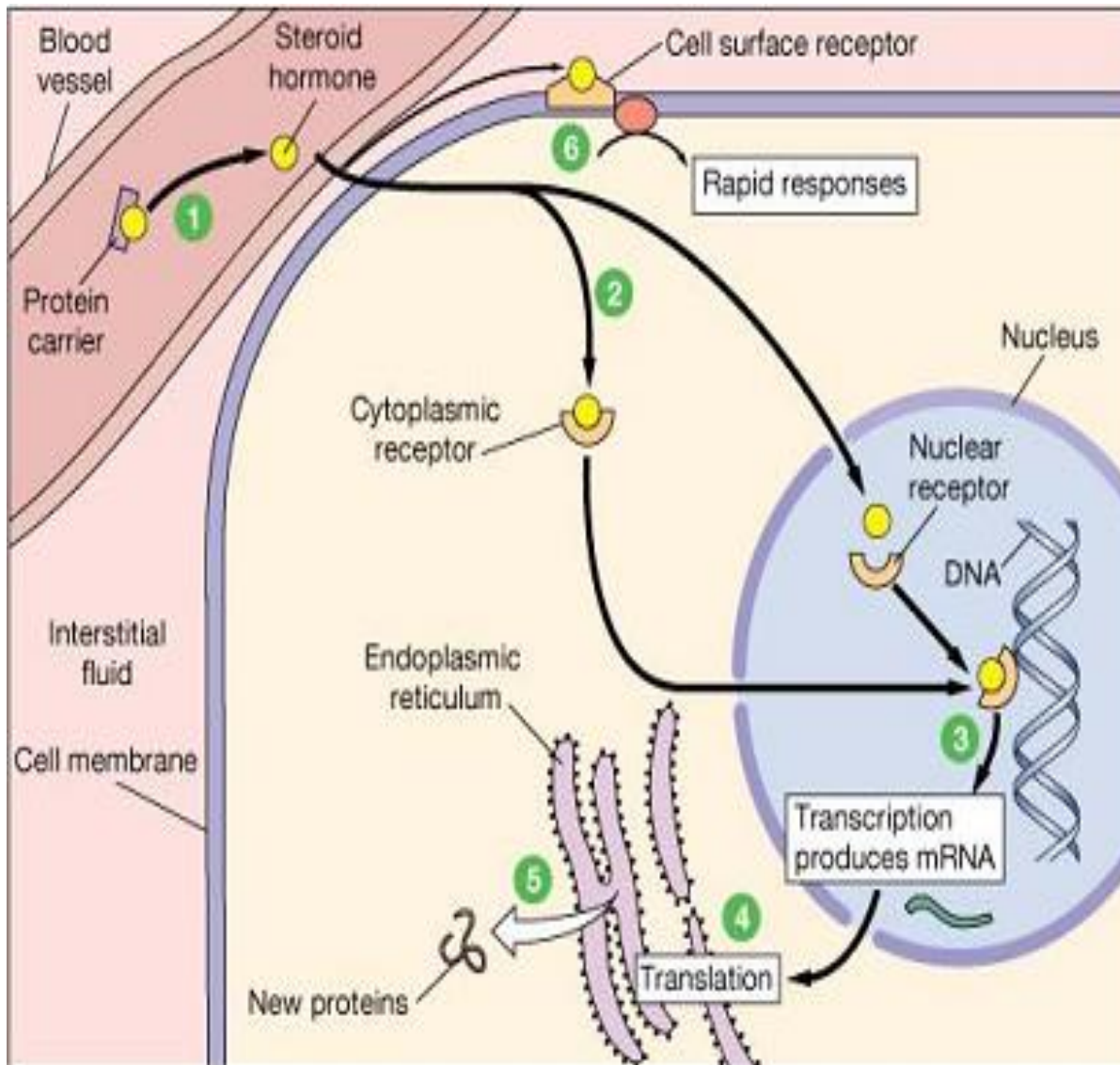


Sambar 4-26 Mekanisme kerja hormon hidrofilik melalui aktivasi simultan jaras perantara-kedua IP_3 - Ca^{2+} dan jaras DAG.

Aksi hormon polipeptida : PIP-Calsium

- Hormon mengikat reseptor, aktifkan protein G
- Protein G mengikat dan mengaktifkan enzim fosfolipase
- Fosfolipasi memecah fosfolipid PIP₂ → IP₃ dan DAG (keduanya merupakan 2nd messenger)
- DAG aktifkan protein kinase; IP₃ memicu pengeluaran Ca²⁺
- Ca²⁺ (3th messenger) merubah respon seluler

Steroid hormones: Action



1 Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.

2 Steroid hormone receptors are in the cytoplasm or nucleus.

3 The receptor-hormone complex binds to DNA and activates or represses one or more genes.

4 Activated genes create new mRNA that moves back to the cytoplasm.

5 Translation produces new proteins for cell processes.

6 Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.

Hormone Transport in the Blood

- Most water-soluble hormone → **free form** in blood circulation
- Lipid-soluble hormone → bound to **transport protein**
- **Fungsi protein pentransport:**
 1. Menjadikan lipid soluble → water soluble secara sementara → solubilitas di darah meningkat
 2. Menahan hormon yang molekulnya kecil untuk tidak terfiltrasi di ginjal → mengurangi hilangnya hormon di urin
 3. Sebagai cadangan hormon yang siap pakai dalam aliran darah
- 0.1–10% of the molecules of a lipid-soluble hormone → free fraction. Free fraction → diffuses out of capillaries, binds to receptors, and triggers responses.
- Ketika molekul free hormone meninggalkan darah → berikatan dg reseptornya, protein carrier akan melepaskan hormon yang dia ikat → free fraction

Hormone concentrations in the blood

- Concentration of circulating hormone reflect:
 - Rate of release
 - Speed of inactivation or removal
- Hormone are removed from blood by:
 - Degrading enzyme (lysosome degradation in target cell)
 - Liver enzyme system (Phase I and II reaction → excretion through feses or urin)

Pengikat/Pembawa Hormon

- Misal : T3-T4 → TBG, Albumin, TBPA (tyrosine binding prealbumin)

Tujuan pengikatan :

- sebagai reservoir → aktif “free” hormon
- cegah degradasi yang cepat dari hormon yang “free/unbound”
- memodulasi konsentrasi “free” hormon
- memperketat akses hormon ke lokasi-lokasi tertentu.

Target cell specificity

- Hormone circulate to all tissues but only activate cells referred to as target cells
- Target cells must have **specific receptors** to which the hormone binds
- These receptors may be intracellular or located on the plasma membrane (surface)
- Examples of hormone activity
 - ACTH receptors are only found on certain cells of adrenal cortex
 - Thyroxin receptors are found on nearly all cells of the body

Target Cell Activation

- Target cell activation depends on three factors
 - Blood level of hormone (either free or bound)
 - Relative number of receptors on target cell
 - Affinity of those receptors for hormone
- Up regulation -- target cells form more receptors in response to lack of hormone
- Down regulation – target cells lose receptors in response to more of hormone

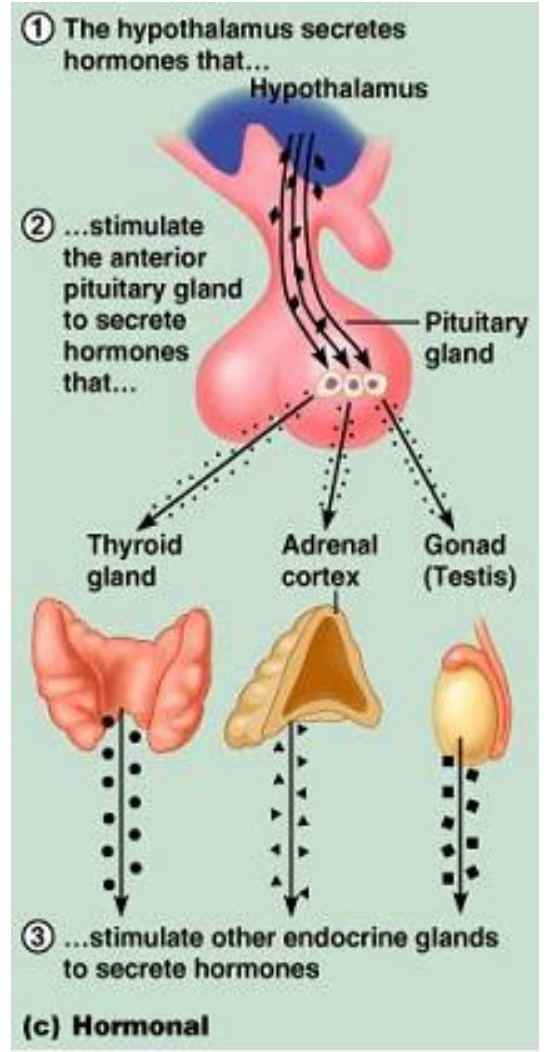
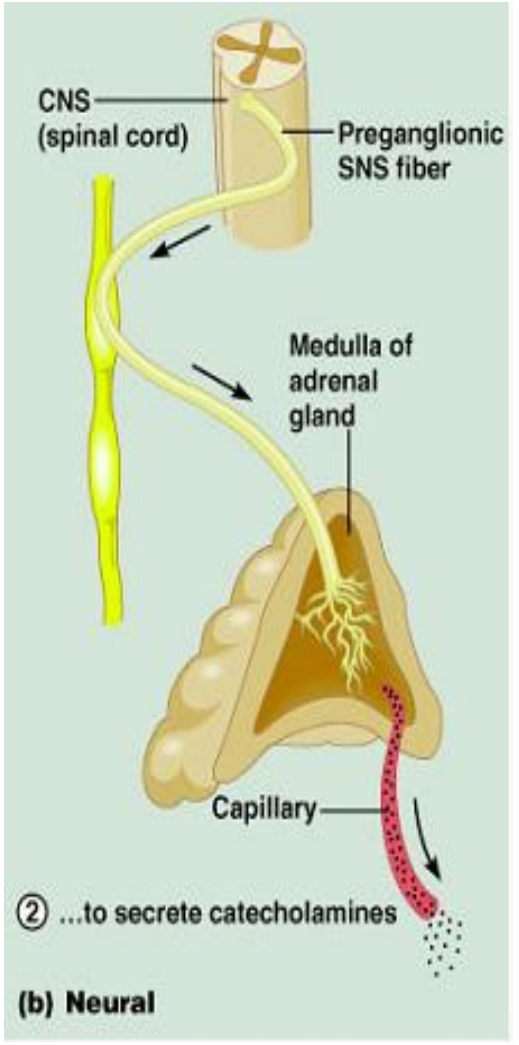
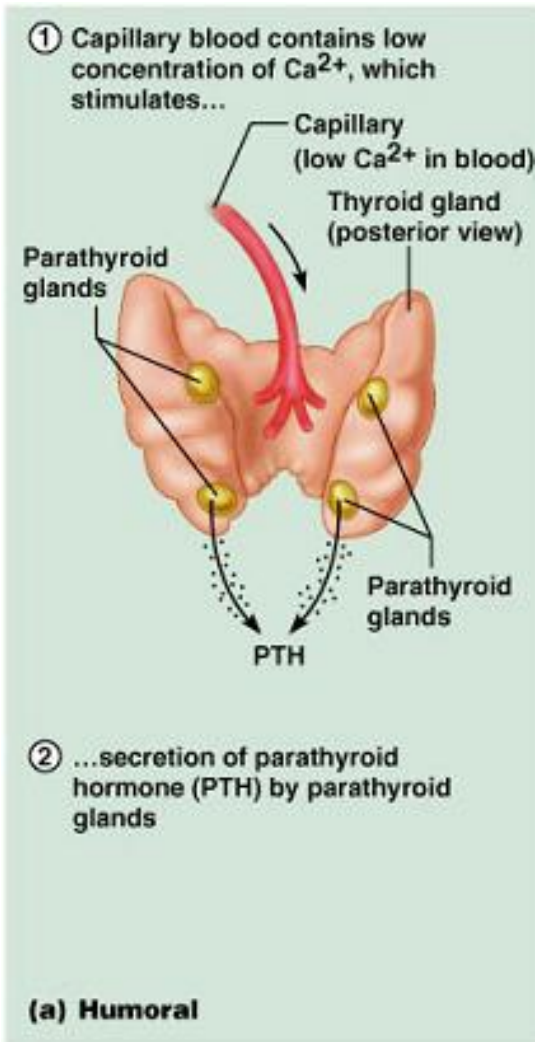
Interaction of Hormones at target cells

- Three type of hormone interaction
 - Permissiveness – one hormone cannot exert its effect without another hormone being present
 - Synergism – more than one hormone produce the same effect on target cell
 - Antagonism – one or more hormone opposes the action of another hormone

Control of hormone release

Hormones are synthesized and released in response to humoral, neural, and hormonal stimuli.

- Humoral stimuli – secretion as direct response to changing blood level of ions and nutrients
- Neural stimuli – nerve fibers stimulate hormone release
- Hormonal stimuli – in response to hormones produced by other endocrine organs



Mechanisms of Controlling Secretion

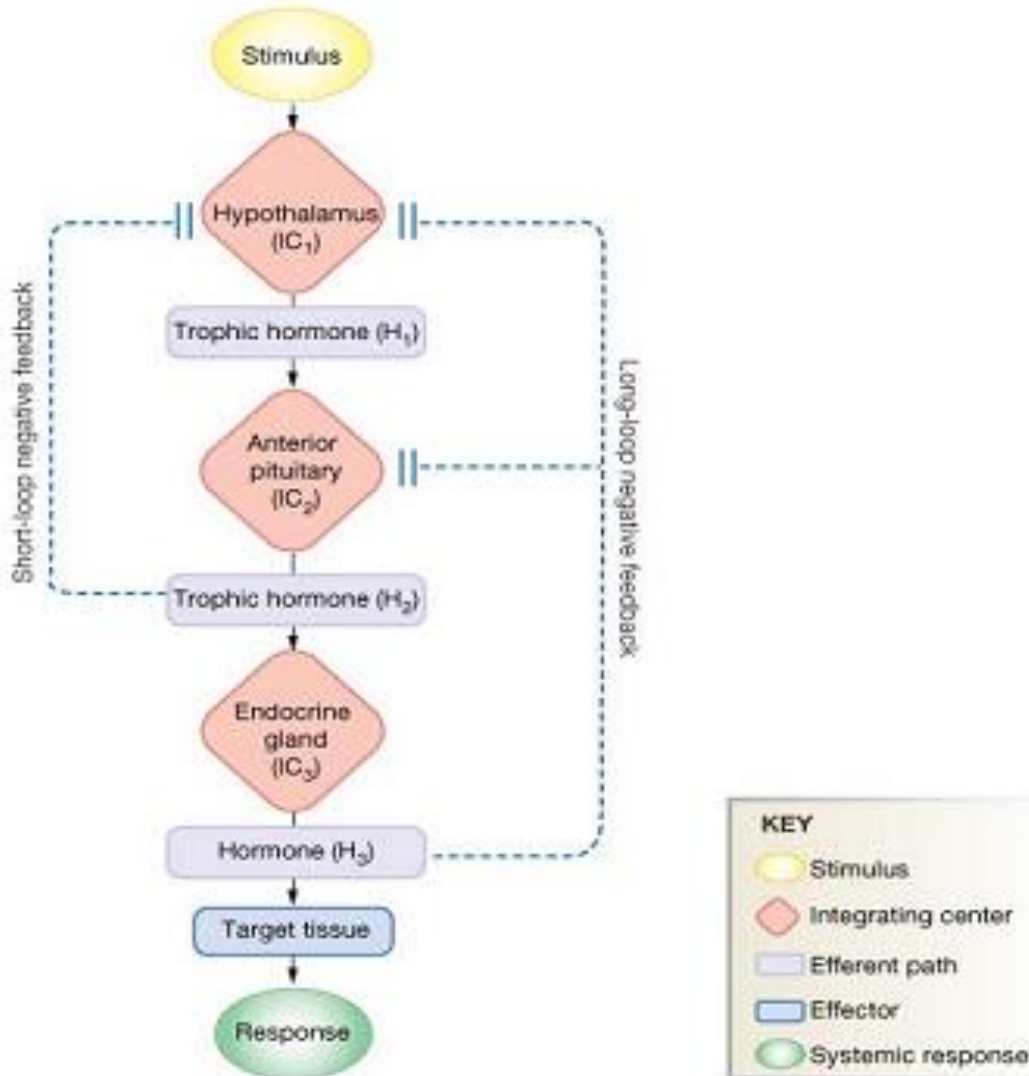
General mechanisms of controlling secretion that are common to many different hormones:

- Negative-feedback control
- Neuroendocrine reflexes
- Diurnal (circadian) rhythms.

Regulation of Hormone feedback

Negative Feedback	Positive Feedback
<p>To maintain hormone level within a relatively narrow range.</p> <p>Ex :</p> <p>TH → TRH, TSH</p> <p>Cortisol → CRH-ACTH</p> <p>Ca²⁺ → PTH</p> <p>Glukosa → inhibition release of insulin</p> <p>And so on</p>	<p>Not well understood</p> <p>Stimulus triggers control mechanism that amplifies effect</p> <p>Ex :</p> <p>Estrogen → LH surge</p> <p>Though, chronic level of Est are inhibitory, gradually rising est level stimulate LH secretion</p>

Negative feedback controls: Long & short Loop reflexes



Neuroendokrin reflexes

- Tujuan refleks : untuk meningkatkan sekresi hormon sbg respon thd stimulus spesifik.
- Beberapa kondisi, input neural ke kllj endokrin adalah satu-satunya faktor yg meregulasi hormon, misal : **sekresi epinefrin medula adrenal karena stimulus saraf simpatis.**
- Beberapa sistem kontrol endokrin, sebaliknya, melibatkan feedback control dan refleks neuroendokrin. Misalnya, peningkatan sekresi cortisol “hormon stress” oleh korteks adrenal selama respon stress.

Diurnal (Circadian) Rhythms

- The most common endocrine rhythm is the diurnal (“day–night”), or circadian (“around a day”) rhythm endocrine rhythms are locked on, or entrained, to external cues such as the light–dark cycle.
- For example, cortisol secretion rises during the night, reaches its peak secretion in the morning before a person gets up, then falls throughout the day to its lowest level at bedtime

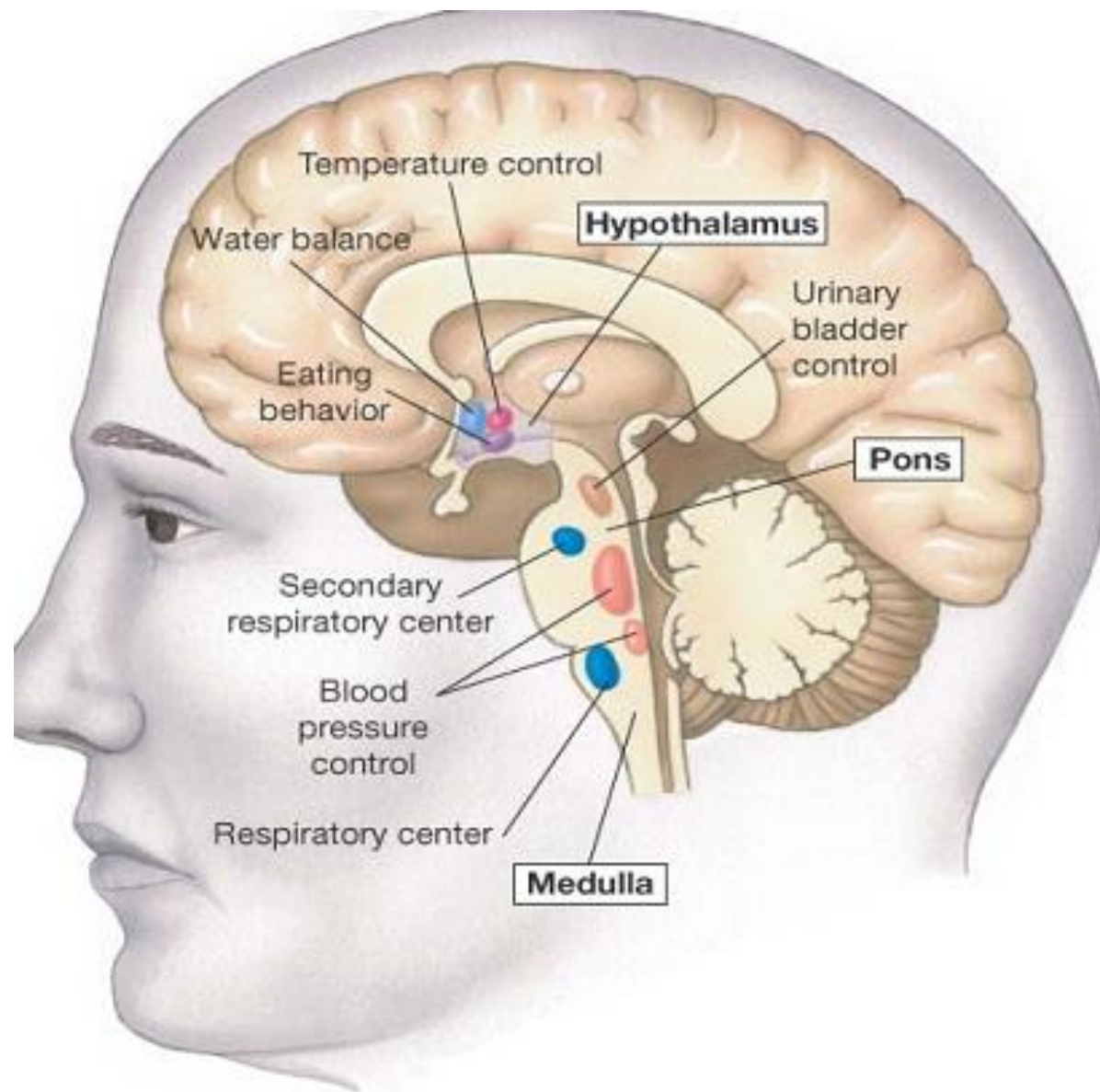


Figure 11-3: Autonomic control centers in the brain

Hypothalamus

- Integrates function that maintain chemical and temperature homeostasis
- Function in limbic system
- **Controls the release of hormones from the anterior and posterior pituitary (hypophysis)**
- **Synthesizes releasing hormones in cell body neurons**
- Hormone are **transported down the axon and stored in nerve endings**
- Hormone are released in pulses

Hypothalamic Releasing Hormones

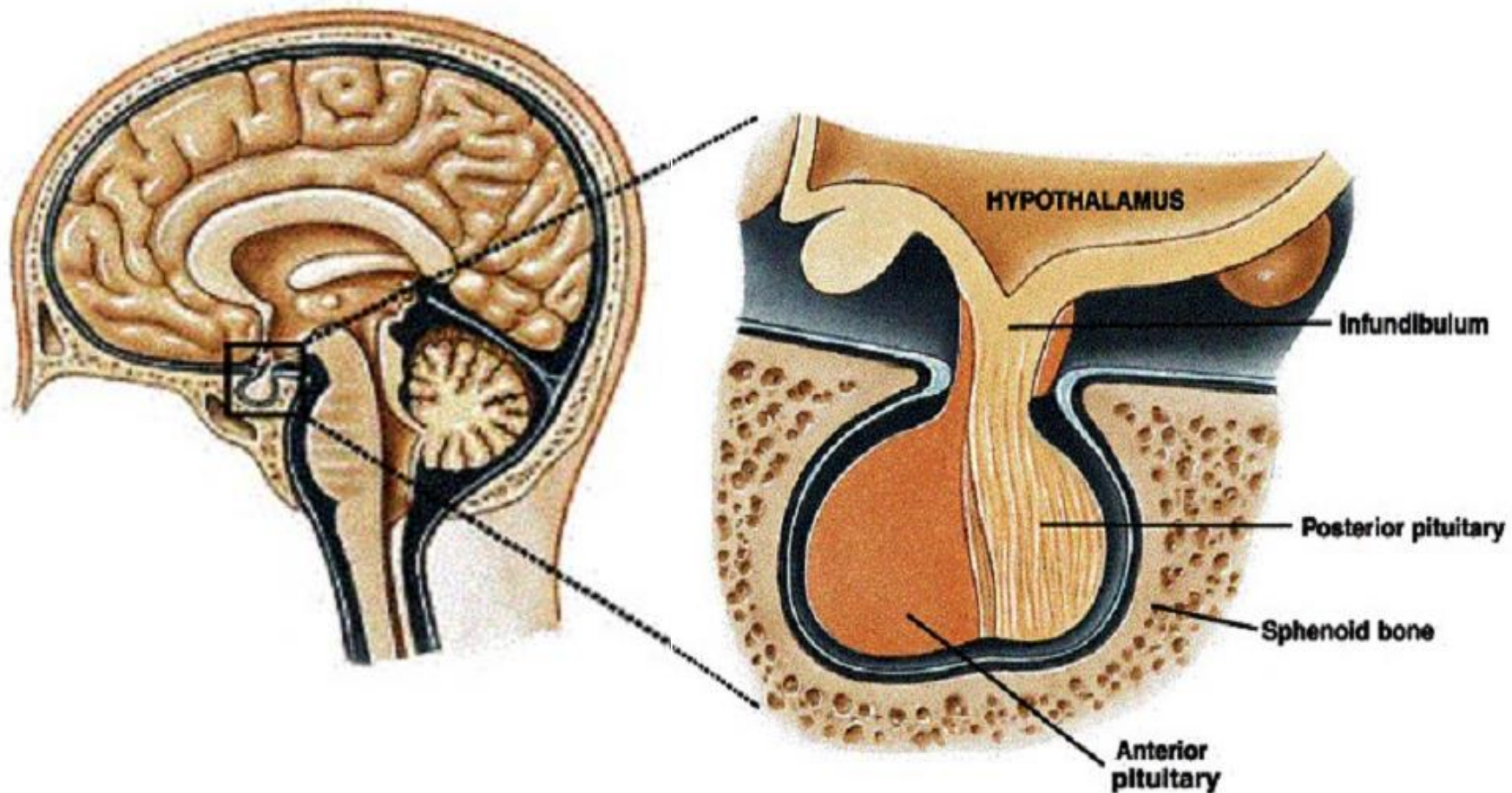
Hormone	Abbreviation	Gland of Origin	Major Actions*
Thyrotropin-releasing hormone	TRH	Hypothalamus	Stimulates secretion of TSH and prolactin
Corticotropin-releasing hormone	CRH	Hypothalamus	Stimulates secretion of ACTH
Gonadotropin-releasing hormone	GnRH	Hypothalamus	Stimulates secretion of LH and FSH
Growth hormone-releasing hormone	GHRH	Hypothalamus	Stimulates secretion of growth hormone
Somatotropin release-inhibiting hormone (somatostatin)	SRIF	Hypothalamus	Inhibits secretion of growth hormone
Prolactin-inhibiting factor (dopamine)	PIF	Hypothalamus	Inhibits secretion of prolactin

Prolactin – releasing hormone PRH Hypothalamus Stimulate secretion of prolactin

Pituitary Gland (Hypophysis)

- Two lobed organ that secretes 9 major hormones
- Neurohypophysis – posterior lobe (neural tissue and infundibulum)
 - Receive, store, and release hormones from hypothalamus
 - Secretes neurohormone
- Adenohypophysis – anterior lobe, made up of glandular tissue (true endocrine tissue)
 - Synthesizes and secretes a number of hormones

Location of pituitary gland



Control of the production of anterior pituitary hormones by hypothalamic regulatory hormones

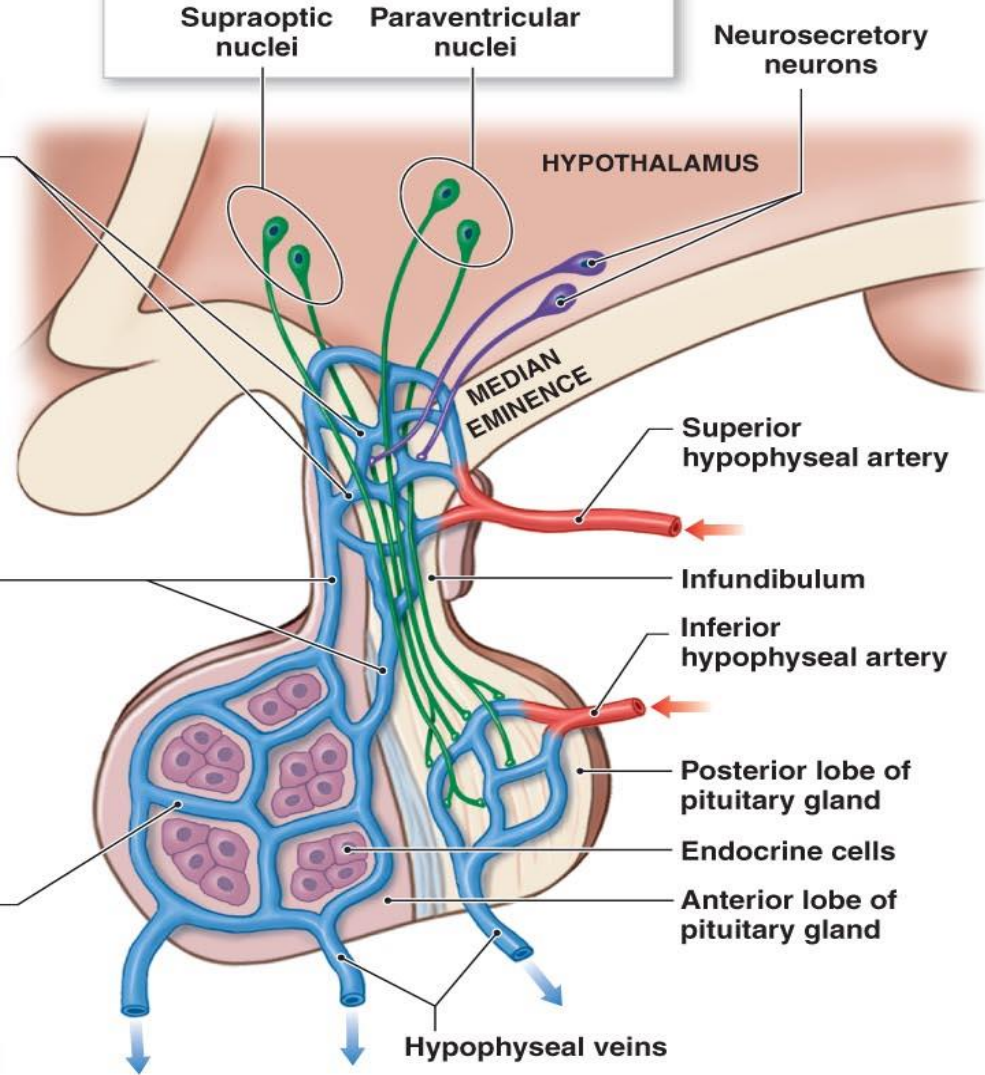
Neurons of these structures manufacture antidiuretic hormone and oxytocin, respectively, which are released by synaptic terminals at capillaries in the posterior lobe of the pituitary gland

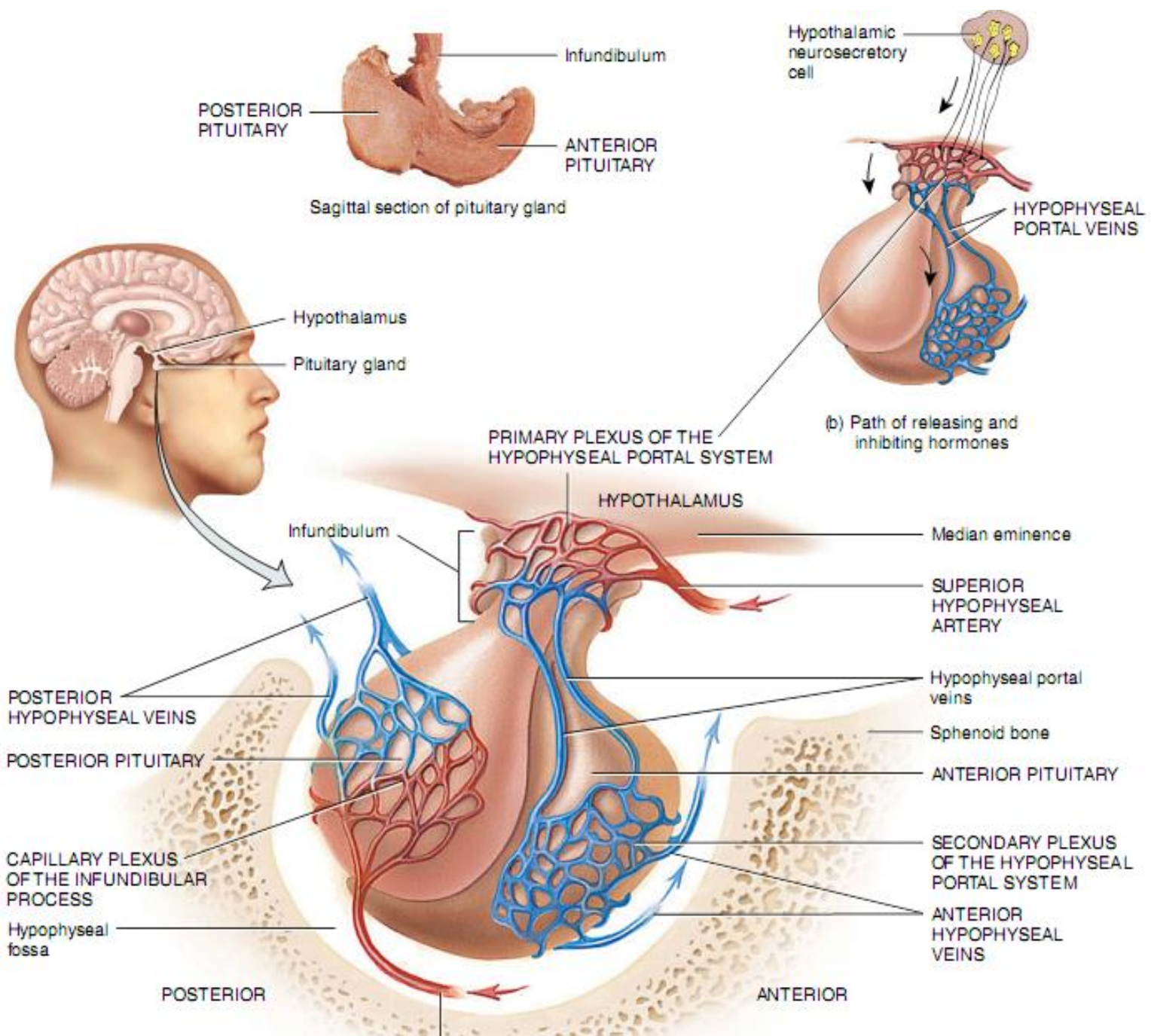
Hypophyseal Portal System

The capillary networks in the median eminence are supplied by the superior hypophyseal artery. **Before leaving the hypothalamus, the capillary networks unite to form a series of larger vessels that spiral around the infundibulum to reach the anterior lobe.**

The vessels between the median eminence and the anterior lobe carry blood from one capillary network to another. **Blood vessels that link two capillary networks are called portal vessels; in this case, they have the histological structure of veins, so they are called portal veins.**

Once within the anterior lobe, these vessels form a second capillary network that branches among the endocrine cells.





Neurosecretory neurons in Hypothalamus

- Synthesize the hypothalamic **releasing and inhibiting hormones in their cell bodies** and package the hormones inside **vesicles**, which reach the **axon terminals** by axonal transport. **Nerve impulses stimulate the vesicles to undergo exocytosis.** The hormones then **diffuse** into the primary plexus of the hypophyseal **portal system**

Adenohypophysis

Hormone	Abbreviation	Gland of Origin	Major action
Thyroid-stimulating hormone	TSH	Anterior pituitary	Stimulates synthesis and secretion of thyroid hormones
Follicle-stimulating hormone	FSH	Anterior pituitary	Stimulates growth of ovarian follicles and estrogen secretion Promotes sperm maturation (testes)
Luteinizing hormone	LH	Anterior pituitary	Stimulates ovulation, formation of corpus luteum, and synthesis of estrogen and progesterone (ovary) Stimulates synthesis and secretion of testosterone (testes)
Growth hormone	GH	Anterior pituitary	Stimulates protein synthesis and overall growth
Prolactin		Anterior pituitary	Stimulates milk production and breast development
Adrenocorticotrophic hormone	ACTH	Anterior pituitary	Stimulates synthesis and secretion of adrenal cortical hormones
β -lipotropin		Anterior pituitary	? in human
Melanocyte-stimulating hormone	MSH	Anterior pituitary	Stimulates melanin synthesis (? humans)

Neurohypophysis

Hormone	Abbreviation	Gland of Origin	Major action
Oxytocin		Posterior pituitary	Milk ejection; uterine contraction
Antidiuretic hormone (vasopressin)	ADH	Posterior pituitary	Stimulates H ₂ O reabsorption by renal collecting ducts

PROLACTIN : Synthesis

- Is synthesized in **lactotropes** which constitute about 2% of anterior pituitary cells
- Lactotrope and somatotropes are derived from a common precursor cell that may give rise to a tumor secreting both PRL and GH
- Marked lactotrope cell hyperplasia develops during the last 2 trimester of pregnancy and first few months of lactation where this transient functional changes are induced by estrogen

PROLACTIN : Secretion

- PRL normal level = 10-25 $\mu\text{g/L}$ in women, 10-20 $\mu\text{g/L}$ in men
- Secretion is **pulsatile** fashion, highest secretory peak during rapid eye movement sleep
- PRL is unique because the predominant central control mechanism is inhibitory. D2 receptors mediate PRL inhibition
- VIP (vasoactive intestinal peptide) induce PRL release, glucocorticoid and TH weakly suppress PRL secretion

PROLACTIN : Secretion

- PRL level increase significantly (10X) during pregnancy and decline rapidly within 2 weeks of parturition. If breastfeeding is initiated, basal PRL level remain elevated.
- Breast suckling stimulates neural afferent pathway in hypothalamus that induce PRL release and encourages continued milk production

ACTH : Synthesis

- Is synthesized by ACTH-secreting **corticotrope** cells which constitute 20% of pituitary cell population
- ACTH is derived from **POMC precursor protein**.
- The **POMC gene is potently suppressed by glucocorticoids**.
- CRH which is synthesized in paraventricular nucleus, is the predominant stimulator of ACTH synthesis and release
- **CRH receptor is a GPCR that is expressed on corticotrope and induces POMC transcription**

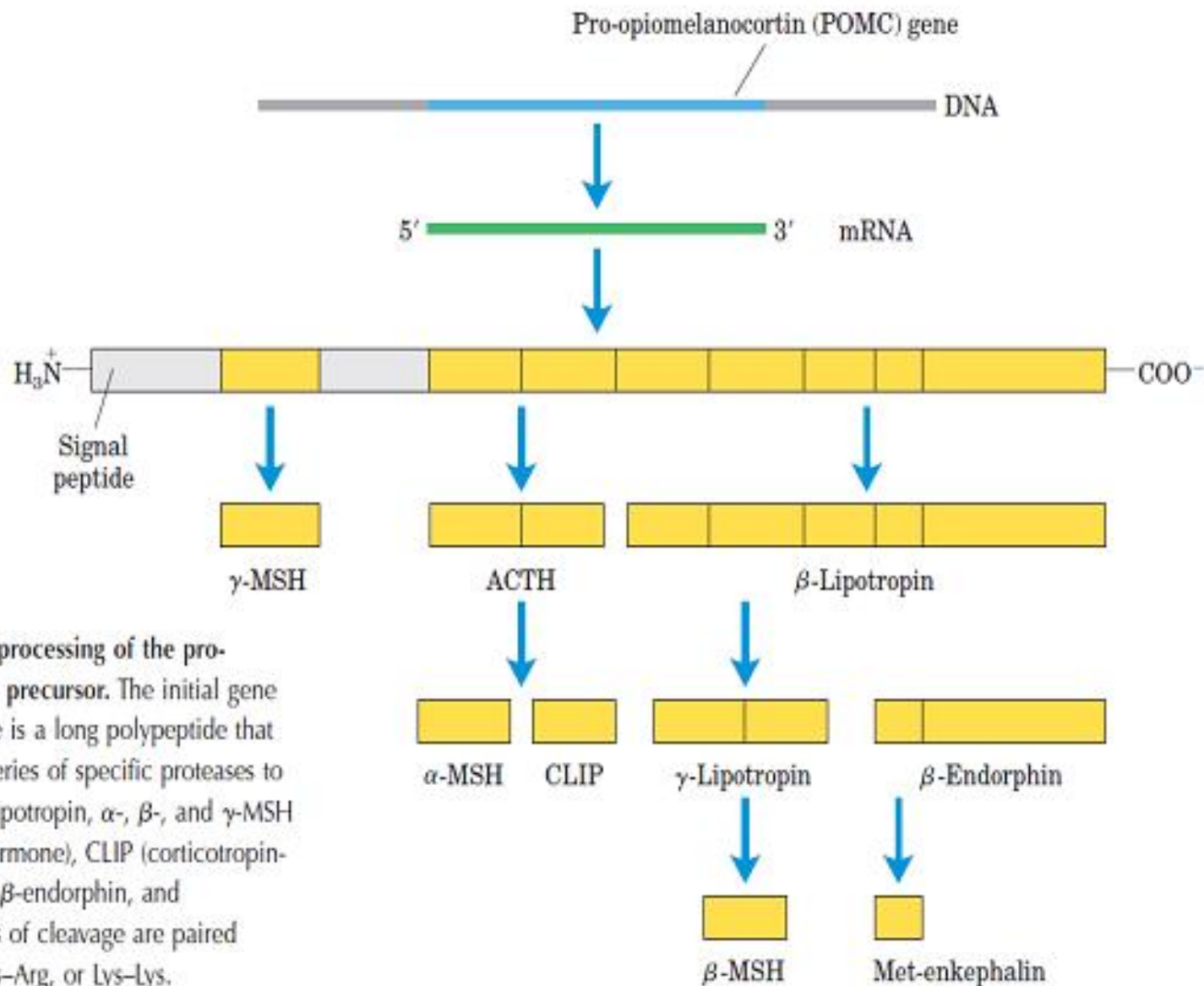
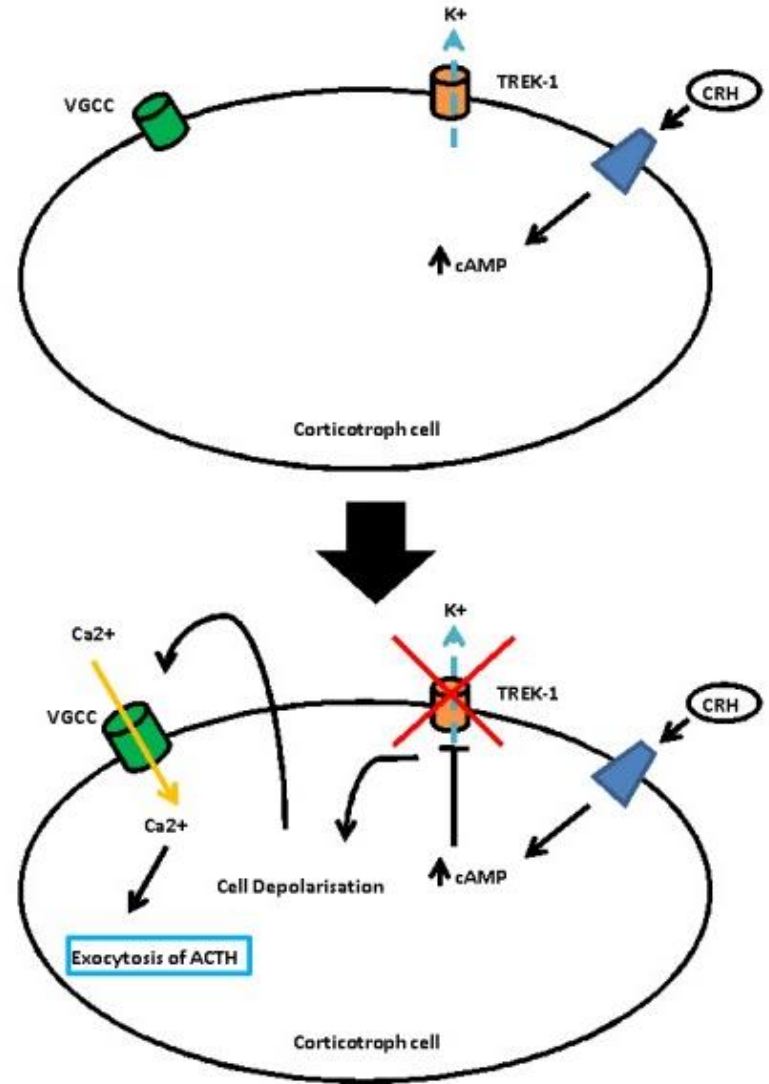


FIGURE 23-6 Proteolytic processing of the pro-opiomelanocortin (POMC) precursor. The initial gene product of the POMC gene is a long polypeptide that undergoes cleavage by a series of specific proteases to produce ACTH, β - and γ -lipotropin, α -, β -, and γ -MSH (melanocyte-stimulating hormone), CLIP (corticotropin-like intermediary peptide), β -endorphin, and Met-enkephalin. The points of cleavage are paired basic residues, Arg-Lys, Lys-Arg, or Lys-Lys.

ACTH : Secretion

Diagram showing the release of ACTH from corticotroph cells. CRH binds to a particular receptor that leads to **activation of cAMP**. The rise in cAMP **inhibits TREK-1**, thus leading to the **depolarisation** of the cell and subsequently **influx of calcium via VGCC** (voltage gated-Calsium channel), The rise in intracellular calcium leads to the **exocytosis** and release of ACTH.



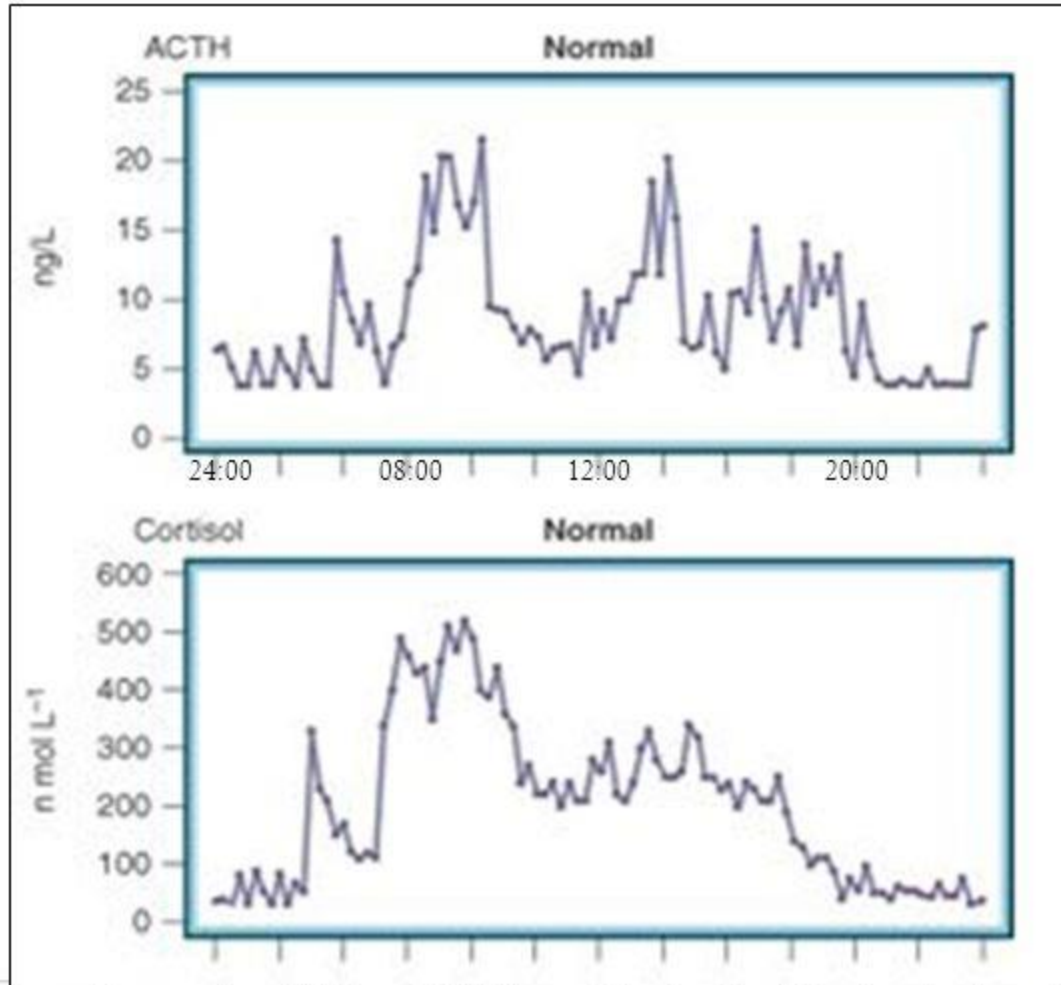
TREK-1 : channel K

VGCC : Voltage gated- Calsium channel

ACTH : Secretion (pulsatile)

STIMULATION	INHIBITION
<ul style="list-style-type: none">•CRH•AVP (arginin vasopresin) stimulate ACTH release, weakly•Stress (physical & Psychological) via CRH & AVP; including Hypoglycemia, exercise, acute illness.	<ul style="list-style-type: none">•Glucocorticoid via negative feedback regulation.•Corticosteroid

ACTH and Cortisol Secretion



- pulsatile secretion
- circadian rhythm
- highest in a.m.

ACTH : Action

- The major function of HPA axis is to maintain **metabolic homeostasis** and to mediate the **neuroendocrine stress response**
- ACTH induces **adrenocortical steroidogenesis** by maintaining adrenal cell proliferation and function

ACTH : Deficiency

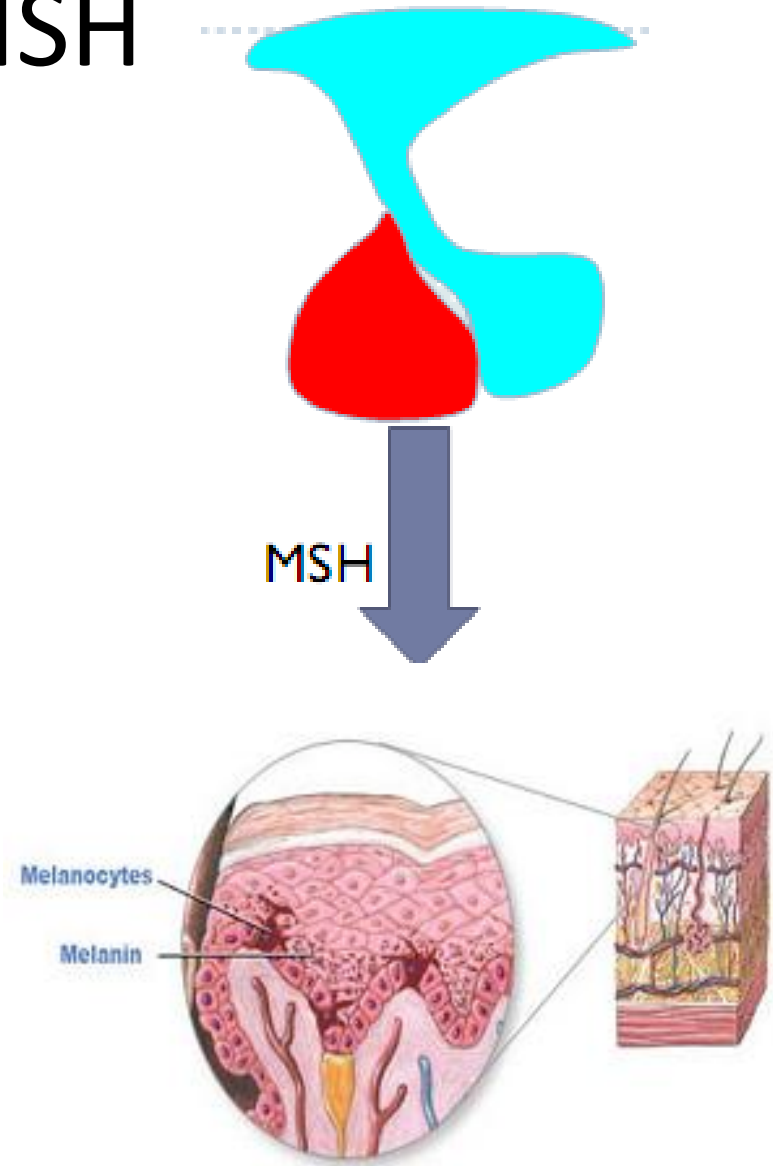
- ACTH deficiency → secondary adrenal insufficiency
- Characterized by : fatigue, anorexia, nausea, vomiting, occasionally hypoglycemia
- Defek pada klj adrenal → primary adrenal insufficiency
- Hipokortisol (sekunder adrenal insuff) → tidak pigmentasi kulit
- Hipokortisol (primer adrenal insuff) → fd (-) → transkripsi POMC gene → ACTH dan MSH >> → pigmetasi kulit

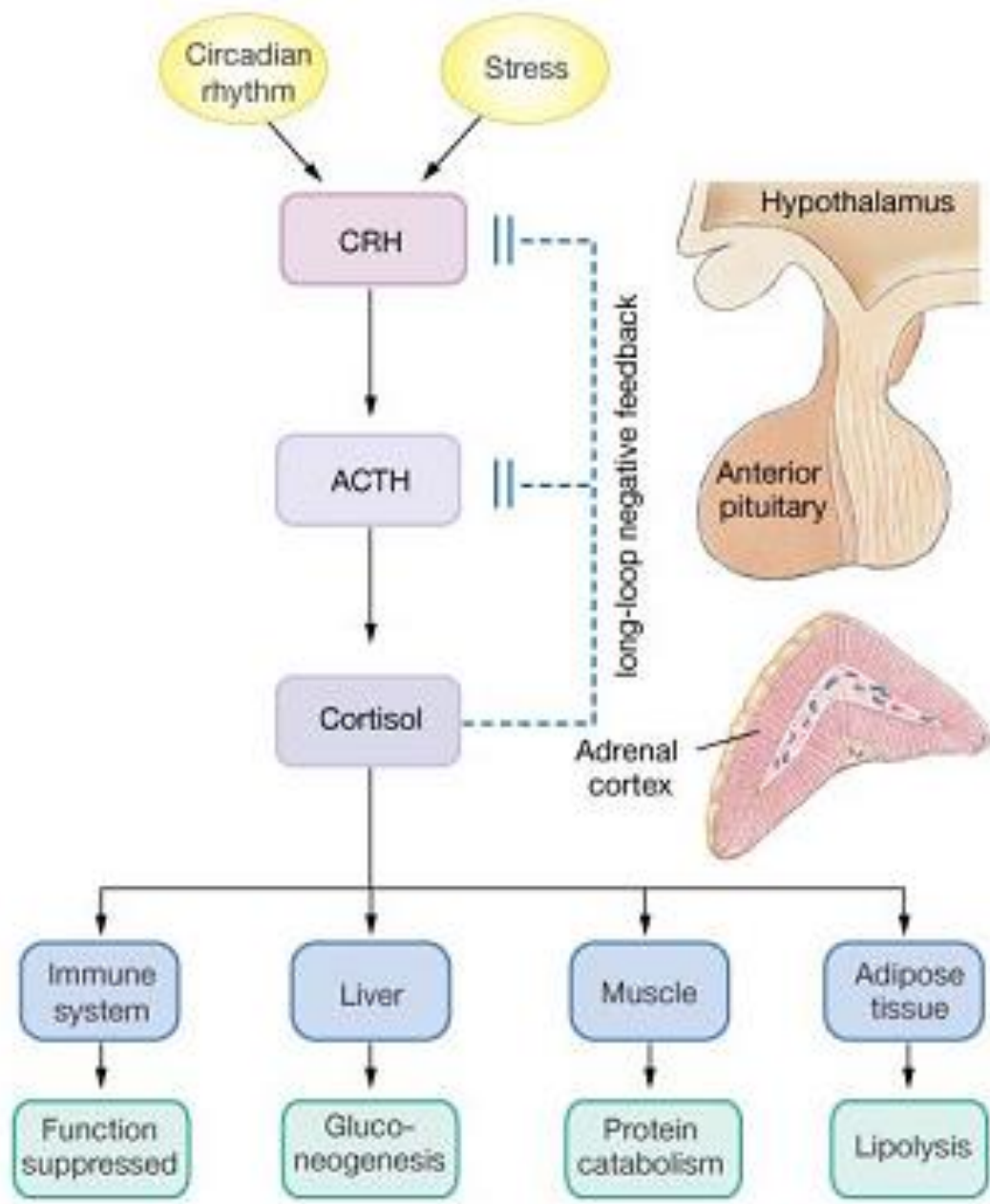
ACTH hypersecretion

- Hypersecretion could be due to:
 - Tumor of pituitary gland → ACTH ↑ → cortisol ↑ (Cushing disease)
 - Where ever tumor that produce CRH/ACTH
- Symptoms :
Moon face, central obesity, Hypertension, Hirsutism.
- Cushing Syndrome vs Cushing disease?
- Primary vs Secondary vs tertiary hypercortisolism

α - MSH

- MSH acts on melanocytes in the epidermis of the skin to stimulate the secretion of melanin
- Melanin controls pigmentation in the skin.





GONADOTROPIN (FSH-LH) :

Synthesis & Secretion

- **Gonadotrope** cells constitute about 10% of anterior pituitary cells and produce 2 gonadotropins : LH & FSH
- In women, the rapidly fluctuating gonadal steroid levels vary throughout the menstrual cycle.
- Hypothalamic GnRH regulate the synthesis and secretion of both LH&FSH
- **Estrogen** act at the hypothalamic & pituitary levels to control gonadotropin secretion.

GONADOTROPIN (FSH-LH) :

Synthesis & Secretion

- Chronic estrogen exposure is inhibitory, whereas **rising estrogen levels exert positive feedback** to increase gonadotropin pulse frequency & amplitude.
- **Testosteron feedback** in men also occur at hypothalamic & pituitary levels
- Testosteron is mediated partially by its conversion to estrogen

Follicle-Stimulating hormone (FSH) & Luteinizing Hormone (LH)

- Regulate the function of ovaries and testes
- FSH stimulate gamete (ovum and sperm) production
- FSH-LH absent from the blood in prepubertal boys and girls
- Triggered by GnRH during and after puberty

Function of Gonadotropins (FSH & LH)

- In females
 - LH works with FSH to cause maturation of the ovarian follicle
 - LH works alone to trigger ovulation (expulsion of the ovum from follicle)
 - LH promote synthesis and release of estrogen and progesterone
- In males
 - LH stimulate interstitial cells of testes to produce testosterone
 - LH is also referred as interstitial cell-stimulating hormone (ICSH)
 - While FSH promote sperm maturation in testes

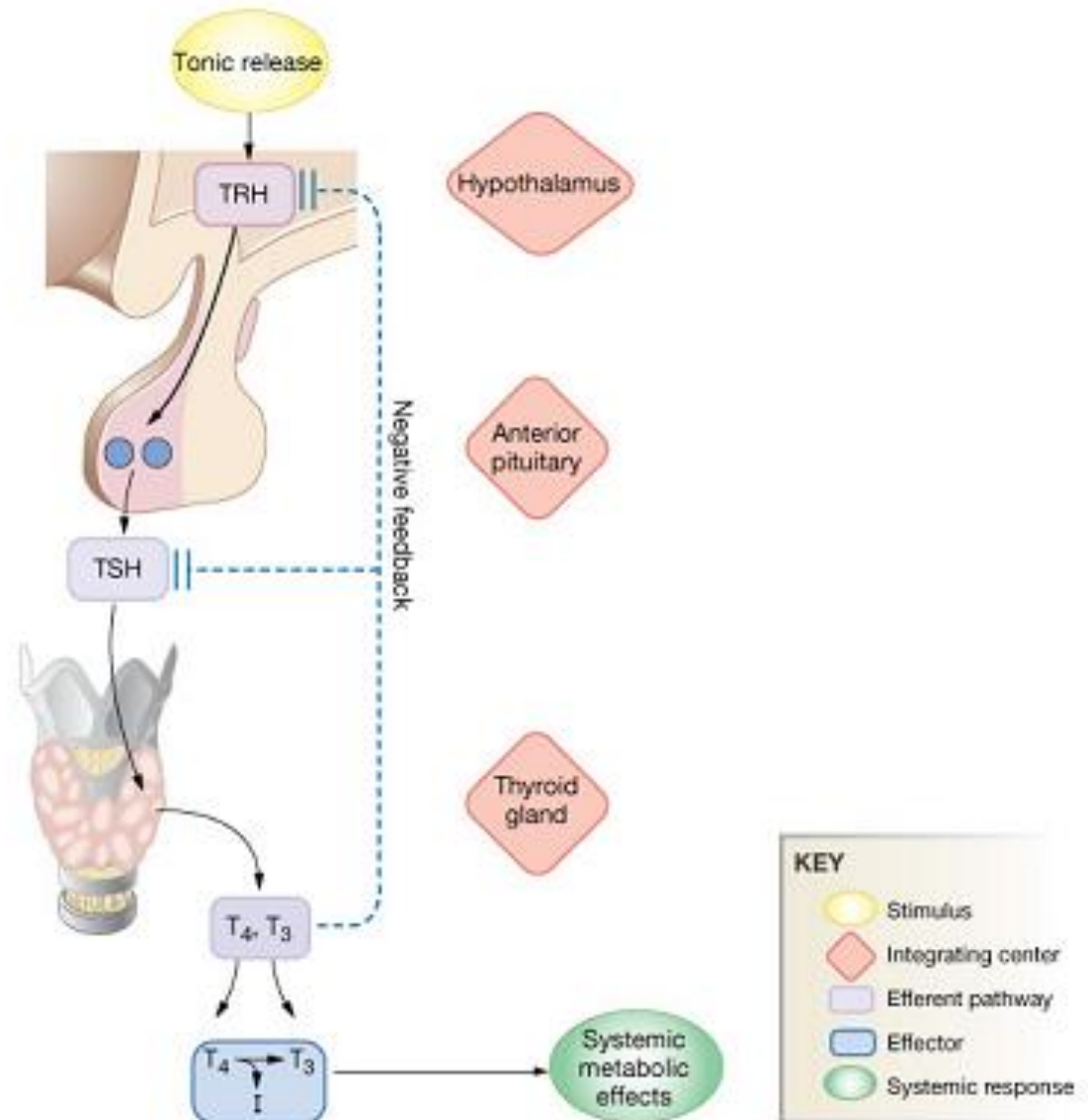
TSH : Synthesis & Secretion

- Is synthesized by TSH secreting **thyrotrope** cells which constitute 5% of the anterior pituitary cell population
- TRH acts through a **GPCR** to stimulate TSH synthesis & secretion
- **Thyroid hormones, dopamine, somatostatin & glucocorticoids** suppress TSH by overriding TRH induction

TSH : Action

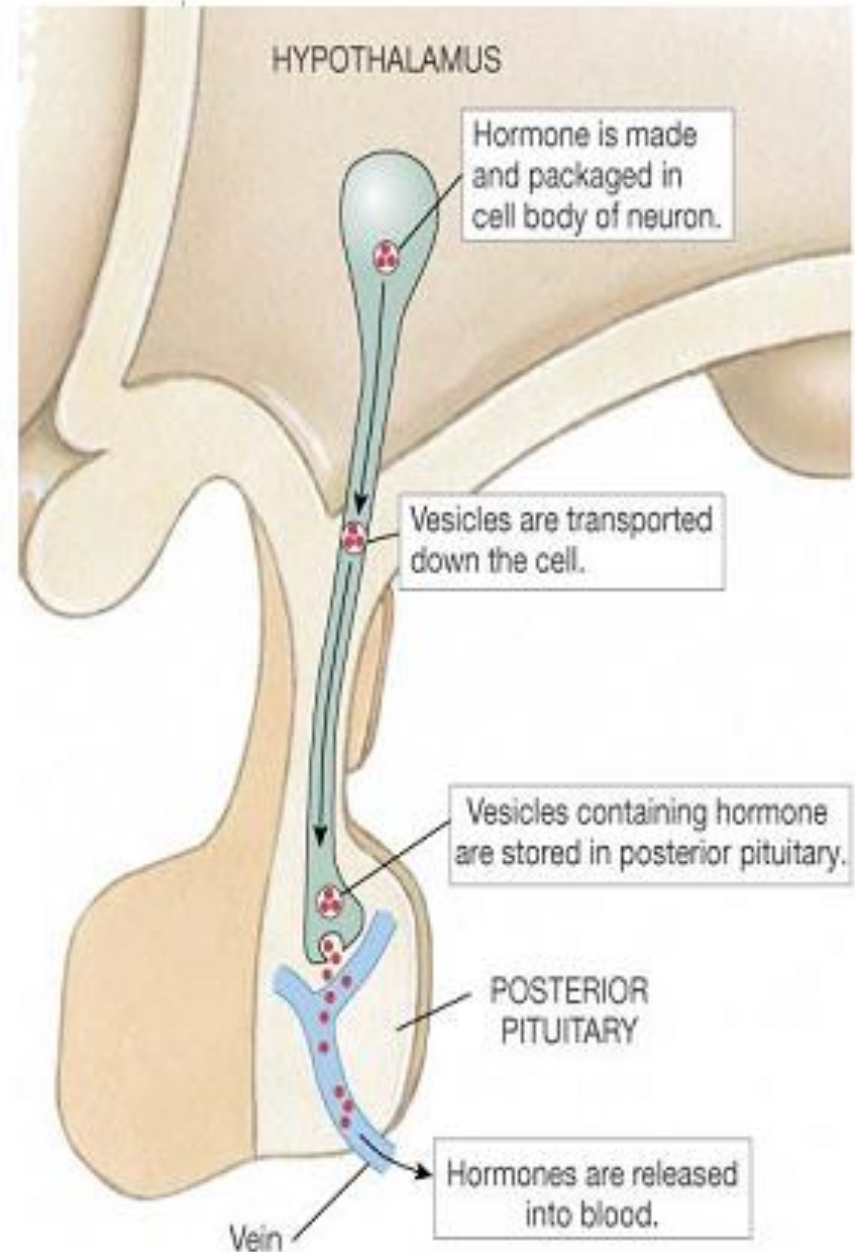
- TSH is secreted in **pulses** with low amplitude of pulses and relatively long half-life
- TSH binds to a GPCR on thyroid follicular cells to stimulate TH synthesis & release

Thyroid hormone control pathway



NEUROHYPOPHYSIS

- Hormone synthesized in the **supraoptic & paraventricular** nuclei of hypothalamus and transport down the axons to posterior pituitary
- Hormones are **stored in vesicle** until it is released into circulation

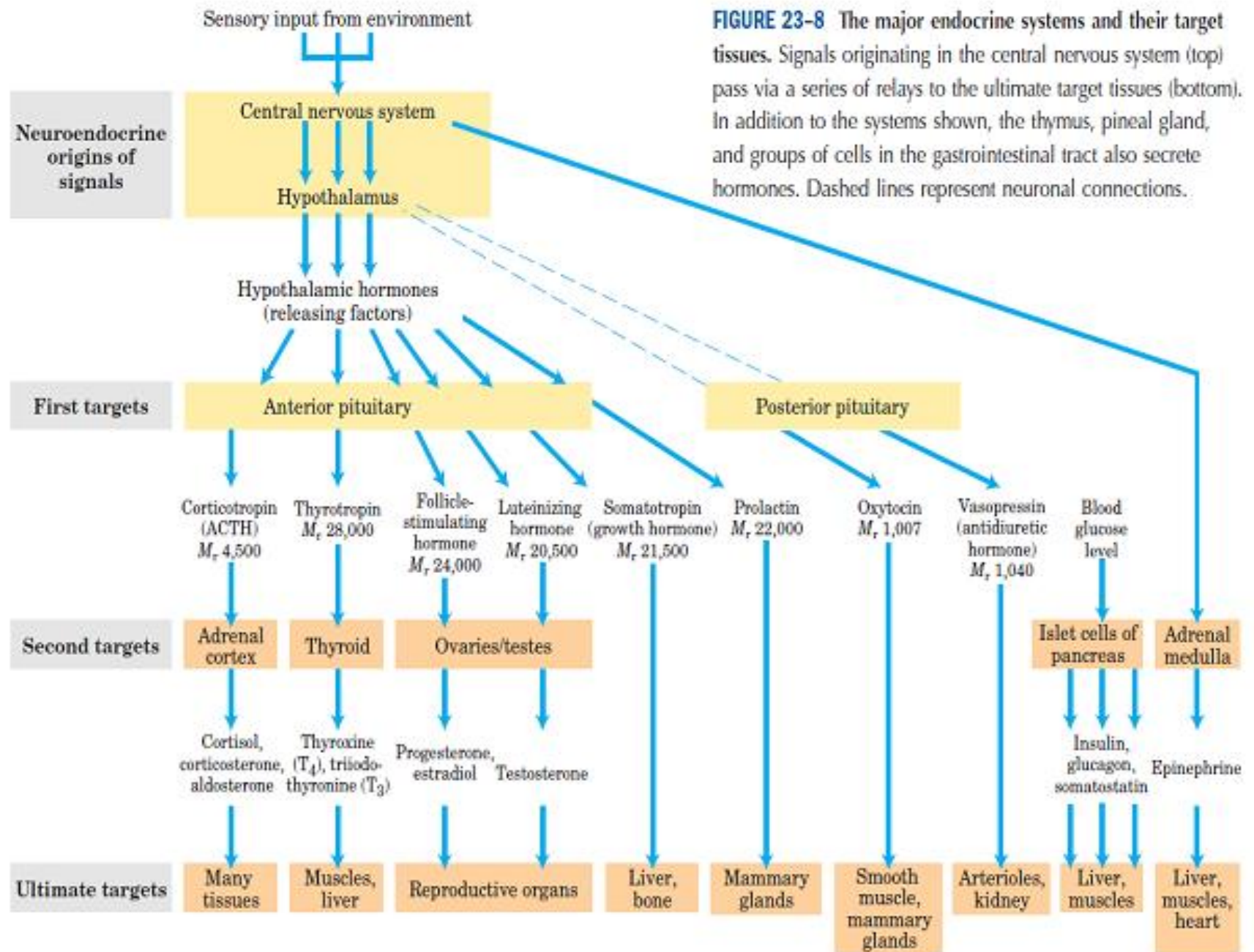


The posterior pituitary hormones : ADH/AVP(arginin vasopressin)

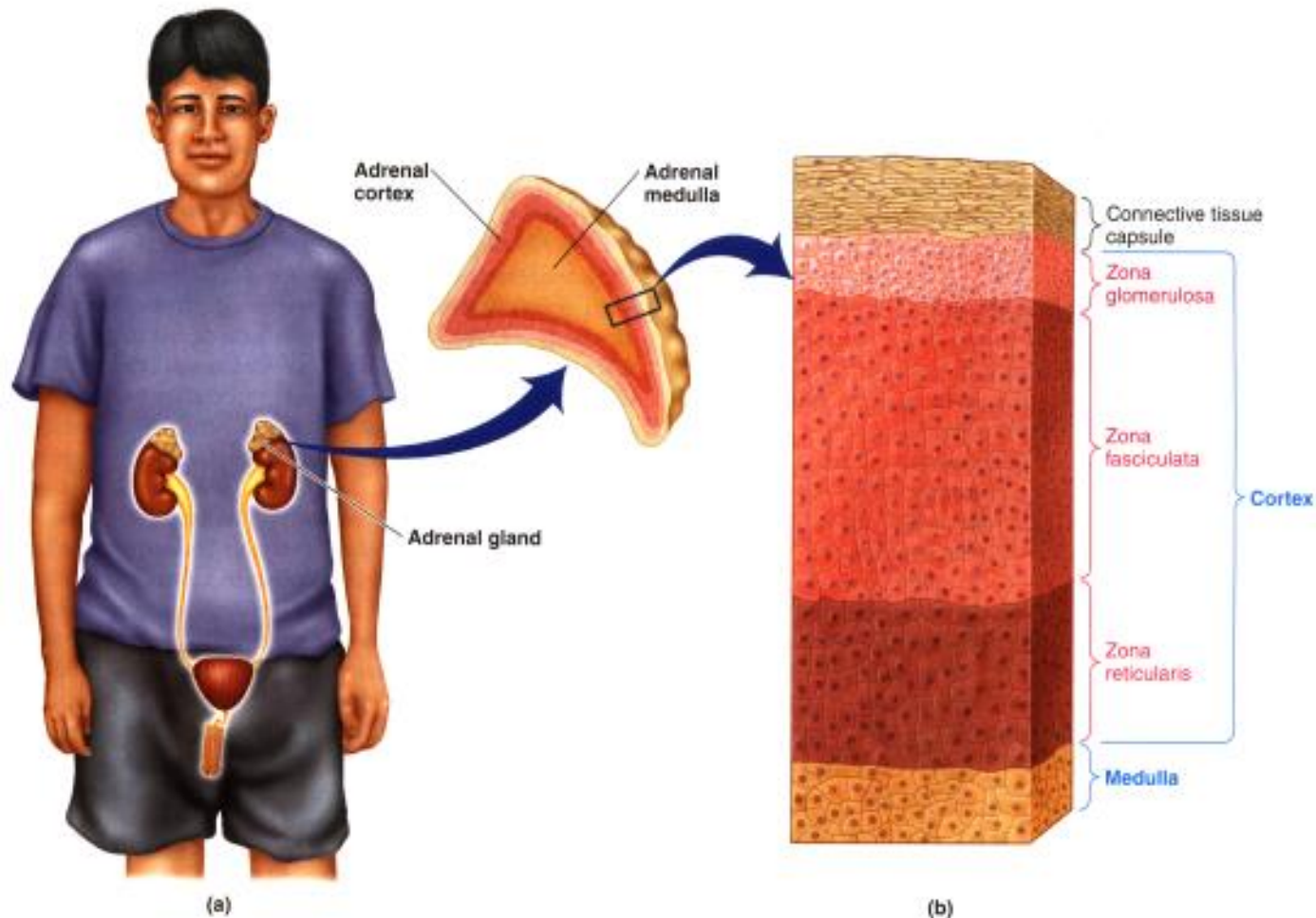
- Plasma osmolality is monitored by osmoreceptors in hypothalamus
- Increase osmolality stimulates secretion of ADH
- High solutes, ADH is released, thus preserving water
- Low solutes, ADH is not released, thus caused water loss from the body

The posterior pituitary hormones : Oxytocin

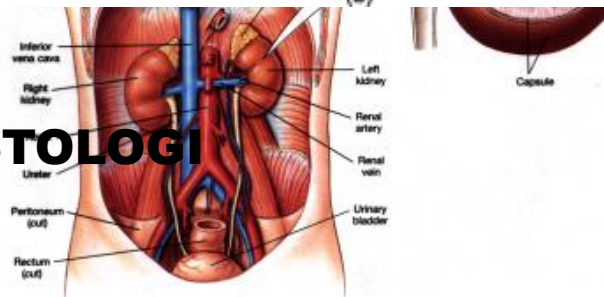
- **Suckling and cervix dilatation** are **physiologic stimuli** of oxytocin secretion
- Oxytocin effects in **uterine contraction** for labor
- Oxytocin triggers milk ejection (“**letdown**” **reflex**) in women producing milk
- It stimulates the breast alveoli contract and squeeze out the milk, pushing it **down** the ducts towards the nipple
- Regulated by positive feedback mechanism to oxytocin in the blood



KELENJAR ADRENAL



ANATOMI DAN HISTOLOGI KLJ.ADRENAL



Korteks Adrenal

- Dibagi menjadi 3 zona : glomerulosa, fasciculata, retikularis.
- Ketiga zona tsb mensekresi kortikosteron, mekanisme enzimatik utk membentuk **aldosteron (mineralokortikoid)** terutama di z.glomerulosa, z.fasciculata terutama mensekresi **glukokortikoid (cortisol)**, dan z.retikularis terutama menghasilkan **hormon sex / androgen adrenal**
- Hormon disintesis dari prekursor kolesterol

- **Glukokortikoid** adrenal penting dalam memodulasi metabolisme intermediet & respon imun
- Tekanan darah, volume vaskular, dan elektrolit diatur melalui **mineralokortikoid**
- Karakteristik seks sekunder (pada wanita) diatur melalui **androgen**
- HPA axis penting dalam respon thd stress dengan meningkatkan secara cepat level kortisol
- Kelainan Adrenal : hyperfunction (Cushing's syndrome) dan hypofunction (adrenal insufficiency)

Transpor Steroid

- Sirkulasi : ada kortisol “free”, berikatan dengan protein, dan metabolit kortisol. Normalnya , **<5%** merupakan kortisol **“free”**
- Kortisol “free” dan metabolitnya saja yang difiltrasi di glomerulus
- Kortisol diikat di plasma oleh ikatan berafinitas tinggi dengan **CBG dan transcortin**, dan ikatan afinitas rendah oleh **albumin**
- Ikatan kortisol dg CBG berkurang di area inflamasi → meningkatkan konsentrasi kortisol “free” lokal
- Metabolit kortisol secara biologis inaktif dan berikatan scr lemah dg protein plasma yg bersirkulasi

Metabolisme dan ekskresi steroid :

Glukokortikoid

- The plasma concentration of cortisol is determined by the **rate of secretion**, the **rate of inactivation**, and the rate of **excretion of free cortisol**
- A major enzyme regulating cortisol metabolism is 11 β -hydroxysteroid dehydrogenase (**11 β -HSD**).
- There are two isoforms: **11 β -HSD 1** is primarily expressed in the liver and acts as a reductase, converting the inactive **cortisone** \rightarrow the active glucocorticoid, **cortisol**
- The **11 β -HSD 2** isoform is expressed in a number of tissues and converts **cortisol** \rightarrow the inactive metabolite, **cortisone**.
- Blood concentration and secretion rate of cortisol fluctuate throughout the day

Metabolisme dan ekskresi steroid :

Mineralokortikoid

- During a single passage through the **liver**, >75% of circulating aldosterone is normally inactivated by conjugation with **glucuronic acid**.
- Diseases of the liver markedly depress the rate of inactivation of adrenocortical hormones, and kidney diseases reduce the excretion of the inactive conjugates.
- The blood concentration of aldosterone, however, depends greatly on several factors, including dietary intake of sodium and potassium.

Metabolisme dan ekskresi steroid :

Androgen adrenal

- The major androgen secreted by the adrenal is dehydroepiandrosterone (**DHEA**) and its sulfuric acid ester (**DHEAS**)
- DHEA is the major precursor of the urinary 17-ketosteroids.
- 2/3 of the urine **17-ketosteroids** in the male are derived from adrenal metabolites, and the remaining 1/3 comes from testicular androgens.
- In the female, almost all urine 17-ketosteroids are derived from the adrenal.

MINERALOKORTIKOID

1. **Aldosterone** (sangat poten, 90% dari semua aktivitas mineralokortikoid)
2. Deoksicorticosterone (sangat sedikit, potensinya 1/30 aldosterone)
3. Corticosterone (aktivitas mineralokortikoid ringan)
4. Cortisol (aktivitas mineralokortikoid ringan, banyak disekresi)
5. Cortisone (aktivitas mineralokortikoid ringan)
6. 9^α-fluorocortisol (sintetik)

GLUKOKORTIKOID

1. **Cortisol** (sangat poten, 95% dari semua aktivitas glukokortikoid)
2. Corticosterone (4% dari aktivitas glukokortikoid total)
3. Cortisone (hampir sama potennya dengan cortisol)
4. Prednisone (sintetik, 4X sama potennya dengan cortisol)
5. Metilprednisolone (sintetik, 5X sama potennya dengan cortisol)
6. Dexamethasone (sintetik, 30X sama potennya dengan cortisol)

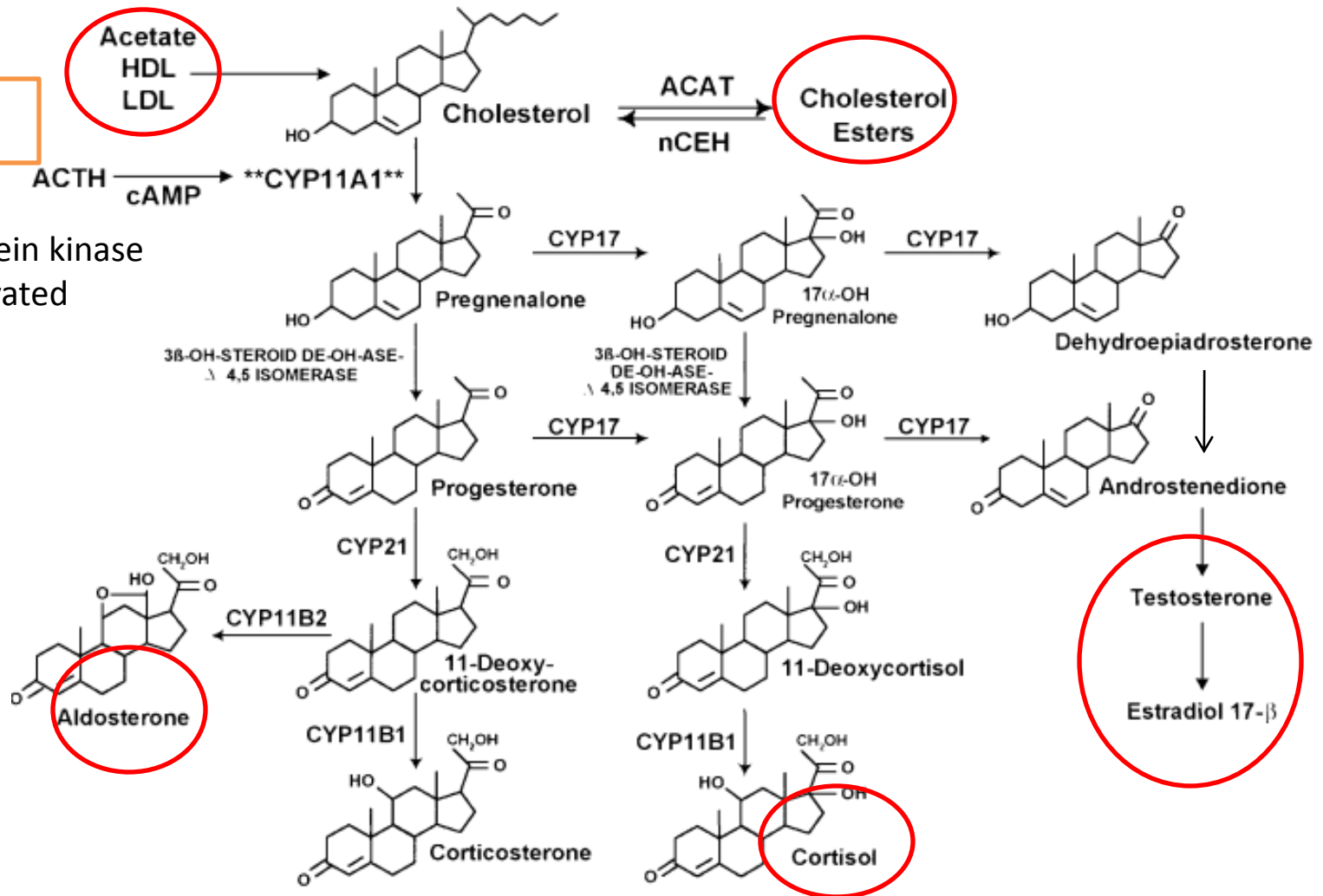
Produksi hormon steroid

ACTH

Acetate
HDL
LDL

Cholesterol
Esters

Protein kinase
activated



Steroid adrenal : action

- Steroids diffuse passively through the cell membrane and bind to intracellular receptors .
- **Glucocorticoids and mineralocorticoids bind with nearly equal affinity to the mineralocorticoid receptor (MR).**
- However, only **glucocorticoids bind to the glucocorticoid receptor (GR).**
- After the steroid binds to the receptor, the steroid-receptor complex is transported to the nucleus, where it binds to specific sites on steroid-regulated genes, altering levels of transcription.

Steroid adrenal : action

- Because cortisol binds to the MR with the same affinity as aldosterone, mineralocorticoid specificity is achieved by local metabolism of cortisol → cortisone by 11β -HSD2.

Glucocorticoid physiology

- The effect of glucocorticoids on **intermediary metabolism** is mediated by the GR.
- Physiologic effects of glucocorticoids include the regulation of **protein, carbohydrate, lipid, and nucleic acid metabolism**.
- Glucocorticoids → ↑ **gluconeogenesis** (hepatic glucose synthesis) , antagonizing the insulin action → ↑ blood glucose level
- The actions on protein metabolism are mainly catabolic → ↑ **protein breakdown** and nitrogen excretion ; inhibit protein synthesis and amino acid uptake

- Glucocorticoids act directly on the **liver** to **stimulate the synthesis of certain enzymes**, such as tyrosine aminotransferase and tryptophan pyrrolase.
- Glucocorticoids regulate **fatty acid mobilization** by enhancing the activation of cellular lipase by lipid-mobilizing hormones (e.g., catecholamines and pituitary peptides).
- The **actions of cortisol on protein and adipose tissue vary in different parts of the body**. **peripheral adipose tissue mass decreases**, whereas **abdominal and interscapular fat expand**

Efek kortisol – metabolis KH (↑glukoneogenesis)

- *Cortisol increases the enzymes required to convert amino acids into glucose in liver cells.*
- *Cortisol causes mobilization of amino acids from the extrahepatic tissues, mainly from muscle*
- *Cortisol antagonizes insulin's effects in liver*
- Cortisol also causes a moderate decrease in glucose utilization in most cell → dengan cara menurunkan translokasi GLUT-4 transporter ke membran sel → resisten insulin
- **Net Effect → ↑ produksi glukosa hepar**

Efek kortisol – metabolisme protein (Reduksi protein seluler dan Increases Liver and Plasma Proteins)

- Decreased protein synthesis and increased catabolism of protein
- Depressed formation of RNA and subsequent protein synthesis in many extrahepatic tissues, especially in muscle and lymphoid tissue
 - Muscle weakness, low immunity

Increased Blood Amino Acids, Diminished Transport of Amino Acids Into Extrahepatic Cells, and Enhanced Transport Into Hepatic Cells

- The increased plasma concentration of amino acids and enhanced transport of amino acids into the hepatic cells by cortisol could also account for **enhanced utilization of amino acids by the liver** to cause such effects as
 - (1) increased rate of deamination of amino acids by the liver
 - (2) increased protein synthesis in the liver
 - (3) increased formation of plasma proteins by the liver, and
 - (4) increased conversion of amino acids to glucose —that is, enhanced gluconeogenesis.

Thus, it is possible that many of the effects of cortisol on the metabolic systems of the body result mainly from this ability of cortisol to mobilize amino acids from the peripheral tissues while at the same time increasing the liver enzymes required for the hepatic effects

Efek kortisol – metabolisme lemak (mobilisasi asam lemak)

- promotes mobilization of fatty acids from adipose tissue → ↑ concentration of free fatty acids in the plasma → ↑ their utilization for energy.
- Have a direct effect to enhance the oxidation of fatty acids in the cells.
- **Excess Cortisol Causes Obesity.** a peculiar type of obesity develops in many people with excess cortisol secretion, with excess deposition of fat in the chest and head regions of the body, giving a **buffalo-like torso** and a rounded **“moon face.”** Although the cause is unclear, it has been suggested that this obesity results from excess stimulation of food intake, with fat being generated in some tissues of the body more rapidly than it is mobilized and oxidized.

- Glucocorticoid have **anti-inflammatory properties** → effects on microvasculature & suppression of inflammatory cytokines
- Glucocorticoid modulate immune response via “Immune adrenal axis” where stress, sepsis → ↑ adrenal secretion → ↑ cortisol level → ↓ immune response
- Glucocorticoids also have a weak mineralocorticoid like properties
- High dose glucocorticoid promote renal tubular sodium reabsorption and urine potassium excretion

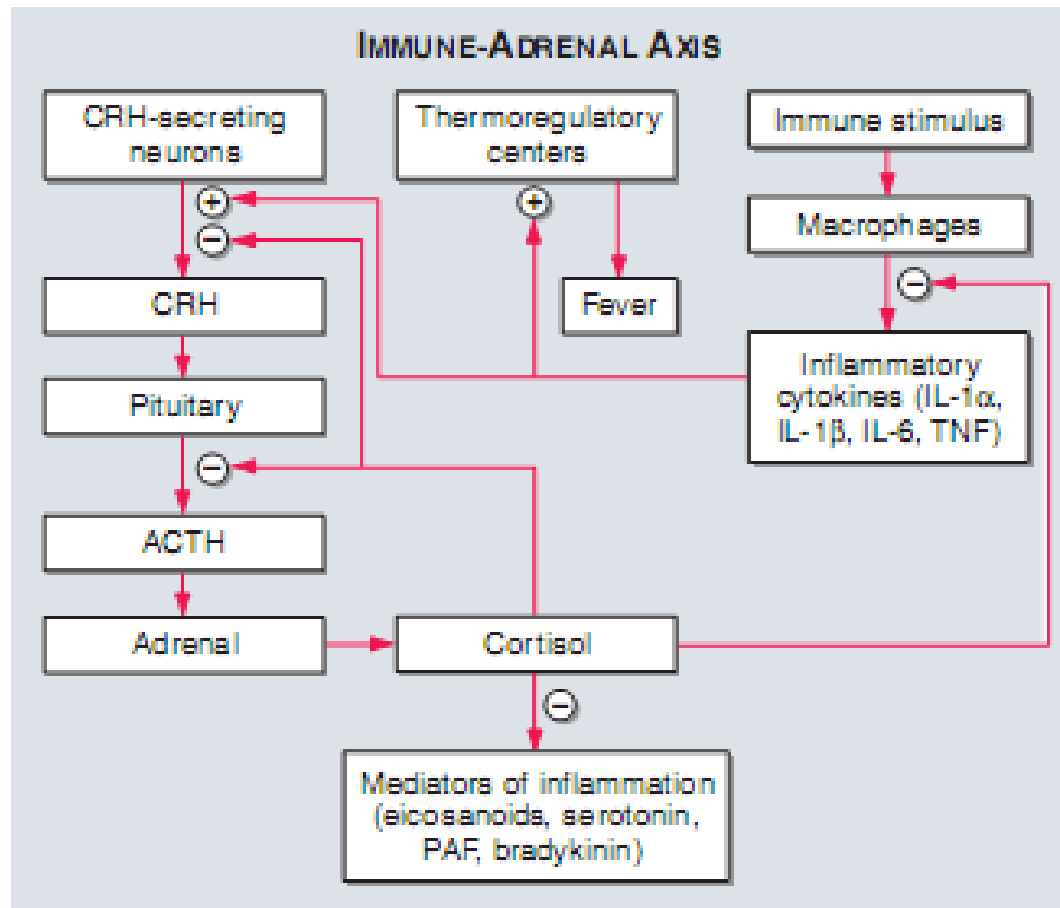
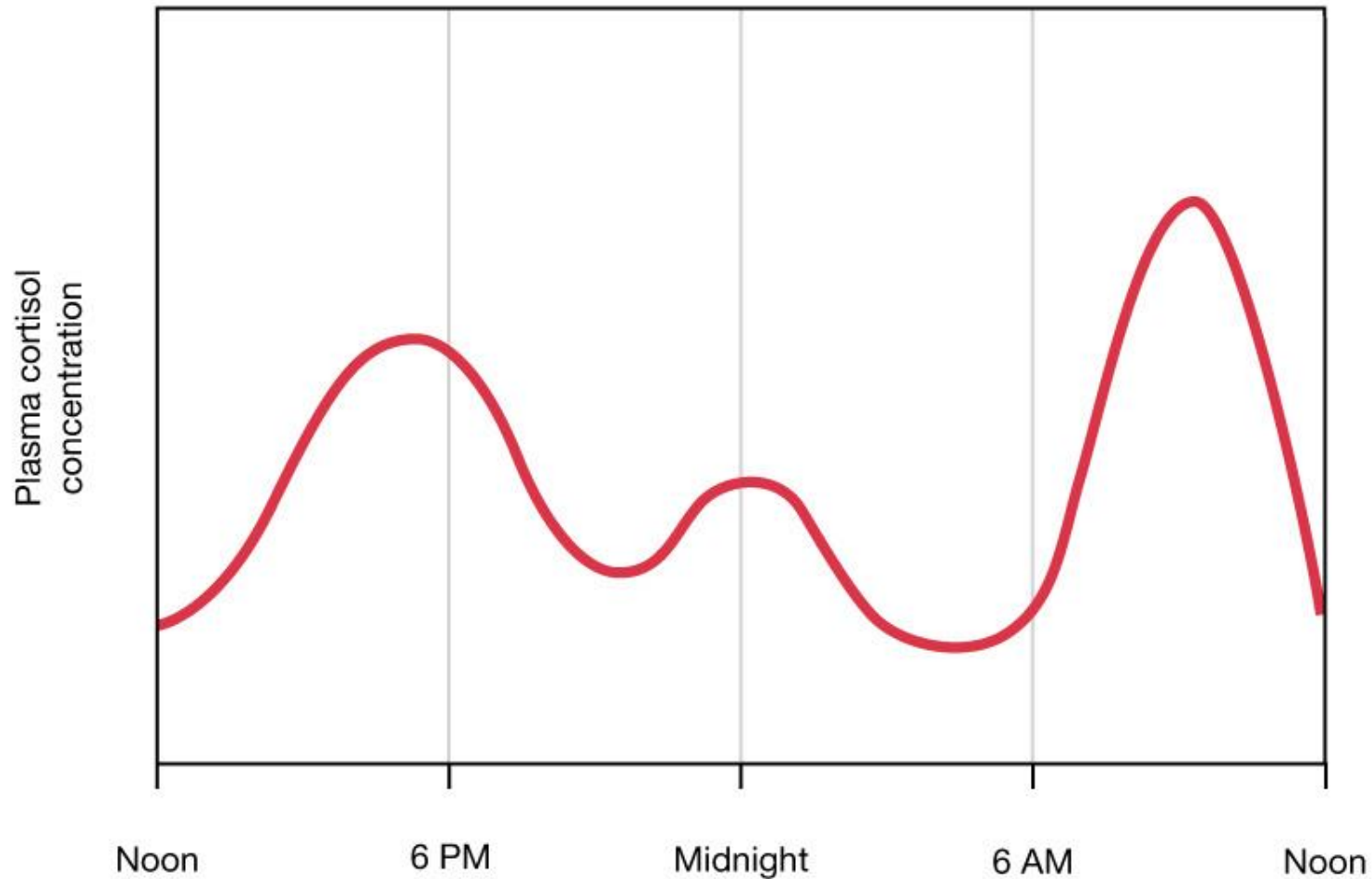


FIGURE 5-4

The immune-adrenal axis. Cortisol has anti-inflammatory properties that include effects on the microvasculature, cellular actions, and the suppression of inflammatory cytokines (the so-called immune-adrenal axis). A stress such as sepsis increases adrenal secretion, and cortisol in turn suppresses the immune response via this system. –, suppression; +, stimulation; CRH, corticotropin-releasing hormone; ACTH, adrenocorticotrophic hormone; IL, interleukin; TNF, tumor necrosis factor; PAF, platelet activating factor.

Irama sirkardian

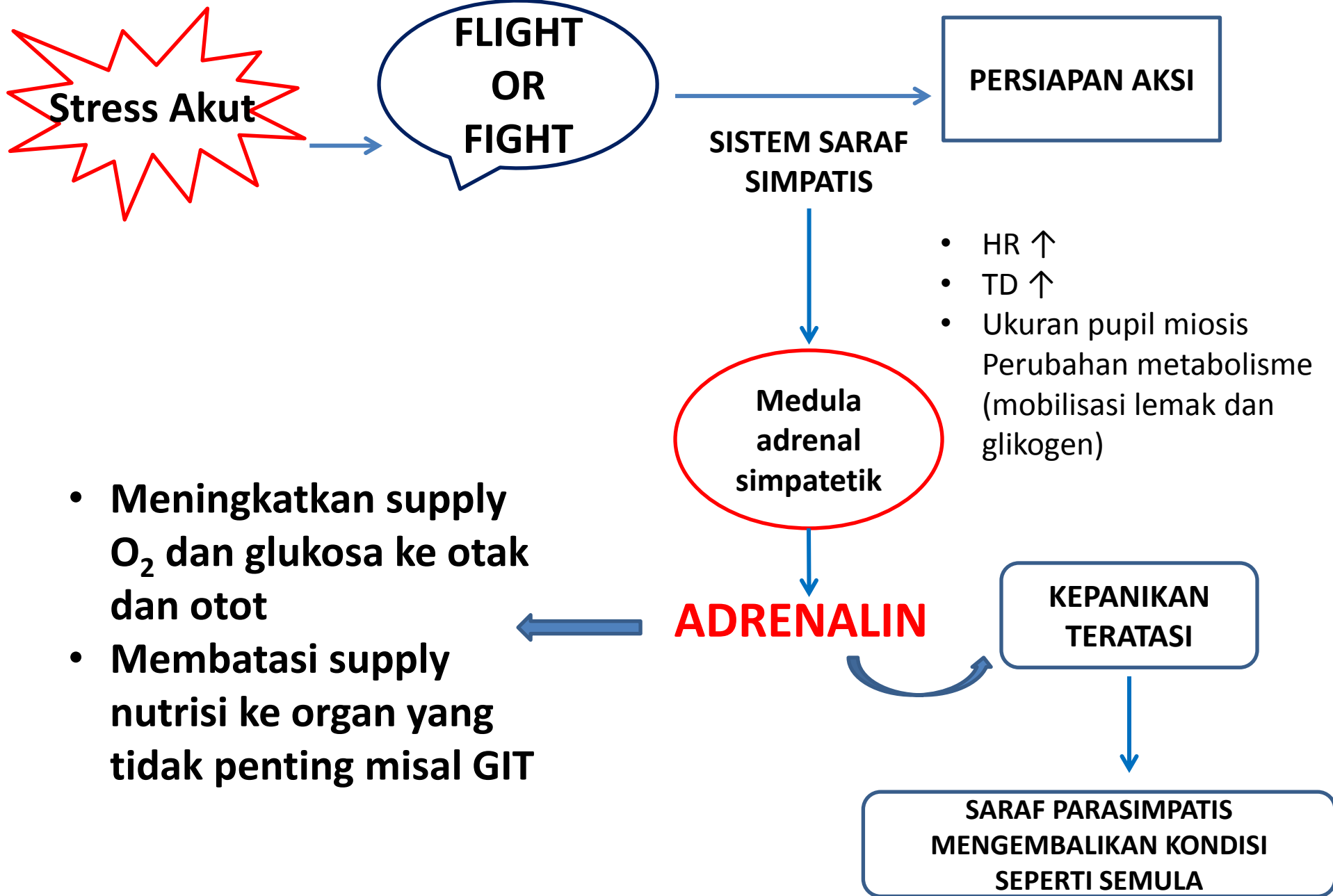


- Binatang nocturnal, sekresi kortisol paling tinggi saat sore menjelang petang. Binatang diurnal, sekresi tertinggi saat pagi

Cortisol Effects: Body Responses to Stress

- Permissive effect on glucagon
- Memory, learning & mood
- Gluconeogenesis
- Skeletal muscle breakdown
- Lipolysis, calcium balance
- Immune depression
- Circadian rhythms

Stress respond (akut)

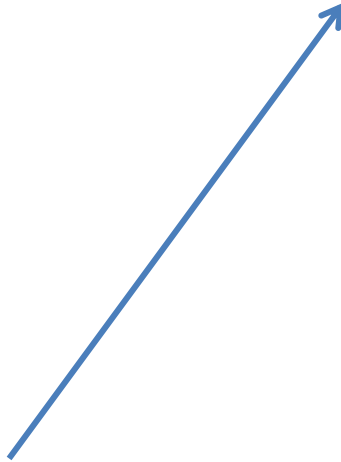


Stress respond (kronik)

LONG TERM

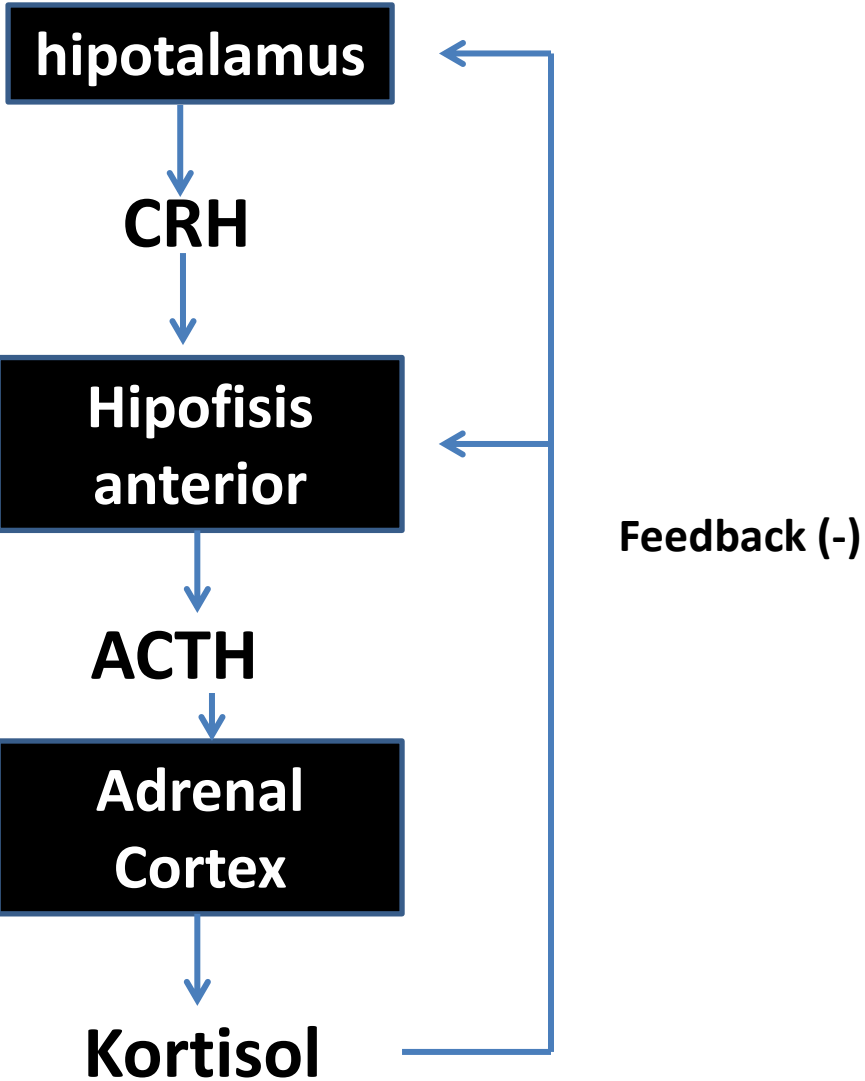


Mebutuhkan Fungsi Otak Yang Lebih Banyak



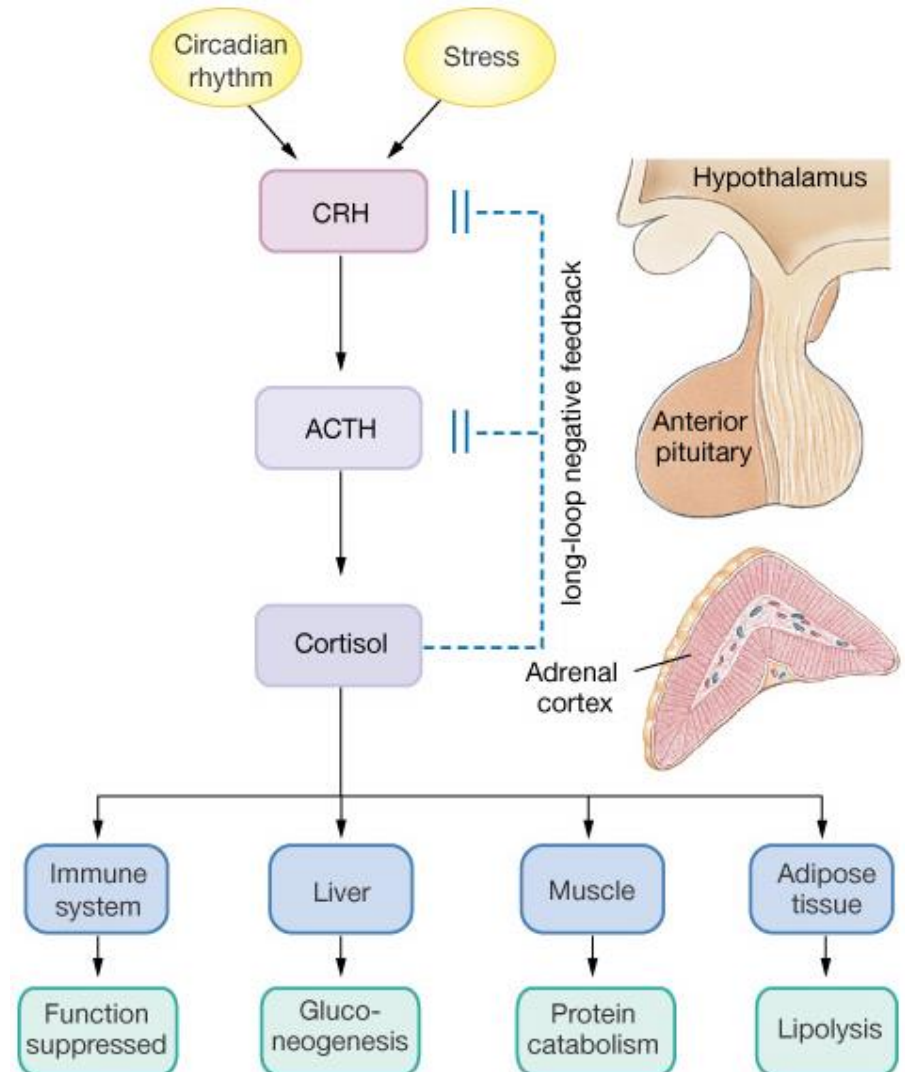
Kortisol :
Punya efek
+ Cepat memBakar energi
+ Meningkatkan ambang nyeri

- TD meningkat
- Pengaruhi kognisi/thinking
- Supresi sistem imun



Kontrol sekresi kortisol : mekanisme feedback

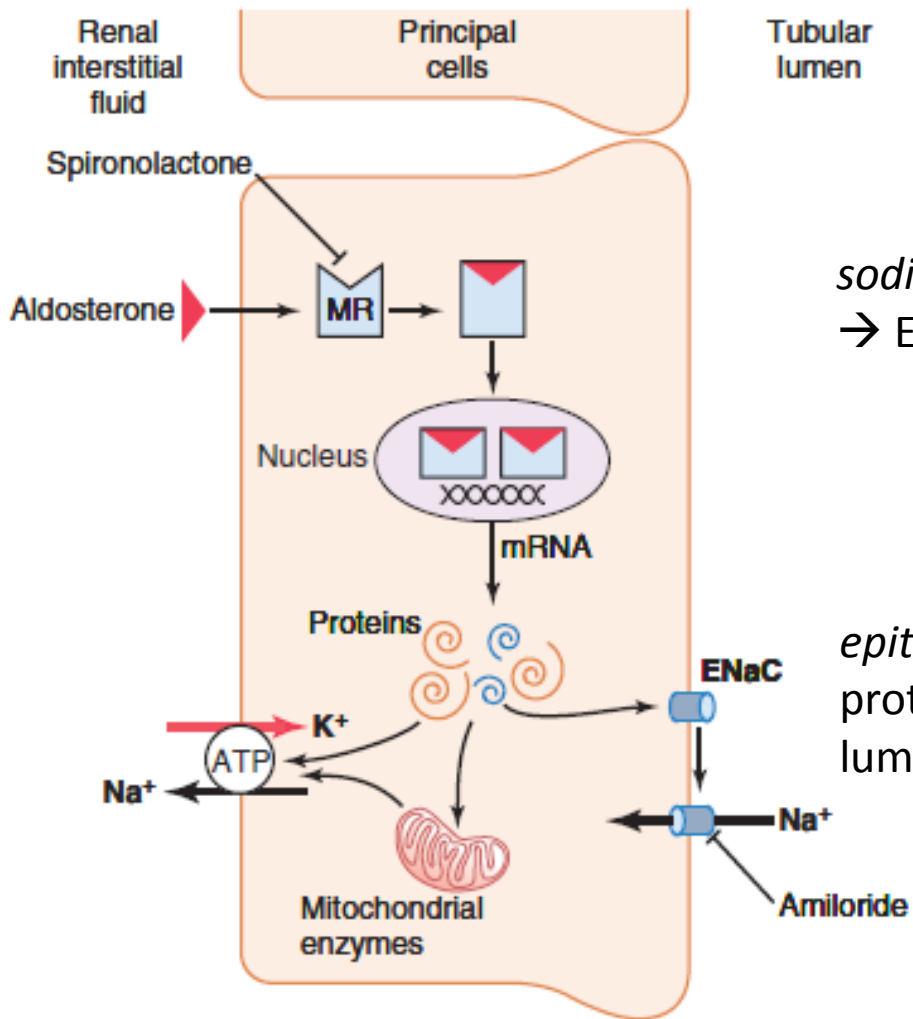
- External stimuli
- Hypothalamic
- Anterior Pituitary
- Adrenal cortex
- Tissues



Mineralocorticoid physiology

- It is modify function in 2 class of cells : epithel and non-epithel
- Effect on epithel :
 - These effects are mediated by the binding of aldosterone to the MR in epithelial cells, **Increase sodium reabsorption and potassium excretion by tubular epithelium** especially *distal tubulus* and *ductus coligentes*.
 - Mineralocorticoids are considered major **regulators of ECFV** and are the major determinants of potassium metabolism

- Aldosterone stimulates all three of these processes by increasing **gene expression** directly (for the sodium pump and the potassium channels) or via a complex process (for epithelial sodium channels) to **increase both the number and activity of the sodium channels**. Water passively follows the transported sodium, thus expanding intra- and extravascular volume.
- Mineralocorticoids also act on the **epithelium of the salivary ducts, sweat glands, and gastrointestinal tract to cause reabsorption of sodium** in exchange for potassium.



sodium-potassium adenosine triphosphatase,
 → Enzim penting dalam pertukaran Na-K

epithelial sodium channel (EnaC) → suatu protein yang mempercepat difusi Na⁺ dari lumen tubulus ke sel epitel tubulus

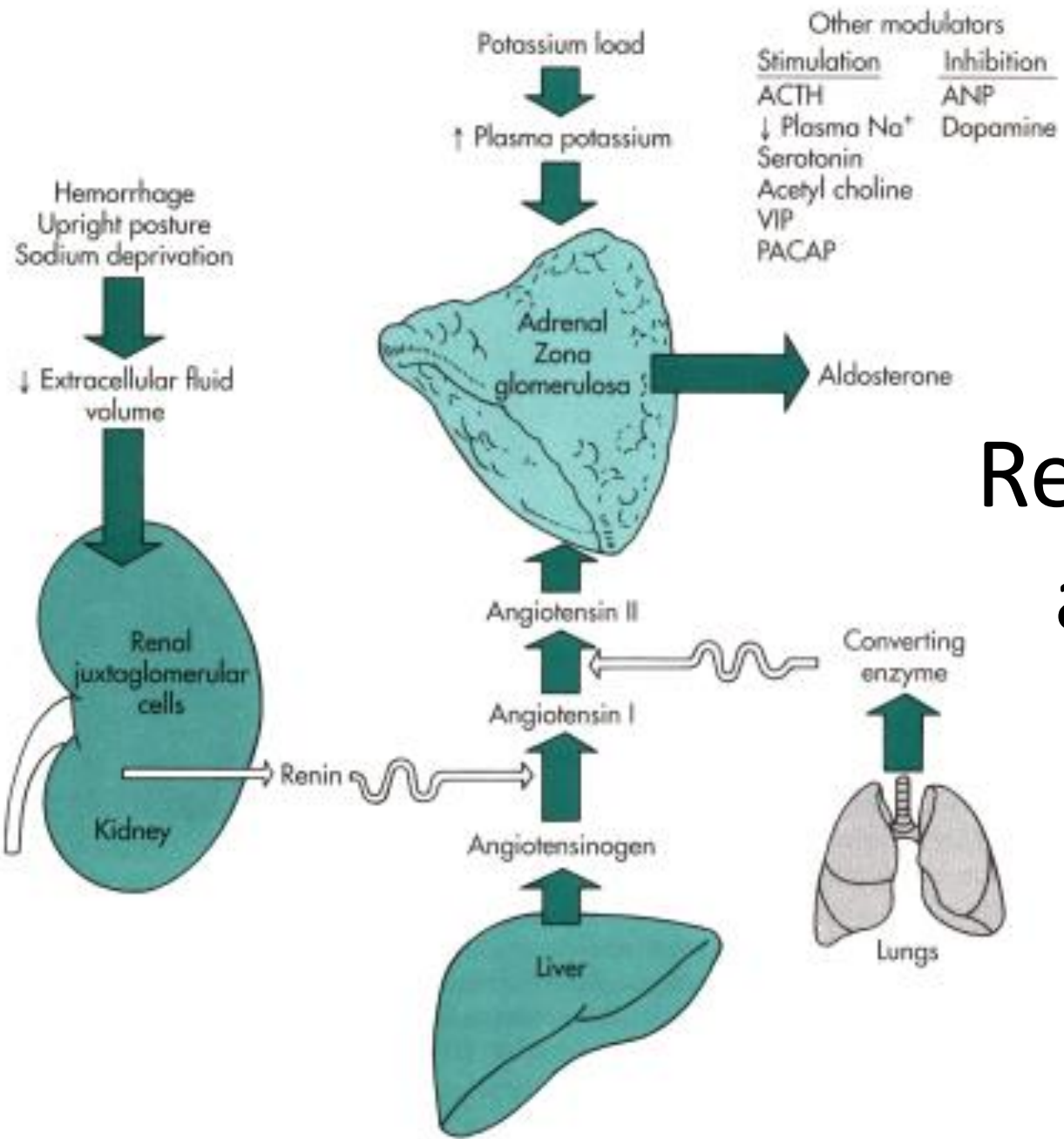
Figure 78-4. Aldosterone-responsive epithelial cell signaling pathways. Activation of the mineralocorticoid receptor (*MR*) by aldosterone can be antagonized with spironolactone. Amiloride is a drug that can be used to block epithelial sodium channel proteins (*ENaC*).

Effect on non-epithel cells

- The MR has been identified in a number of nonepithelial cells, e.g., neurons in the brain, myocytes, endothelial cells, and vascular smooth-muscle cells. In these cells, the actions of aldosterone differ from those in epithelial cells in several ways:
 - Not modify Na-K homeostasis
 - Modifies the expression of several collagen genes controlling tissue growth factors
 - Via rapid non-genomic mechanism

Regulation of aldosterone secretion

- Three primary mechanisms control adrenal aldosterone secretion: **the renin-angiotensin system, potassium, and ACTH** (*it is needed but has very small effect on secretion rate*).
- **RAS maintain circulating blood volume constant** by causing aldosterone induced sodium retention during volume deficiency
- K^+ directly stimulates aldosterone secretion
- K^+ also modifies aldosterone secretion *indirectly* by **activating the local RAS** in the zona glomerulosa
- ACTH which release in pulsatile fashion stimulate aldosterone secretion.



Regulasi sekresi aldosterone

Androgen physiology

- The principal adrenal androgens are DHEA, androstenedione, and 11-hydroxyandrostenedione.
- DHEA and androstenedione are weak androgens and exert their effects via conversion to the potent androgen testosterone in extraglandular tissues
- Androgens regulate male secondary sexual characteristics and can cause virilizing symptoms in women
- Adrenal androgens have a minimal effect in males, whose sexual characteristics are predominately determined by gonadal steroids (testosterone).
- In females, however, several androgen-like effects, e.g., sexual hair, are largely mediated by adrenal androgens.
- Adrenal androgens are suppressed by exogenous glucocorticoid administration

MEDULLA ADRENAL

Medula adrenal : ganglion simpatetik yang dimodifikasi

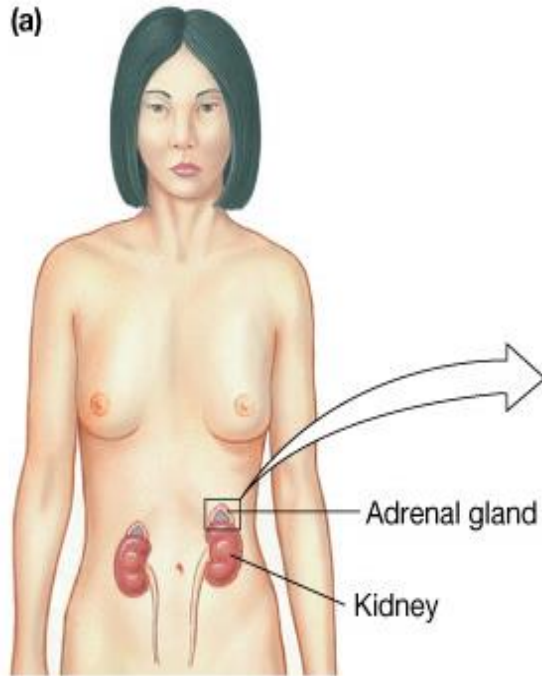
- Sympathetic stimulation
 - Catecholamine release to blood
 - Epinephrine
 - Norepinephrine
 - Travel to:
 - Multiple targets
 - Distant targets

Medula Adrenal

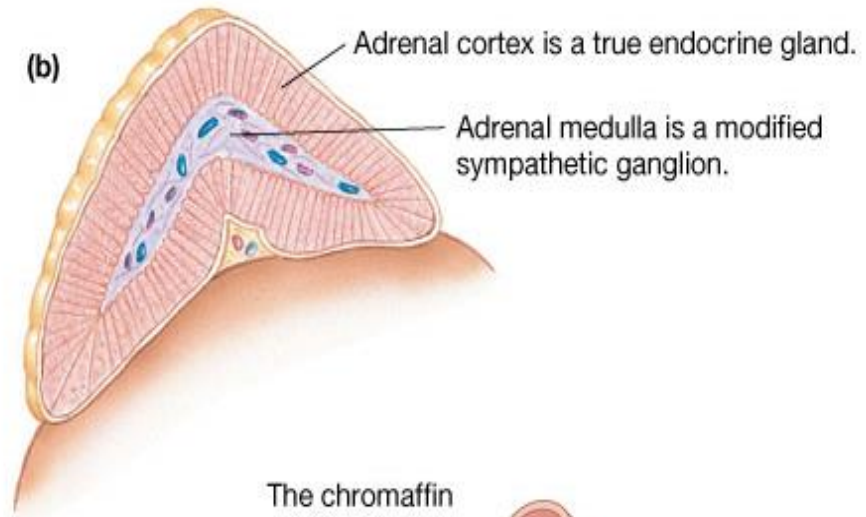
- Mensekresi katekolamin (norepinefrin, epinefrin, dan dopamin)
- Pada manusia, terutama mensekresi epinefrin (80%), sisanya NE 20%.
- NE utamanya disintesis SSP, dan E → catecholamine yg utamanya disintesis medula adrenal.

- The biological actions of the catecholamines are initiated through their interaction with two different types of specific cell membrane receptors, the α -adrenergic and β -adrenergic receptors
- **NE** primarily interacts with **α -adrenergic** receptors, whereas **E** interacts with both α and **β -adrenergic** receptors.

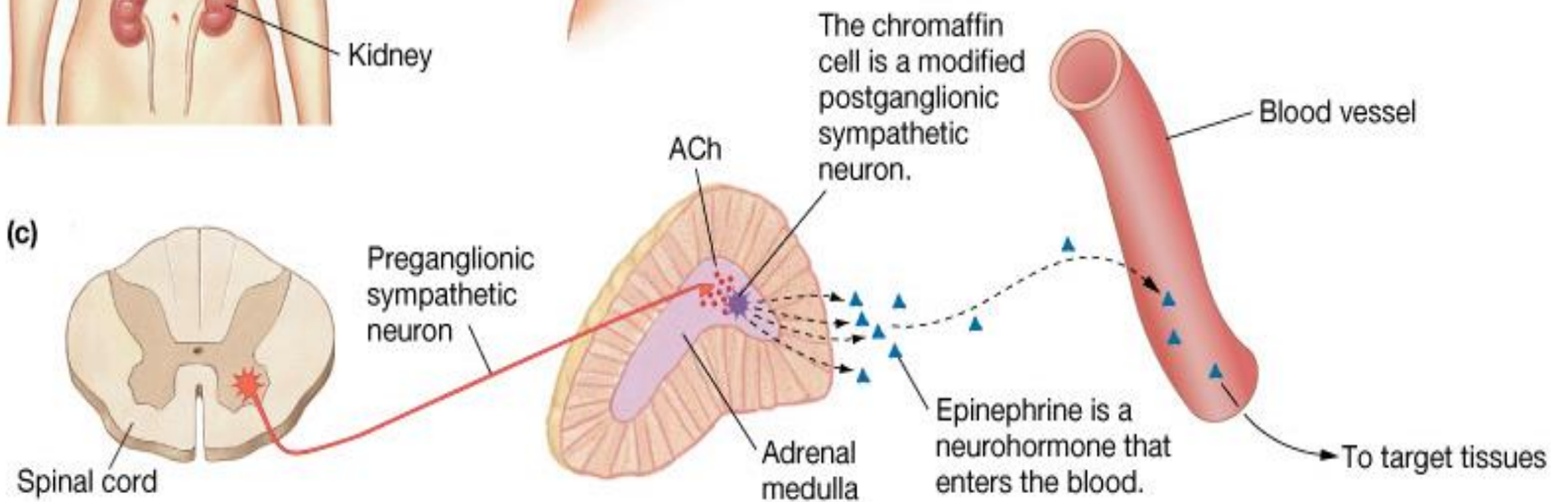
(a)



(b)



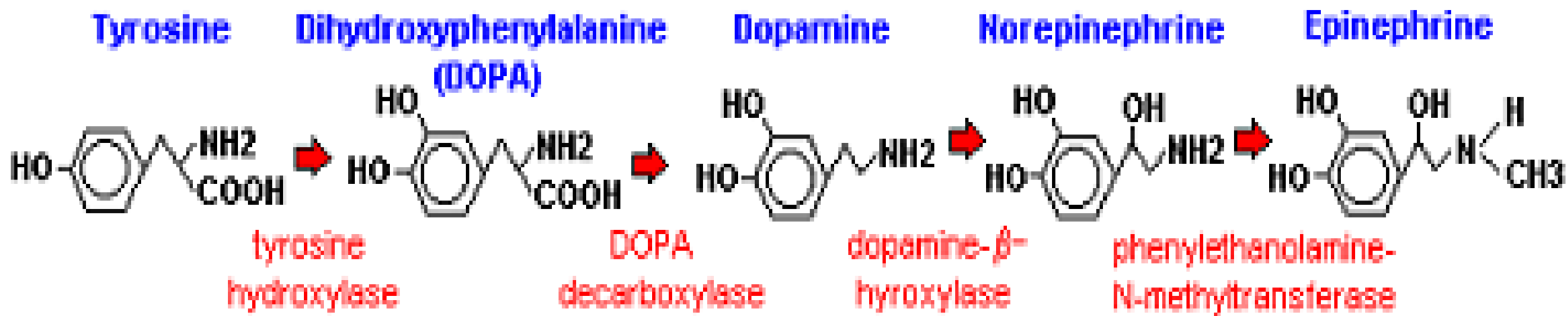
(c)



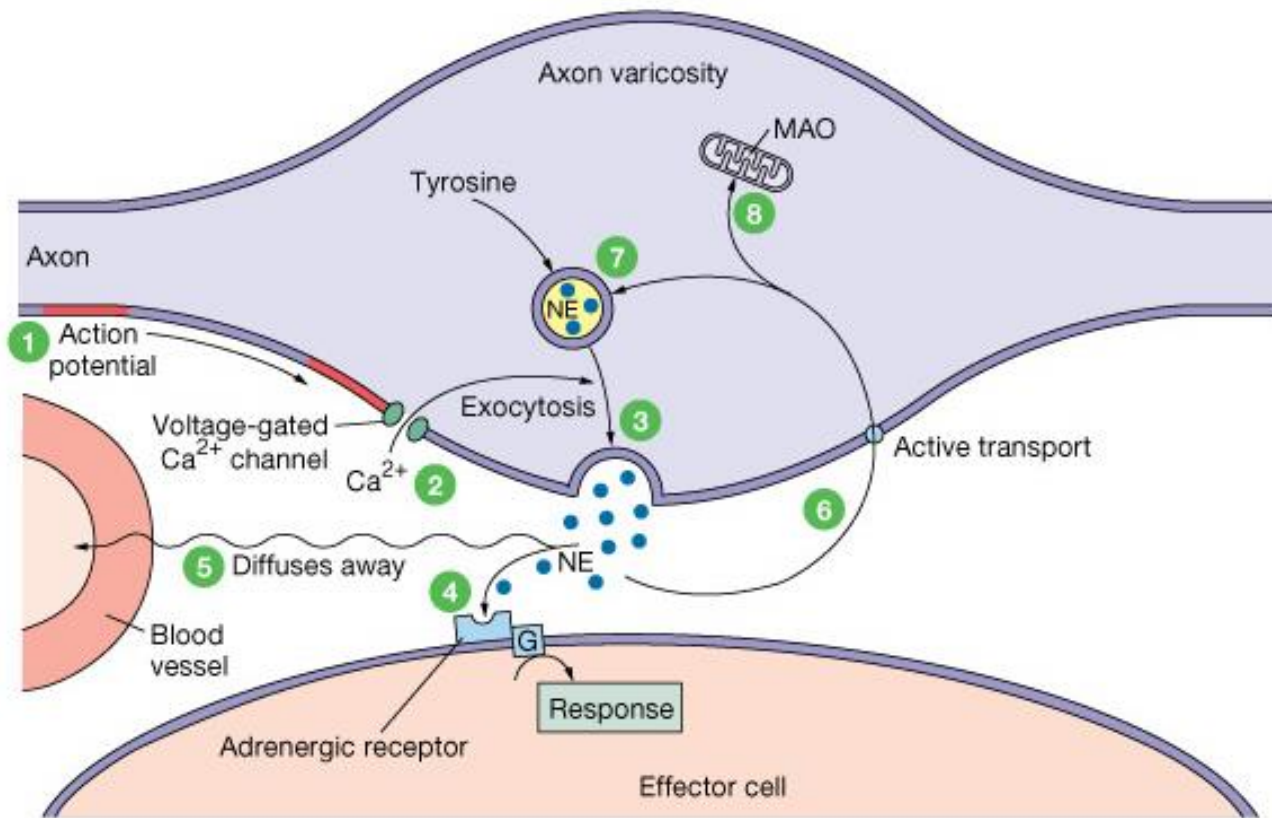
Synthesis & Release

- The catecholamines are released from the adrenal medulla in response to **hypotension, hypoxia, exposure to cold, muscular exertion, pain, and emotional disturbances**
- Following secretion into blood, the catecholamines bind loosely to and are carried in the circulation by **albumin** and perhaps other serum proteins.

- Synthesis of catecholamines begins with the amino acid tyrosine, which is taken up by chromaffin cells in the medulla and converted to NE and E through the following steps:



Mechanism: Norepinephrine Release and Recycling

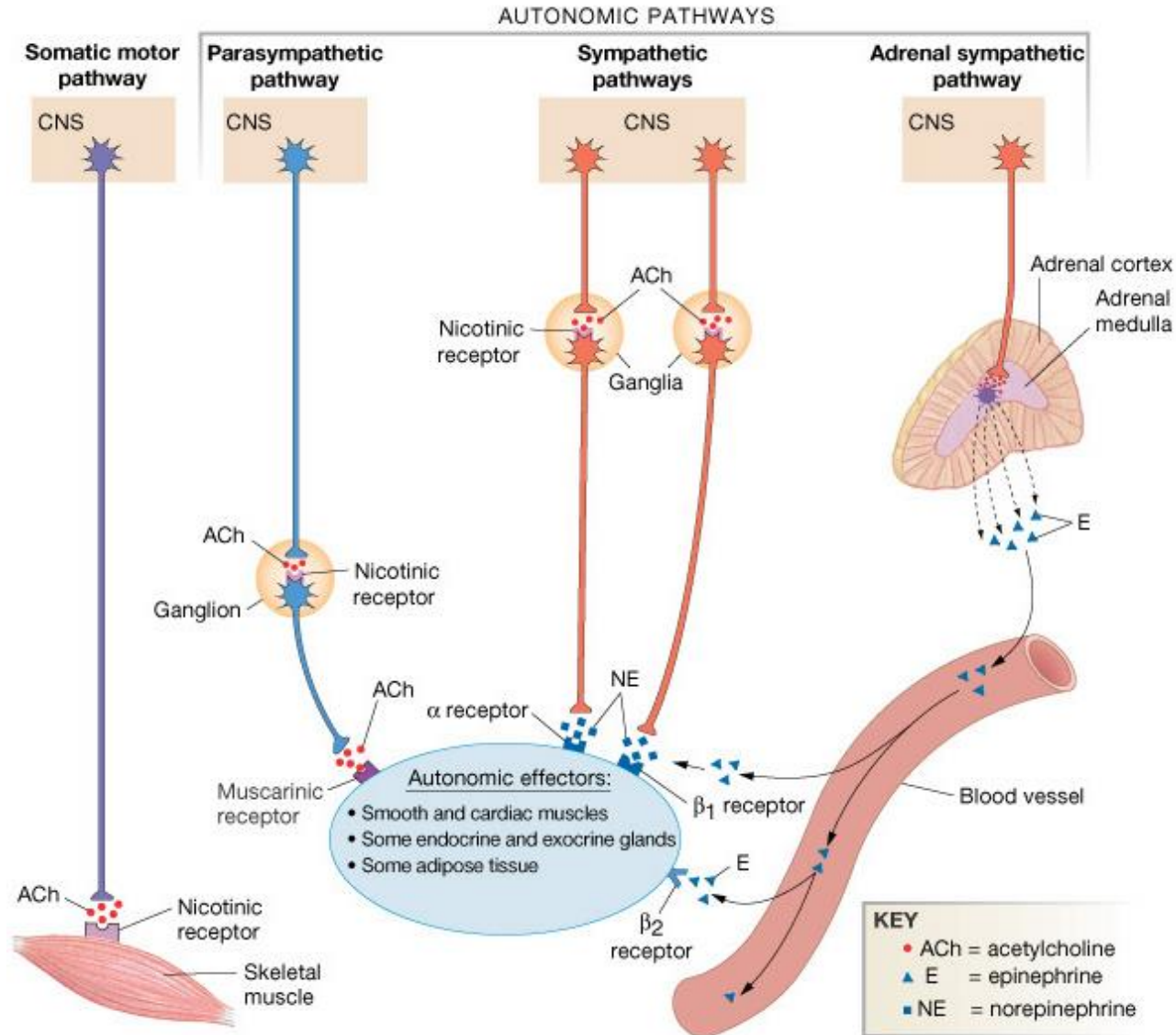


- 1 Action potential arrives at the varicosity.
- 2 Depolarization opens voltage-gated Ca^{2+} channels.
- 3 Ca^{2+} entry triggers exocytosis of synaptic vesicles.
- 4 NE binds to adrenergic receptor on target.
- 5 Activity ceases when NE diffuses away from the synapse.
- 6 NE is transported back into the axon.
- 7 NE can be taken back into synaptic vesicles for re-release.
- 8 NE is metabolized by monoamine oxidase (MAO).

KEY

- NE (norepinephrine)

Efferent pathway : Motor and Autonomic



Effect of catecholamin in reseptor

- Stimulation of **α -adrenergic** receptors results in:
 - vasoconstriction,
 - decrease in insulin secretion,
 - sweating,
 - piloerection ,
 - and stimulation of glycogenolysis in the liver and skeletal muscle leading to an increase in blood glucose concentration.
- Stimulation of **β -receptors** leads to:
 - vasodilatation;
 - stimulation of insulin release;
 - increased cardiac contraction rate;
 - relaxation of smooth muscle in the intestinal tract;
 - bronchodilatation by relaxation of smooth muscles in bronchi;
 - stimulation of renin release, which enhances sodium resorption from the kidney – and enhanced lipolysis.

Efek katekolamin

- NE&E meningkatkan kewaspadaan (kecemasan&ketakutan → E>NE)
- NE&E meningkatkan glukosa plasma (glikogenolisis di hati dan otot rangka)
- NE&E meningkatkan kekuatan dan kecepatan kontraksi jantung
- NE → vasokonstriksi sebagian besar organ
- E → vasodilatasi vaskular di otot rangka dan hati (sebagai kompensasi vasokonstriksi krn E di tempat lain)
- Meningkatkan fungsi metabolik

Catecholamines: Activity

- Stimulates the “**fight or flight**” reaction
- Increased plasma glucose levels
- Increased cardiovascular function
- Increased metabolic function
- Decreased gastrointestinal and genitourinary function

DOPAMINE

- Naturally produced in the body.
- In the brain, dopamine functions as a neurotransmitter, activating dopamine receptors.
- Dopamine is also a neurohormone released by the hypothalamus.
- Its main function as a hormone is to inhibit the release of prolactin from the anterior lobe of the pituitary

Efek Dopamin

- Belum jelas peran dopamin di perifer
- Meningkatkan *food intake* , mengontrol metabolisme glukosa dan berat badan
- Meregulasi aksi insulin di jaringan yang berbeda-beda
- Regulasi kontraktibilitas vaskular dengan menurunkan tekanan darah

*Rubi B and Maechler P. Minirevie: New roles for peripheral dopamine on metabolic control and tumor growth. Endocrinology. December 2010. 151(1):5570-5581

TERIMA KASIH

- ♥ This is only <1‰ of Endocrine system on the human body
- ♥ Keep study and keep searching, and
- ♥ Knowing that we know almost nothing