HELLENIC REPUBLIC
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ADRENAL GLAND HORMONES

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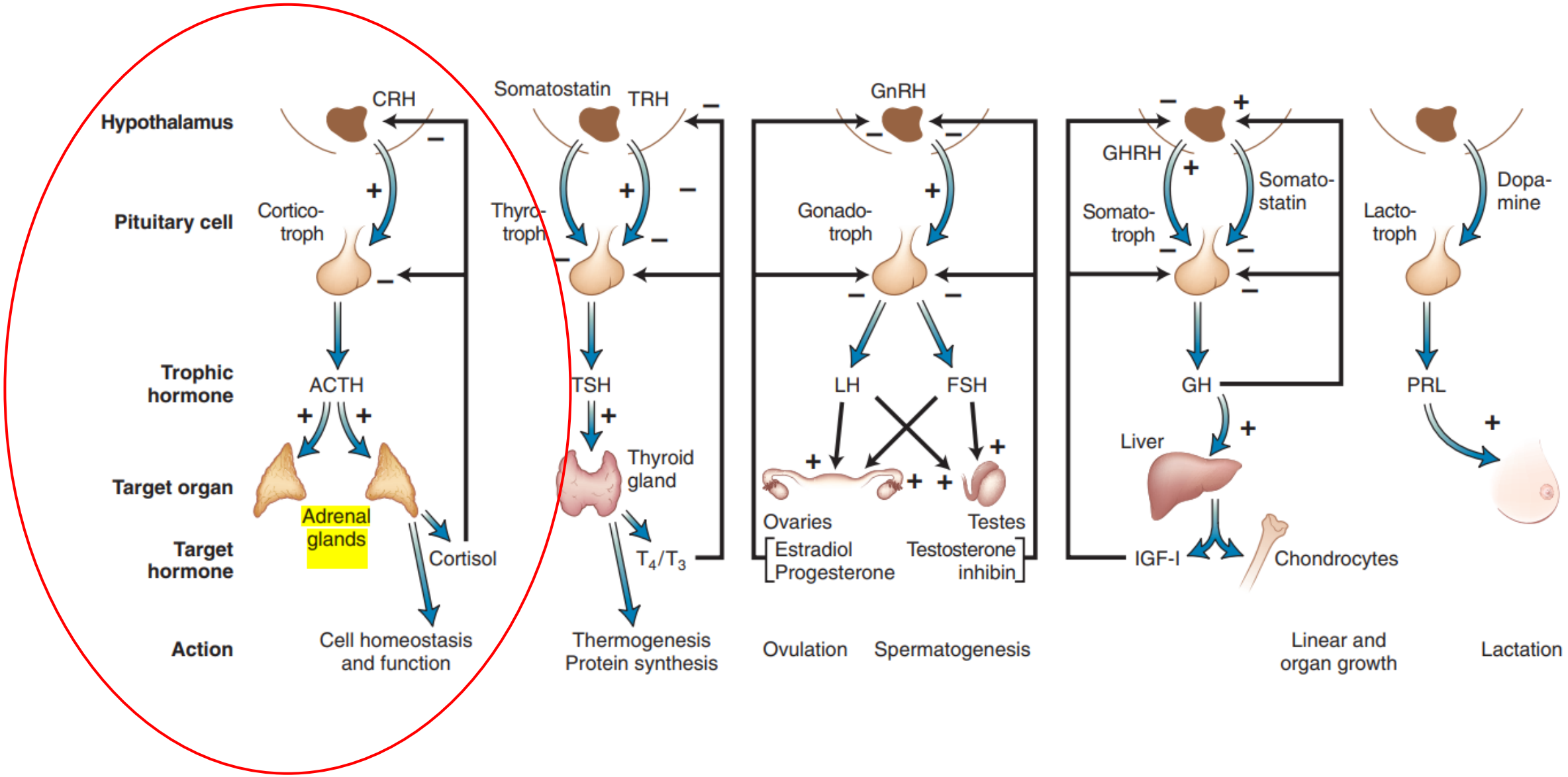
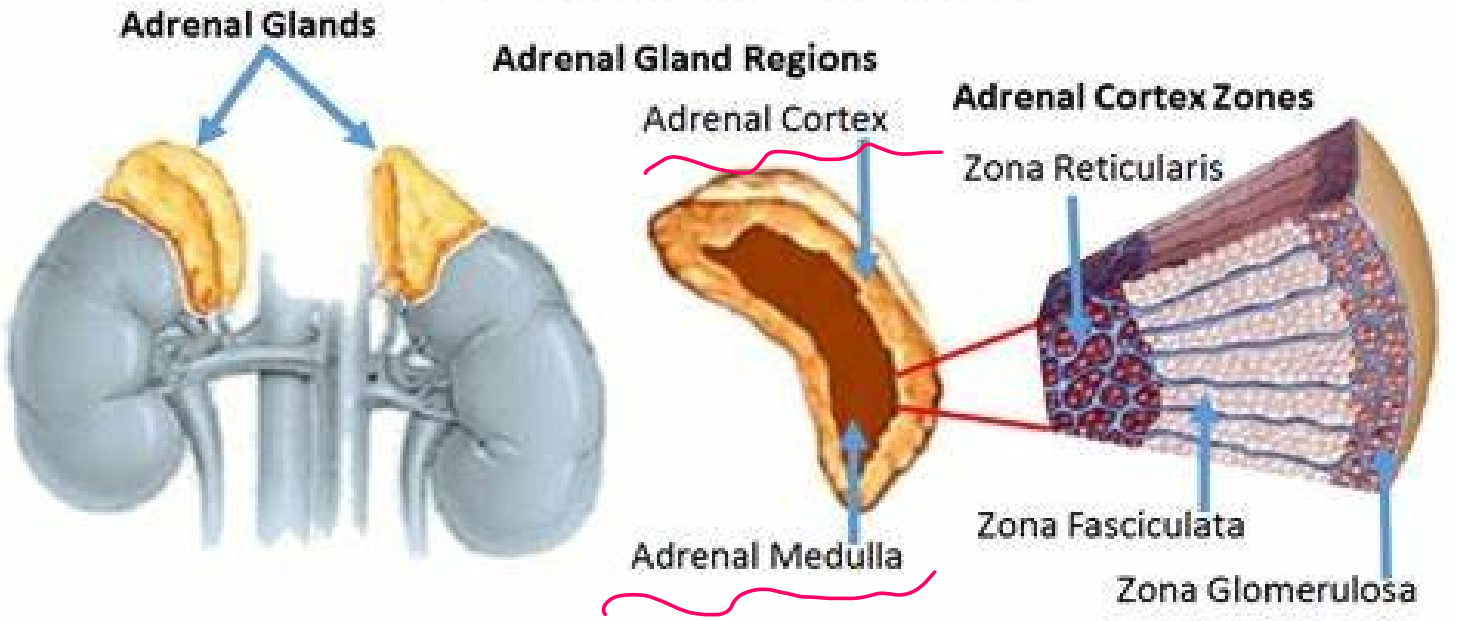
Educational aims

- Understand the structure of the cortex and adrenal medulla hormones.
- Understand their biosynthesis and metabolism.
- Understand their molecular mechanism action and regulation.
- Understand their action on tissues and organs.
- Understand their function through clinical examples.

Control of hypothalamic-pituitary target organ axes



Adrenal Glands

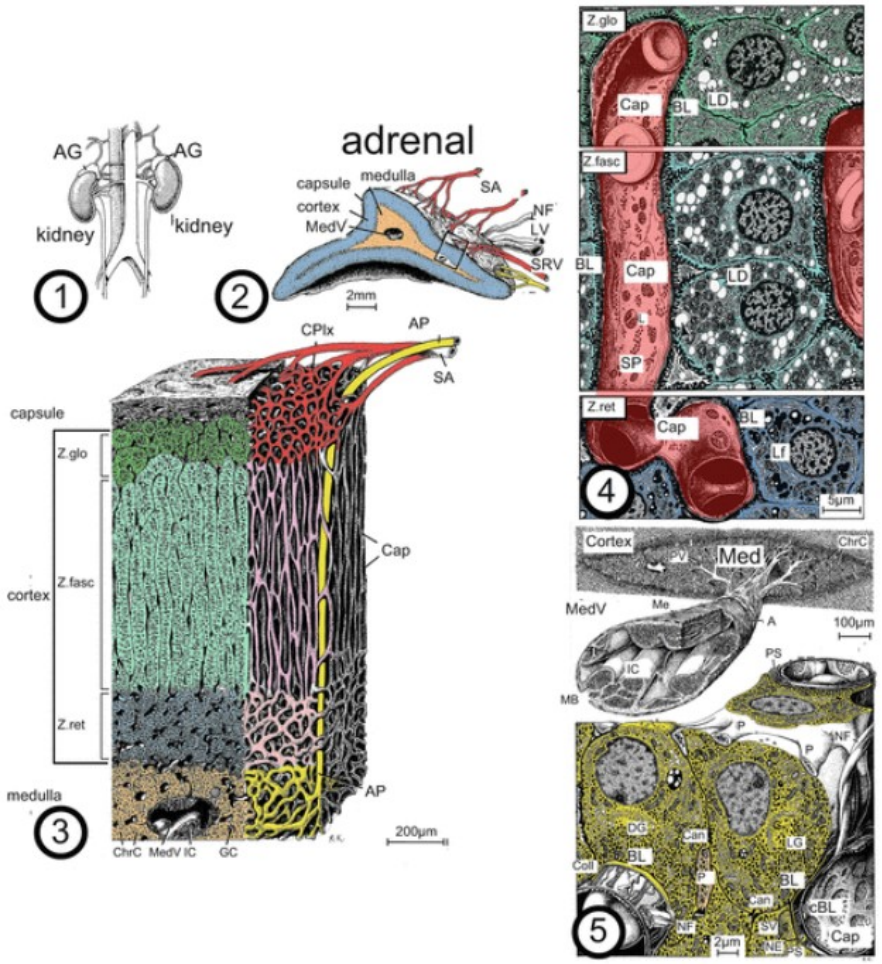


- The right adrenal gland is pyramidal, whereas the left one is more crescentic, extending toward the hilum of the kidney.
- Computer tomography revealed that the left adrenal gland is larger than the right adrenal
- Men have larger adrenal glands than women

- On the kidneys the adrenal glands are like caps consisting of **cortex and medulla.**
- Histologically, it is divided into the **outer cortex and the inner medulla under a common capsule.**
- **Major regulators of body homeostasis and the endocrine stress response**

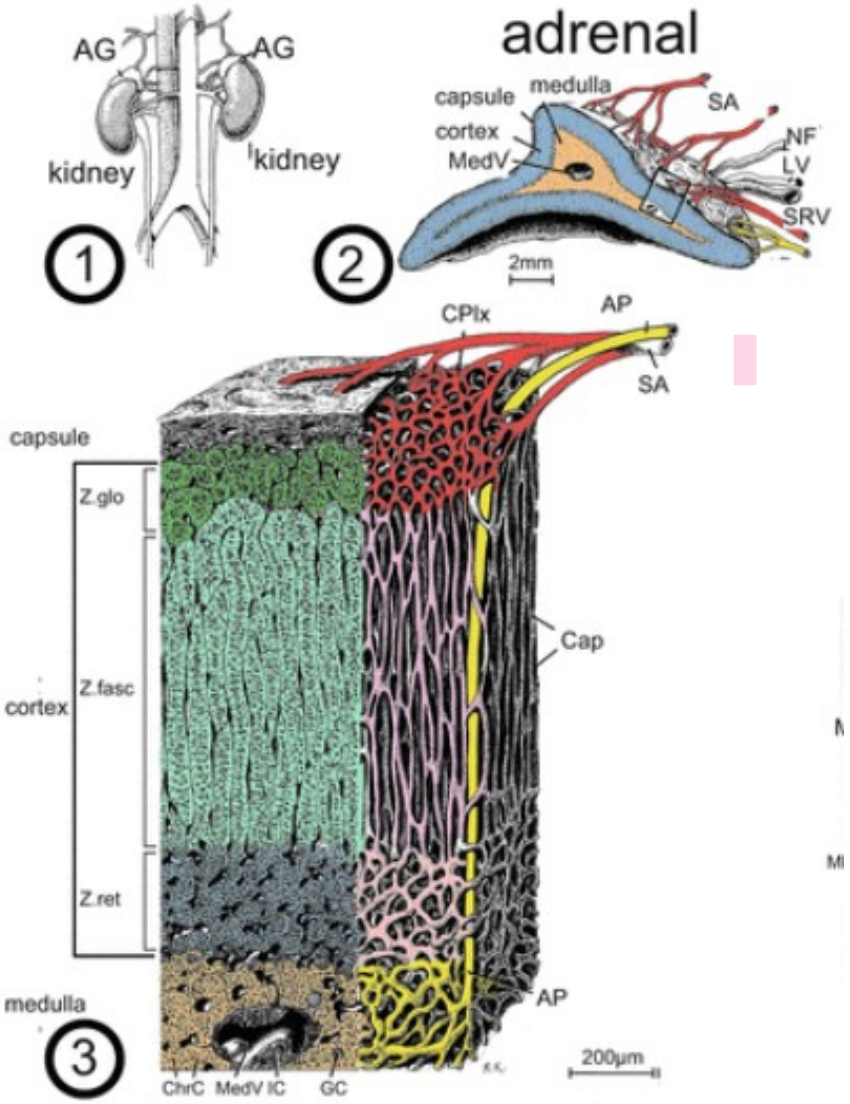
Adrenal Glands

- The adrenal gland **forms a cap on top of the kidney.**
- **Like all glands, the adrenal glands are covered by capsules**. A yellowish cortex **surrounds the white medulla.**
- Below the capsule there is the adrenal cortex and the adrenal medulla.
- **Adrenal arteries enter the capsule at several sites, and nerves and lymphatic vessels enter the adrenal gland via the hilus,** where the adrenal vein leaves the organ.

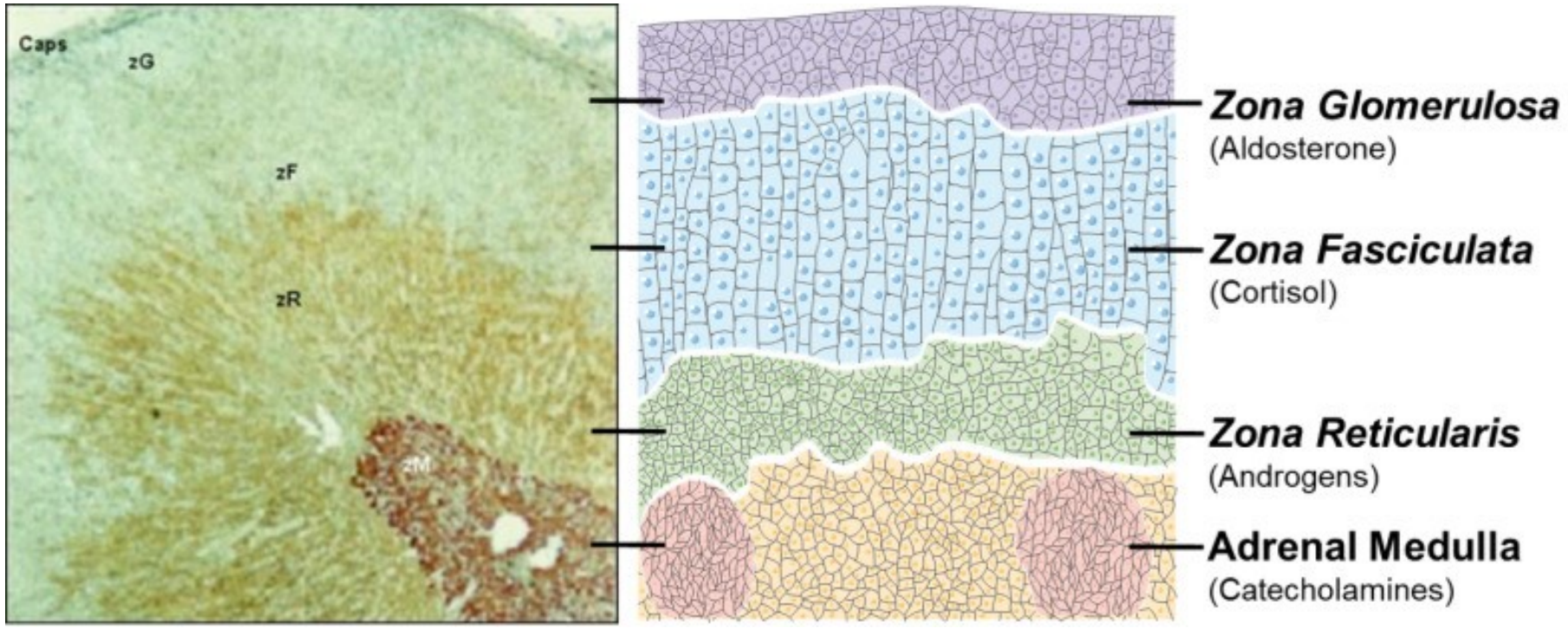


Adrenal Glands

- The adrenal glands **have one of the greatest blood supply rates** per gram of tissue of any organ and several small arteries may enter each gland
- The adrenal glands obtain their blood supply from branches arising from three sources**; the inferior phrenic artery, the renal artery, and the aorta**



Adrenal Cortex



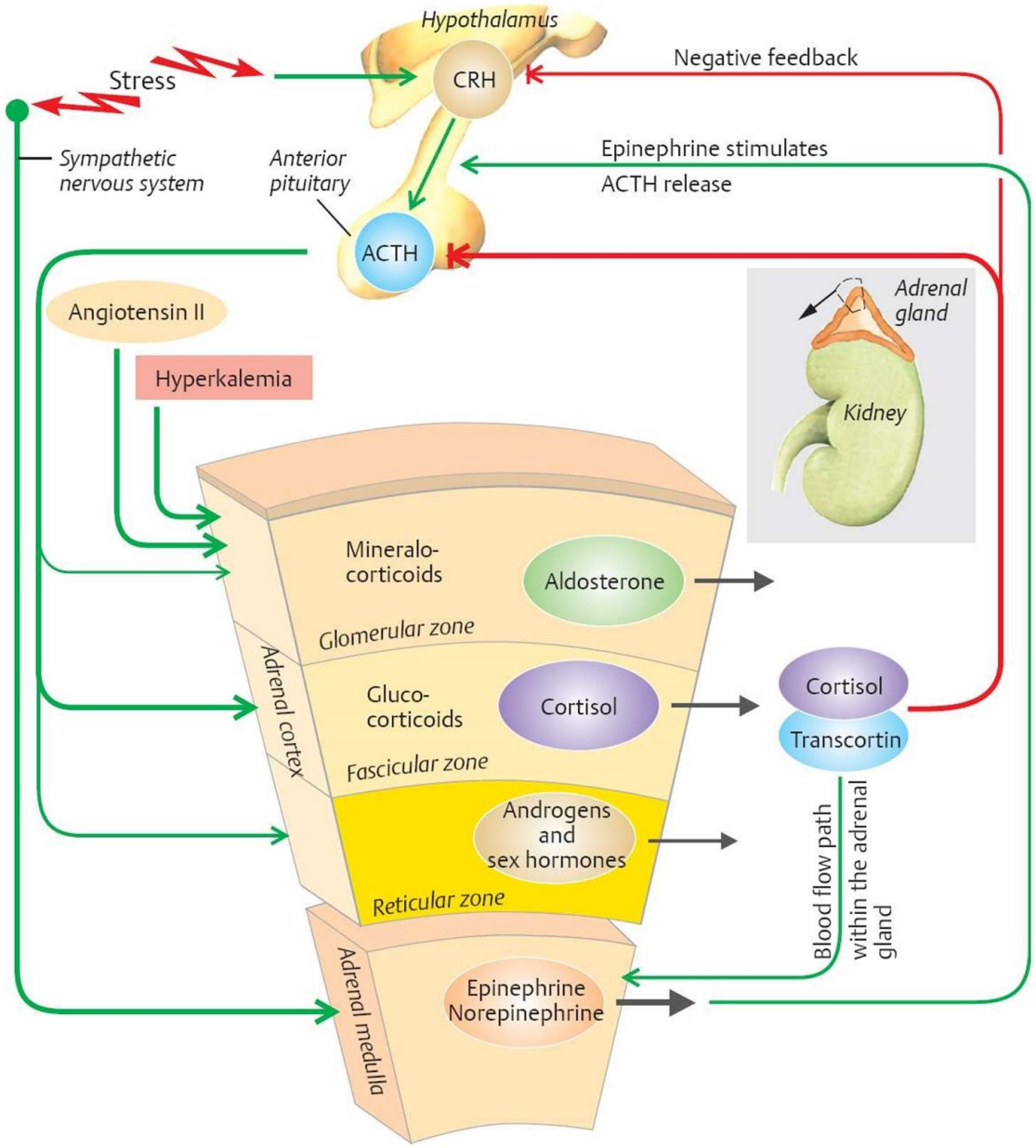
Nicolaides NC, Willenberg HS, Bornstein SR, et al. Adrenal Cortex: Embryonic Development, Anatomy, Histology and Physiology. [Updated 2023 Jun 12]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK278945/

- The adrenal cortex **takes part in steroidogenesis, producing glucocorticoids, mineralocorticoids, and androgen precursors.**
- It has **3 distinct functional and histological zones**: the zona glomerulosa (outermost layer), the zona fasciculata (middle layer), and the zona reticularis (innermost layer).

ADRENAL CORTEX

- **<u>Each layer produces steroid hormones from the precursor cholesterol.</u>**

- The specific steroid hormone produced **differs** in each layer **because of zonal specific enzymes.**

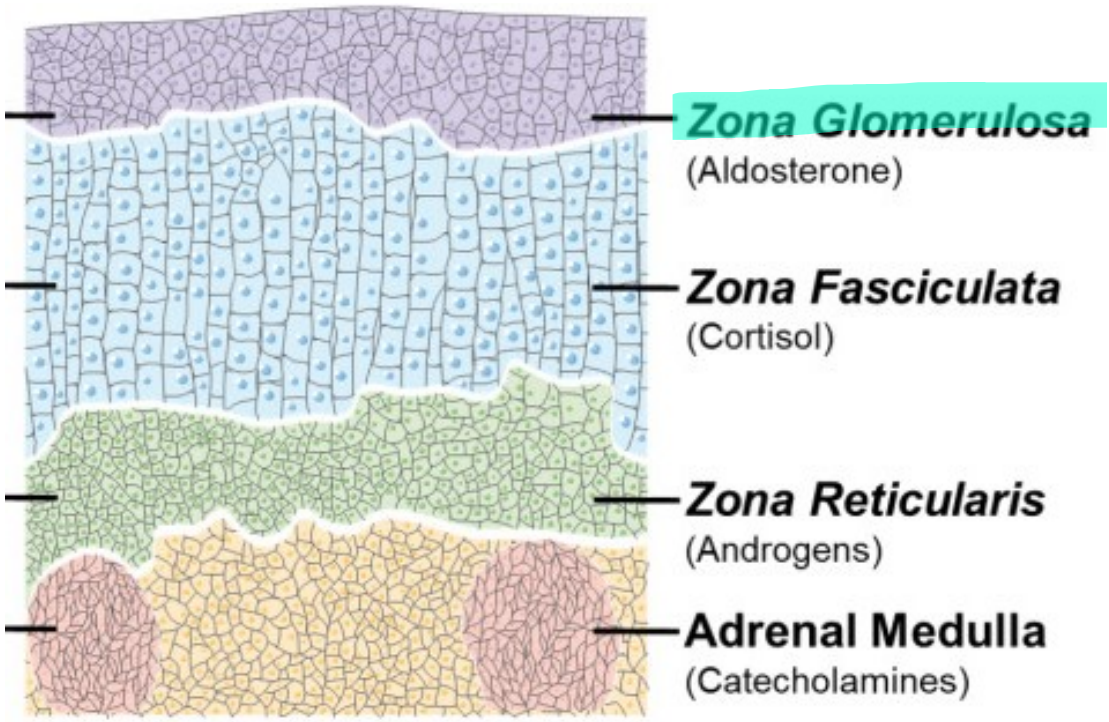


OUTERMOST LAYER/ ZONA GLOMERULOSA

ADRENAL CORTEX

The zona glomerulosa produces mineralocorticoids that help in the **regulation of blood pressure and electrolyte balance.**

The outermost layer, site of mineralocorticoid production (mainly aldosterone): regulated by angiotensin II, potassium, and ACTH
✓dopamine, atrial natriuretic peptide (ANP) and other neuropeptides modulate adrenal zona glomerulosa function



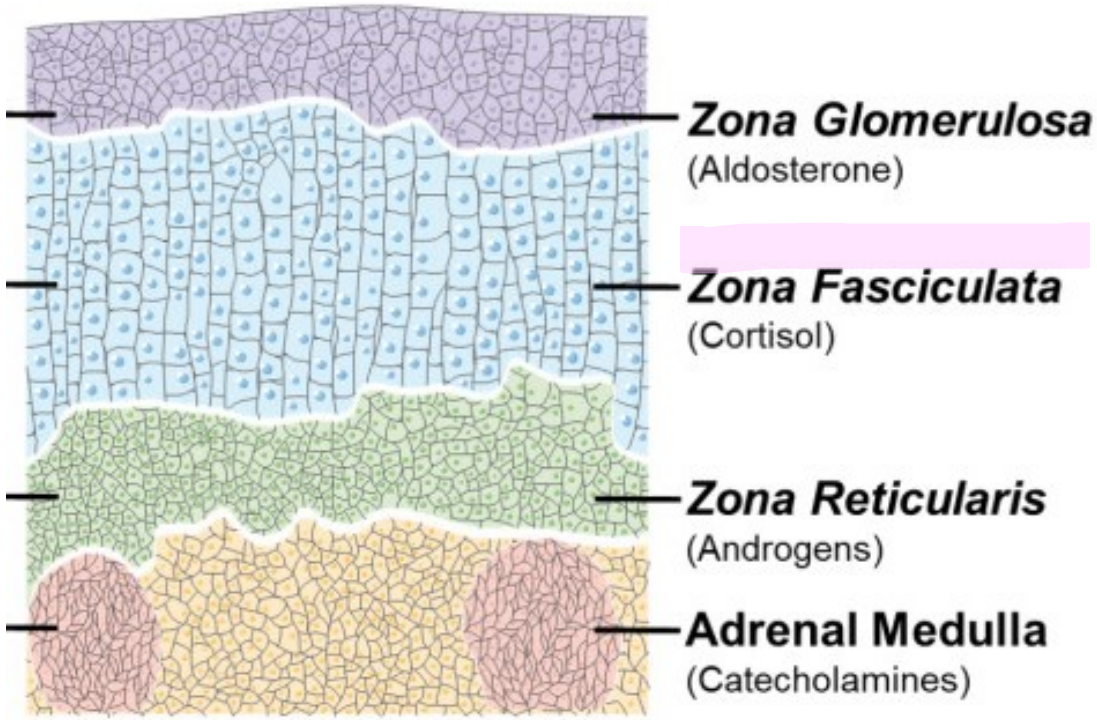
MIDDLE LAYER/ ZONA FASCICULATA

- **The middle layer, responsible mainly for glucocorticoid synthesis, is regulated by ACTH.**

✓**Several cytokines (IL-1, IL-6, TNF), neuropeptides, and catecholamines influence the biosynthesis of glucocorticoids.**

ADRENAL CORTEX

The zona fasciculata produces glucocorticoids that help in the regulation of blood pressure and electrolyte balance.

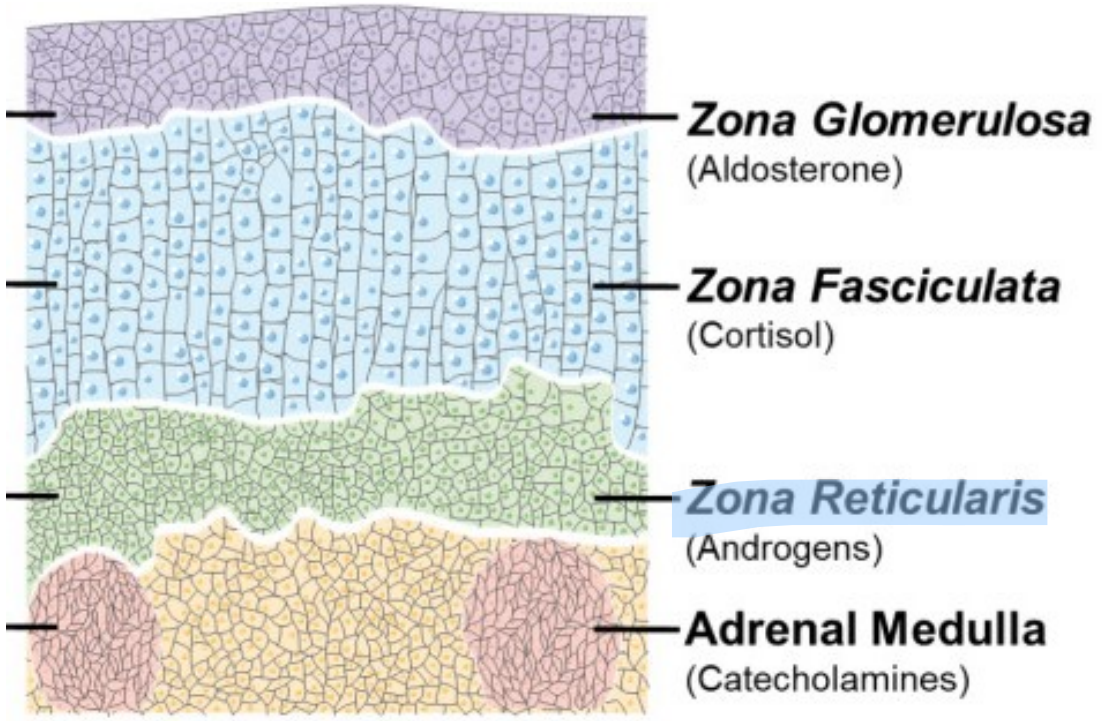


INNERMOST LAYER/ ZONA RETICULARIS

ADRENAL CORTEX

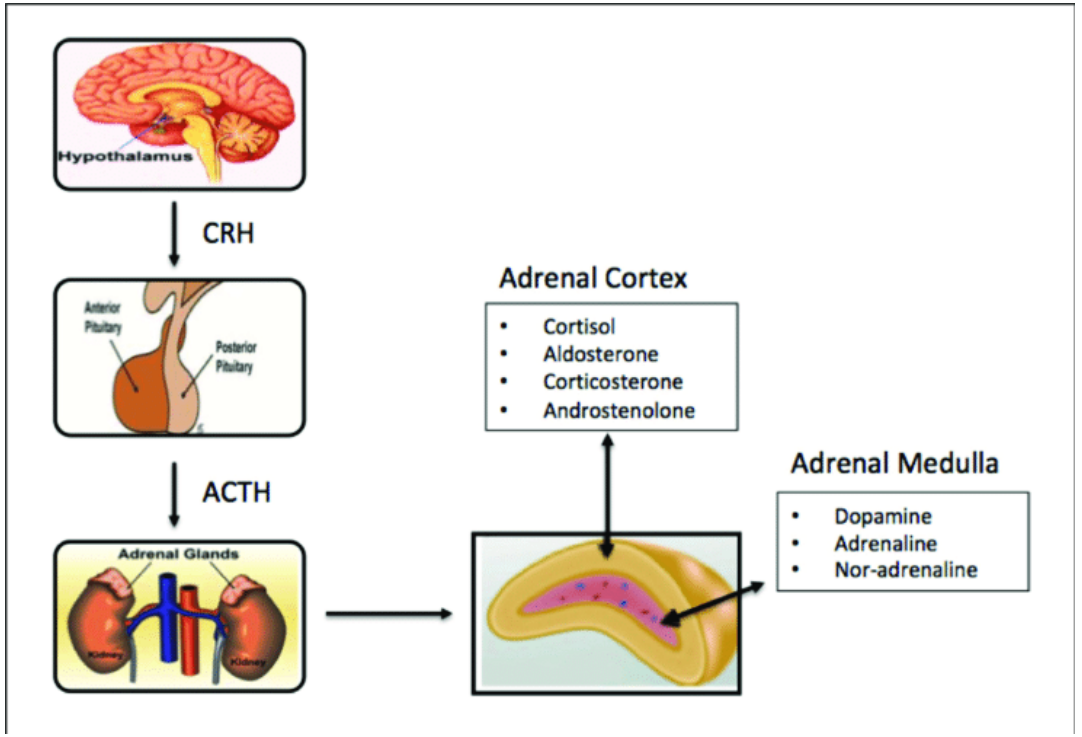
The zona reticularis produces androgen precursors that are converted to fully functional sex hormones in the gonads and other target organs

- The innermost layer, **site of adrenal androgen (predominantly dehydroepiandrostenedione [DHEA], DHEA sulfate [DHEA-S] and Δ4-androstenedione) secretion**, as well as some glucocorticoid production (cortisol and corticosterone).



Adrenal Cortex and HPA axis

- **Regulation of stress:** cortex of the adrenal gland via the hypothalamic-pituitary-adrenal (HPA) axis
- A variety of external and internal stimuli induce the release of corticotropin releasing hormone (CRH) from the hypothalamus.
- CRH then mediates the release of adrenocorticotropic hormone (ACTH) from the pituitary ⇒ Adrenal glands
- **Adrenal cortex:** cortisol/ aldosterone/ corticosterone/ androsterone
- **Adrenal medulla: dopamine/ epinephrine/ nor-epinephrine**



ADRENAL FUNCTIONAL IMPAIRMENT

Can lead to:

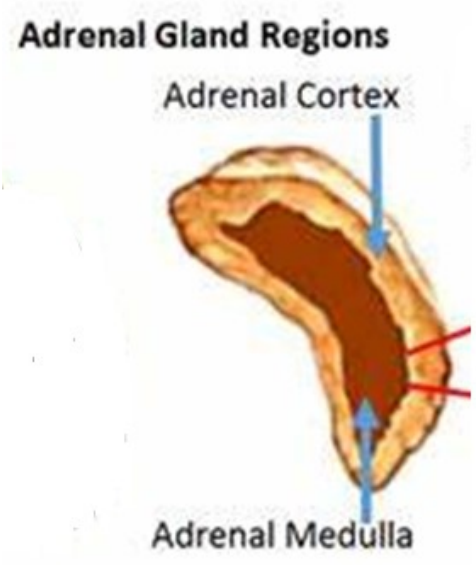
Insufficiency and overproduction of hormones

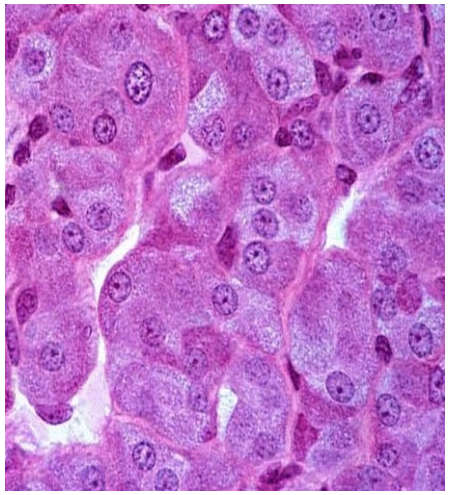
Eliciting:

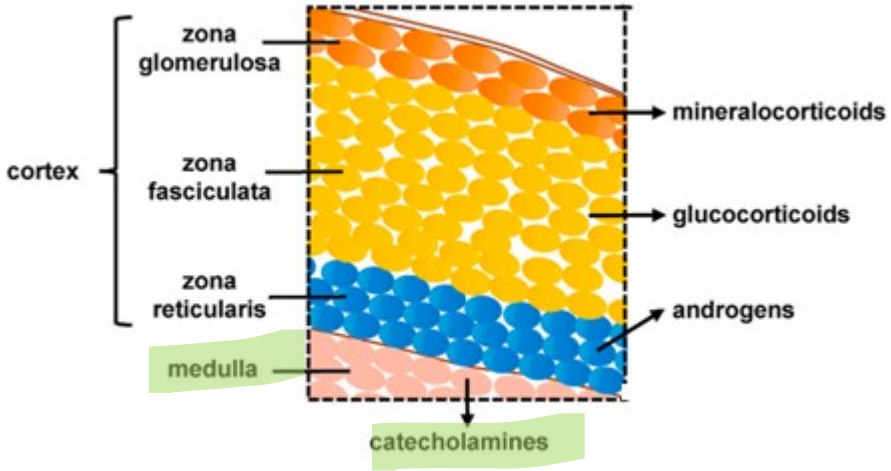
- ❑ **Addison's disease (primary hypo-adrenalism)**
- ❑ **Cushing's syndrome (hypercortisolism)**
- ❑ **Conn's disease (primary hyperaldosteronism)**
- ❑ **Adrenal androgen excess**
- ❑ **Pheochromocytoma**

Adrenal Medulla

- **Situated below the cortex, filled with neurosecretory cells.**
- **In the medulla, catecholamines, epinephrine (adrenaline) and nor-epinephrine (nor-adrenaline, are synthesized, stored in granules, and on cholinergic stimulation released.**
- In the medulla there are also ganglion cells, and nerve fibers forming synapses to the chromaffin cells with acetylcholine-containing storage granules.
- **Chromaffin cells- the main cell type- so called due to their easy staining with chromium salts**







NOR-EPINEPHRINE

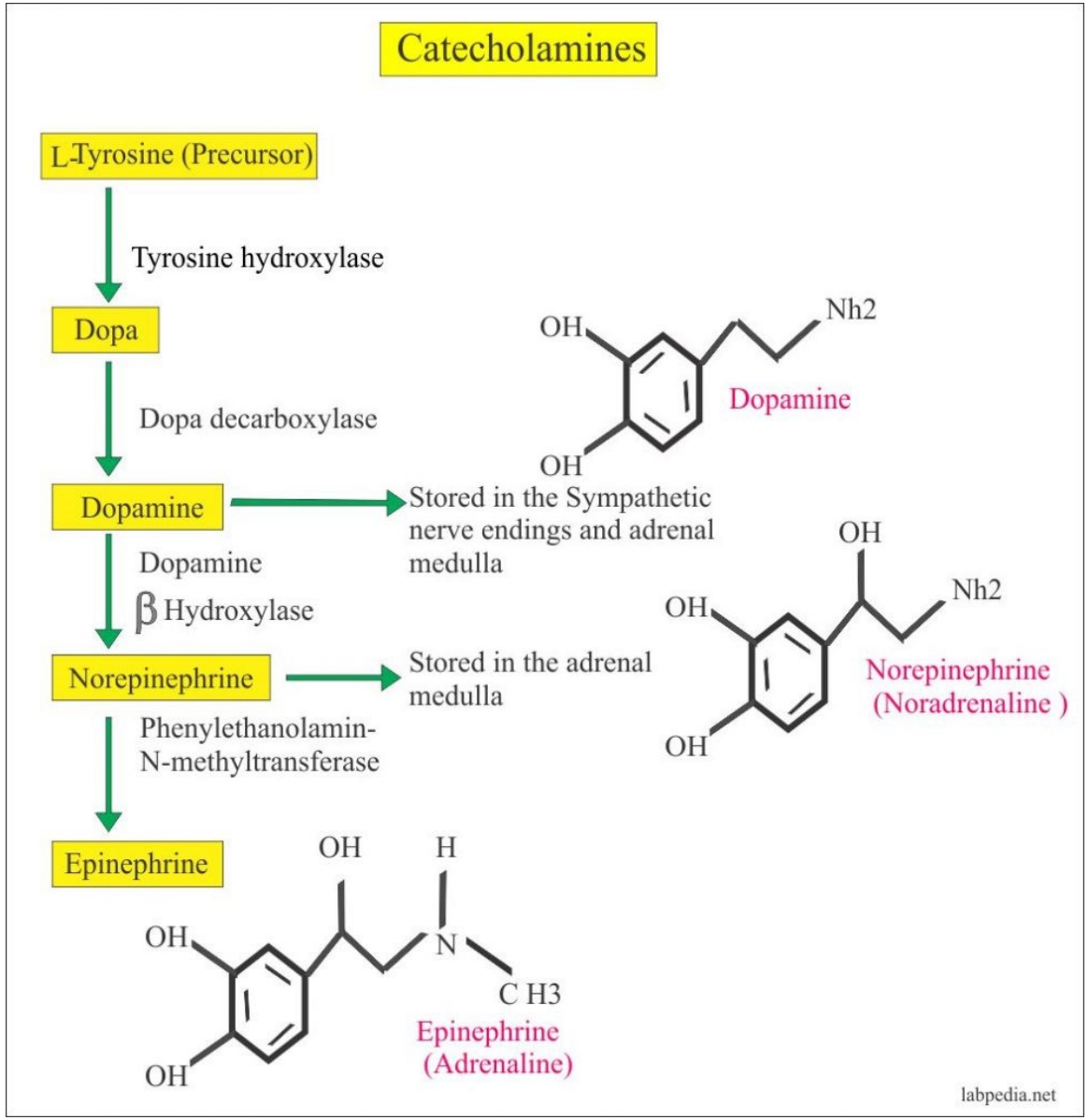
- Is a neurotransmitter **acting directly from noradrenergic neurons on target cells such as muscle cells via synapses**.
- A hormone from the adrenal medulla acting in an endocrine manner on cells other than those in the adrenal medulla.

On a given heart cell, nor-epinephrine acts via synapses, whereas epinephrine acts via circulation.

EPINEPHRINE

- **A hormone distributed via the circulation and acting on receptors on a variety of target cells—for example, nerve cells.**
- Accelerates the pulse, contracts blood capillaries, and **is the hormone of "fight or flight" reactions in the brain.** In response to stress, coldness, fatigue, shock, or hypoglycemia: epinephrine is secreted with acetylcholine as a neurotransmitter.
- In the liver, epinephrine stimulates emptying of glycogen stores and gluconeogenesis to cause enhanced glucose consumption.
- **Under the influence of catecholamines, lipid catabolism is accelerated and lipid and ketone body levels in the blood are increased.**

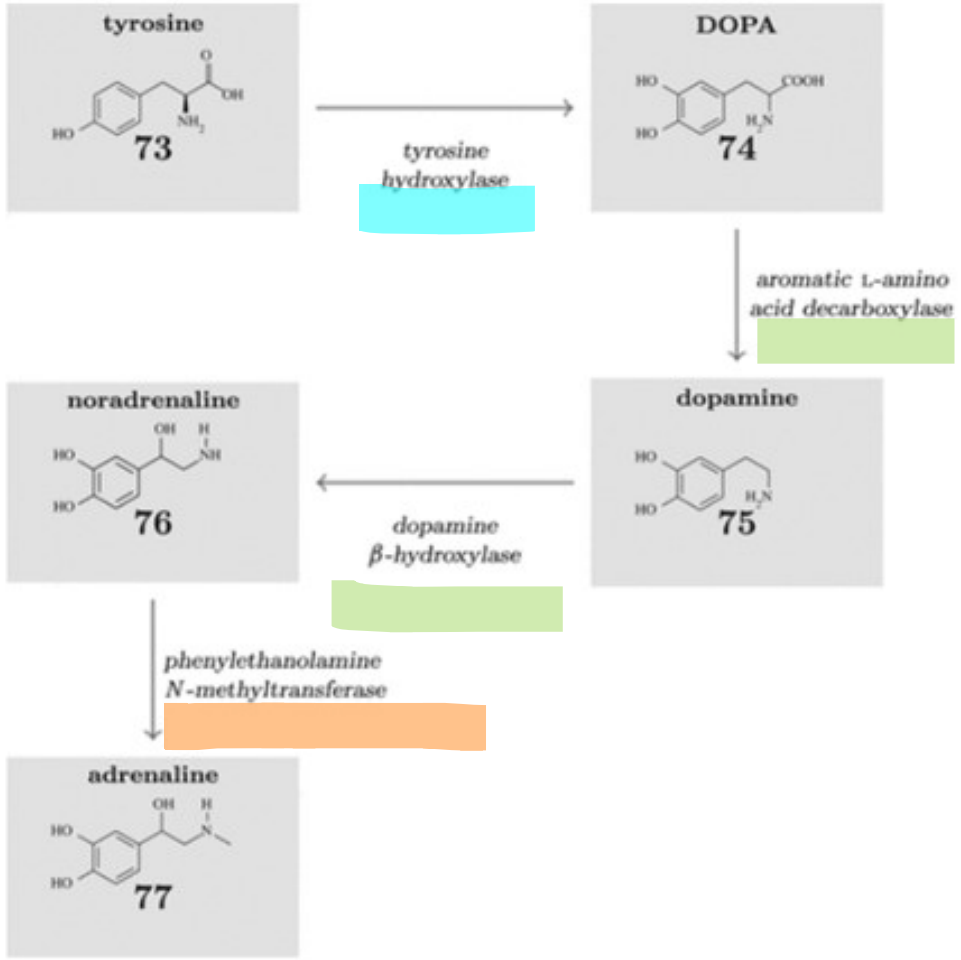
ADRENAL MEDULLA HORMONES



- **The first two reactions from tyrosine to dopamine occur in the cytosol.**
- The key enzyme is **tyrosine hydroxylase.** Its activity determines the amount of nor-epinephrine and epinephrine produced.
- Dopamine is active within vesicles.

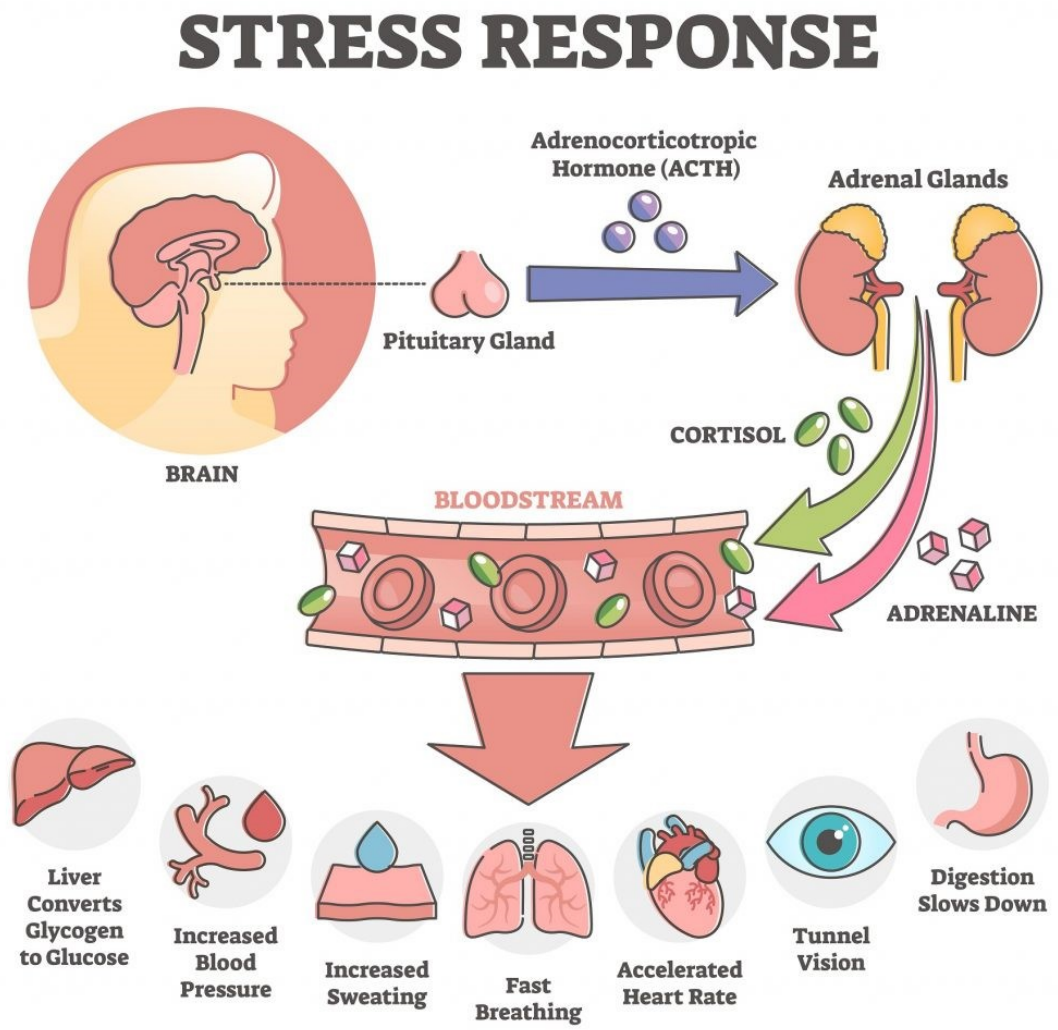
ADRENAL MEDULLA HORMONES

- Dopamine β-hydroxylase, is active only inside vesicles. It is expressed in noradrenergic neurons and in the adrenal medulla.
- The last enzyme of catecholamine biosynthesis, **phenylethanolamine N-methyltransferase, is the characteristic enzyme of chromaffin cells of the adrenal medulla and is stimulated by adrenocorticotropic hormone.**



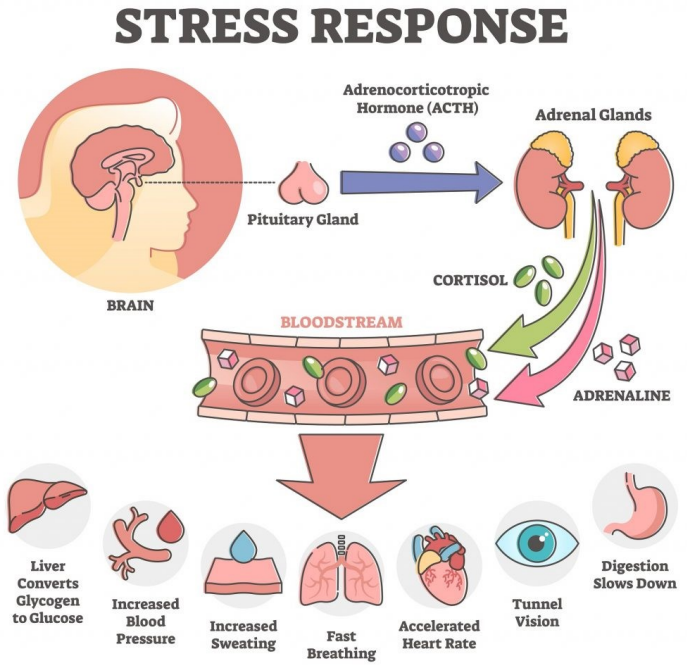
ADRENAL MEDULLA HORMONES

- Adrenal catecholamines, epinephrine, and norepinephrine are involved in executing the fight-or-flight response of the sympathetic nervous system.
- Increase blood pressure via alpha-1 receptors on vascular smooth muscle.
- Increase serum glucose by activating glycogenolysis and increasing glucagon secretion via beta-2 receptors and decreasing insulin secretion via alpha-2 receptors.



Catecholamine Synthesis

1. After an external stimulus triggers the body's stress response, the pituitary-adrenal axis and sympathetic division of the autonomic nervous system are activated.
2. Glucocorticoids production increases in the adrenal cortex, and acetylcholine (Ach) is released from sympathetic splanchnic nerves.
3. Ach binds to nicotinic receptors located on the membrane of chromaffin cells in the adrenal medulla
4. These receptors promote exocytosis of catecholamine-filled vesicles for transport in the bloodstream.
5. In the blood, catecholamines target alpha and beta-adrenergic receptors, a family of g protein-coupled receptors (GPCRs).
6. The adrenergic receptors utilize either cyclic adenosine monophosphate (cAMP) or phosphoinositol second messenger systems to activate ion channels that ultimately mediate the body's sympathetic response.

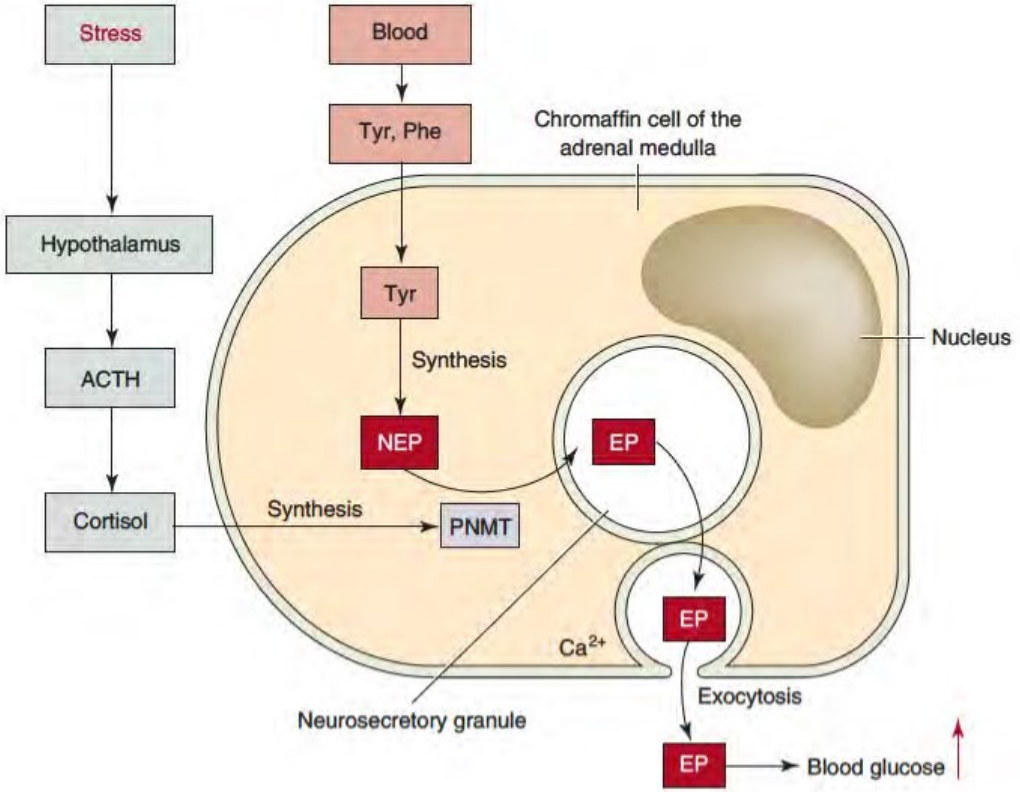


Acute stress: the neurosecretory chromaffin cells of the adrenal medulla, secrete the catecholamines epinephrine (adrenaline) and norepinephrine (nor-andrenaline) in the **fight-or-flight response**

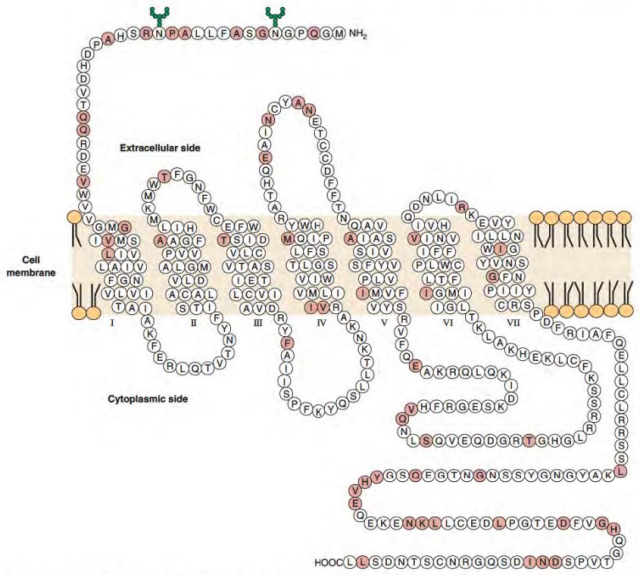
The stress response at the level of the adrenal cortex ensures the production of epinephrine from the adrenal medulla

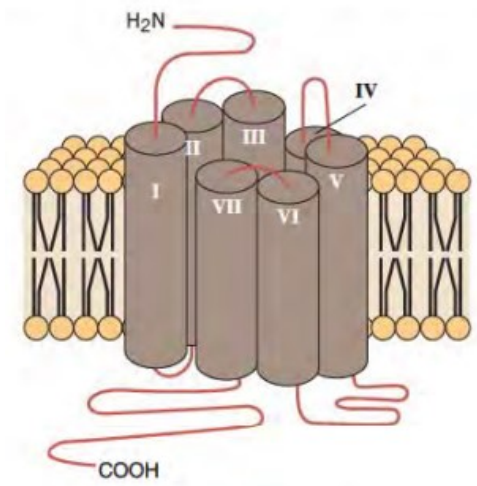
Cortisol induces methyltransferase that converts norepinephrine into epinephrine

Biosynthesis, packaging, and release of epinephrine in adrenal medulla chromaffin cell.



ADRENERGIC RECEPTORS



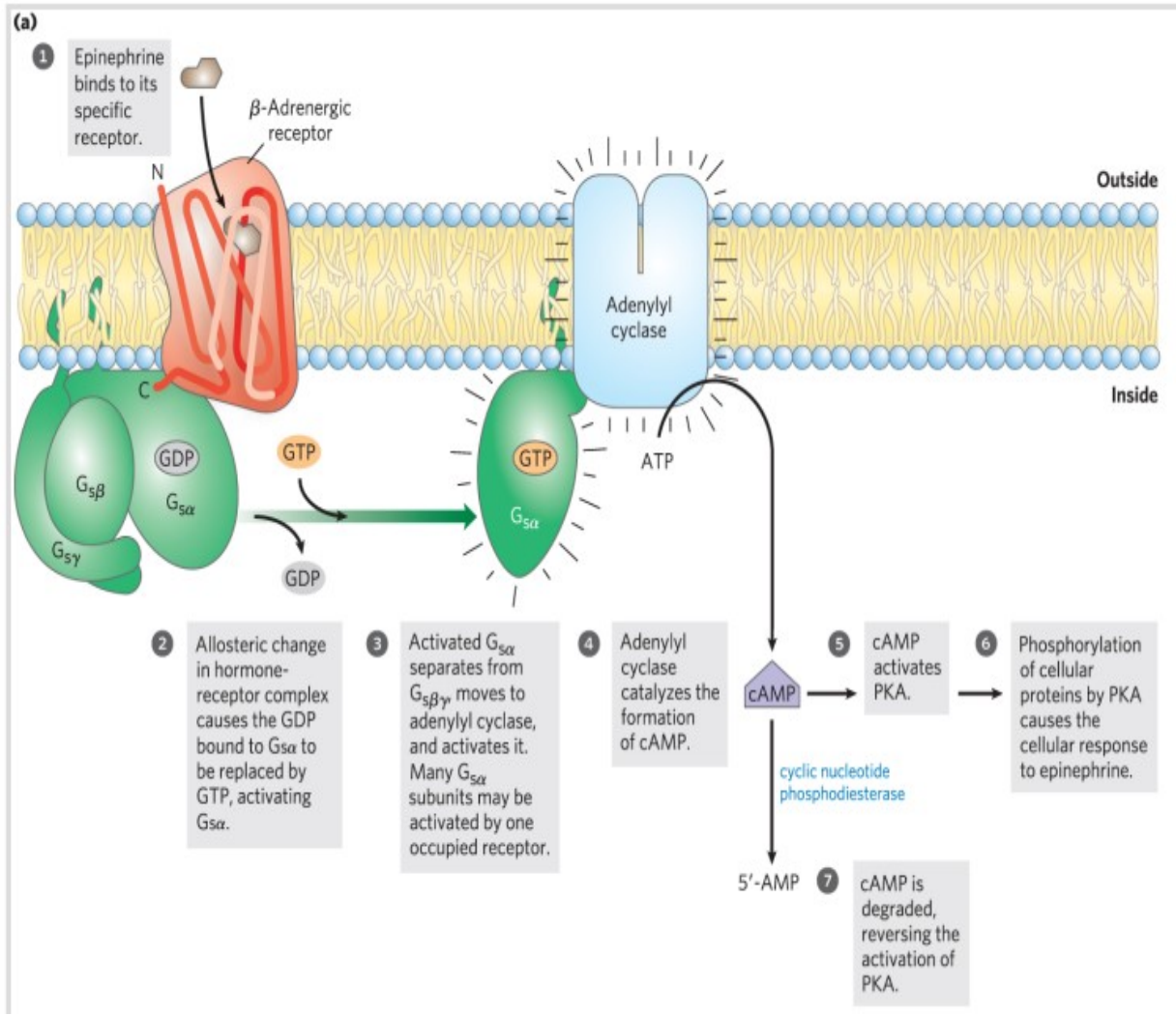


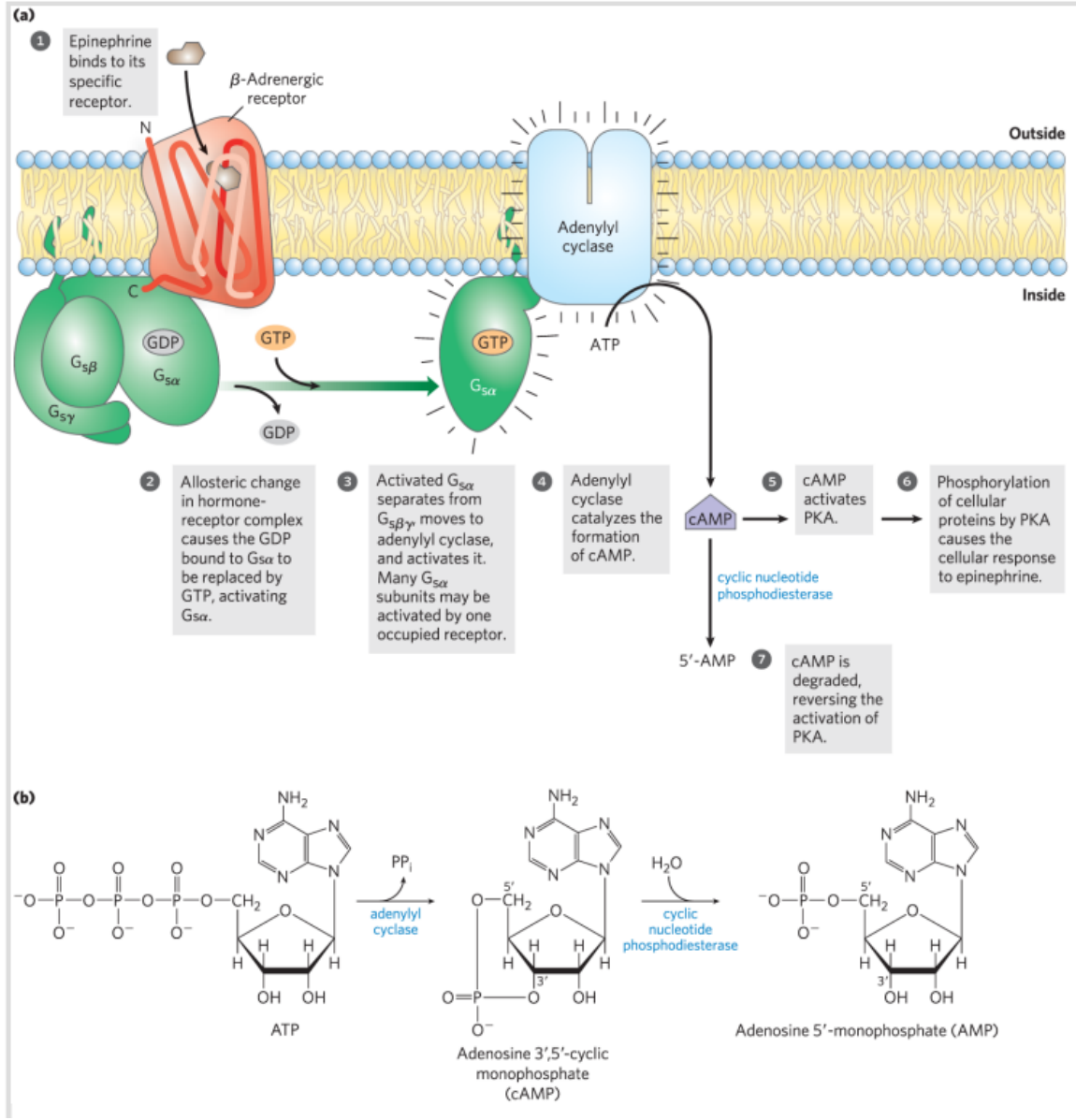
- Adrenergic receptors: four general types, α1, α2, β1, and β2, defined by differences in their affinities and responses to a group of agonists and antagonists.
- Agonists are molecules (natural ligands or their structural analogs) that bind a receptor and produce the effects of the natural ligand
- Antagonists are analogs that bind the receptor without triggering the normal effect and thereby block the effects of agonists, including the natural ligand.

Like all GPCRs, **the β-adrenergic receptor is an integral protein with seven hydrophobic**, helical regions of 20 to 28 amino acid residues that span the plasma membrane seven times, thus the alternative names for GPCRs: **seven-transmembrane (7tm) or heptahelical receptors.**

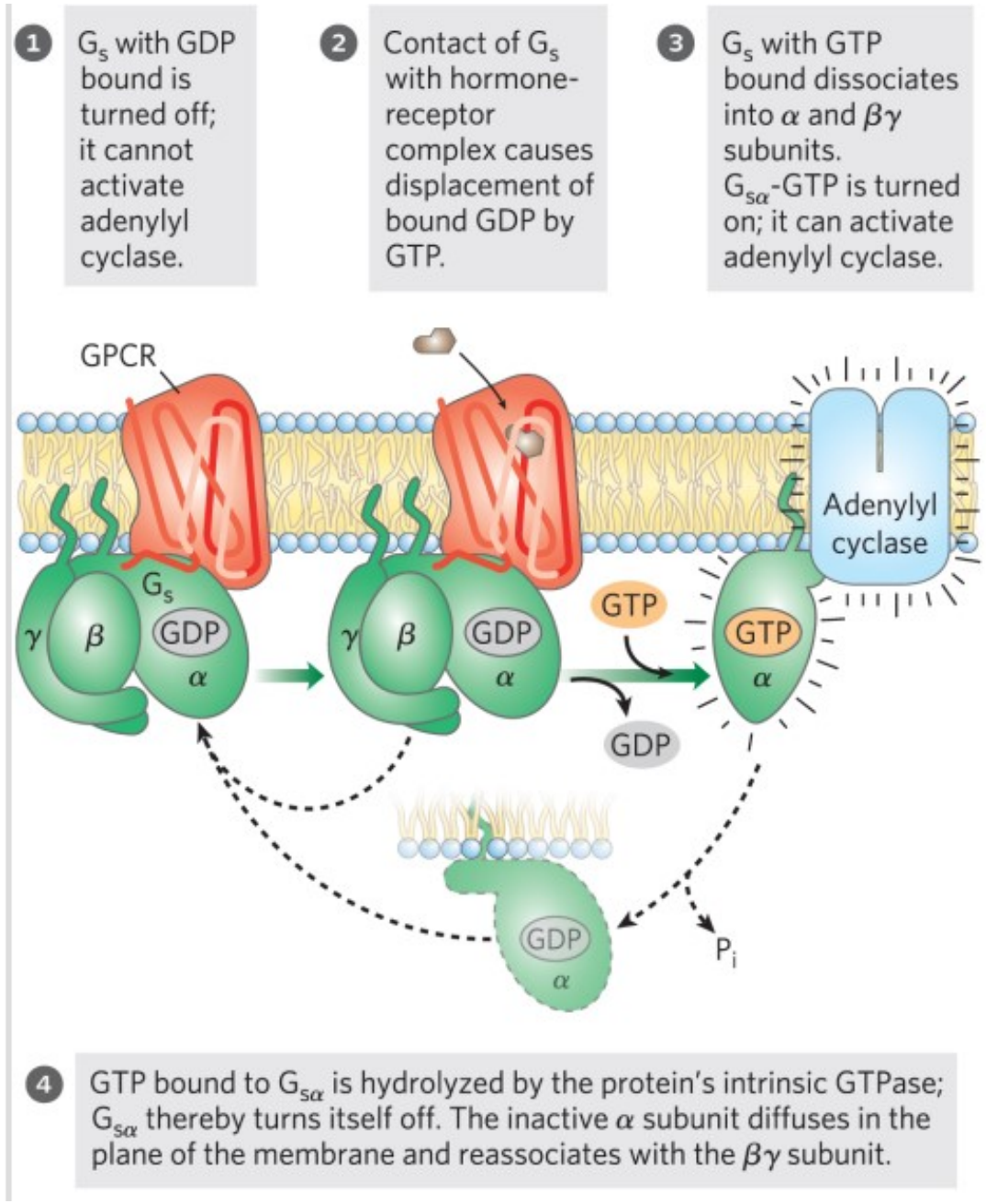
GPCRs effect signal transduction through interaction with heterotrimeric G proteins, a **conserved family of signaling proteins with three subunits, α, β, and γ.**

The binding site for GDP or GTP is on the α subunit.
When **GDP is bound, the G protein is in its trimeric, inactive form**.





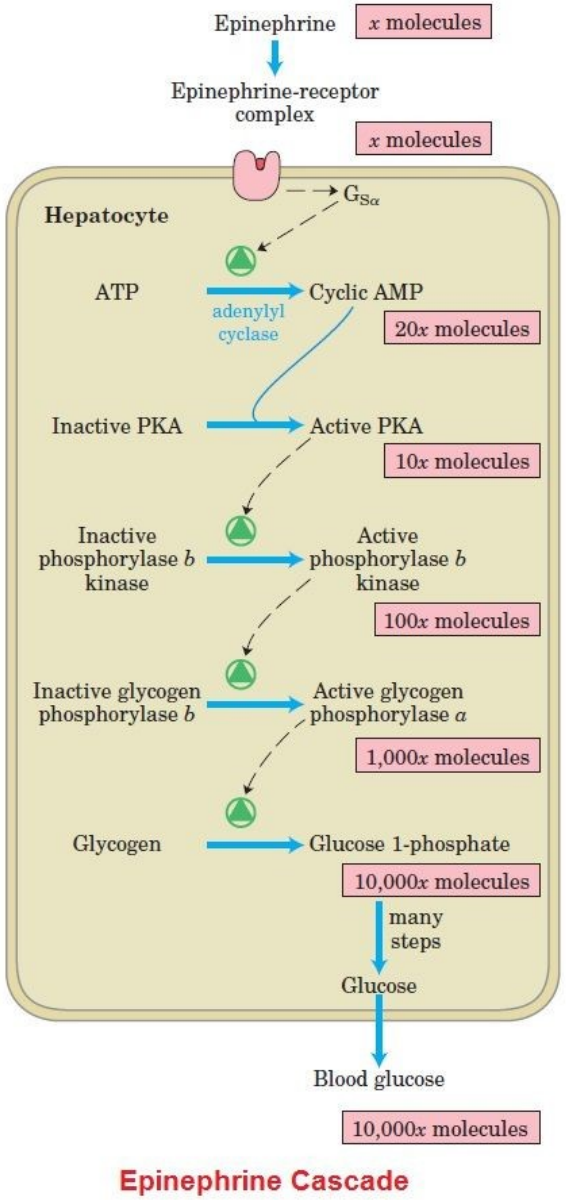
- **GPCRs are allosteric proteins.**
- The **hormone-bound GPCR** acts as a guanosine nucleotide–exchange factor (GEF).
- In this **active form, the G protein can transmit the signal from the activated receptor to the downstream effector protein, adenylyl cyclase.**
- **G protein stimulates its effector**, it is referred to as a stimulatory G protein, **or Gs.**
- **In the active form, the β and γ subunits of Gs dissociate from the α subunit as a βγ dimer**, and Gsα, with its bound GTP, **moves in the plane of the membrane from the receptor to a nearby molecule of adenylyl cyclase**



- **Gsα has intrinsic GTPase activity that switches Gsα to its inactive form by converting its bound GTP to GDP.**
- **The inactive Gsα dissociates from adenylyl cyclase, rendering the cyclase inactive.**
- **Gsα reassociates with the βγ dimer (Gsβγ), and inactive Gs is again available to interact with a hormone-bound receptor.**

Amplification of the original hormone signal

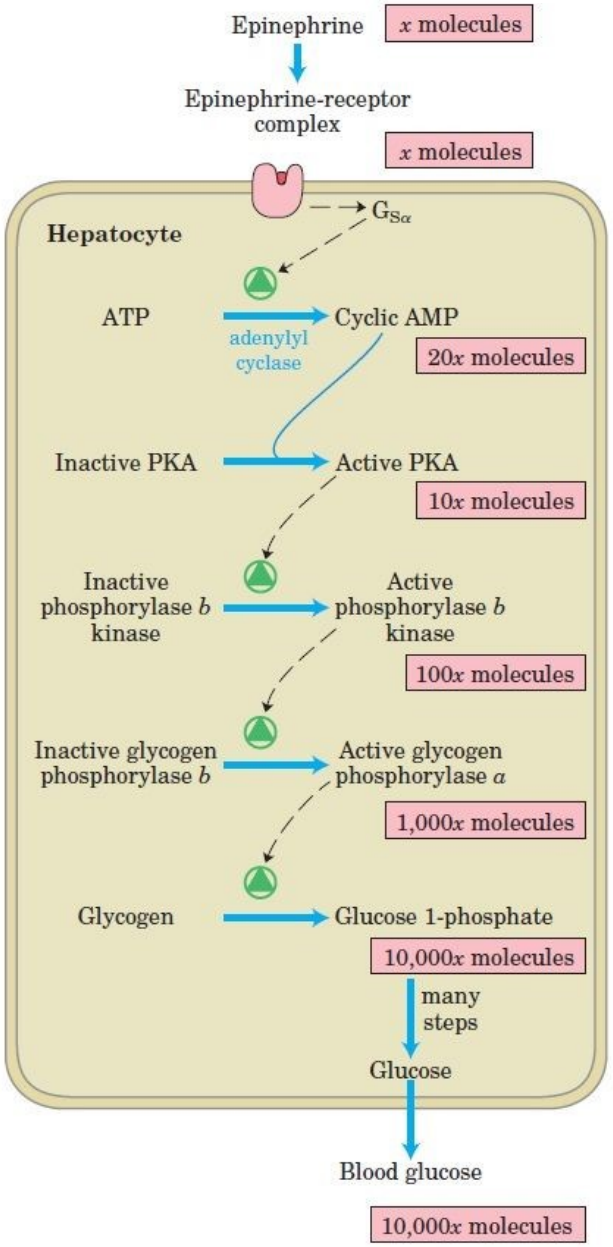
Signal transduction by the β-adrenergic receptor and adenylyl cyclase entails several steps that amplify the original hormone signal



Epinephrine Cascade

Signal transduction by the β-adrenergic receptor and adenylyl cyclase entails several steps that amplify the original hormone signal

- **Epinephrine triggers a series of reactions resulting in great amplification of the original hormone signal.**
- Binding of one molecule of epinephrine to one β-adrenergic receptor on the cell surface activates many (possibly hundreds of) G proteins, one after the other each of which goes on to activate a molecule of the enzyme adenylyl cyclase.
- Adenylyl cyclase acts catalytically, producing many molecules of cAMP for each activated adenylyl cyclase.



Epinephrine Cascade

SIGNALING- SHUTING OFF MECHANISMS

1. **Systems shut off or adapt to the continued presence of the signal by becoming less sensitive to it, by desensitizing.**
2. **The β-adrenergic system illustrates both.**
3. **The response to β-adrenergic stimulation will end when the concentration of the ligand (epinephrine) in the blood drops below the Kd for its receptor.**
4. The epinephrine then dissociates from **the receptor, which reassumes its inactive conformation**, in which it can no longer activate Gs.

A second means of ending the response is the hydrolysis of GTP bound to the Gα subunit, catalyzed by the GTPase activity of the G protein.

A third mechanism for terminating the response is to remove the second messenger: cAMP is hydrolyzed to 5 ′ -AMP (which is not active as a second messenger) by cyclic nucleotide phosphodiesterase

The β-Adrenergic Receptor Is Desensitized by Phosphorylation and by Association with Arrestin

- **Desensitization, damps the response even while the signal persists.**
- The mechanisms for signal termination described above **take effect when the stimulus ends.**

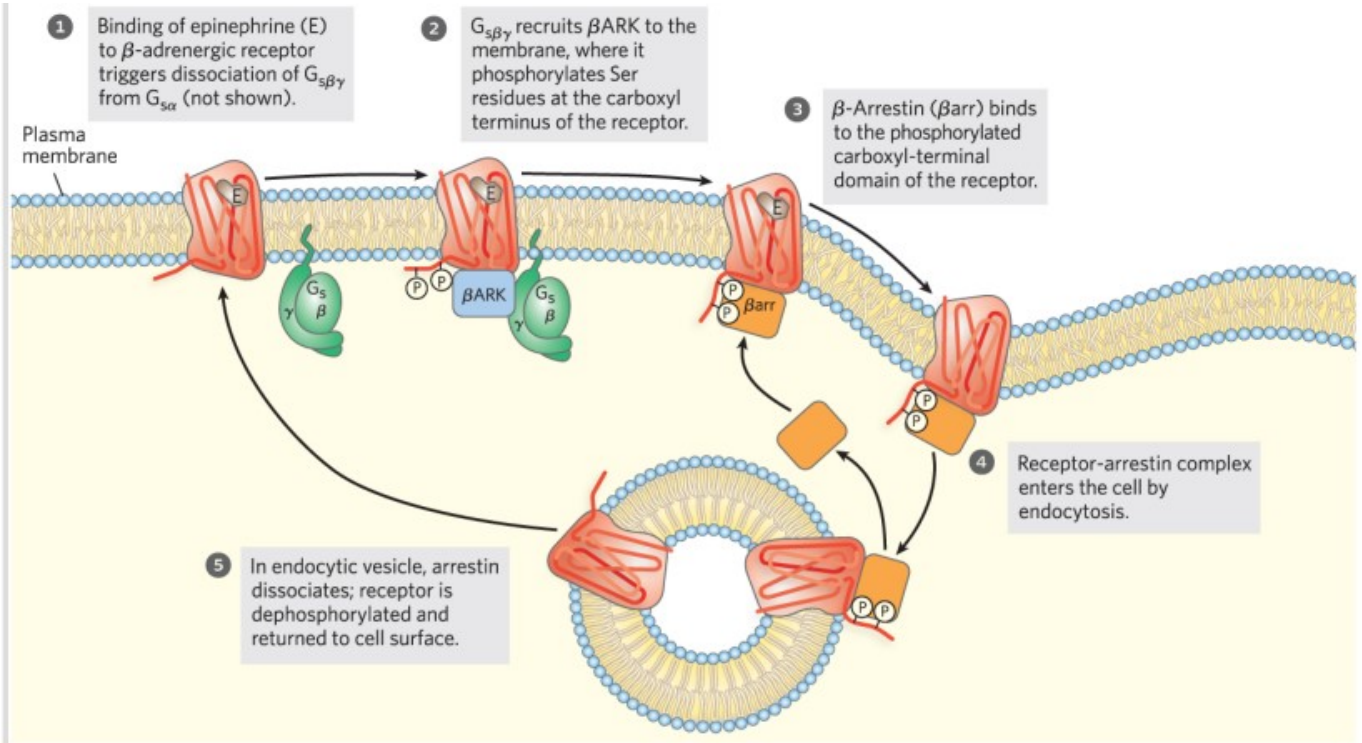
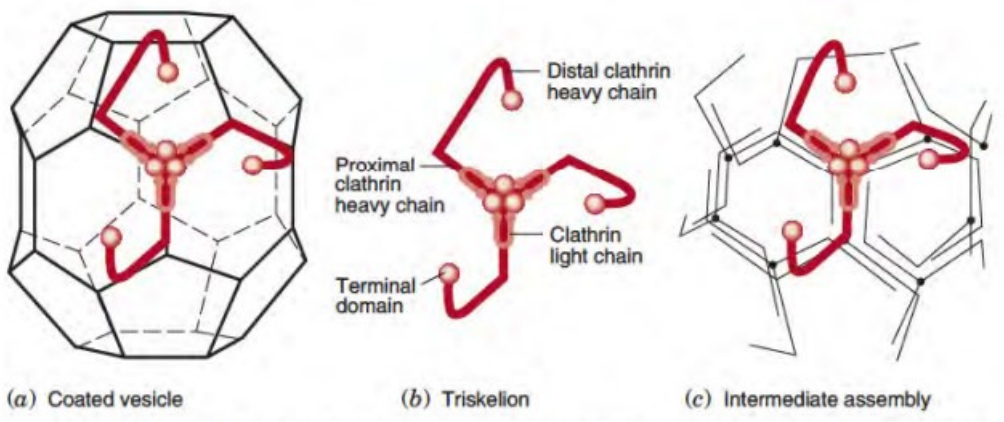


FIGURE 12-9 Desensitization of the β-adrenergic receptor in the continued presence of epinephrine. This process is mediated by two proteins: β-adrenergic protein kinase (βARK) and β-arrestin (βarr). Not shown here is the phosphorylation and activation of βARK by PKA. PKA is activated by the rise in [cAMP] in response to the initial signal (epinephrine).

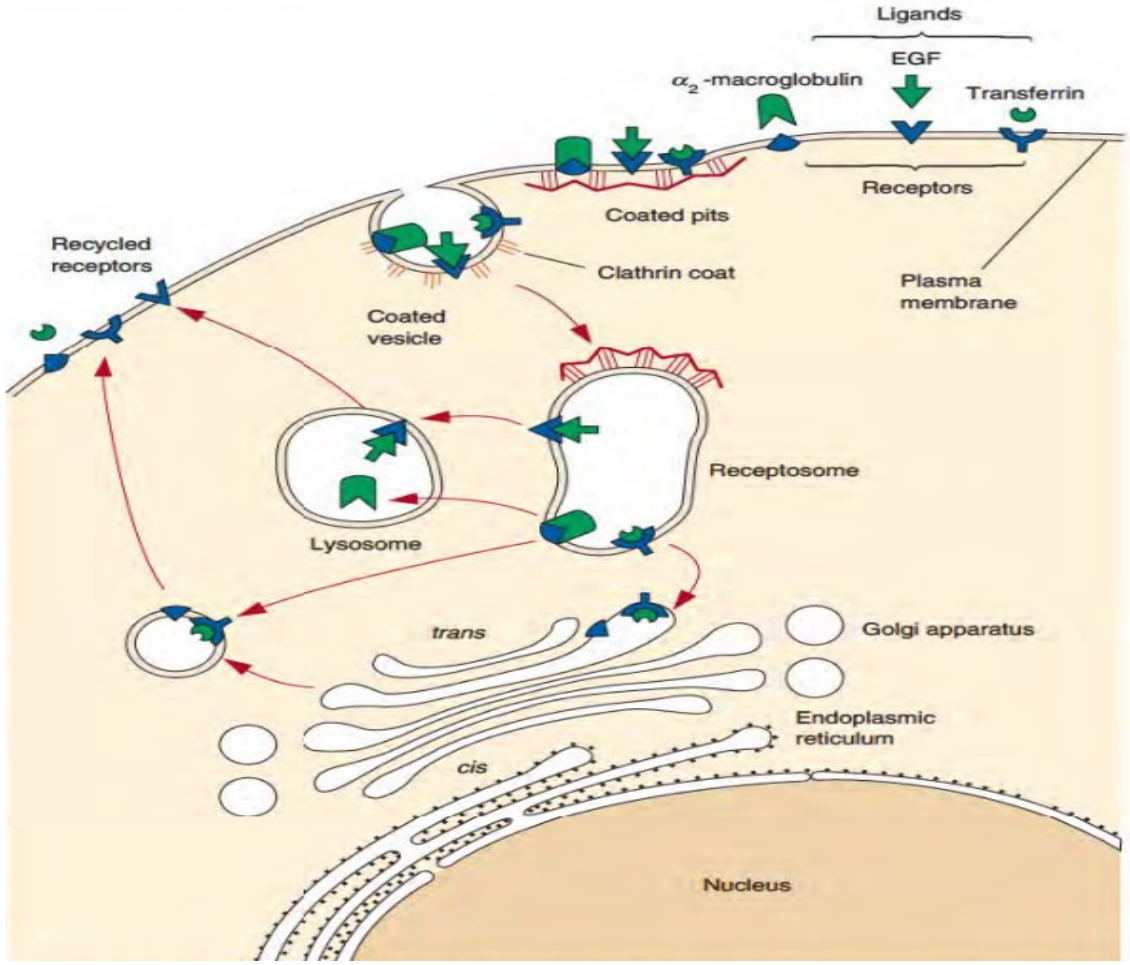
Clathrin Directs Internalization of Hormone-Receptor Complexes from Plasma Membrane

- Protein component of a coated vesicle is **clathrin**: a nonglycosylated protein (180 k.Da) whose amino acid sequence is highly conserved.
- The coated vesicle contains 70% clathrin, 5% polypeptides of about 35 kDa, and 25% polypeptides of50 - 100 kDa.
- **Coated vesicles have a lattice-like surface structure composed of hexagons and pentagons**



Endocytosis introduces an intact receptor or ligand to the cell interior in cases where the nucleus may contain a receptor-binding site or a ligand-binding site- DECREASE IN HORMONE SENSITIVITY

- Endocytosis renders a cell less responsive to hormone, since it **reduces the number of cell surface receptors.**
- Internalization of receptors by endocytosis thus leads to **receptor down-regulation and a decrease in hormone sensitivity**



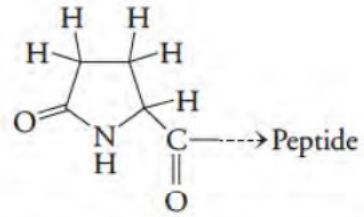
Inactivation and Degradation of Amino-Acid-Derived Hormones

- Most **polypeptide hormones** are **degraded by proteases in lysosomes**.
- Some hormones contain modified amino acids, the cyclic glutamate ring or the C-terminal amide
- **Breakage of the cyclic glutamate ring or cleavage of the C-terminal amide inactivates many of these hormones**.
- Such reactions have been reported to occur in **blood and may account for the short half-life of some hormones in plasma.**

TABLE 22.4 • Hypothalamic Releasing Hormones Containing an N-Terminal Pyroglutamate,[a] a C-Terminal Amino Acid Amide, or Both

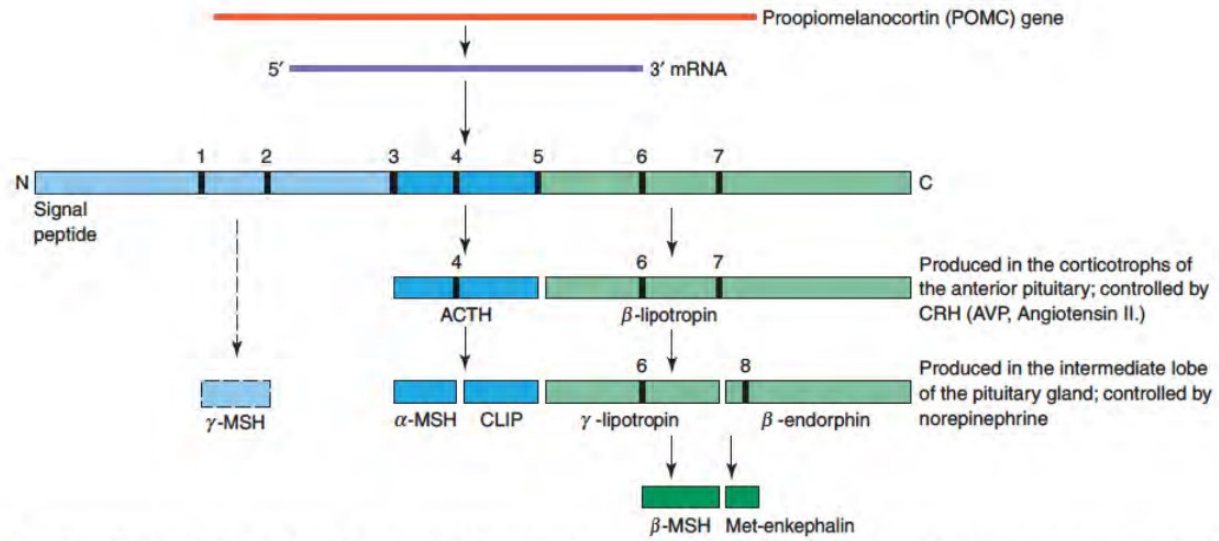
Hormone	*Sequence*
Thyrotropin-releasing hormone (TRH)	*pGlu*-H-*Pro*-NH_2
Gonadotropin-releasing hormone (GnRH)	*pGlu*-HWSYGLRP-*Gly*-NH_2
Corticotropin-releasing hormone (CRH)	SQEPPISLDLTFHLLREVLEMTKADQLAQQAHSNRKL-LDI-*Ala*-NH_2
Growth hormone-releasing hormone (GRH)	YADAIFTNSYRKVLGQLSARKLLQDIMSRQQGESNQE-RGARAR-*Leu*-NH_2

[a]The pyroglutamate structure is



[b]Single-letter abbreviations used for amino acids: Ala, A; Arg, R; Asn, N; Asp, D; Cys, C; Glu, E; Gln, Q; Gly; G; His, H; Ile, I; Leu, L; Lys, K; Met, M; Phe, F; Pro, P; Ser, S; Thr, T; Trp, W; Tyr, Y; Val, V.

Inactivation and Degradation of Amino-Acid-Derived Hormones



- Some hormones contain **cystine disulfide bonds, and these may be degraded by cystine aminopeptidase and glutathione transhydrogenase**
- Alternatively, the peptide may undergo partial proteolysis to shorter peptides, some of which may have hormonal actions.
- **Maturation or processing of prohormones into mature hormones involves selective proteolysis**

METABOLIC FUNCTIONS OF EPINEPHRINE

1. Stimulates glycogenolysis in liver-muscles:↑ GLUCOSE
2. Stimulates gluconeogenesis in the liver: ↑ BLOOD GLUCOSE
3. Stimulates lipolysis in adipose tissue: ↑ FATTY ACIDS IN THE BLOOD
4. Stimulation of glucagon by A-cells in the islets of the pancreas:

↑ BLOOD GLUCOSE

5. Stimulation of glycolysis in muscles

EPINEPHRINE-SIGNALING

- Epinephrine is synthesized from phenylalanine/tyrosine in the adrenal medulla.
- This catecholamine hormone is secreted along with some norepinephrine, enkephalins, and dopamine β hydroxylase by medullary chromaffin cells.
- Its secretion is signaled by the neuronal response to stress, which is transmitted by way of preganglionic acetylcholinergic neurons.
- This signal increases intracellular Ca^{2+}, which in turn stimulates exocytosis and release of hormone stored in the chromaffin granules

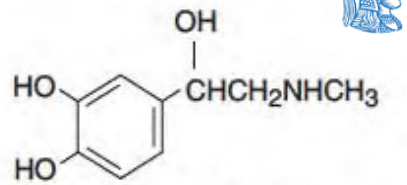
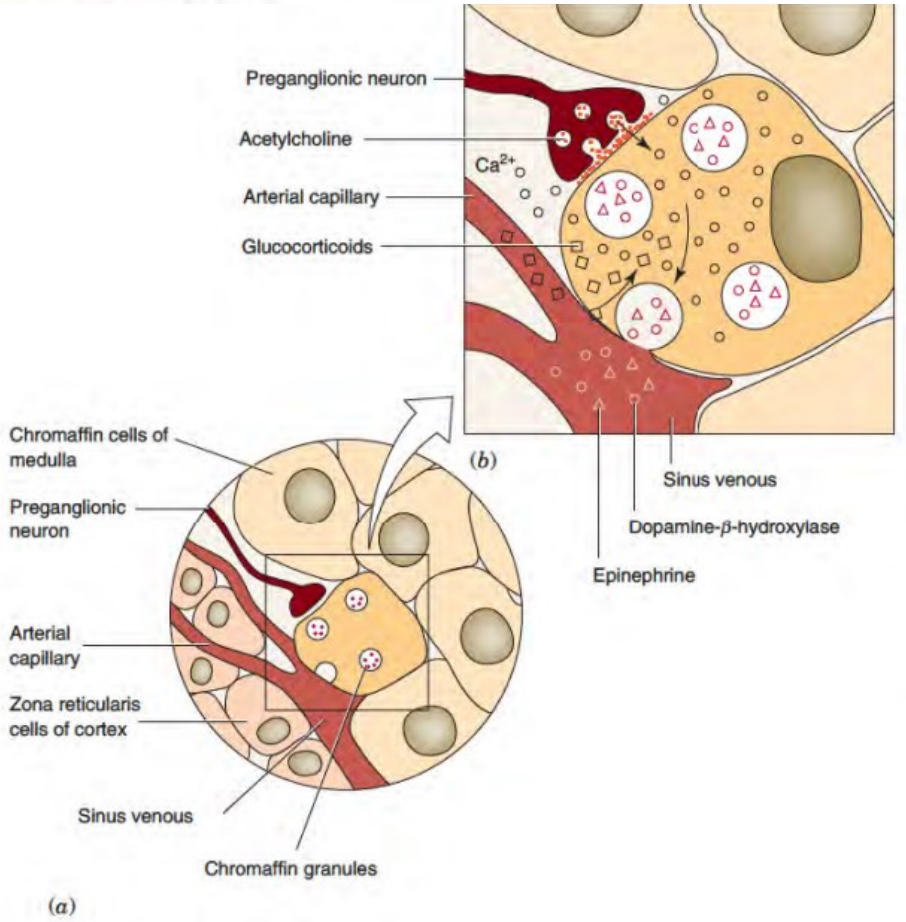
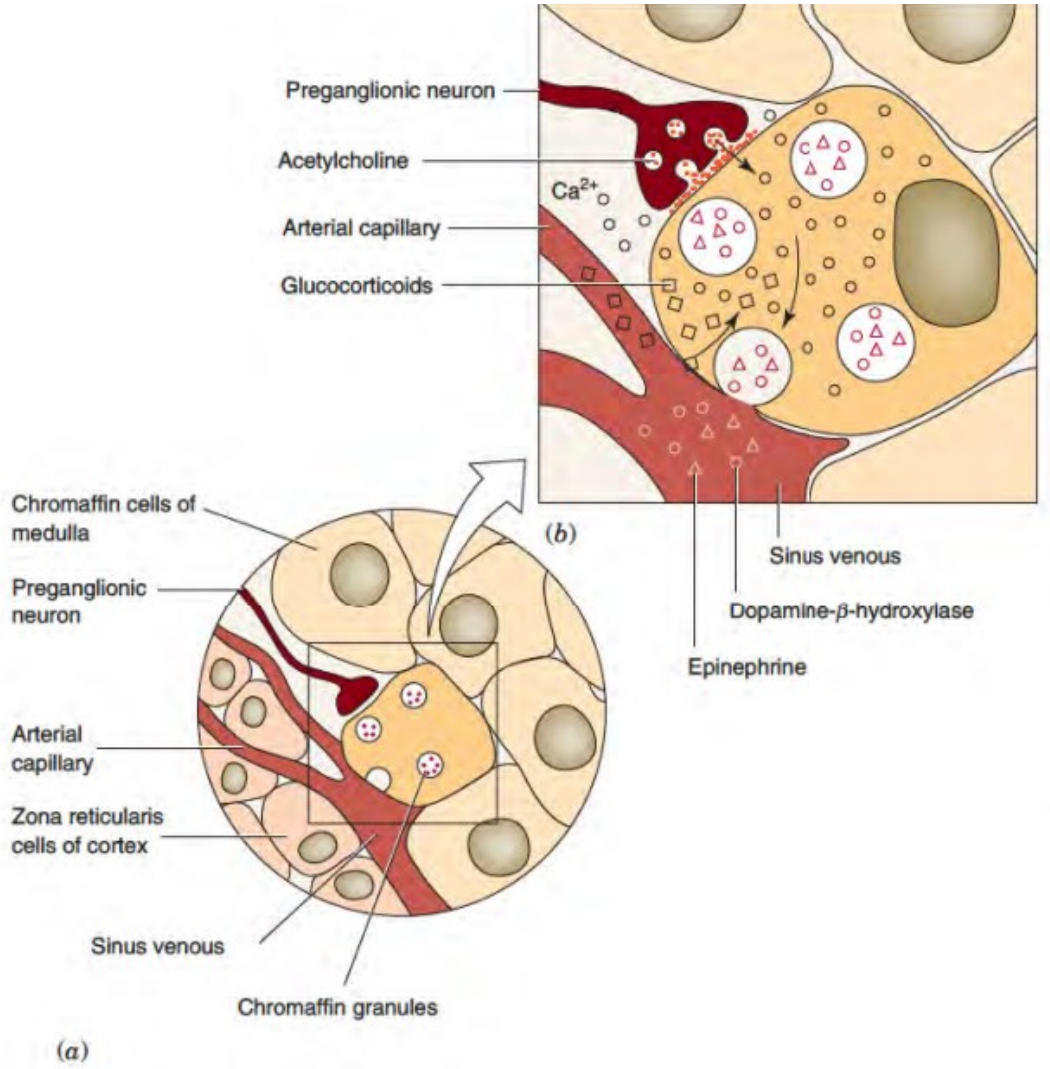


Figure 22.10 **Structure of catecholamine hormone epinephrine.**



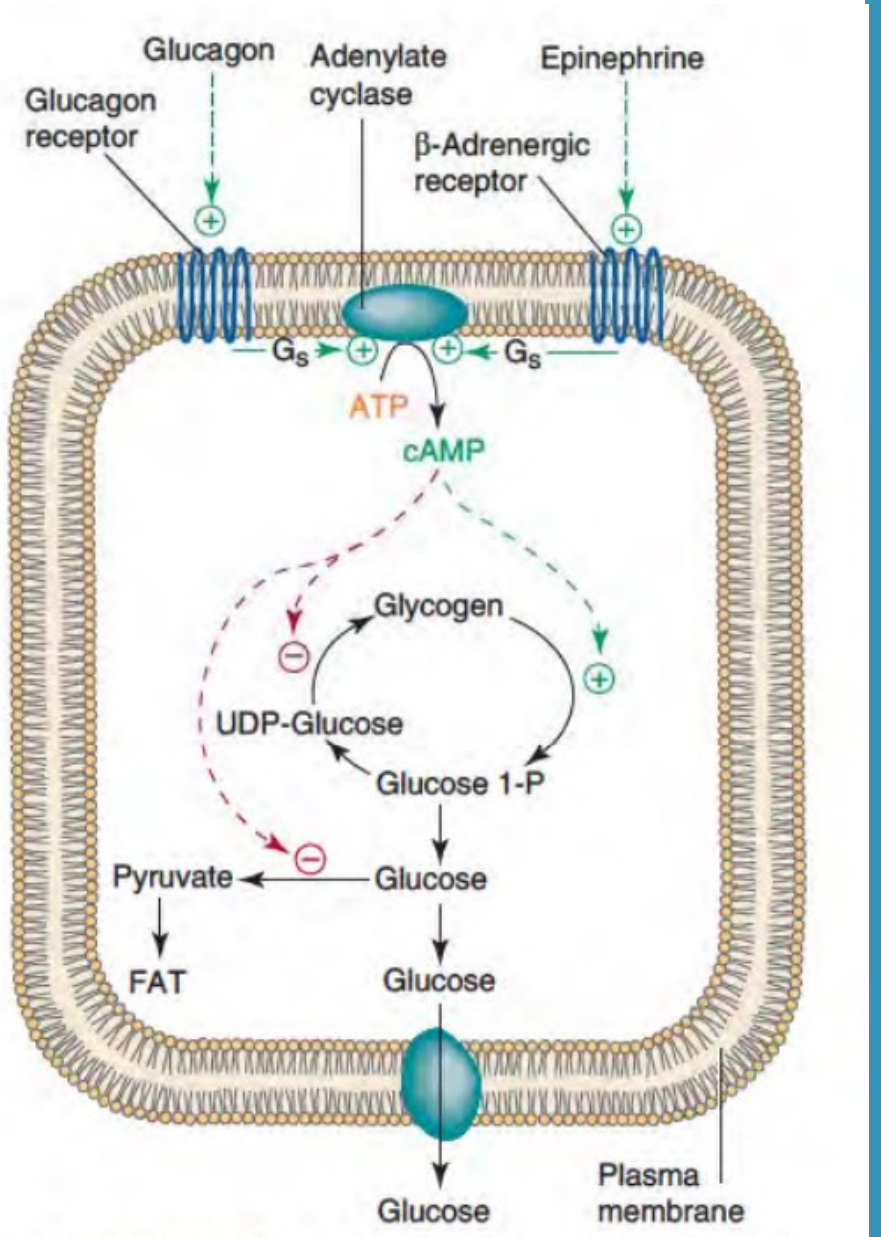
EPINEPHRINE-SIGNALING

- Once secreted, epinephrine and norepinephrine mediate their specific effects by interacting with receptors located on the plasma membranes of target cells.
- <u>These receptors are generically grouped as a and β.</u>
- <u>Epinephrine has a greater affinity for β-receptors than a-receptors, while norepinephrine acts primarily via a receptors.</u>

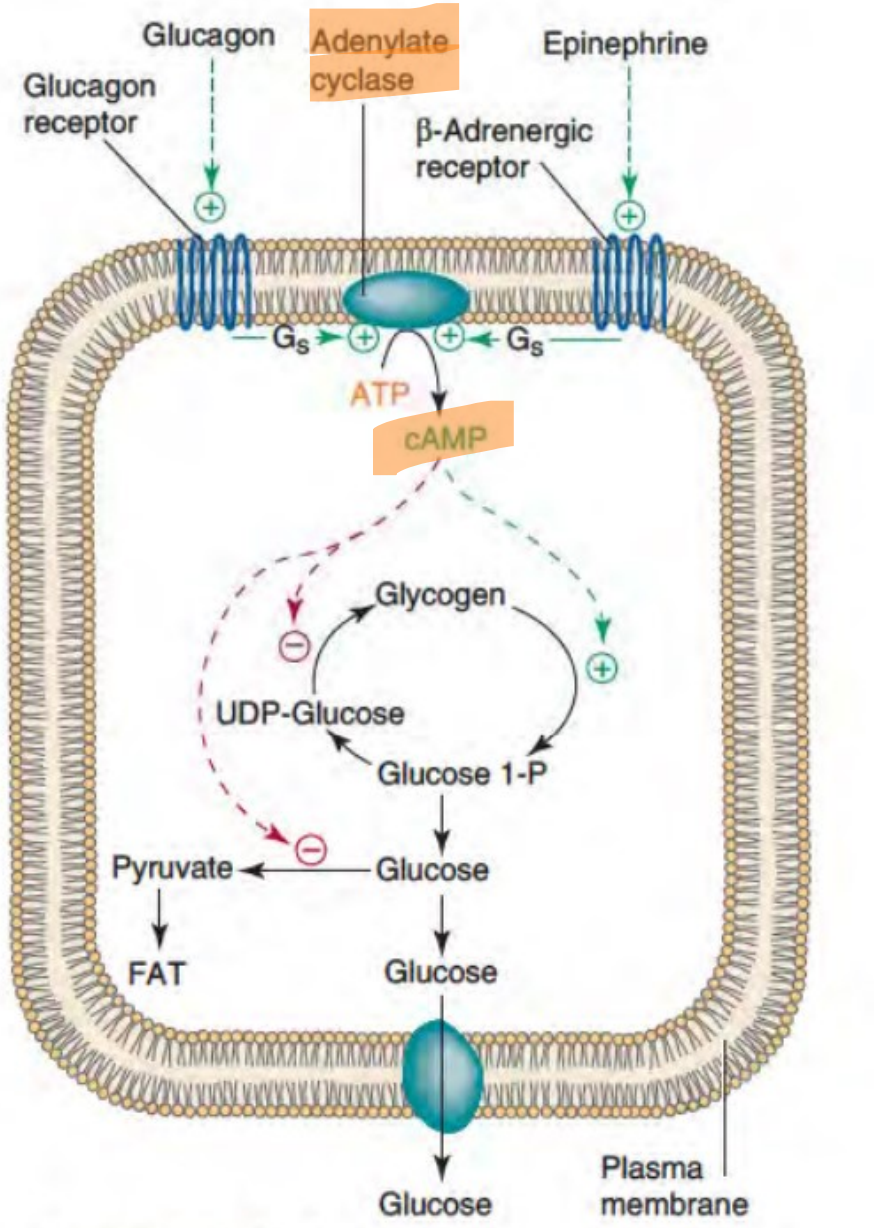


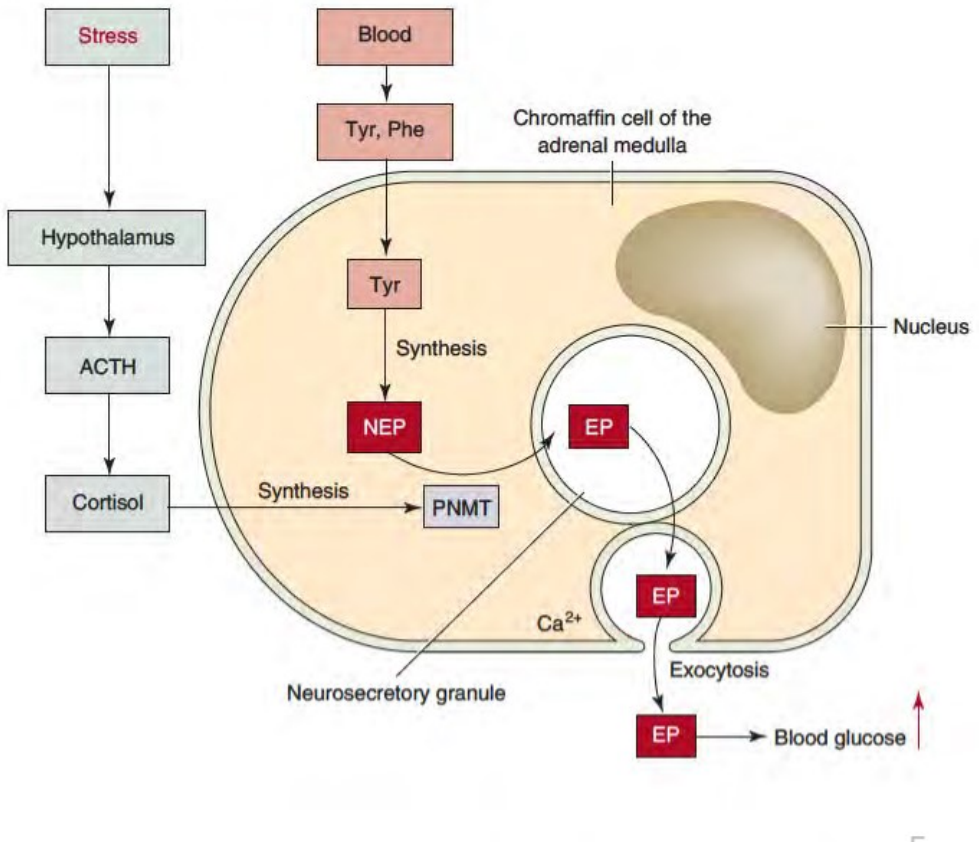
EPINEPHRINE MECHANISM

- **Epinephrine is released into blood from chromaffin cells of the adrenal medulla in response to stress.**
- This "**fright, flight or fight" hormone** prepares the body for either combat or escape.
- **Binding of epinephrine with β-adrenergic receptors on liver cells activates adenylate cyclase and cAMP has the same effects as glucagon, that is, activation of glycogenolysis and inhibition of glycogenesis and glycolysis to maximize the release of glucose**



- **Epinephrine exerts its downstream effects through the increase in [cAMP] that results from activation of adenylyl cyclase.**
- Cyclic AMP, the second messenger, allosterically activates cAMP-dependent protein kinase, also called protein kinase A or PKA , which catalyzes the phosphorylation of specific Ser or Thr residues of targeted proteins, such as glycogen phosphorylase b kinase.
- **The latter enzyme is active when phosphorylated and can begin the process of mobilizing glycogen stores in muscle and liver in anticipation of the need for energy, as signaled by epinephrine.**

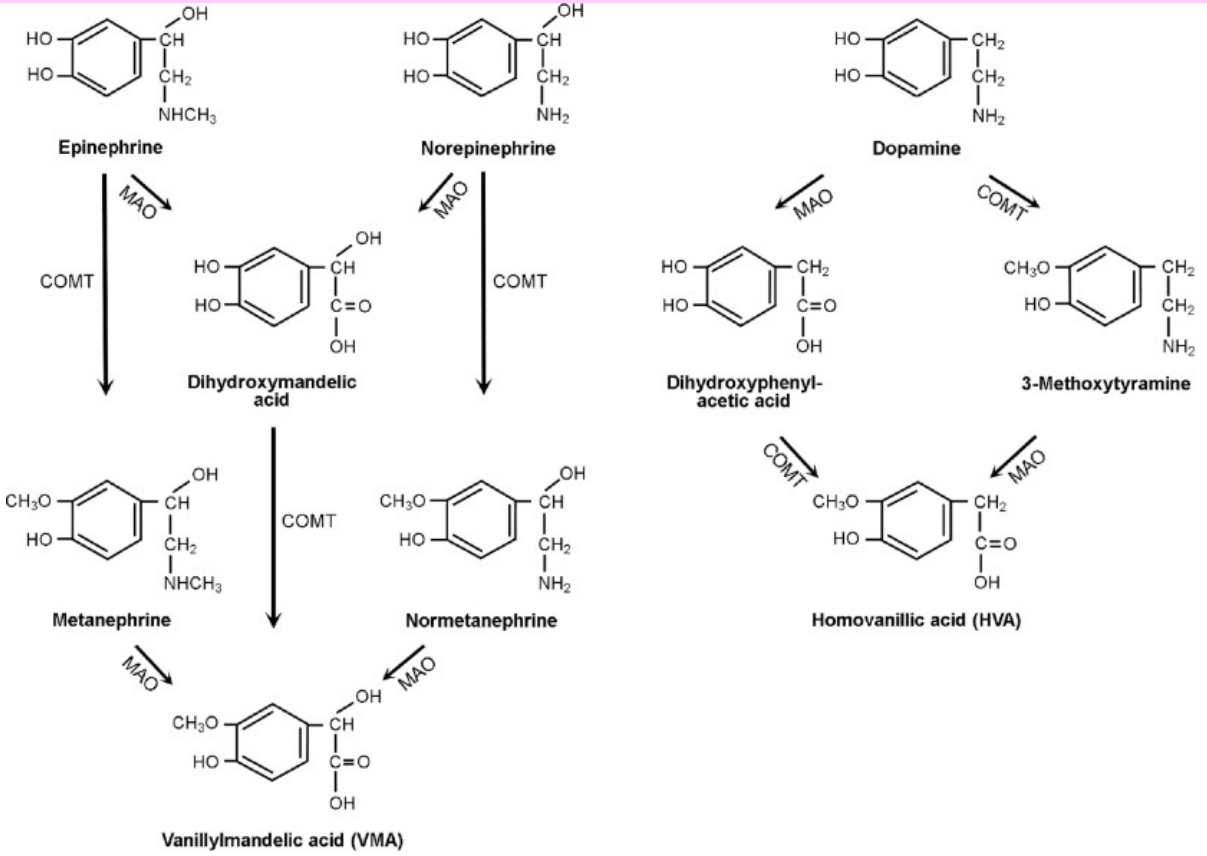




- In contrast to the catecholamine hormones, the steroid hormones including aldosterone, cortisol, and dehydroepiandrosterone are synthesized and secreted by cells in the adrenal cortex
- Like epinephrine, the secretion of cortisol by the adrenal cortex is increased in response to stress.
- This secreted cortisol perfuses the adrenal medulla where it induces phenylethanolamine N-methyltransferase (PNMT) that converts norepinephrine to epinephrine .

Metabolism of catecholamines to homovanillic acid (HVA) and vanillylmandelic acid (VMA)

Catecholamines last only a short time and are quickly broken down by the body into molecules called metanephrines.



When released into circulation, catecholamines are rapidly metabolized.

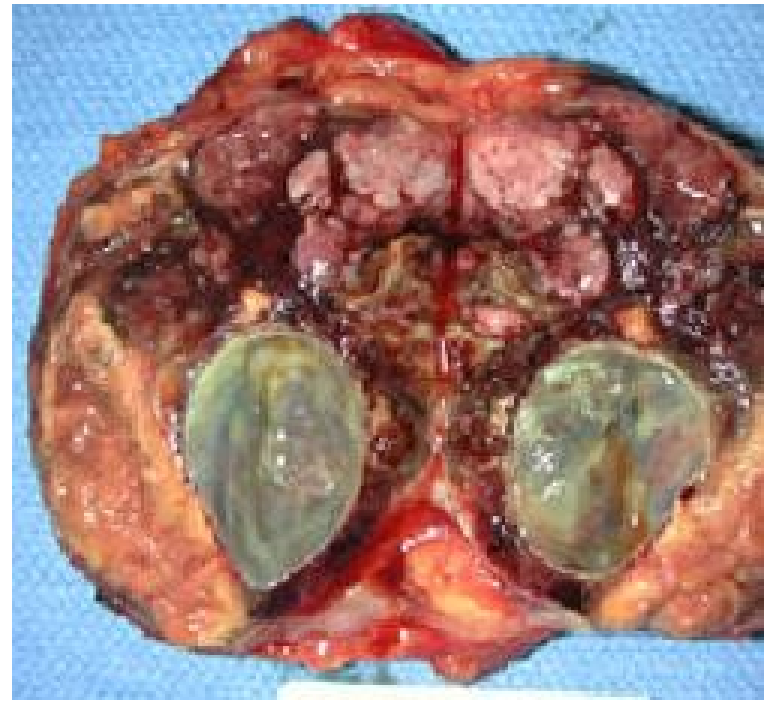
✓ **Their half-life is 1-2 minutes, which explains their low level in the blood.**

✓ Removing them from circulation:

- by their reinstatement by nerve endings of sympathetic Nerve
- by their catabolism by enzymes Catechol-O-methyltransferase (COMT) and monoamine oxidase (MAO)

Pheochromocytomas

- **Pheochromocytomas** are **tumors arising from chromaffin cells of the adrenal medulla.**
- About **80-85% of pheochromocytomas grow in the inner layer of the adrenal gland**, called **the adrenal medulla.**
- About **15-20% of pheochromocytomas** grow outside of this area and are **called extra-adrenal pheochromocytomas or paragangliomas**.
- Similar tumors that arise from extra-adrenal chromaffin cells have been referred to as **paragangliomas.** These tumors are **predominantly benign** but can be malignant in a minority of cases.



- The clinical manifestations of these tumors are primarily related to the **excessive secretion of catecholamines.**
- **Pheochromocytomas release these catecholamines in various patterns ranging from paroxysmal, continuous, and mixed patterns, as well as long asymptomatic intervals.**
- Norepinephrine is released continuously and can result in persistent hypertension, while **epinephrine is released in a paroxysmal pattern resulting in tachyarrhythmias**.

Symptoms:

- Hypertension 80-90%

Paroxysmal (50-60%)/ Continuous (30 %)

- Tachycardia (50-70 %)
- Anxiety (20-40 %)
- Diaphoresis (50-70 %)
- Pallor (40-45 %)
- Weight loss (20-40 %)
- Hyperglycemia (40 %)
- Nausea (40-60 %)

The classic clinical triad of symptoms includes headache, palpitations and sweating

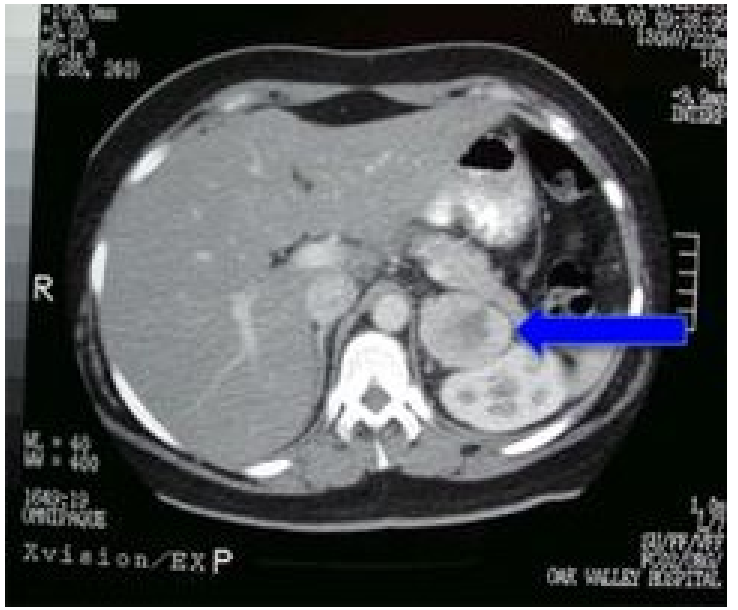
through β-adrenergic stimulation

DIAGNOSIS

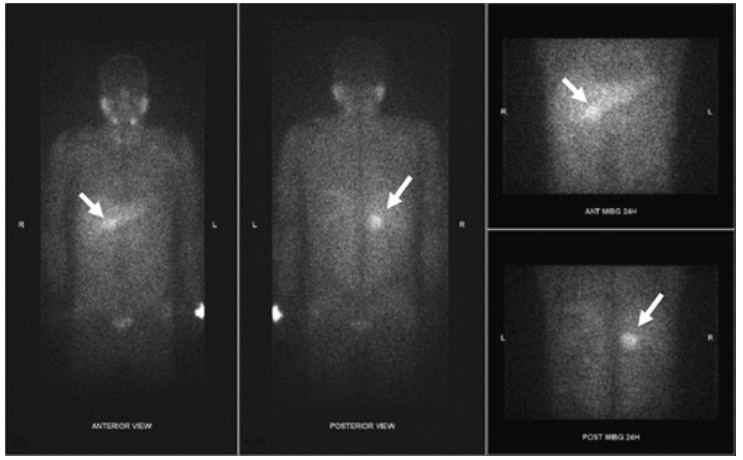
<u>Blood Tests:</u> Metanephrines last much longer and are easier and more accurate to measure than catecholamines.

- **<u>Catecholamines and metanephrines may be measured in the blood or in a 24-hour collection of urine.</u>**
- Depending on the patient's age, family history, and other factors, **plasma (i.e. blood) and/or urine tests will be ordered.**
- **<u>Levels that are at least twice the upper limit of normal mean that the patient is almost certain to have a pheochromocytoma.</u>**

IMAGING TESTS



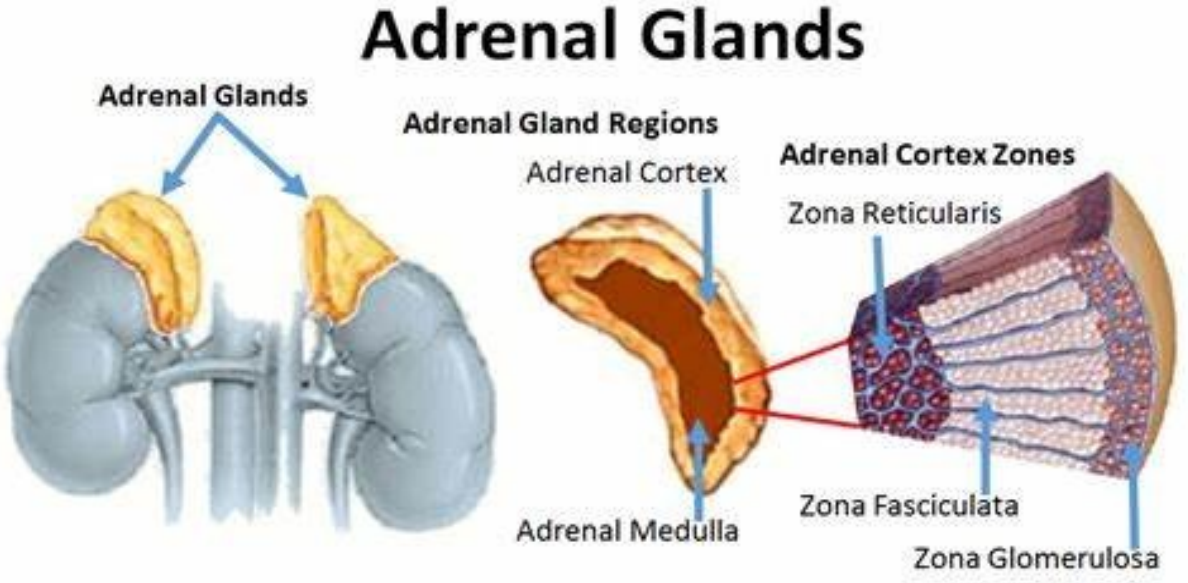
MRI



MIBG

Anyfanti P, Mastrogiannis K, Lazaridis A, Tasios K, Vasilakou D, Kyriazidou A, Aroutsidis F, Pavlidou O, Papoutsopoulou E, Tiritidou A, Kotsis V, Triantafyllou A, Zarifis I, Douma S, Gkaliagkousi E. Clinical presentation and diagnostic evaluation of pheochromocytoma: case series and literature review. Clin Exp Hypertens. 2023 Dec 31;45(1):2132012. doi: 10.1080/10641963.2022.2132012. Epub 2022 Oct 11. PMID: 36218060.

ADRENAL CORTEX HORMONES



1. **Glucocorticoids:** cortisol
2. **Mineralocorticoids:**
   Aldosterone
3. **Androgens (adrenal):**

dehydroepiandrosterone (DHEA)
dehydroepiandrosterone sulfate (DHEA-S)
androstenedione (D4)

HPA axis

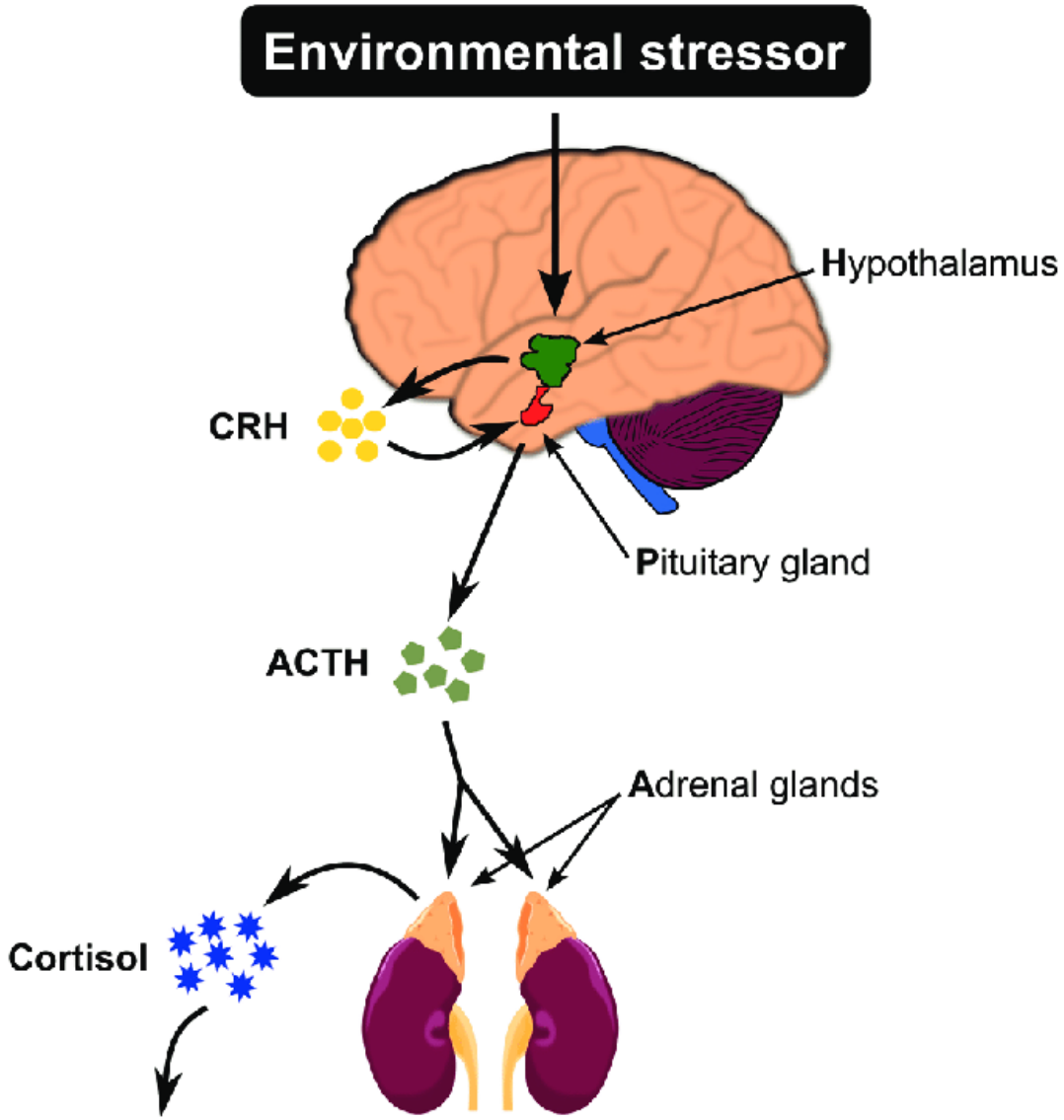
- The secretion of glucocorticoids and adrenal androgens is subject to control of HPA axis.
- The stimulus for secretion is given by **ACTH, excreted after stimulation of adenohypophysis by hypothalamic CRH.**

The secretion of CRH is regulated

1) extrahypothalamic centers operating as pulsators and cause the secretion of CRH by impulses at a 24-hour secretion rate

2) by various stress stimuli but also from

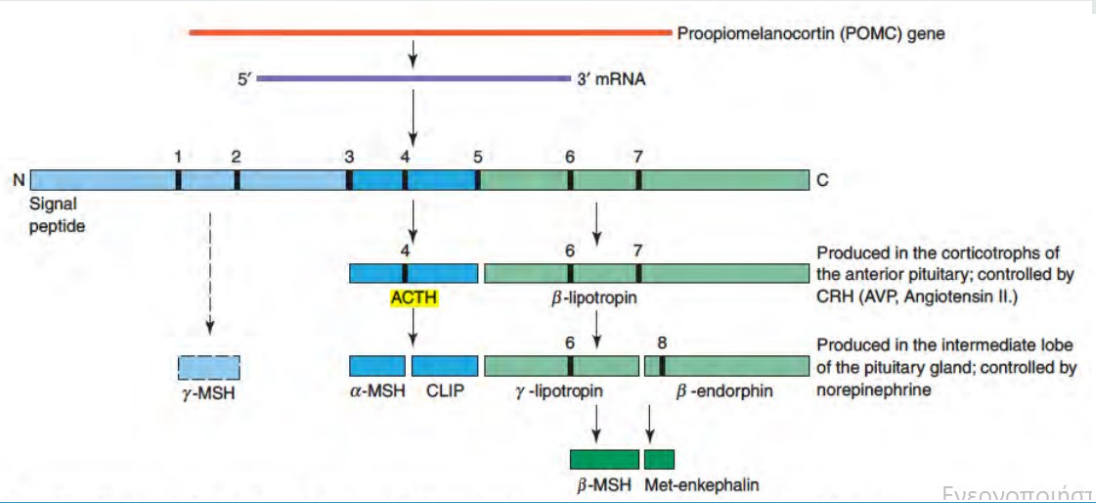
3) Negative feedback system



Negative feedbacks regulation is exercised by glucocorticoids

Proopiomelanocortin Is Precursor for Numerous Hormones

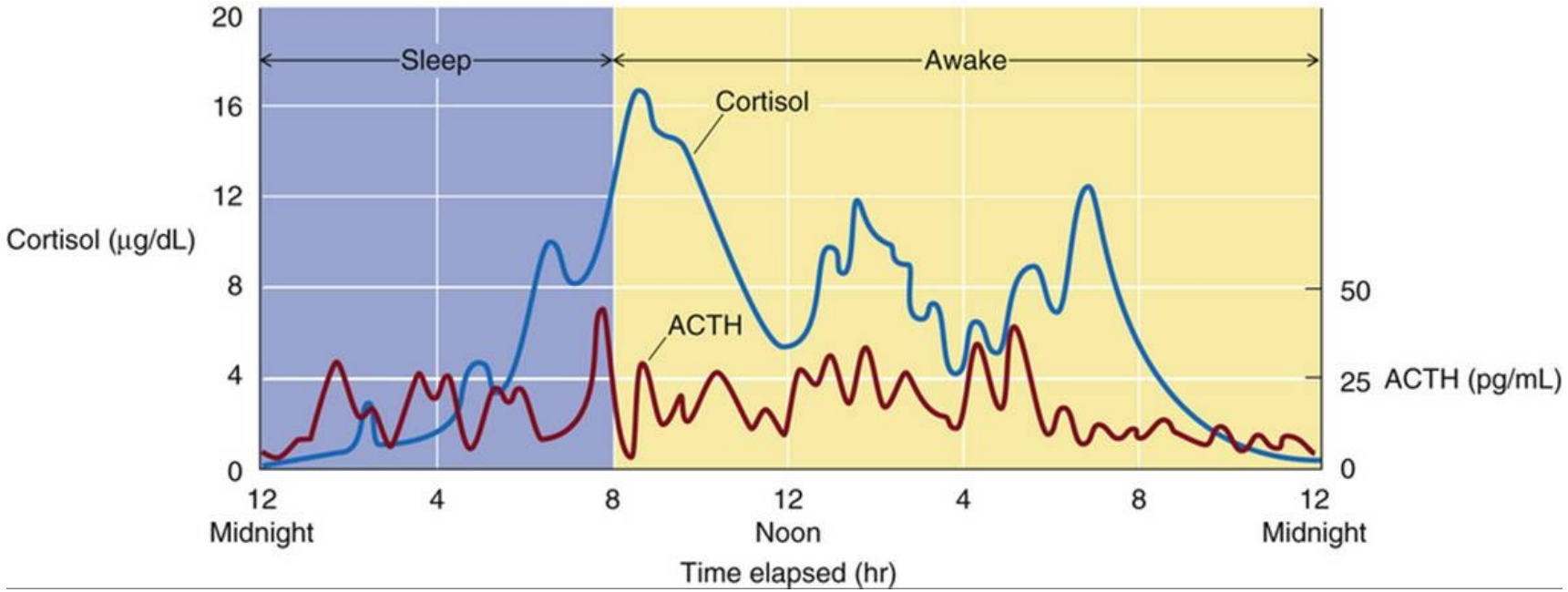
- Proopiomelanocortin is a precursor for several hormones including: ACTH , β-lipotropin, and γ-lipotropin, γ-MSH, a-MSH, CLIP, and β-endorphin, and potentially β-MSH and enkephalins.
- All of these are not expressed simultaneously in a single cell type but are produced in separate cells depending on their content of specific proteases, metabolic controls, and regulators.
- While proopiomelanocortin is expressed in both corticotropes of the anterior pituitary and pars intermedia cells, the stimuli and products are different



CIRCADIAN RYTHM

Cortisol secretion manifests circadian rhythm with fluctuations during the 24h, which reflect proportional fluctuations in ACTH and CRH secretion

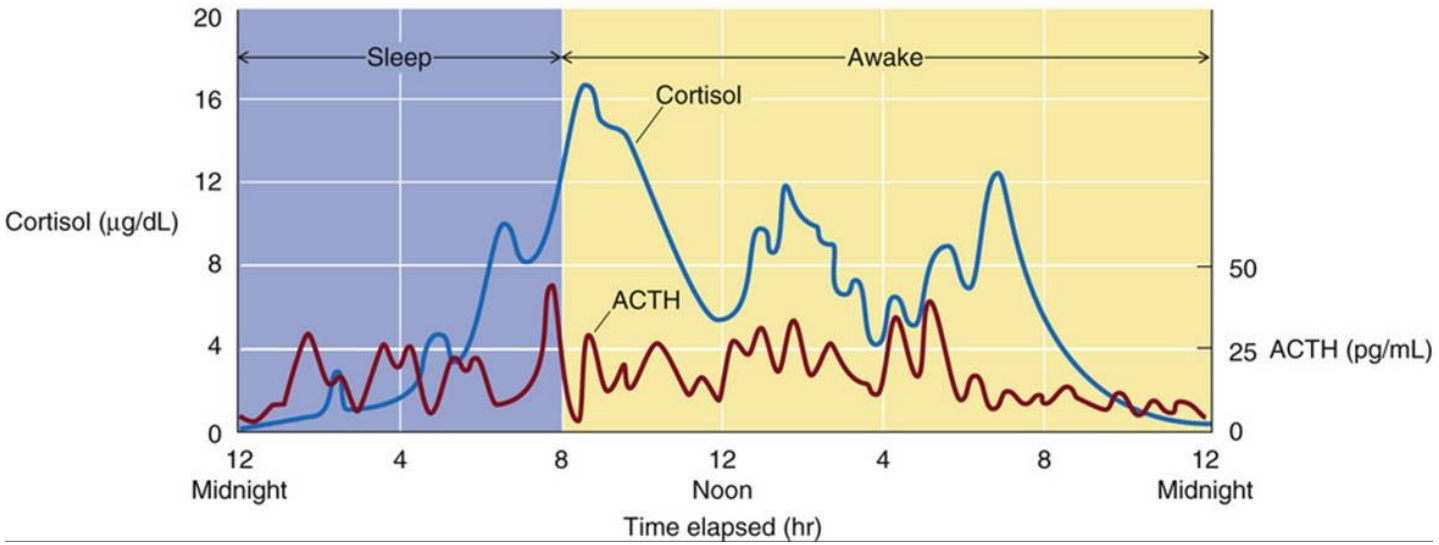
Cortisol is secreted in a pulsatile fashion (i.e. in short bursts) from the adrenal glands, and the time-specific 6.6 fold variation in the size (i.e. amplitude) of these bursts that occur every 60 to 90 minutes creates the circadian rhythms observed in the human



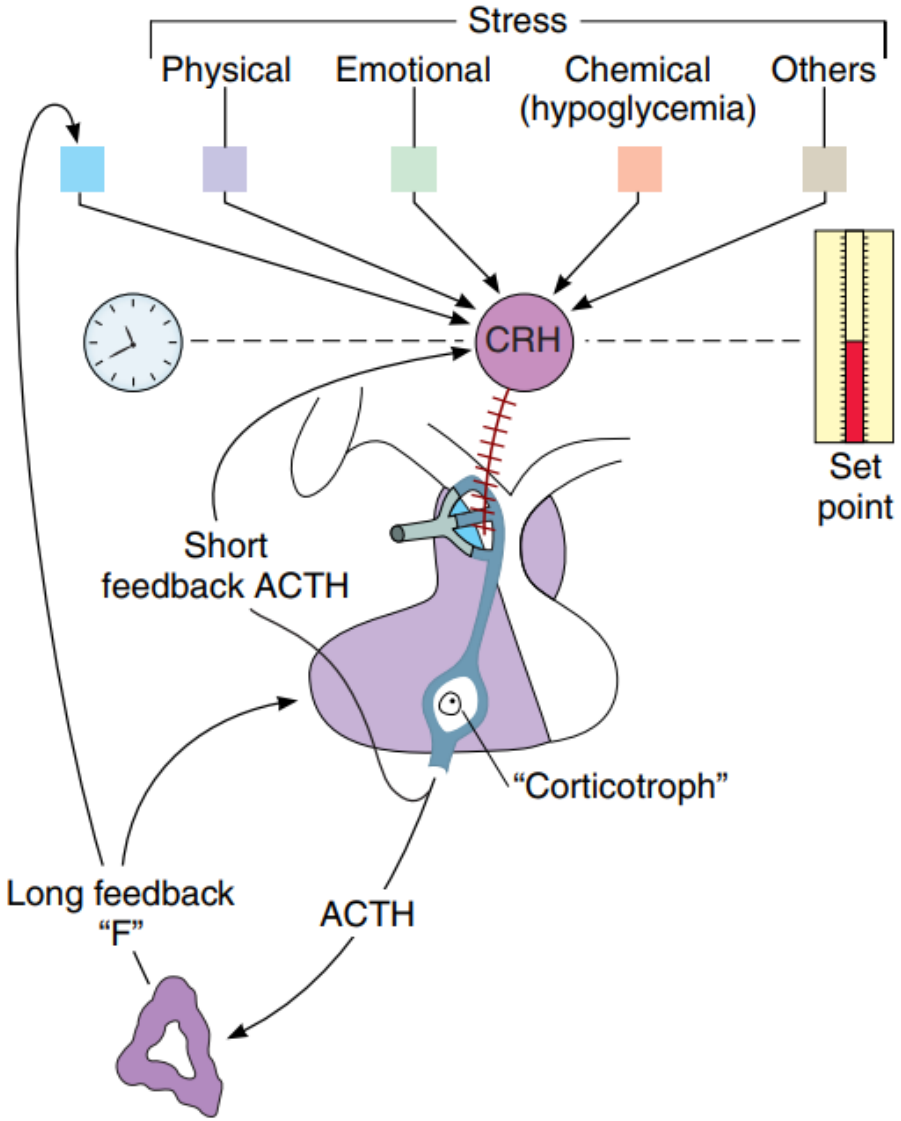
CIRCADIAN RYTHM

Cortisol secretion is low in the late evening and continues to decline
In the first several hours of sleep: **time plasma cortisol levels may be nearly undetectable.**
3rd and 5th hours of sleep: **increase in secretion**
major secretory episodes: begin in the sixth to eighth hours of sleep

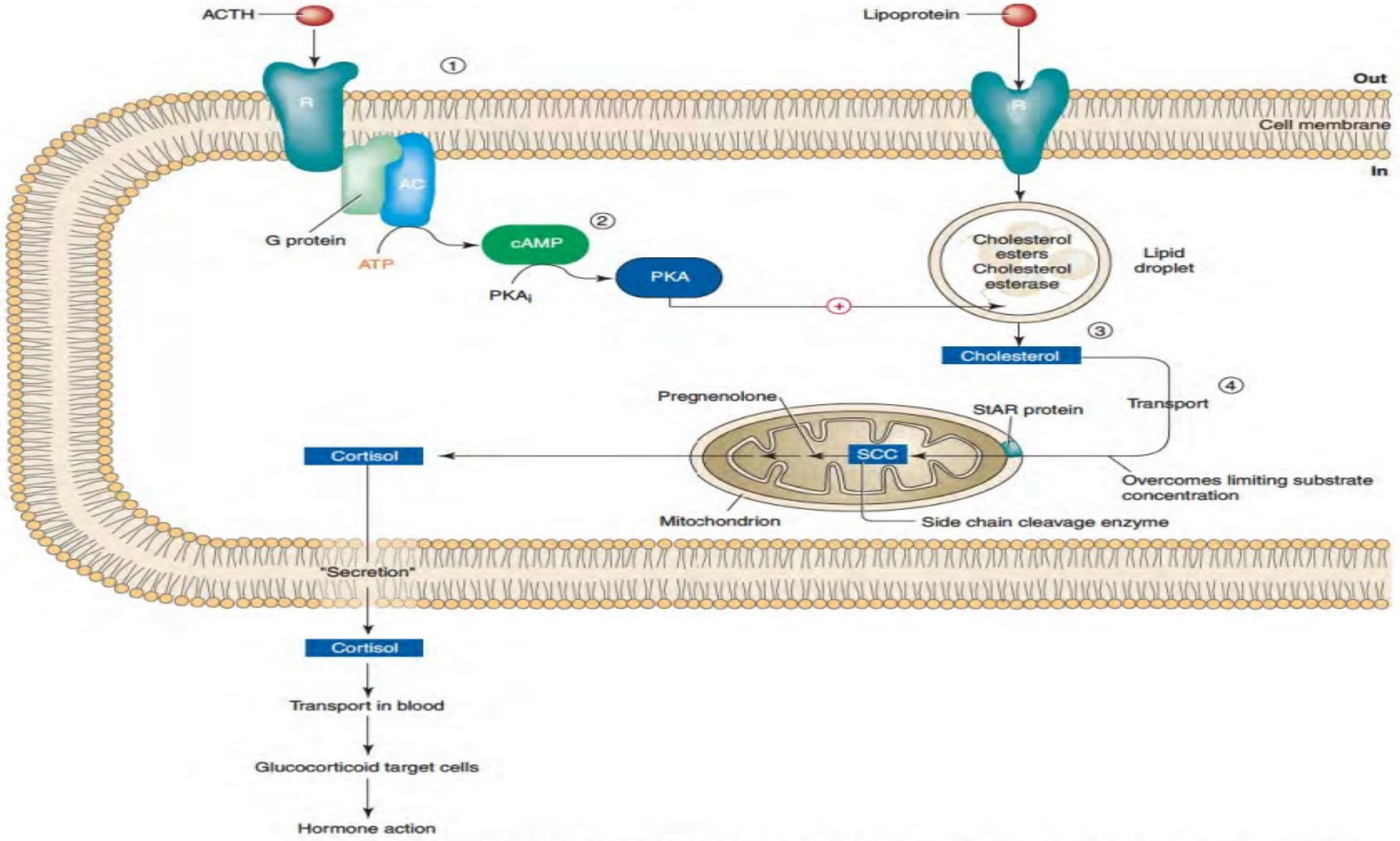
begin to decline as wakefulness occurs



Consistent pattern BUT <u>considerable intra- and inter-individual variability,</u> and the circadian rhythm may be altered by changes in sleep pattern, light-dark exposure, and feeding times- ALSO STRESS/ DISORDERS/ CUSHING SYNDROME/ ALCOHOL/ LIVER DISEASE etc.

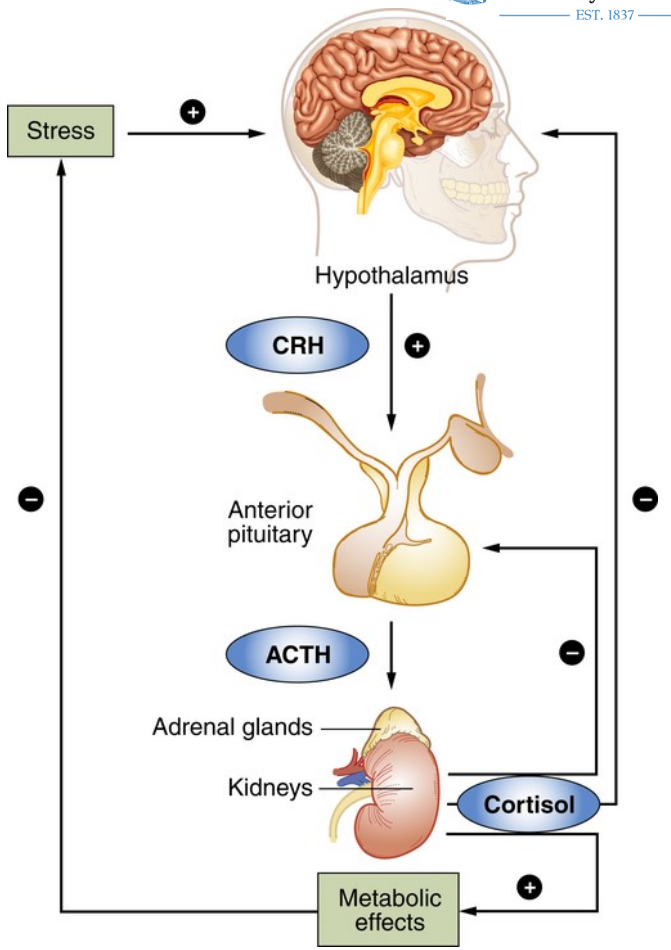


- **The physiologic secretion of ACTH is mediated by CRH.**
- **CRH stimulates ACTH in a pulsatile manner**: diurnal rhythmicity causes a peak before awakening and a decline as the day progresses. During night, the quantity of ACTH is twice to thrice as high as during daytime
- **ACTH secretion also increases in response to feeding** in both humans and animals.
- Physical, emotional, and chemical stresses such as pain, trauma, hypoxia, acute hypoglycemia, cold exposure, surgery, depression, and interleukin-1 and vasopressin administration have all been shown to **stimulate ACTH and cortisol secretion.**
- **The increase in ACTH levels during stress is mediated by vasopressin as well as CRH.**
- **Negative feedback of cortisol and synthetic glucocorticoids on ACTH secretion occurs at both the hypothalamic and pituitary levels**


ACTH
Lipoprotein
1
R
R
Out
Cell membrane
In
AC
G protein
ATP
2
cAMP
PKA
PKA$_i$
Cholesterol esters
Cholesterol esterase
Lipid droplet
+
3
Cholesterol
4
Transport
Pregnenolone
StAR protein
SCC
Cortisol
Overcomes limiting substrate concentration
Mitochondrion
Side chain cleavage enzyme
"Secretion"
Cortisol
Transport in blood
Glucocorticoid target cells
Hormone action

• Glucocorticoids

- **Steroid hormones produced from the cortex of adrenal glands.**
- **Pivotal role in the glucose, protein, and fat metabolism of the body.**
- They originate from **steroid precursors** and are synthesized primarily in the **zona fasciculata of the adrenal cortex.**
- Their medical significance arises from their **anti-inflammatory, anti-allergic, and immune-suppressive role in the body**



The essential glucocorticoid in the body is cortisol.
It is released in a diurnal circadian pattern, with the highest levels released at around 8 AM and its lowest levels between midnight and 4 AM.

Form of stress (physical, psychological) is an acute inducer of **cortisol** secretion: the stress hormone of the body.

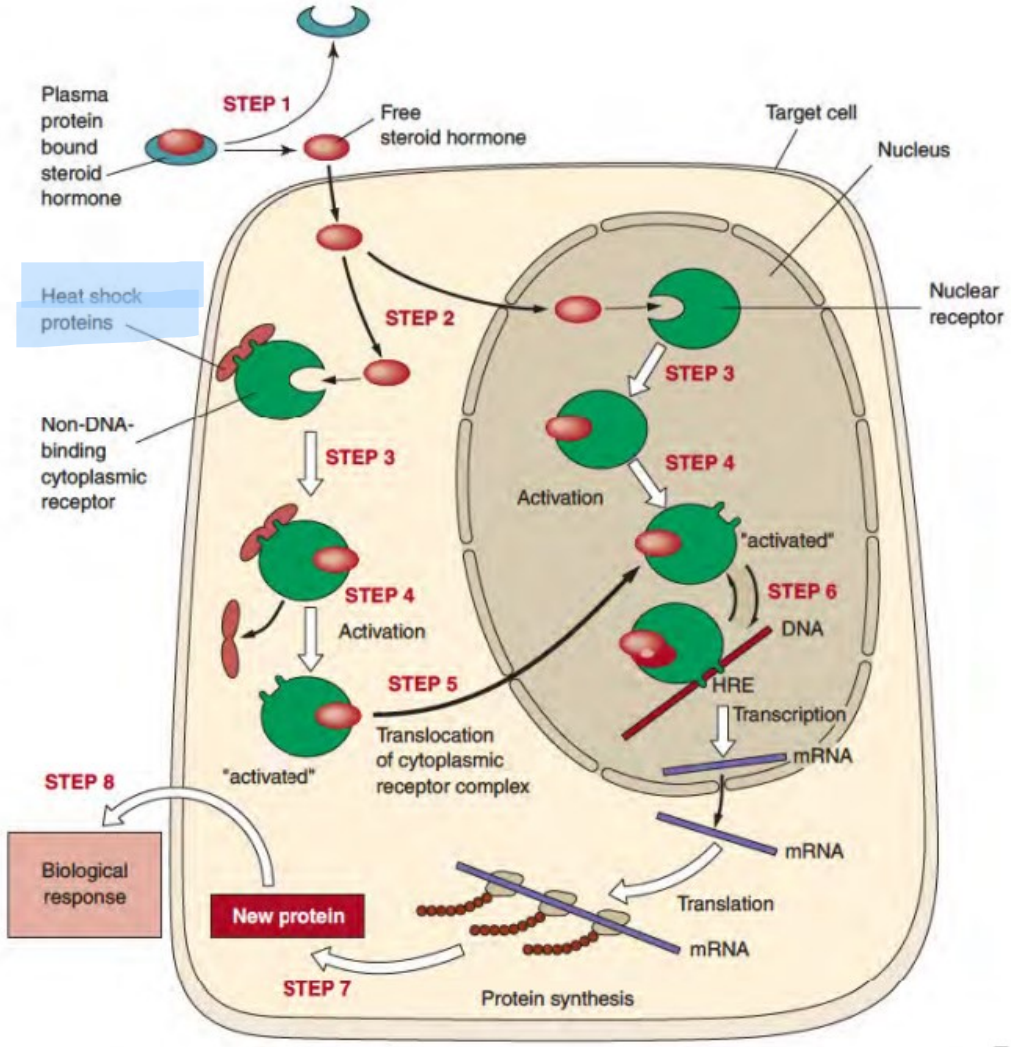
Receptors for steroids and receptors for nonsteroid hormones (i.e., thyroid hormone, retinoic acid, and Vitamin D3) are located intracellularly (in the cytoplasm) or within the nucleus

Model of steroid hormone action- Cortisol

Glucocorticoid receptor binding happens intracellularly /in the cytoplasm or directly to the nucleus

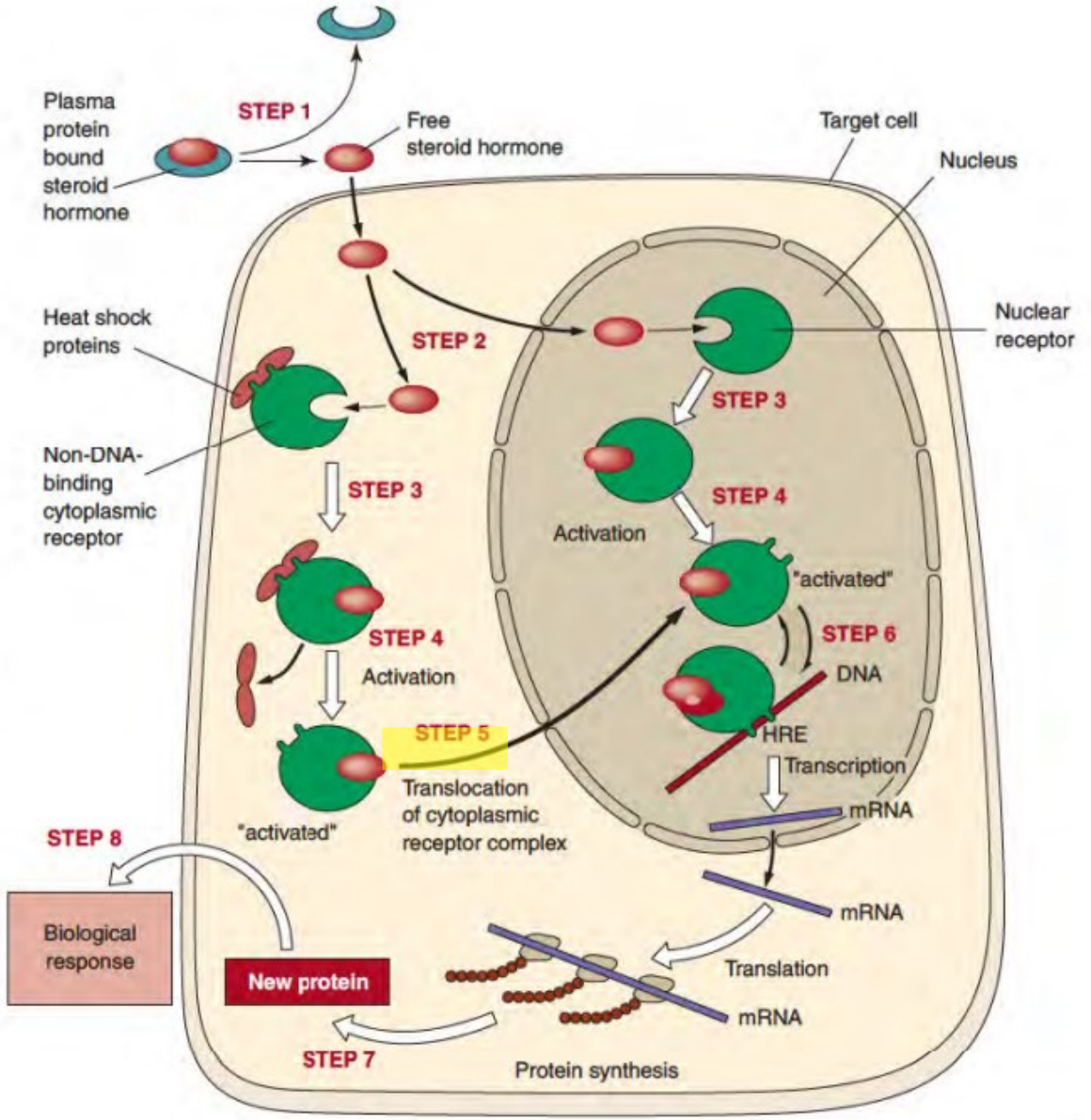
✓ In the cytoplasm the receptor is associated with heat shock proteins and is inactivated.

✓ **3+4 Cortisol binding results in the release of HSP and the receptor's activation.**



5. The cortisol-receptor complex enters the nucleus and connects to **specific DNA sequences, the HRE (Hormone Response Elements)**

✓ acts as a **transcription factor that promotes or does not promote gene transcription, regulating protein synthesis**



Glucocorticoids-Regulators

Metabolic Effects:

- Stimulation of glucose production in cells, particularly in the liver.
- Stimulation of fat breakdown in adipose (fat) tissues.
- Inhibition of glucose and fat storage in cells.

Anti-Inflammatory Effects:

Suppress the production of proteins involved in inflammation /suppress inflammation by activating a group of enzymes known as lipocortins.

Brain Effect:

Glucocorticoid excess leads to euphoria and psychosis, whereas deficiency results in lethargy, apathy, and depression.

Immunosuppressant Effect:

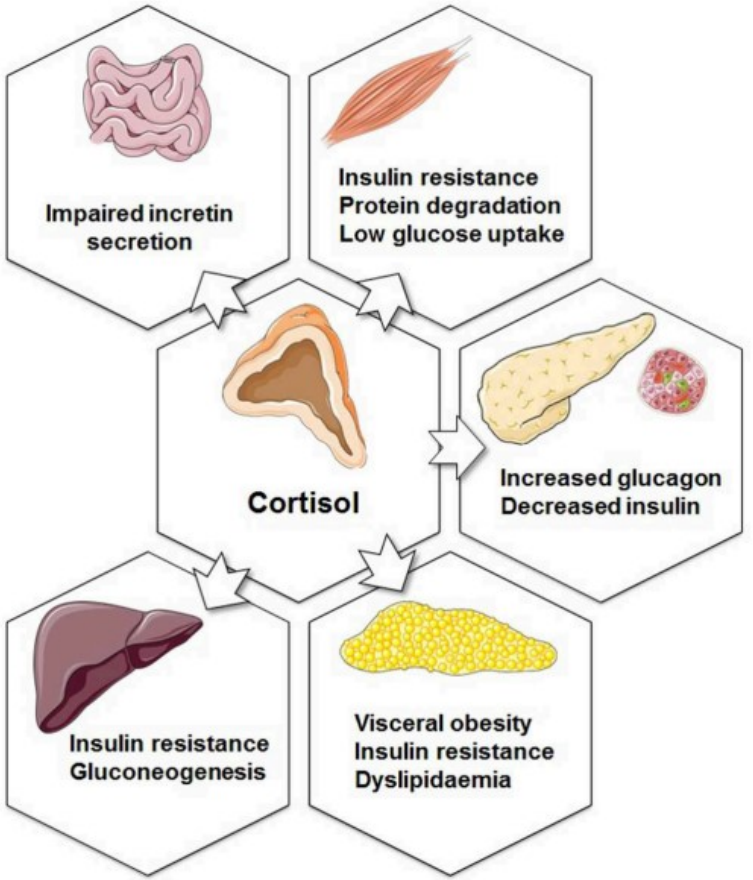
Inhibit certain aspects of leukocyte function

Bone Effect:

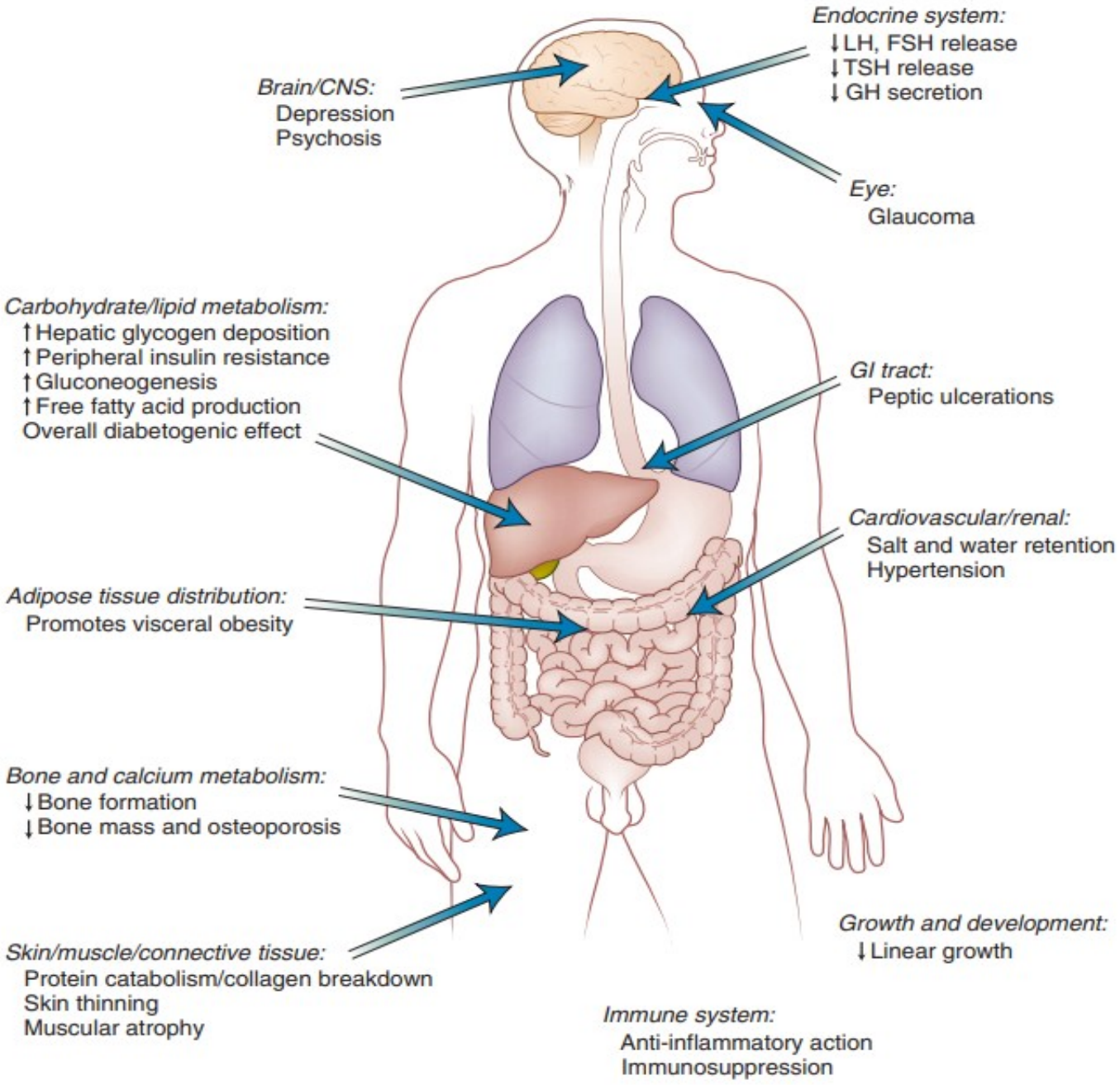
Inhibit osteoblast function: osteoporosis (avascular necrosis)

Decrease calcium absorption in the gastrointestinal system

Increase the urinary excretion of calcium



Akalestou, Elina & Genser, Laurent & Rutter, Guy. (2020). Glucocorticoid Metabolism in Obesity and Following Weight Loss. Frontiers in Endocrinology. 11. 10.3389/fendo.2020.00059.

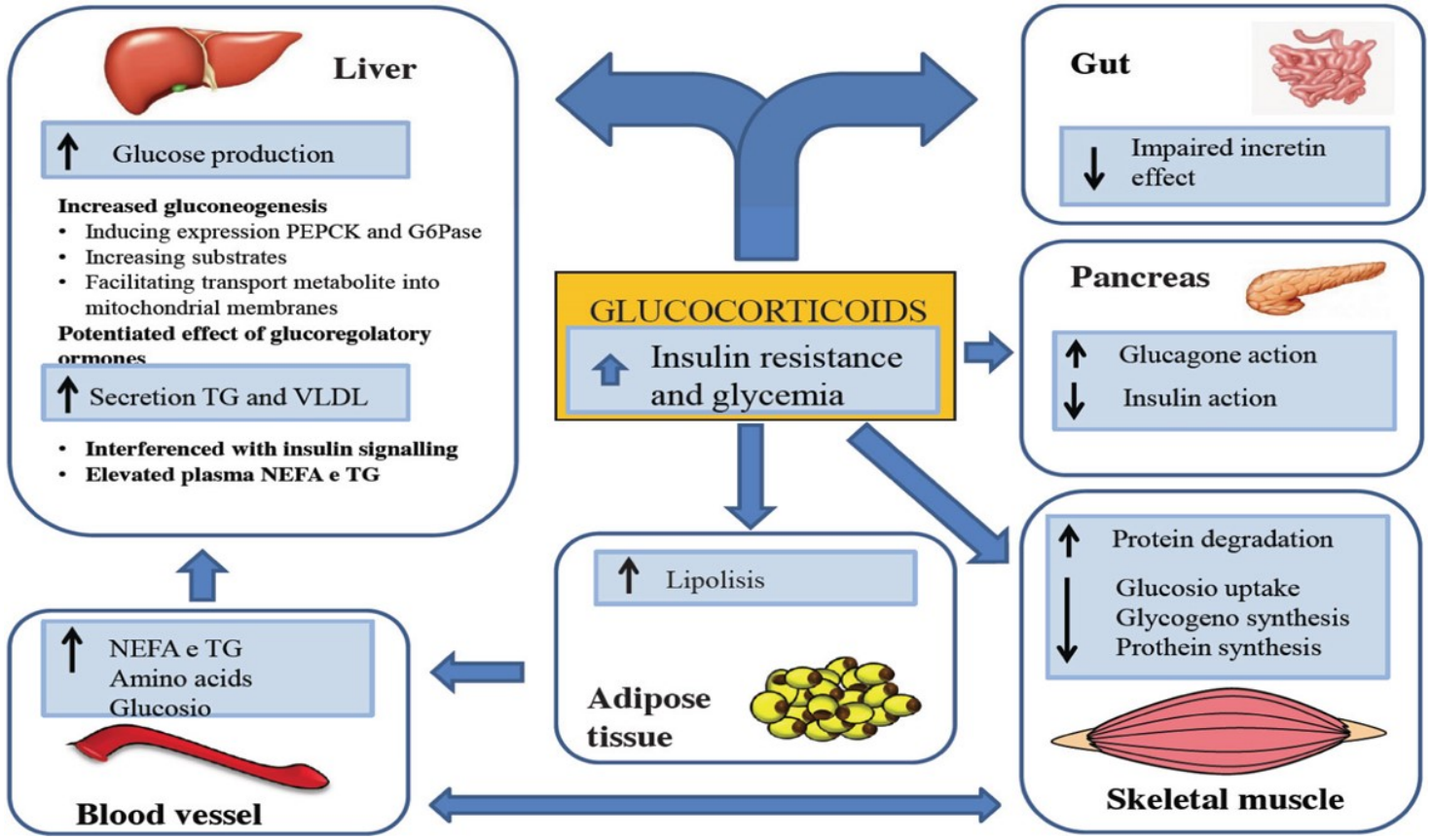


The principal sites of action of glucocorticoids in humans, highlighting some of the consequences of glucocorticoid excess

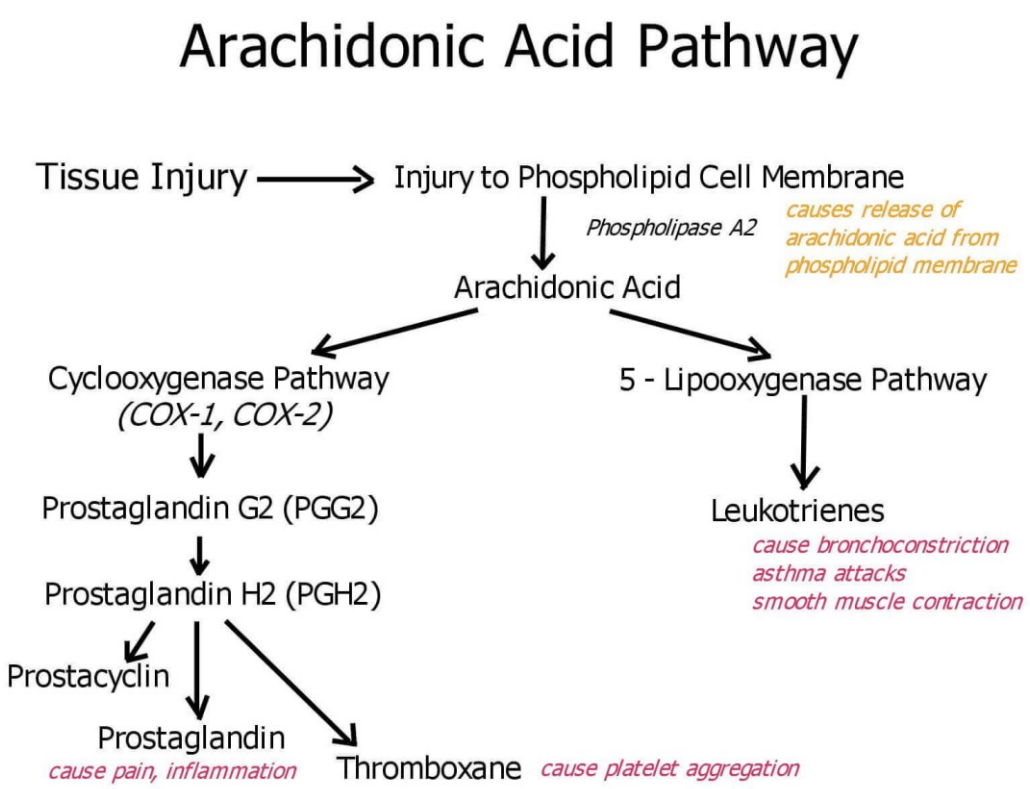
CORTISOL DEFICIENCY

Excess glucocorticoid levels result in profound <u>metabolic disturbances of intermediate metabolism</u>

abdominal obesity,
insulin resistance and dyslipidaemia
insulin sensitivity,
decreased energy expenditure
decreased protein loss



Hyperglycemia and Diabetes Induced by Glucocorticoids in Nondiabetic and Diabetic Patients: Revision of Literature and Personal Considerations
Author(s): Ceccarelli Elena*, Mattaliano Chiara, Brazzi Angelica, Marinetti A. Chiara, Nigi Laura, Chirico Chiara, Corallo Claudio, Fioravanti Antonella and Giordano NicolaVolume 19, Issue 15, 2018



Glucocorticoids: anti-inflammatory- inhibit prostaglandin production.

1. Glucocorticoid- receptor complexes induce annexin-1 (or lipocortin), a 40-kD protein , which inhibits membrane phospholipase A2, and hence the release of arachidonic acid for prostaglandin synthesis.

2. Glucocorticoids also inhibit expression of cyclooxygenase (COX) that generates prostaglandins and related compounds.

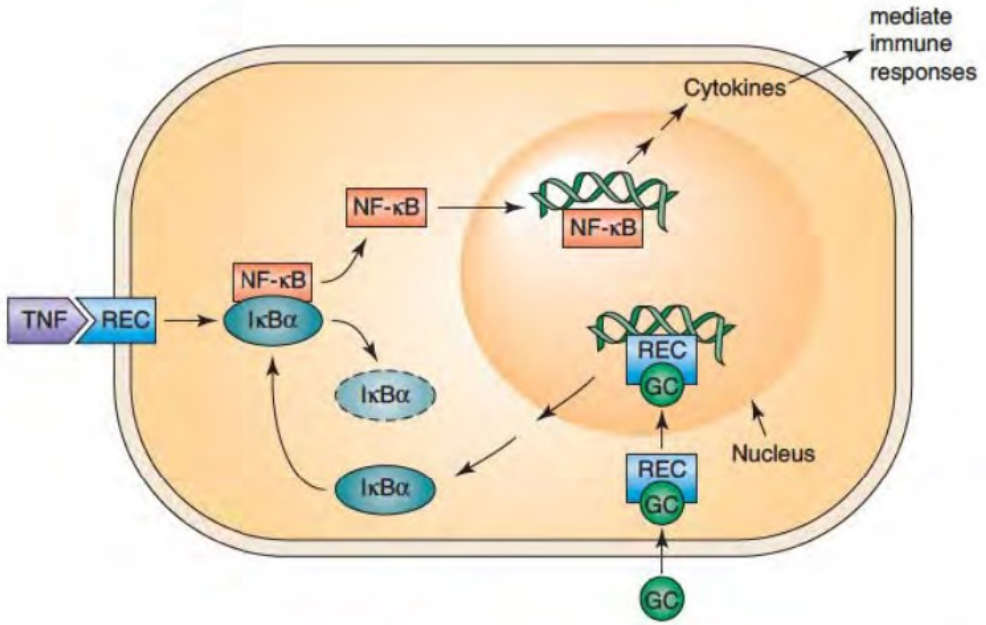
COX-1 is constitutively expressed and produces prostaglandins under noninflammatory conditions.

COX2 is induced in inflammatory cells and suppression of its synthesis by glucocorticoids accounts for a major part of their anti-inflammatory effects

Glucocorticoids interfere with the transcription factor nuclear factor kappa B (NF-KB).
Stimulation: causes **phosphorylation of IKBa which leads to ubiquitination and subsequent degradation via proteasomes.**

Degradation releases NF-KB, which has been trapped in the cytoplasm in an inactive form, from this complex and **it migrates into the nucleus.**

In the nucleus it induces genes for cytokines: activates immune cells, cell adhesion molecules that draw immune cells into inflammatory sites.



Glucocorticoids suppress this immune cell activation by inducing lKBa gene transcription and ensuring that NF-KB is retained in the cytoplasm in its inactive form under conditions where it should migrate into the nucleus and induce gene transcription .

Cushing Syndrome

Elevated cortisol levels- HYPERCORTISOLISM

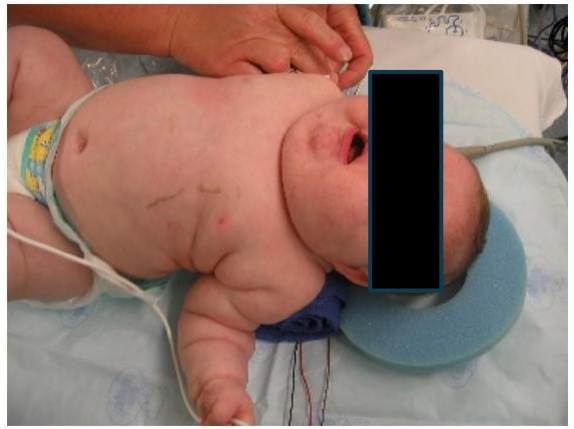
There are **two main etiologies** of Cushing syndrome:

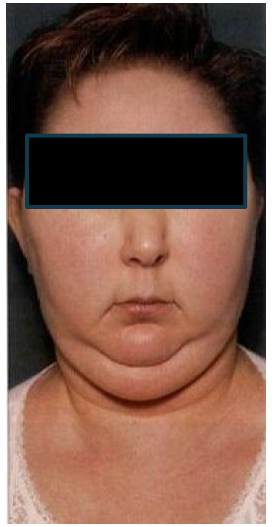
endogenous hypercortisolism:

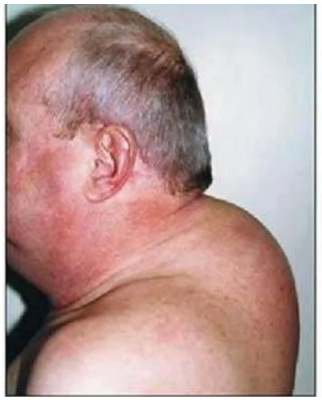
- increased ACTH release- ectopic ACTH release
- hyperplasia of CRH- or ACTH-secreting cells
- primary cortisol-releasing adrenal tumors- Adrenal hyperplasia, adenoma, and carcinoma

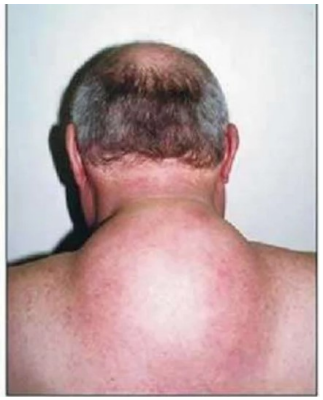
exogenous hypercortisolism (iatrogenic):

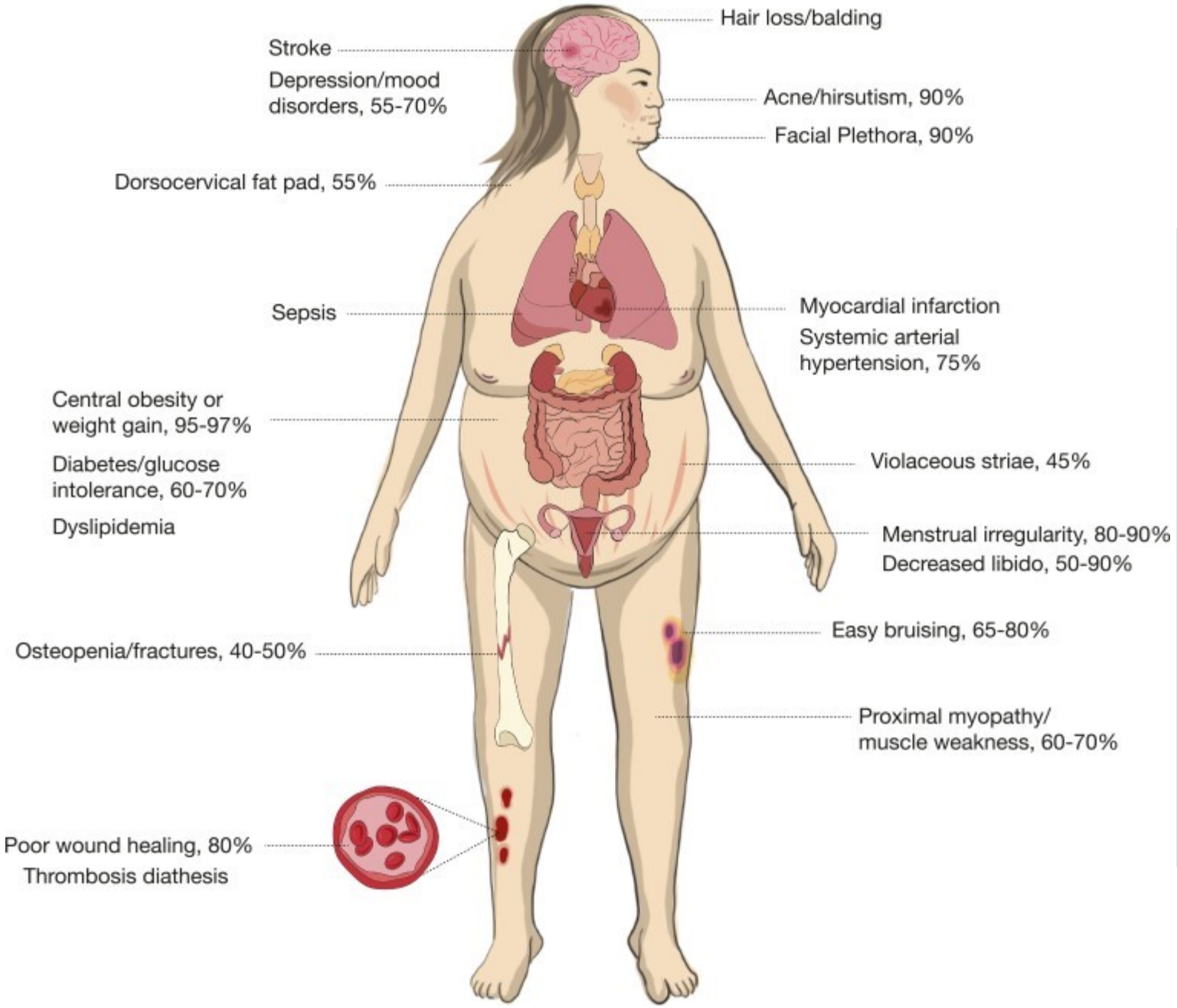
- prolonged use of glucocorticoids











Cushing Syndrome

Cushing syndrome is associated with:
hyperglycemia,
protein catabolism,
immunosuppression,
hypertension,
weight gain,
neurocognitive changes,
mood disorders

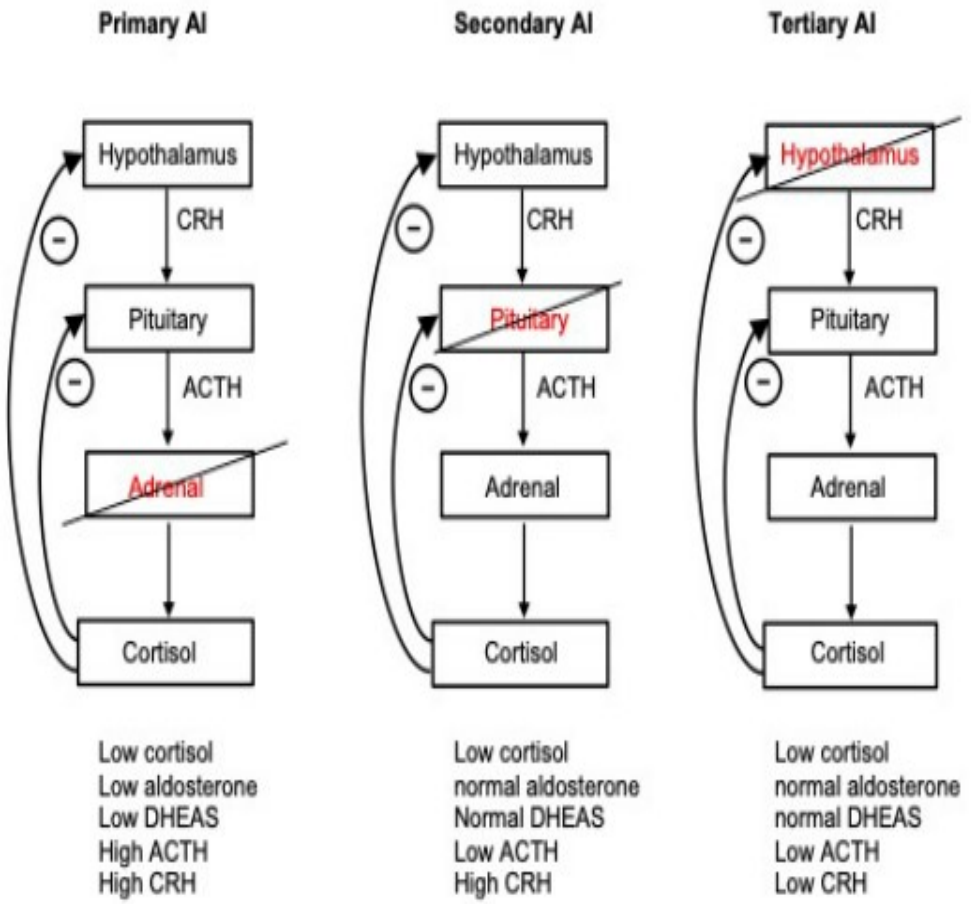
Savas M, Mehta S, Agrawal N, van Rossum EFC, Feelders RA. Approach to the Patient: Diagnosis of Cushing Syndrome. J Clin Endocrinol Metab. 2022 Nov 23;107(11):3162-3174. doi: 10.1210/clinem/dgac492. PMID: 36036941; PMCID: PMC9681610.

What causes adrenal insufficiency?

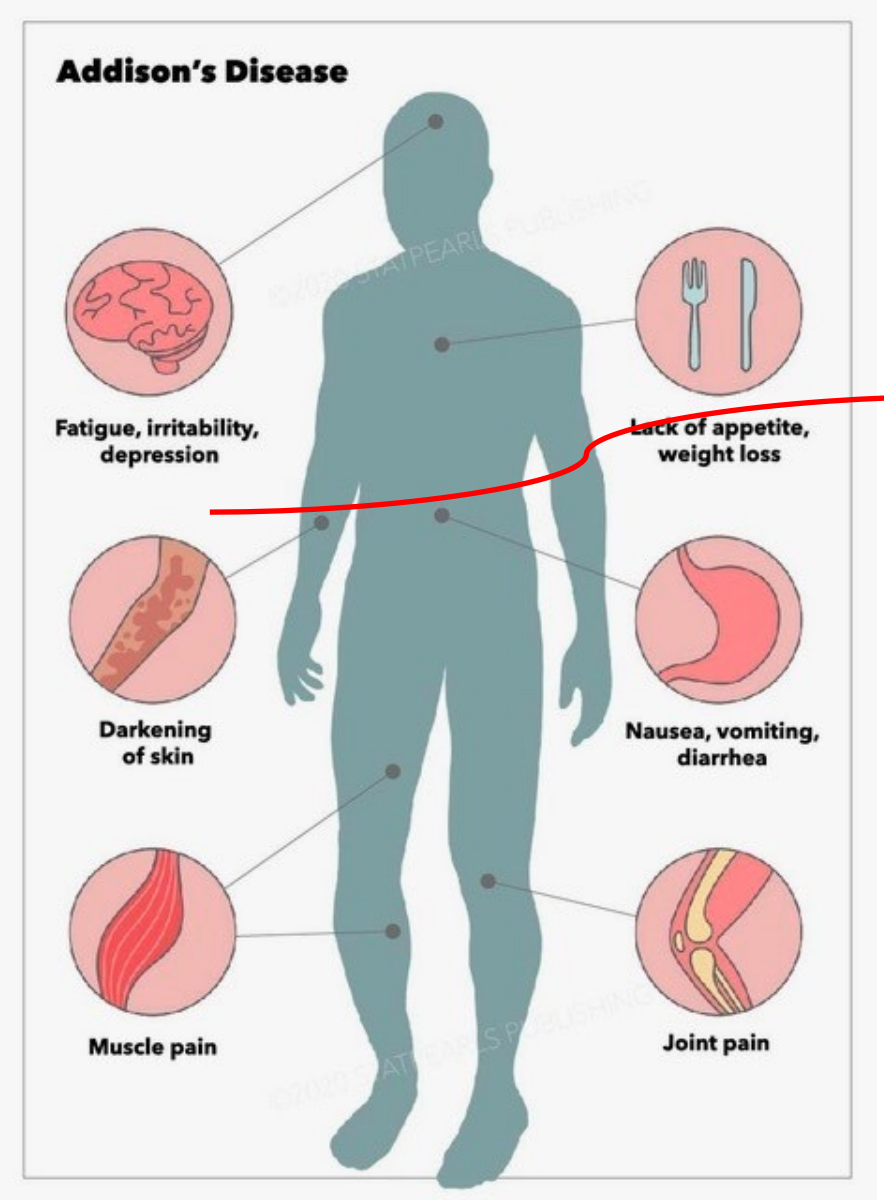
Primary adrenal insufficiency (PAI)- Addison's Disease
Adrenal glands are damaged.
Not enough cortisol/ aldosterone
Rare, at any age, women more frequently than men

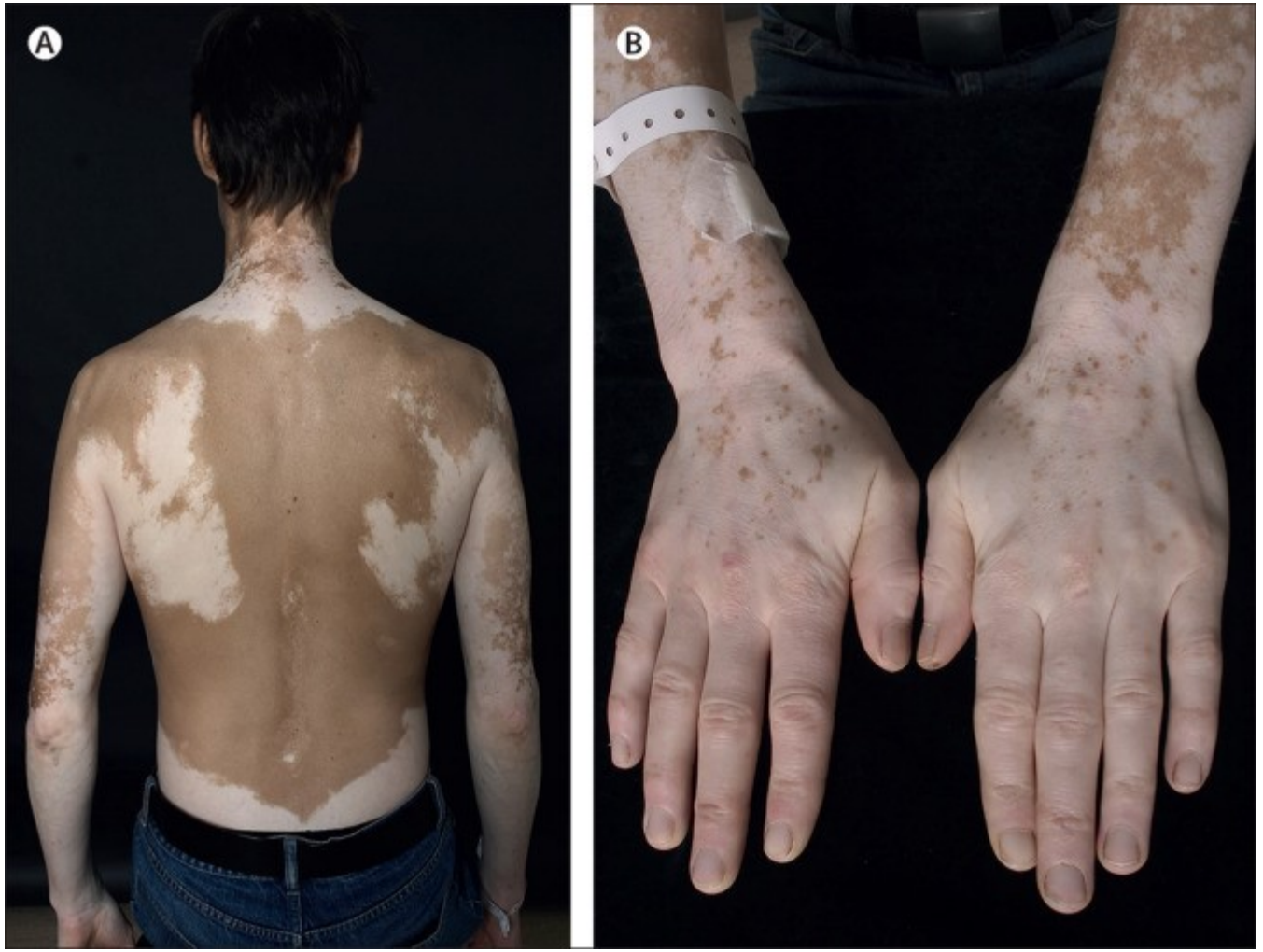
Secondary adrenal insufficiency (SAI)
Pituitary gland: not enough ACTH
Not enough cortisol, normal aldosterone
More common, prevalence: 150–280 per million , more common in women than men.

Tertiary adrenal insufficiency (TAI)
Defect at hypothalamic level, mostly caused by **exogenous steroid treatment.** Any disease involving the hypothalamus that interferes with **corticotropin-releasing hormone (CRH) secretion will result in TAI**



Kumar R, Wassif WS Adrenal insufficiency
Journal of Clinical Pathology 2022;**75:**435-442





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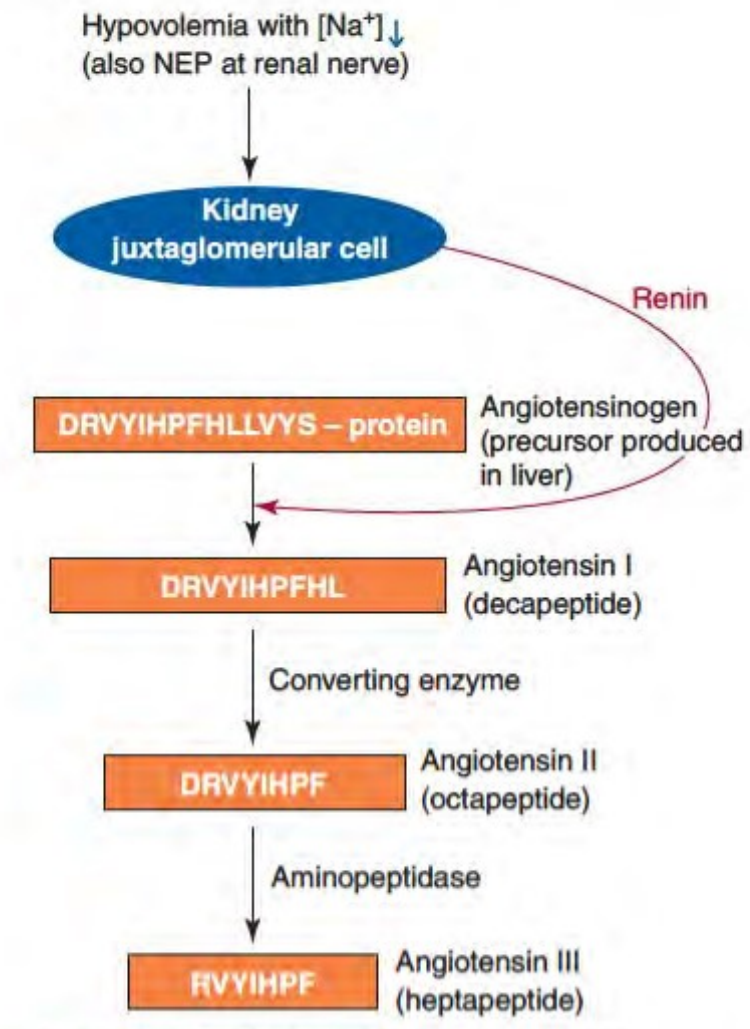
Mineralocorticoids

A major driving force for aldosterone biosynthesis is angiotensin II, which is generated by the renin-angiotensin system

The **signal** for **aldosterone secretion** is generated under conditions when blood Na^+ concentration and blood pressure (blood volume) need to be increased.

Hypovolemia (rise in serum K^+ concentration), stress, Hypervolemia (increase blood volume)



Mineralocorticoids

Promote sodium reabsorption in transporting epithelia of the kidneys, salivary glands, and large intestine.

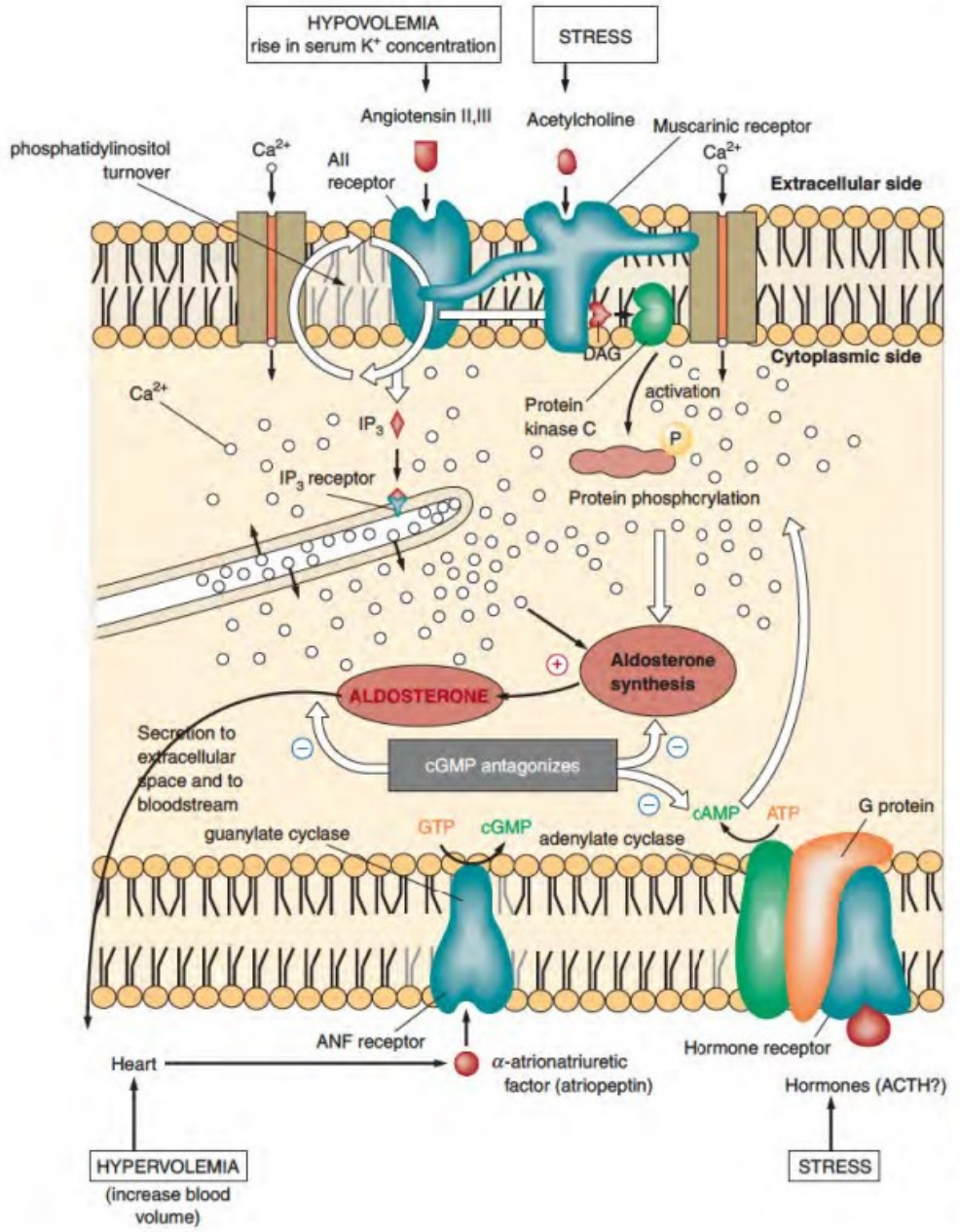
Sodium reabsorption is followed by passive reabsorption of water.

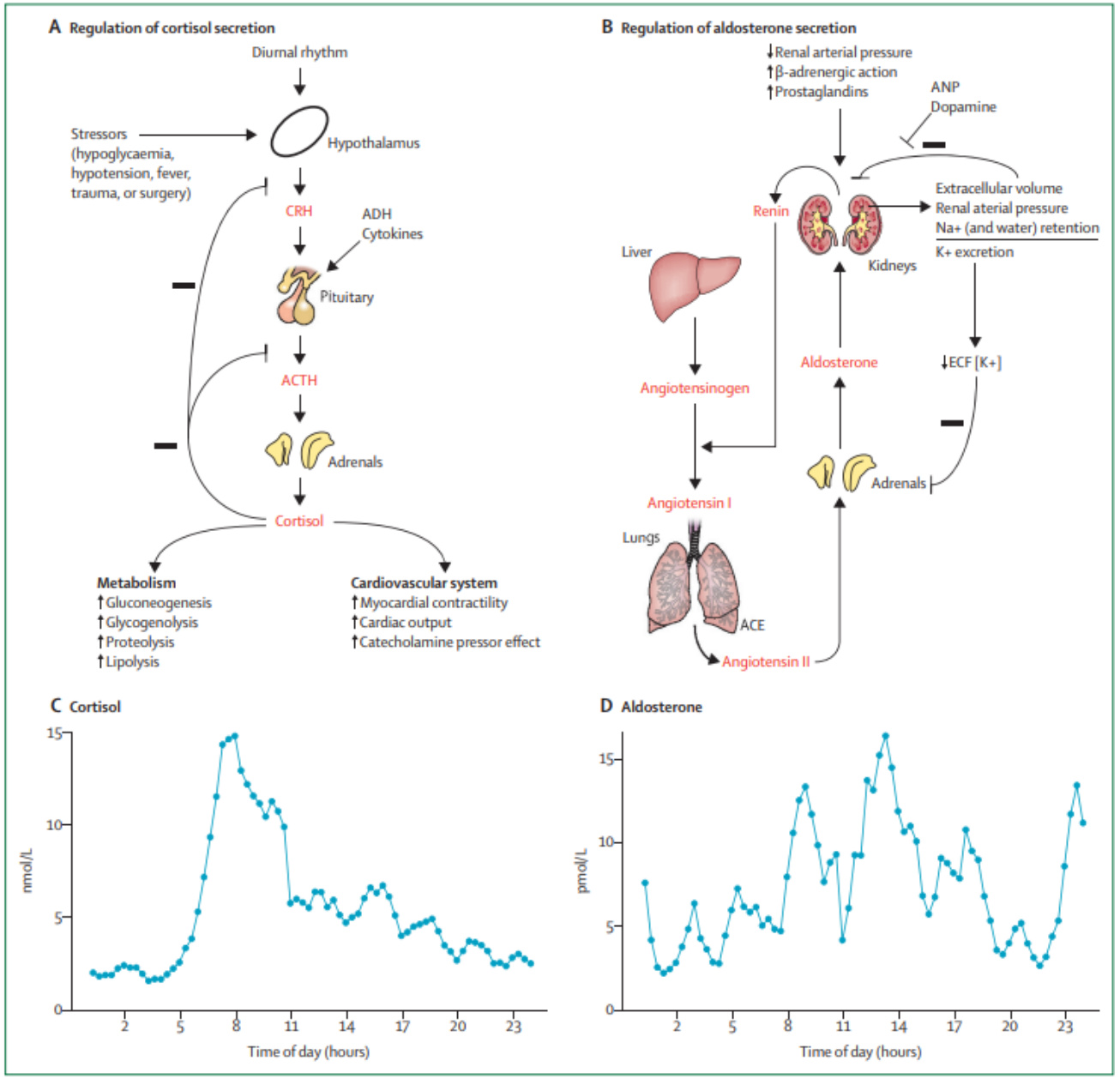
Circulating aldosterone concentrations rise in response to low blood volume or sodium depletion under control of the renin-angiotensin system (RAS).

The kidneys release renin, which converts angiotensinogen to angiotensin I.

Angiotensin I is then cleaved by angiotensin-converting enzyme (ACE) to active angiotensin II.

Angiotensin II stimulates mineralocorticoid production by the zona glomerulosa of the adrenals.





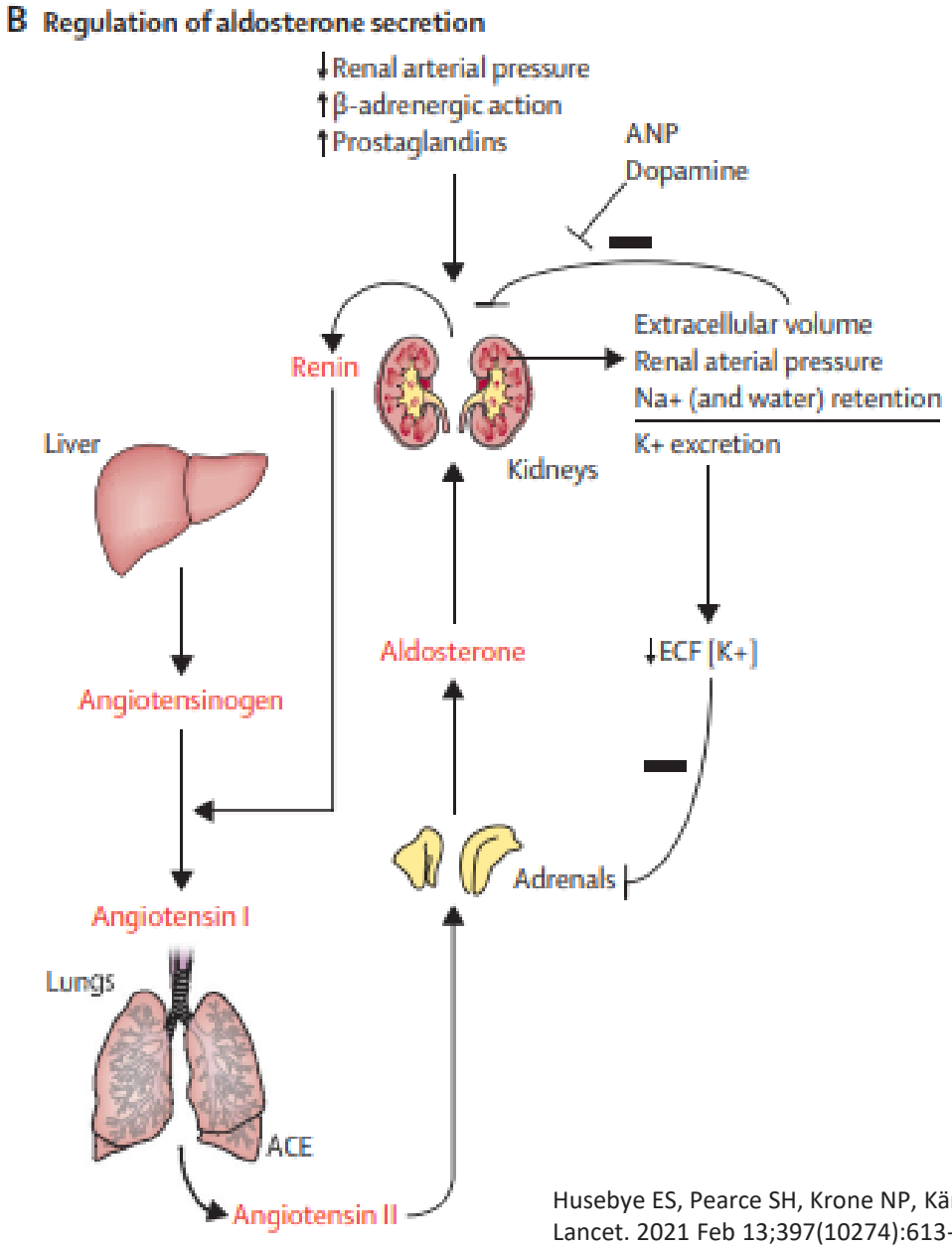
Adrenal steroid secretion is tightly regulated at multiple levels

The hypothalamic–pituitary–adrenal axis regulates cortisol production in response to light, stress,

A robust, but adaptable, circadian and ultradian cortisol rhythm, characterised by secretory bursts every 60–90 min

Aldosterone production is mainly regulated by the renin–angiotensin system, but the HPA axis also causes circadian variation of aldosterone

Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet. 2021 Feb 13;397(10274):613-629. doi: 10.1016/S0140-6736(21)00136-7. Epub 2021 Jan 20. PMID: 33484633.

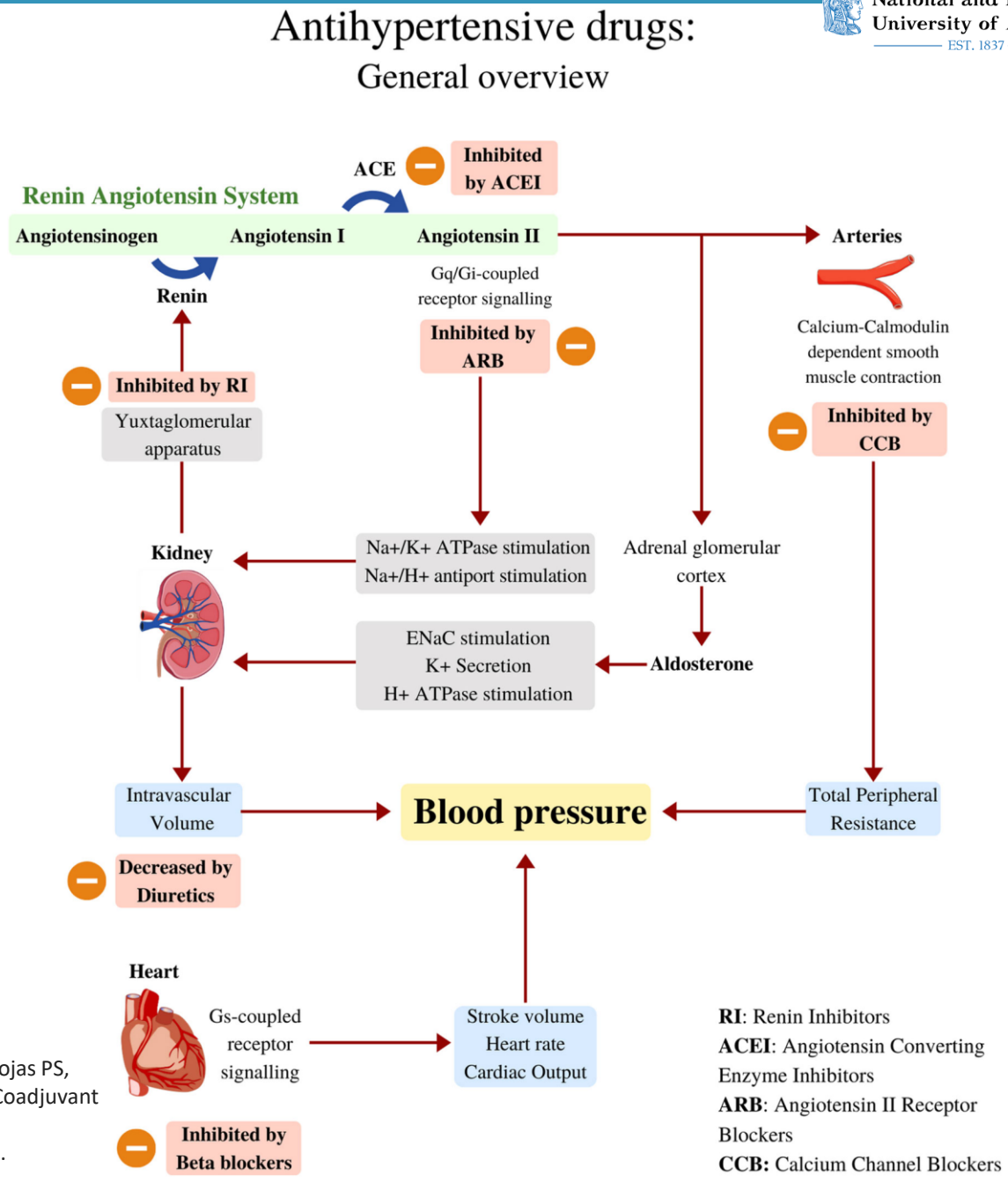


The renin-angiotensin-aldosterone pathway, also known as the renin-angiotensin system (RAS), is a complex physiological mechanism in the human body that **helps regulate blood pressure, fluid balance, and electrolyte homeostasis. It plays a crucial role in maintaining overall cardiovascular and renal health**

Dysregulation of this pathway can contribute to various medical conditions, including hypertension (high blood pressure), congestive heart failure, and kidney diseases

Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet. 2021 Feb 13;397(10274):613-629. doi: 10.1016/S0140-6736(21)00136-7. Epub 2021 Jan 20. PMID: 33484633.

Antihypertensive drugs are medications designed to lower high blood pressure (hypertension).



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Hyperaldosteronism

Excessive production of ALDOSTERONE ➡ Balances potassium and sodium in the body

- **Primary hyperaldosteronism:**

excess production: zona glomerulosa: presents as a primary tumor in the gland known as **Conn syndrome** or bilateral adrenal hyperplasia.

- **Secondary hyperaldosteronism**

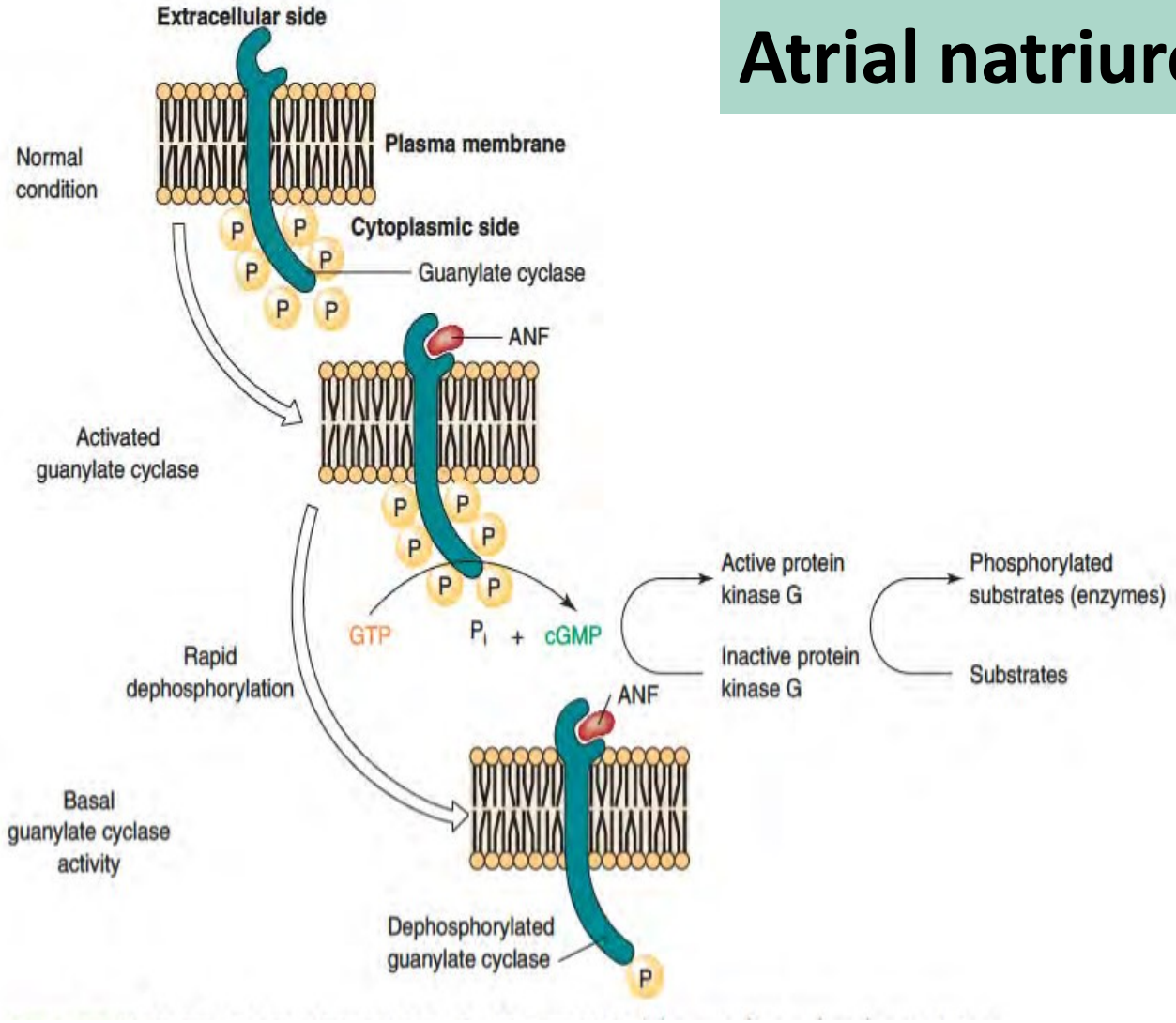
occurs due to excessive activation of the renin-angiotensin-aldosterone system (RAAS). **This activation can be due to a renin-producing tumor, renal artery stenosis etc.**

Primary hyperaldosteronism is an important and increasingly prevalent cause of hypertension that is characterized by UNREGULATED ALDOSTERONE EXCESS

90% of primary hyperaldosteronism cases are attributable to either idiopathic adrenal hyperplasia or aldosterone-producing adenomas.

This results in:
low renin levels
more sodium and less potassium
elevated blood pressure

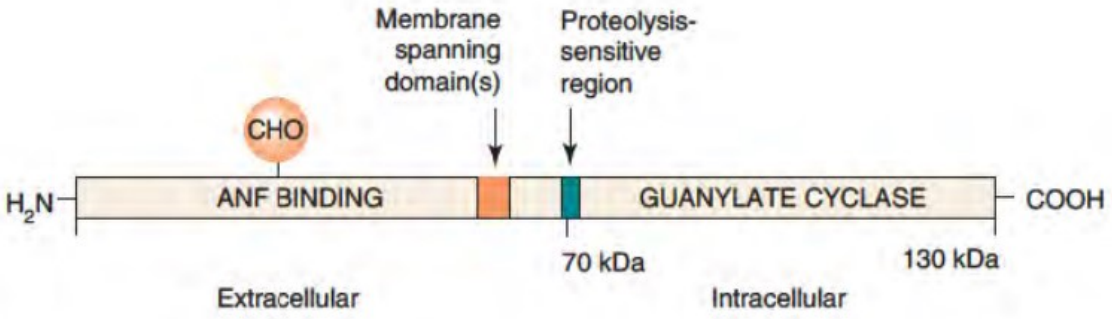
Atrial natriuretic factor



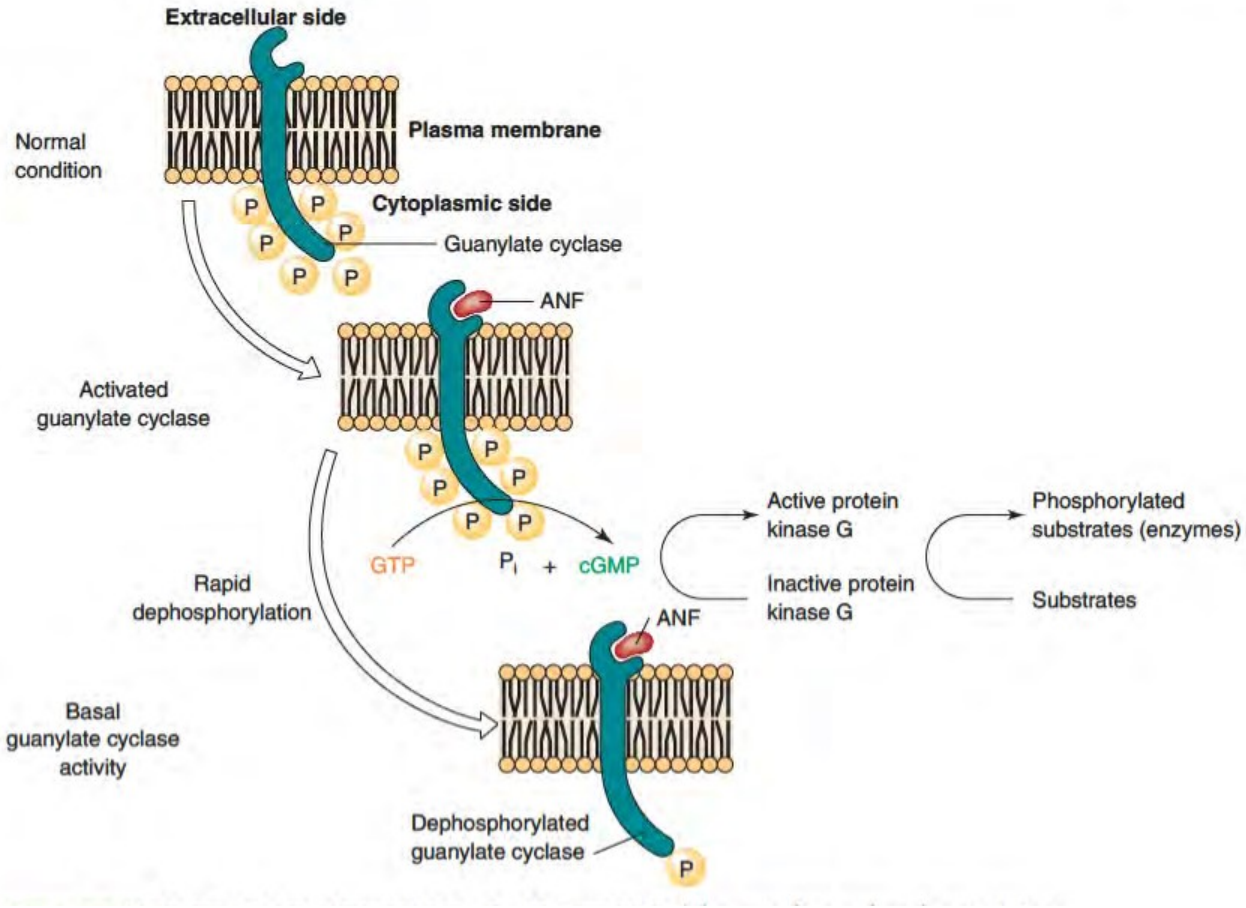
ANF: Peptide from 33 amino acids which is synthesized in the right atrium of the heart

- Stimulus: ↑arter. Pressure, ↑tension

1) increases renal excretion of water and sodium
2) inhibits sodium reabsorption in tubular epithelium
3) **inhibits the release of aldosterone**
4) **inhibits the release of renin** by kidney and acts through a membrane connector Guanylate cyclase (↑ c-GMP within the cell)

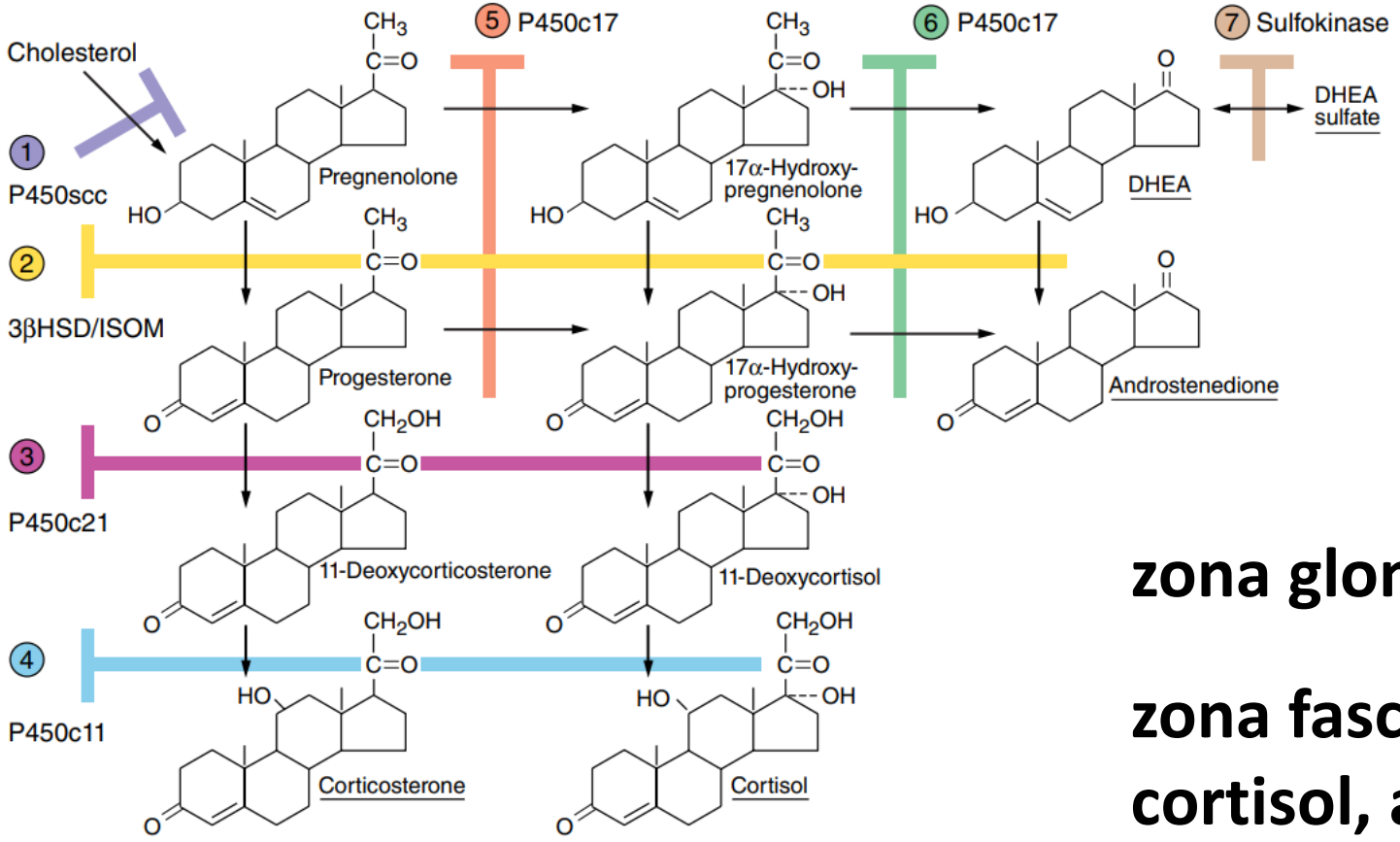


ANF is secreted by cardiac myocytes in response to signals such as blood volume expansion, high salt intake, increased right atrial pressure, and increased heart rate. Its secretion is **stimulated by activators of cardiac protein kinase C and decreased by activators of protein kinase A.**



ANF increases the glomerular filtration rate, leading to increased urine volume and excretion of sodium ion

Zones-Stereidogenesis



Because of enzymatic differences between the zona glomerulosa and the inner two zones, the adrenal cortex functions as two separate units, with differing regulation and secretory products.

zona glomerulosa: aldosterone

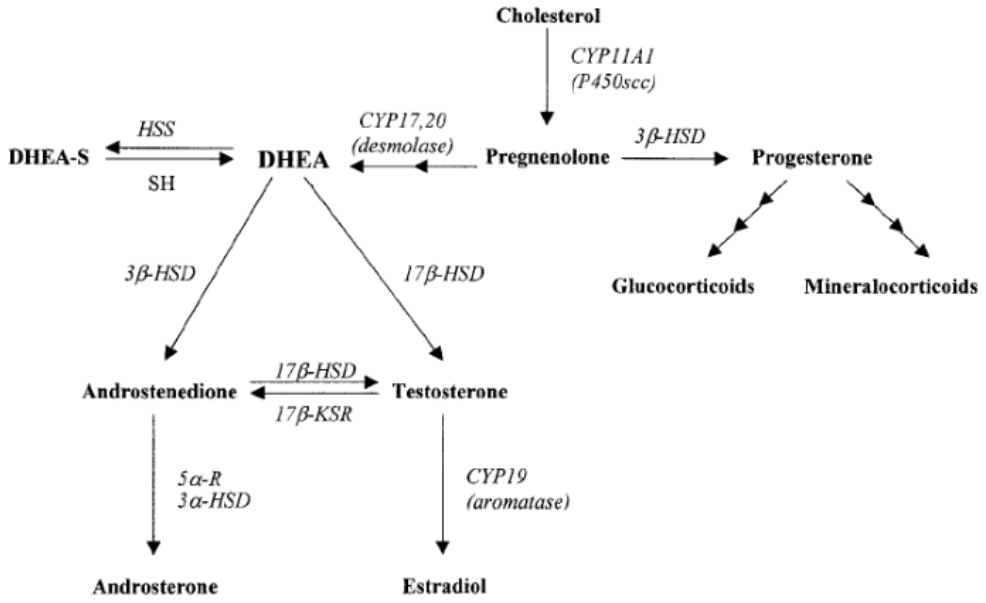
zona fasciculata and zona reticularis: cortisol, androgens and small amounts of estrogens

Adrenal Androgens-DHEA-DHEA-S

MEN

- DHEA, DHEA sulfate, and androstenedione, have minimal intrinsic androgenic activity, and they contribute to androgenicity by their **peripheral conversion to the more potent androgens testosterone and dihydrotestosterone.**
- DHEA and DHEA sulfate are secreted in greater quantities

BUT **Androstenedione is qualitatively more important, because it is more readily converted peripherally to testosterone**



Biologic Activity: Function primarily as **precursors for peripheral conversion to the active androgenic hormones, testosterone and dihydrotestosterone.**

Adrenal Androgens-DHEA-DHEA-S

FEMALES

- Total androgen production by the peripheral conversion of **androstenedione to testosterone.**
- In the follicular phase of the menstrual cycle, **adrenal precursors account for two-thirds of testosterone production and one-half of dihydrotestosterone production.**
- **During midcycle**, the ovarian contribution increases, and the adrenal precursors account for only 40% of testosterone production.
- Abnormal adrenal function as seen in Cushing syndrome, adrenal carcinoma, and congenital adrenal hyperplasia results **in excessive secretion of adrenal androgens, and their peripheral conversion to testosterone results in androgen excess, manifested by acne, hirsutism, and virilization**

Produced as free hormone (DHEA) and as a compound with sulfate radical (DHEA-S).

In pregnancy, DHEA-S is the precursor, where the adrenal glands of the fetus and placenta produce huge quantities of estrogens

DHEA-S → DHEA → Δ4-androstenedione → testosterone

LEARNING OBJECTIVES

Define adrenal glands.

Which are the hormones of the cortex and medulla of adrenal glands?

From which amino acids do catecholamines originate and describe their biosynthesis.

How does cortisol contribute to the synthesis of catecholamines?

How is the action of catecholamines terminated? Describe the shutting off mechanisms.

How is cortisol secretion regulated?

What is the molecular mechanism of action of cortisol in the cell?

Describe the metabolic and anti-inflammatory role of cortisol.

Describe the renin-angiotensin-aldosterone axis.

Which is the main stimulator of aldosterone secretion?

Describe aldosterone.

Explain the molecular mechanism of action of ANF.

Define adrenal androgens.

Describe adrenal functional impairment diseases (Addison's, Cushing, Conn's, Adrenal androgen excess, Pheochromocytoma)

Which hormones can cause arterial hypertension in hypersecretion?

SUGGESTED BIBLIOGRAPHY

Williams "Textbook of Endocrinology"

Chapter 15

Devlin "Textbook of Biochemistry with clinical correlations"

Chapters 22.1-22.5

Greenspans "Basic and Clinical Endocrinology", Chapters 10 +11, material covered in lecture only

e-class slides

SAMPLE QUESTIONS

QUESTION 1

Which of the following statements concerning G proteins is correct?

A. G proteins bind the appropriate hormone at the cell surface
B. G proteins interact with cytoplasmic receptors.
C. G proteins are second messengers.
D. G protein causes the regulatory subunits of the protein kinase to dissociate from the catalytic subunits.
E. Activated G protein may either activate or inhibit the production of second messenger.

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D. G protein causes the regulatory subunits of the protein kinase to dissociate from the catalytic subunits.
E. Activated G protein may either activate or inhibit the production of second messenger. **There are both stimulatory and inhibitory G protein subunits**

QUESTION 2

Epinephrine

A. mediates its effects by binding co cytoplasmic receptors
B. is synthesized in the adrenal cortex
C. is synthesized from norepinephrine by a methyl transferase (PNMT)
D. leads to the formation of cGMP
E. produces DAG and IP3

QUESTION 2

Epinephrine

A. mediates its effects by binding co cytoplasmic receptors
B. is synthesized in the adrenal cortex
C. is synthesized from norepinephrine by a methyl transferase (PNMT) This is induced by cortisol under stress
D. leads to the formation of cGMP
E. produces DAG and IP3

QUESTION 3

Each adrenal cortex layer produces steroid hormones from the precursor:

A. cholesterol

B. cortisol

C. aldosterone

D. CRH

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QUESTION 4

On a given heart cell, epinephrine acts

A. via synpases
B. As a neurotransmitter
C. via circulation
D. As CRH

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QUESTION 5

The ….. of the adrenal medulla, secrete the catecholamines epinephrine and norepinephrine in the fight-or-flight response

A. hepatocyte cells

B. neuroaminergic cells

C. neurosecretory cells

D. neurosecretory chromaffin cells

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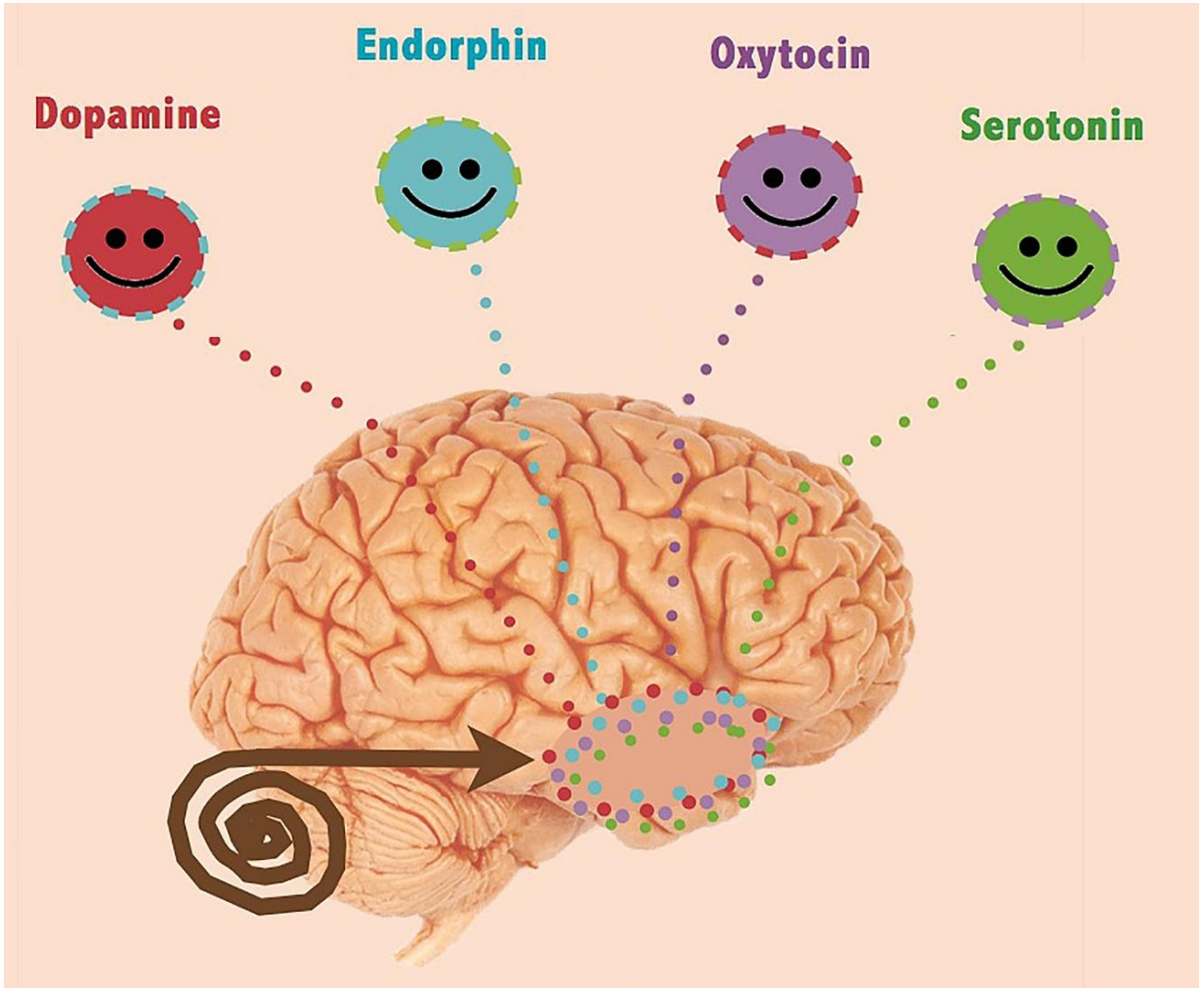

THANK YOU!