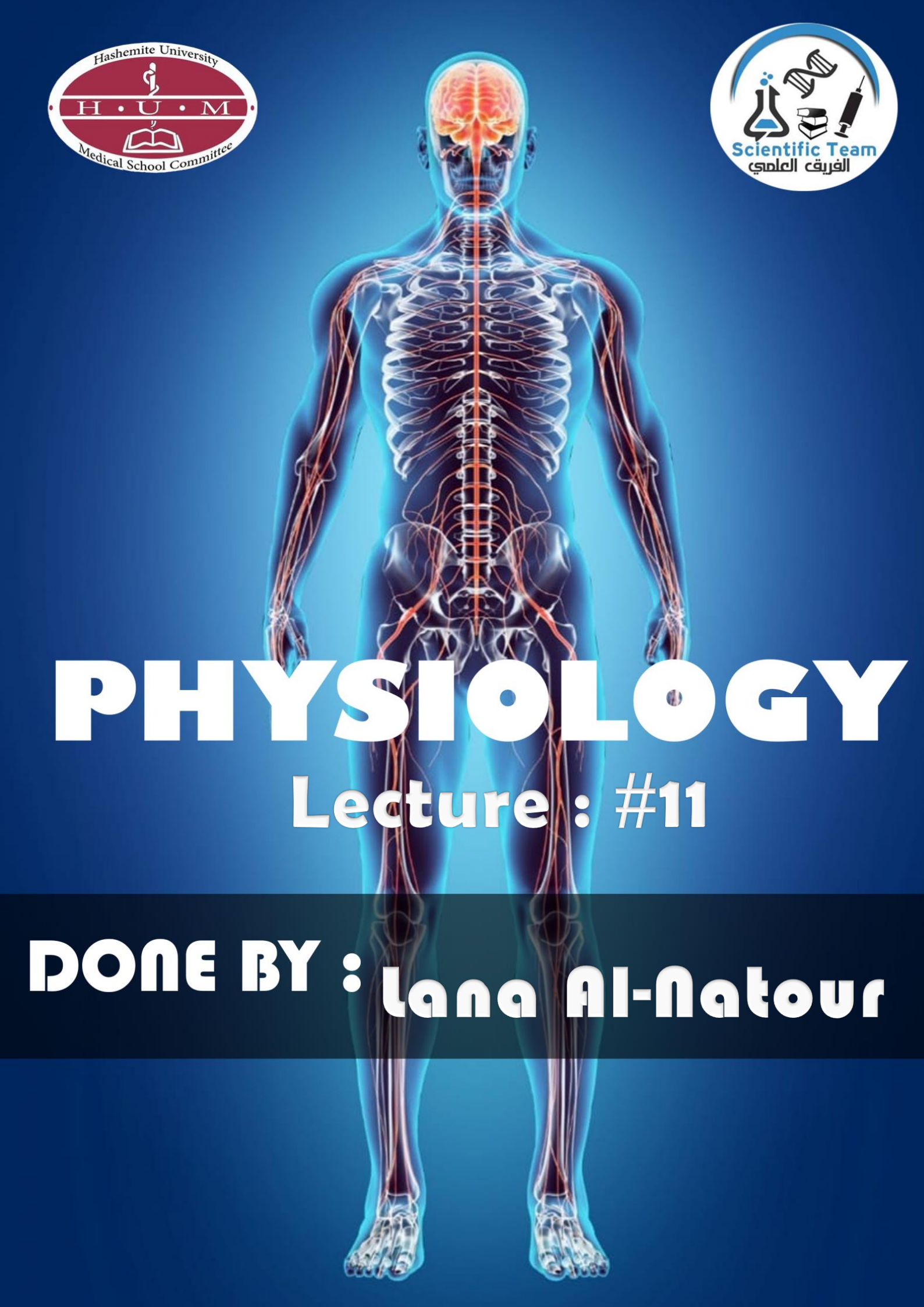


PHYSIOLOGY

Lecture : #11

DONE BY : Lana Al-Natour

Adrenal Gland Medullary and cortical hormones I

Introduction

-The adrenal gland is composed of the adrenal medulla (the central 20%) and the adrenal cortex (80% of the gland).

تسمى بالغدة الكظرية وتقع فوق الكليتين لذا ففي الجسم الانسان يوجد غدتين كظرتين وتتكون كل غدة من اللب (related to nervous sytem)والقشرة من الخارج (related to pituitary gland)

-The medulla is functionally related to the sympathetic nervous system. It is derived from a subpopulation of neural crest cells. It synthesizes and secretes epinephrine, norepinephrine, and dopamine (function?) in response to direct sympathetic stimulation. These hormones cause almost the same effects as direct stimulation of the sympathetic nerves.

مراجعة سريعة لsympathetic nervous system هو involuntary ويتكون من
2 neurons: preganglionic and postganglionic هلا preganglionic بيخرج من spinal cord وينتهي في synapse مع postganglionic وبالتالي بدنا نعتبر انه adrenal medulla عبارة عن
Postganglionic without axon وبس preganglionic رح نتنتهي
بال adrenal medulla cell bodies
وايشي مهم لازم نعرفه انه acetylcholine بيطلع من عند preganglionic وreceptor تاعه هو Nicotinic receptor يلي بكون موجود على adrenal medulla (postganglionic) اما
على target tissue رح يكون فيه muscarinic receptor
بالعادة postganglionic بتفرز noradrenaline اول ما توصله اشارة عصبية ولكن adrenal medulla اول ما توصلها اشارة عصبية رح تحول هاي الاشاة لهرمونات تطلقها في الدم
وبالتالي postganglionic sympathetic nervous system بيطلق neurotransmitters و adrenal medulla بتطلق hormones
سؤال ليش طيب 3 هرمونات ليش مش واحد؟لانه حسب تركيب الكيميائي كلهم بيتكونوا من amino acid tyramine وبالتالي رح يتحول الى dopa ومنه بيتصنع dopamine(اول هرمون يصنع)وثم dopamine رح يتحول الى norepinephrine وهاد biosynthesis موجود قي postganglionic وبس يستطيع تصنيع norepinephrine وما بيقدر يصنع epinephrine لانه لا يستطيع تحويل norepinephrine الى epinephrine((الفرق بينهم عبارة عن methyl group)) وبالتالي بما انه الانزيم يلي بحولهم مش موجود فهاد يعني انه postganglionic بيطلع norepinephrine فقط بينما adrenal medulla بيطلع الاثنين((epi+nor)) وعمل الاثنين نفس الايشي سواء طالع من sympathetic postganglionic او طالع من adrenal medulla ولكن dopamine يلي طالع من adrenal medulla مش معروف شو وظيفته بس انه ما بشبه من يلي طالع من nervous system

The Adrenal Medulla

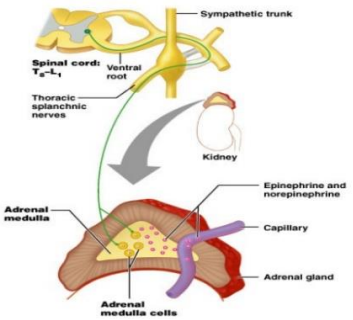
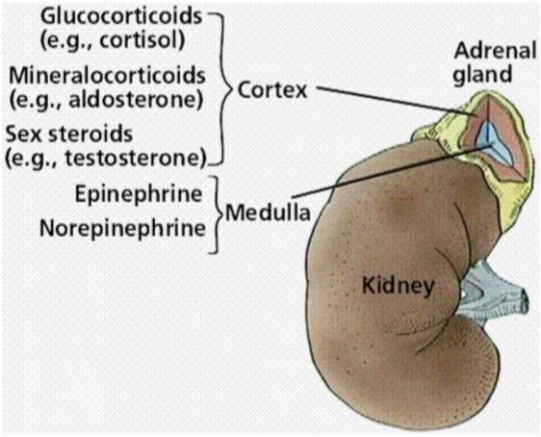


Figure from google to understand better ☺

- The adrenal cortex is derived from mesodermal tissue and secretes corticosteroids. These hormones are synthesized from the cholesterol

اي steroids معناها مصنوعة من كوليسترول وبالتالي بتقدر تمر من خلال cell membrane و receptor تاعهم بكون intercellular وطبعا ما بتقدر تمر freely عشانها lipophilic فبتحتاج carrier



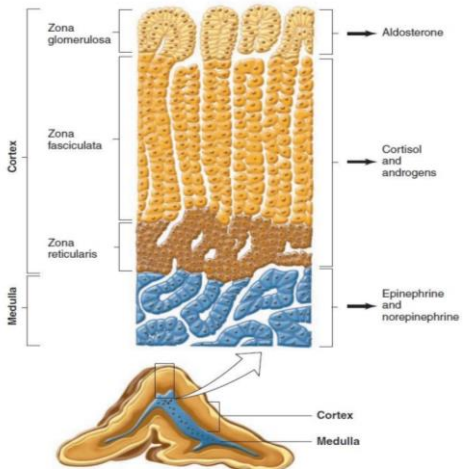
Here we have to know that cortex gives us 3 types of hormones :

1-glucocorticoids

2-minerallcorticoids

3-sex hormones

While medulla gives us norepinephrine and epinephrine



This is a cross-sectional of adrenal medulla so as we see the cortex is made from 3 zones :

1-zona glomerulsa gives aldestrone

2-zona fasiculata gives cortisol and little amount of androgens

3-zona reticularis gives androgens

وهاد المقطع هو من adult وليس من طفل لانه طفل بتكون عنده zones لسا مش كاملين

The medulla gives epi+nor

The adrenal medullary hormones

-Catecholamines are amino acid-derived hormones, synthesized from the amino acid tyrosine by the medullary pheochromocytes in response to nicotinic cholinergic receptors stimulation. The type of cell that secretes dopamine is unknown.

-The half-life of circulating catecholamines is short (2-3 minutes). Most (>50%) of the catecholamines released circulate bound to albumin with low affinity.

وعمره اطول من عمر ACH

-Catecholamines do not cross the blood-brain barrier easily, therefore they exert their effects almost exclusively in peripheral tissues and not in the brain.

-About 80% of the secretion is epinephrine (E) and 20% is norepinephrine (NE). These proportions can change under different physiological conditions.

فمثلا في حالة الخوف يفرز adrenaline في كميات كبيرة ويفرز noradrenaline في كميات كبيرة في حالات توتر غير معروفة السبب

بما انه catecholamines تفرز منها في nervous system ما سبب وجود adrenal medulla ؟؟لانه postganglionic axon لا يستطيع الوصول لكل خلية من الخلايا وبالتالي الهرمونات تأثيرها سريع على جميع خلايا جسم الانسان لانه بتفرز في الدم وهاي الغاية ليش sympathetic nervous system جزئين جزء عن طريق((nor)) axons وجزء عن طريق الهرمونات من((nor+epi)) adrenal medulla

Note :adrenaline is the same as epinephrine but British authors said adrenaline and American authors said epinephrine ☺

-Humoral catecholamines((from adrenal medulla)) have the same effects caused by direct sympathetic stimulation, except that the effects last 5-10 times longer. Postganglionic sympathetic neurons also produce and secrete NE but do not produce epinephrine

هلا norepinephrine بس ينفرز ك neurotransmitter جزء منه رح يرجع ياخده preganglionic وجزء منه بذوب ويدمر ببطيءعشان هيك half life تاعته طويلة مش زي ACH

هلا شو الفرق بين nor/epi في العمل ؟؟هلا epinephrine بيشتغل ك universal stimulator على alpha receptors وعلى beta receptors بينما norepinephrine بيشتغل على alpha receptor وعلى beta 1 ولكنه لا يعمل على beta 2

فمثلا في vascular system في عنا alpha and beta receptors فاذا كانت beta receptor اكثر رح تكون نتيجة عمل adrenalineعبارة عن vasodilation اما اذا كان alpha receptor اكثر رح يصير vasoconstriction بينما بالنسبة ل noradrenaline لن يحصل لنا الا vasoconstriction

-two hormones are known to produce upregulation of adrenergic receptors: the glucocorticoids and thyroid hormone. Receptor upregulation by thyroid hormone is critical in hyperthyroid patients because the combined effects of thyroid hormone and catecholamines can exacerbate cardiovascular manifestations of disease.

Receptors تعون catecholamines ليس ثابتا انما يتغير على سطح الخلية فيعني مريض thyrotoxicosis احد الاعراض يلي رح يعاني منها المريض هي tachycardia و hypertension بسبب زيادة beta receptors وبالتالي رح يزيد sympathetic stimulation ويزود beta 1 في vasoconstriction في heart وبرفع resistanceورح يزيد sympathetic stimulation في vascular system

-Chronic exposure to adrenergic receptor agonists can reduce the number of receptors in the plasma membrane because of decreased synthesis of the receptor (downregulation). Examples include β-agonist-promoted desensitization in asthma and α-agonist-stimulated tachyphylaxis (a rapid and short-term onset of drug tolerance) in patients receiving sympathomimetic nasal decongestants.

عندما تستخدم ادوية مشابهة لل catecholamine فمثلا منستخدم beta agonist في asthma حتى يصير عنا bronchodilation ولكن الاستخدام المفرط لهذه الادوية رح يقلل من sympathetic stimulation response بسبب downregulation يلي صار لل receptors وفي انواع من الادوية منستخدمها في الزكام وبسوي decongestion يلي هي alpha agonist حتى تسوي vasoconstriction و edema تخف بس مع الاستخدام المتكرر رح يصير tolerance

-Epinephrine is a universal adrenergic receptor stimulator; and since it stimulates β receptors it causes powerful cardiac stimulation, mild rise in blood pressure, and grater metabolic effect (5-10 times) compared to that of norepinephrine

وذلك لان norepipherine بيشتغلوا على alpha receptor بشكل كبير فتأثيره رح يكون انه يزود الضغط بشكل كبير ولكن epinephrine رح يشتغل على alpha +beta receptors فبزود الضغط بشكل اقل من norepinepherine

هلا حكينا انه epinephrine بيشتغل على alpha and beta receptors فعلى سبيل المثال splanchnic circulationالدورة الدموية يلي بتغذي الجهاز الهضمي في هذه الدورة alpha receptors اكثر وبالتالي رح يصير vasoconstriction اكثرولكن في beta receptors يلي واصلة vessels رح يصير skeletal muscle vasodilation اكثر بكثير منvasoconstriction وبالتالي رح تكون اقل resistance

-The metabolic effects ((sympathetic stimulation))include an increase in BMR, ↑ glycogenolysis and gluconeogenesis (β2) in the liver and muscles, ↑ lipolysis (β1), and ↑ glucose and lactate release into the blood (hyperglycemia and hyperlactatemia). The metabolic effect of humoral catecholamine cannot be substituted by direct sympathetic stimulation as small proportion of all the cells in the body are innervated directly by sympathetic fibers.

Lipolysis:in the adipose tissue it's hormonal effect not neuronal

-Most of the increase in fat utilization occurs during heavy exercise. This results almost entirely from release of E and NE by the adrenal medulla. Both hormones activate triglyceride lipase in fat cells →liberation of free fatty acids.

اثناء exercise و stress يلي رح يصير انه sympathetic system رح يصيرله stimulation وبالتالي خلال exercise الجسم رح يحتاج energy سواء من glucose او FA بحيث يطلق جلوكوز من liver او FA عن طريق lipolysis

-There is basal secretion of E and NE by the adrenal medulla (0.2 µg/kg/min for E and about 0.05 µg/kg/min for NE). This basal rate of secretion maintains the blood pressure. The gland increases its secretion rate in alarm or stress response (= mass discharge of sympathetic system) such as during physical exercise, mental stress (anger, anxiety, pain), cold, hypoglycemia, hypoxia, bleeding(decrease in blood volume), injury, etc.

دائما هناك افراز لل catecholamines بشكل قليل من adrenal medulla بشكل دائم للحفاظ على tone blood pressure لكن يوجد حالات بأنه sympathetic لما يصيرله stimulation

-The overall reaction to the sudden release of catecholamines is known as the "fight-or-flight" response

تجارب بتصيرعلى حيوانات بحيث لما يكون حيوان قوي بكون جاهز لل fight واذا كان حيوان ضعيف بكون جاهز لل flight

-The regulatory sympathetic centers are mainly present in the brain stem reticular substance. However, signals from the hypothalamus and even from the cerebrum can modulate activities of all autonomic control centers.

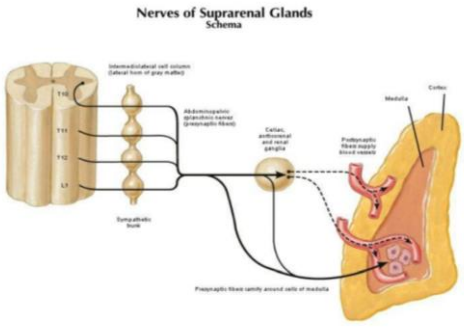
اوامر من hypothalamus بتغير وبتخفف sympathetic nervous system وهذا يفسر خلال العملية المريض يتنفس وبيضل قلبه شغال السبب؟لانه المراكز المسؤولة يلي موجودة في medulla oblongata and pons وبتعمل modulate لل sympathetic ما بتتوقف في البنج وما بتتأثراذا توقف عمل cerebral cortex

-Pheochromocytomas are adrenal medullary tumors that mostly secrete NE. They cause episodic or sustained hypertension

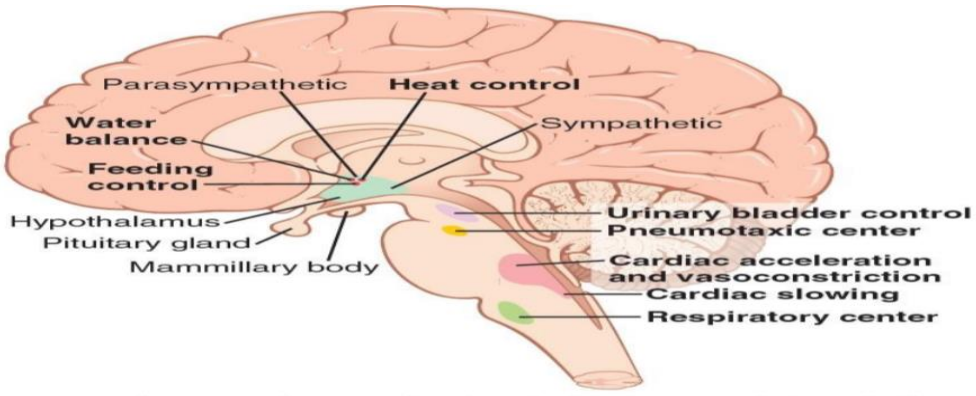
Episodes يعني بيرتفع ضغط بشكل كثير كبير لما sympathetic nervous system يزيد و sustained يعني دائما الضغط مرتفع

عشان هيك وقت خلع السن رح يزيد sympathetic وبالتالي بيسأل الدكتور المريض اذا عنده ارتفاع ضغط الدم عشان ما يصير نزيف ..

-Dopamine has positive inotropic effect (↑ systolic blood pressure but has no effect on diastolic blood pressure). Therefore, moderate doses are useful in treatment of traumatic and cardiogenic shock



The supply of sympathetic vessels in the adrenal medulla



Autonomic control areas in the brain stem and hypothalamus.

<u>A list of some major effects</u> mediated by epinephrine and norepinephrine

-Increase alertness: E and NE are equally potent in this regard, although in humans epinephrine usually evokes more anxiety and fear.

-Increased rate and force of contraction of the heart muscle: this is predominantly an effect of epinephrine acting through beta receptors.

-Constriction of blood vessels: norepinephrine, in particular, causes widespread vasoconstriction, resulting in increased resistance and hence arterial blood pressure.

-**Dilation of bronchioles**: **assists in pulmonary ventilation.**

-**Stimulation of lipolysis in fat cells**: **this provides fatty acids for energy production in many tissues and aids in conservation of dwindling reserves of blood glucose.**

-**Increased metabolic rate**: **oxygen consumption and heat production increase throughout the body in response to epinephrine. Medullary hormones also promote breakdown of glycogen in skeletal muscle to provide glucose for energy production.**

-**Dilation of the pupils:** **particularly important in situations where human or animal are surrounded by conditions of low ambient light.**

-**Inhibition of certain "non-essential" processes:** **an example is inhibition of gastrointestinal secretion and motor activity**

The adrenal cortical hormones

-**The adrenal cortex synthesizes and secretes mainly mineralocorticoids, glucocorticoids, and androgens (male sex hormones) in response to hypothalamic-pituitary-adrenal hormone stimulation.**

-**The mineralocorticoids are those hormones in which effects on Na+ and K+ excretion predominate. Glucocorticoids are those hormones in which effects on glucose and protein metabolism predominate.**

-**Aldosterone hormone is the principal mineralocorticoid secreted by the zona glomerulosa, whereas, cortisol is the principal glucocorticoid secreted by the zona fasciculata. This latter zone secretes Corticosterone and small amounts of adrenal androgens (Dehydroepiandrosterone, DHEA) as well.**

The main Androgen ((testosterone))is from testes while DHEA ((small amount))is from adrenal cortex

-**The zona reticularis develops postnatally and is recognizable at approximately age 3 years; it also produces androgens, as well as small amounts of estrogens and some glucocorticoids.**

هرمون ذكري ممكن يتحول الى هرمون انثوي (estrogen) قبل ان يدمر في الكبد لكن بعد تدميرها تصبح water soluble ويصيرله conjugation وينطرح في kidney

-**All steroids have some degree of mineralocorticoids activities, i.e. they cause salt and water retention.**

قاعدة عامة اينما يحبس الصوديوم يحبس الماء وبالتالي اي ستيرويد ممكن يحبس ماء بس بدرجة اقل من aldosterone فمثلا حبوب منع الحمل (steroids :estrogen/progesterone) قبل ما نعطيها لازم نسأل المريضة اذا عندهم بالعيلة hypertension حتى ما يزيد water retention...وممكن يصير عندها hypertension

Adrenal cortex- outer layer

Zone layer	Production	Principal steroid
zona glomerulosa	Mineralocorticoids	Aldosterone
zona fasciculata	Glucocorticoids	Cortisol
zona reticularis	Androgens	Dihydroepiandrosterone & Androstenedione (and Corticosterone)

Angiotensin II increase the output of aldosterone and cause hypertrophy of the zona glomerulosa, and has no effect on the other two zones. ACTH increase secretion of cortisol and adrenal androgens and cause hypertrophy of the zona fasciculata and zona reticularis. ACTH has little effect on the zona glomerulosa

The Aldosterone

-It is essential for life. Its main function is to:

1. Regulates sodium and potassium ions

2. Promotes secretion of H+ so helps control pH

3. Regulates BP and blood volume

هرمون مهم واذا ما كان موجود يؤدي اللى الموت بسبب hypotension

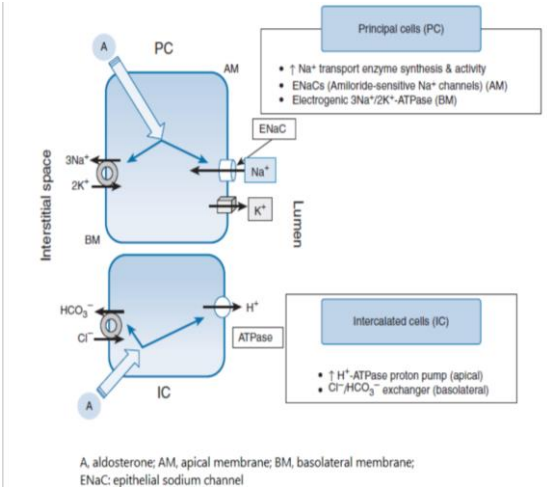
**هلا معظم الهرمونات يلي بتشتغل على kidney بتشتغل على distal tubule وبالتالي 90% بصيرلها امتصاص بال proximal tubule و 10% بيوصل لل distal tubule اذا بحب الجسم يسترجعها بيسترجعها حسب اذا الجسم بحتاجها او لا

-Aldosterone binds to a cytoplasmic receptor, and the receptor-hormone complex moves to the nucleus where it alters the transcription of mRNAs.

-Aldosterone ↑ absorption of Na+ and ↑ secretion of K+ (to maintain electricity) especially by the principal cells of the collecting tubules and to a lesser extent in the distal tubules and collecting ducts → conserve Na+ in the extracellular compartment → expansion of the extracellular fluid volume.

لما يصير عنا سحب لكمية كبيرة من الصوديوم يلي رح يصير انه البوتاسيوم رح يصيرله excretion بشكل كبير مع الهيدروجين وبالتالي رح يصير عنا alkalosis +hypertension و urine بصير more acidic

-The epithelium of the second half of renal distal tubule and collecting tubule has two types of cells, the principal and intercalated cells. Principal cells (express more aldosterone receptors) are responsible for Na+ and water reabsorption and secretion of K+. This function is controlled by aldosterone and K+ concentration in blood



A, aldosterone; AM, apical membrane; BM, basolateral membrane; ENaC: epithelial sodium channel

The effect of aldosterone on principal cells and intercalated cells

So in PC // the aldosterone enters the cell and sodium channels will open inside the cell and the potassium will excrete outside ,,the sodium will enter interstitial space and potassium enters the cell by the pump

And in IC//proton pump will be activated and the hydrogen will be excreted ,,CO2+H2O will form $H_2CO_3 \longrightarrow HCO_3^- + H^+$ ((H^+ will be pumped out and HCO_3^- will be absorbed))

-Intercalated cells reabsorb K+ and secrete H+ , a process that requires H+-ATPase (i.e. responsible for acidification of urine).

This mechanism is similar to that in stomach and can create [H+] gradient of 1/1000. Cellular H+ion is obtained from the carbonic acid synthesized in these cells by the enzyme carbonic anhydrase.

-Aldosterone has almost the same effects on sweat glands, salivary gland, and content of the GIT as it has on the renal tubules

-The regulation of aldosterone is multifactorial and secretion is achieved by the following mechanisms:

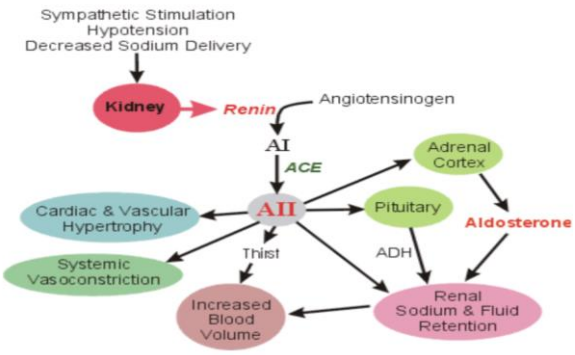
1. ↑ in plasma K+ concentration → ↑ aldosterone secretion

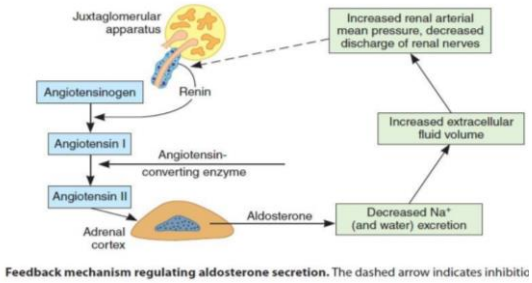
الصوديوم ايون آمن ولكن البوتاسبوم ايون خطير بحيث لو اعطينا normal saline لمريض ما رح يأثر كثير لانه الصوديوم not permeable to water ورح يضل بال extracellular compartment وما رح يغير بال polarity وهي آمن بالنسبة لل cardiac muscle اما بالنسبة للبوتاسيوم فهو very permeable to the cell membrane وبالتالي دخول البوتاسيوم لداخل الخلية رح يقلل negativity لداخل الخلية قمثلا cardiac muscle رح تصير بدل 90- تصير 100- بصير arrhythmia وdeath

عشان هيك hyperkalemia اكبر محفز لل aldosterone

2. ↑ in angiotensin II level → ↑ aldosterone secretion

تفرز لما يكونBP قليل بتصير لما ينخفض الضغط رح تحس kidney بهاد الايشي وبالتالي رح تفرز renin و رح تحول angiotensinogen ل angiotensin 1 وبعدين بتتحول angiotensin 11 وبتروح على zona glomerulasa وبتطلع aldosterone





Feedback mechanism regulating aldosterone secretion. The dashed arrow indicates inhibitio

3. ACTH from anterior pituitary gland is necessary for basal aldosterone secretion. Great ↑ in ACTH → ↑ secretion of all cortical hormones including the aldosterone

لازم ACTH تكون بكميات كبيرة حتى ينفرز aldestrone

Note: Factors that <u>suppress aldosterone secretion include atrial naturetic hormone, high sodium concentration and potassium defiency</u>.

ANPيطلب من kidney ان تطرح الصوديوم في urine وبالتالي هو عكس هرمون aldosterone

Test Questions:

Q. Which autonomic receptor mediates secretion of epinephrine by the adrenal medulla?

A. Adrenergic α receptors

B. Adrenergic β1 receptors

C. Adrenergic β2 receptors

D. Cholinergic muscarinic receptors

E. Cholinergic nicotinic receptors

Answer :E

Q. A 60-year-old man suffers from elevated blood pressure (185/130 mmHg). Lab tests reveal an increase in plasma renin activity, plasma aldosterone level, and left renal vein renin level. His right renal vein renin level is decreased. What is the most likely cause of the patient's hypertension?

A. Aldosterone-secreting tumor

B. Adrenal adenoma secreting aldosterone and cortisol

C. Pheochromocytoma

D. Left renal artery stenosis

E. Right renal artery stenosis

Answer:D