ENDOCRINE BLOCK

ADRENAL GLAND

Correction File

Case .. 36-year-old woman with no significant medical history presents to her primary care physician with a 6-month history of amenorrhea, weight gain, and excessive facial hair growth. She denies any recent diet or medication changes. Her vital signs are notable for a pulse of 80/min and blood pressure of 148/90 mm Hg. Physical examination reveals a well-developed hirsute female with truncal obesity, abdominal striae, and peripheral edema. She has difficulty arising from a chair during her neurological exam. Relevant laboratory findings are as follows:
Sodium: 140 mEq/L Chloride: 92 mEq/L Bicarbonate: 25 mEq/L Glucose: 225 mg/dL Potassium: 3.4 mEq/L

What is the most likely diagnosis?
Cushing syndrome results from excess glucocorticoids, either from increased cortisol production or exogenous glucocorticoid therapy. **Common causes include the following:**
1-Iatrogenic (eg, steroid ingestion, most common).
2- Pituitary adenoma (Cushing disease).
3-Adrenal tumor/hyperplasia.
4-Adrenocorticotropic hormone (ACTH)-producing tumor (most commonly secondary to small cell lung cancer).

What laboratory tests can help confirm the diagnosis?
Screening tools for Cushing syndrome or glucocorticoid excess include the following:
1- 24-hour urine free cortisol test. ↑ cortisol level indicates hypercortisolism.
2-Dexamethasone suppression test. A normal result is a decrease in cortisol after administration of low- dose dexamethasone. In glucocorticoid excess due to Cushing disease, low-dose dexamethasone will not suppress cortisol levels.

After identifying elevated cortisol levels, what diagnostic tests help define the source of the hormonal abnormality?
Serum ACTH levels:
1- ↑ ACTH: Pituitary adenoma or an ectopic ACTH-producing neoplasm.
2- ↓ ACTH: Adrenal tumor/hyperplasia or exogenous glucocorticoid administration.
3- A high-dose dexamethasone suppression test can differentiate between a pituitary adenoma and an ectopic ACTH-producing tumor. Pituitary adenomas are suppressed by high-dose ACTH, whereas ectopic ACTH-producing tumors usually are not.

What are the appropriate treatments for this condition?
The most appropriate treatment for adrenal tumors is surgery. Treatments for nonresectable tumors or hyperplasia are as follows:
Ketoconazole: Inhibits glucocorticoid production.
Metyrapone: Inhibits cortisol formation in adrenal pathway.
Aminoglutethimide: Inhibits the synthesis of steroids.

Case ... 40-year-old woman visits her physician because of fatigue and weakness, which she has experienced for several months. She says she often feels lightheaded when she first gets out of bed in the morning or stands suddenly. Review of symptoms is positive for frequent headaches, nausea, and vomiting. Her vital signs are notable for a blood pressure of 125/75 mm Hg seated and 105/60 mm Hg standing. Physical examination reveals several patches of hyperpigmentation on the skin. Relevant laboratory findings are as follows:
Sodium: 126 mEq/L Bicarbonate: 19 mEq/L Potassium: 5.2 mEq/L Cortisol: 4.3 mg/dL Chloride: 97 mEq/L

What is the most likely diagnosis?
Addison disease, or primary adrenal insufficiency

Mention the causes of adrenal Insuffciency (Hypoandrenalism)?
A-Primary : 1-autoimmune (addison disease) 2- TB 3- Radiation 4- Malignancy
B- seconday : ↓ ACTH

What is the cause of this patient's metabolic abnormalities?
Adrenal insufficiency causes a deficiency of cortisol. Hyponatremia, hyperkalemia, and a low bicarbonate level can result from low aldosterone levels associated with primary adrenal insufficiency.

How would this patient's cortisol level change if she were administered adrenocorticotropic hormone (ACTH)?
The cortisol level should not change appreciably since it is low because of a primary adrenal insufficiency (ie, the problem is within the adrenal gland itself). This is suggested by the hyperpigmentation, which is due to the attempt of the pituitary gland to overcome the cortisol deficiency by increasing ACTH production. ACTH, in turn, stimulates the release of melanocyte-stimulating hormone, causing hyperpigmentation

Mention the symptoms of addisonian crisis ?
1- Profound fatigue 2- Dehydration 3- vascular collapse 4- Renal shudt down 5- decrease serum Na 6- Increase serum K

Case ..

50-year-old woman presents to the emergency department complaining of 2 hours of vertigo, headache, palpitations, blurry vision, and diaphoresis. She has a history of occasional tension headaches but no significant cardiac history. She does not smoke and has no history of hypertension. At presentation her blood pressure is 200/140 mm Hg, her heart rate is 120/min, and she is afebrile. Her skin is sweaty and flushed. Noncontrast imaging of the brain is negative for blood or other mass lesions. Her blood pressure is stabilized pharmacologically. Laboratory testing reveals increased plasma metanephrine and normetanephrine levels. Results of a serum thyroid-stimulating hormone test are within normal limits. Twenty-four-hour urine catecholamines and meta/normetanephrines are elevated.

What is the most likely diagnosis?
Pheochromocytoma is a catecholamine-secreting tumor of chromaffin cells of the adrenal medulla.

What are the key steps in epinephrine catabolism?
Catecholamines are substrates for monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). Epinephrine can undergo two paths of catabolism. In the first, COMT converts epinephrine into metanephrine, which MAO then converts into 3-methoxy-4- hydroxymandelic acid.
In the second, MAO converts epinephrine into dihydroxymandelic acid, which COMT then converts into 3-methoxy-4- hydroxymandelic acid (the same product as the first pathway).

What receptors do catecholamines act on to produce hypertension?
Catecholamines act on $\alpha 1$ and $\beta 1$ receptors. Activation of $\alpha 1$ receptors contracts vascular smooth muscle, and activation of $\beta 1$ receptors in the heart increases heart rate, conduction velocity, and contractility.

During removal of an adrenal gland, the surgeon must secure the adrenal vasculature, especially the adrenal vein. How is the blood supplied to the adrenal gland?
The arterial blood supply to the adrenal gland can be variable, with blood supply from the superior suprarenal artery originating from the inferior phrenic artery; the middle suprarenal artery originating from the aorta; and the inferior suprarenal artery originating from the renal artery. The adrenal gland typically has a dominant vein, which empties into the left renal vein (left adrenal gland) and the inferior vena cava (right adrenal gland).

What is the structure and function of the adrenal gland?
The adrenal gland is composed of the cortex and medulla, each with its own secretory products. The zones of the adrenal cortex can be remembered with the memory trick, "the deeper you go, the sweeter it gets": salt-related hormones (aldosterone) from the zona glomerulosa, sugar-related hormones (cortisol) from the zona fasciculata, and sex-related hormones (testosterone, DHEAS) in the zona reticularis. The adrenal medulla produces catecholamines such as epinephrine and norepinephrine.

Anatomy & Embryology

•The **suprarenal (adrenal) gland** is a component of the **hypothalamic-pituitary-suprarenal** axis that is responsible for coordinating **stress response and metabolism.**
•The suprarenal gland is enclosed within the renal fascia with the kidney but in a separate compartment, that allow the two organs to be separated easily during surgery.
•It is separated from the kidney by the perirenal fat

Describe the Location of adrenal glands ?

- They are yellowish retroperitoneal They lie on the upper poles of the kidneys, At the level of the last thoracic vertebra (T12).
- Each gland has an outer yellow cortex and an inner dark brown medulla.

What are the functions of the cortex and medulla of adrenal glands ?

<table>
<tr><th colspan="3">Function</th></tr>
<tr><th colspan="2">Cortex</th><th>Medulla</th></tr>
<tr><td>Mineral corticoids</td><td>which are concerned with the control of fluid & electrolyte balance</td><td rowspan="3">catecholamines: epinephrine & norepinephrine</td></tr>
<tr><td>Glucocorticoids</td><td>which are concerned with the control of the metabolism of carbohydrates, fats, & proteins</td></tr>
<tr><td>Small amounts of Sex hormones</td><td>which probably play a role in the prepubertal development of the sex organs.</td></tr>
<tr><th colspan="3">Development</th></tr>
<tr><th colspan="2">Cortex</th><th>Medulla</th></tr>
<tr><td colspan="2">Mesodermal in origin,develops from the celomic epithelium of the posterior abdominal wall & It appears during the 6th week of development by aggregation of the mesenchymal cells between dorsal mesentery & developing gonads
•A second wave of mesenchymal cells arise from the mesothelium, enclose the fetal cortex & forms a thinner definitive (permanent) cortex.
•Differentiation of the characteristic suprarenal cortical zones begins during the late fetal period. <u>Zona glomerulosa & zona fasciculata</u> are present at birth, but <u>zona reticularis</u> is not recognizable until the end of third year.</td><td>Ectodermal in origin, develops from the adjacent Sympathetic ganglion, derived from Neural crest cells
•It forms a mass medial to the fetal cortex</td></tr>
</table>

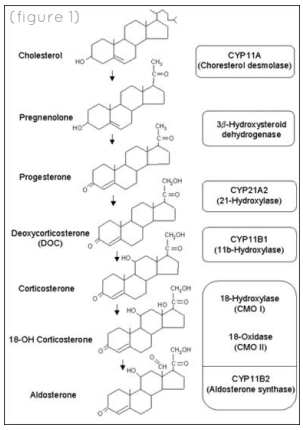
	LEFT adrenal gland	RIGHT adrenal gland
Shape & location	Is **crescentic** in shape . Extends along the medial border of the left kidney from the upper pole to the hilus.	Is **pyramidal** in shape. -Caps the upper pole of the right kidney.
Anterior	pancreas, lesser sac, and stomach	- right lobe of the liver - inferior vena cava.
Posterior	diaphragm.	
Medial	Celiac plexus and ganglia	
blood supply	- Superior suprarenal from inferior phrenic artery. - Middle suprarenal from abdominal aorta - Inferior suprarenal from renal artery.	
Venous Drainage	A single vein emerges from the hilum of each gland and drains into	
	into the left renal vein	into the inferior vena cava
Nerve supply	**Preganglionic sympathetic** fibers derived from the **splanchnic nerves** supply the glands. Most of the nerves end in the **medulla** of the gland	
lymph drainage	into the **lateral aortic lymph nodes.**	

•**The suprarenal glands of the fetus** is **10-20 times larger than the adult glands** relative to the body weight, and are large compared with the kidneys. This is because of the extensive size of the fetal cortex. The medulla remains relatively small until after birth.
•The suprarenal glands rapidly become smaller during the **first 2-3 weeks** after birth, due to the rapid regression of the fetal cortex.
•Its involution is largely **completed in the first year of life.**
•During the process of involution, the cortex is friable and **susceptible to trauma at birth** leading to severe hemorrhage

Congenital adrenal hyperplasia (CAH)

• inherited as autosomal recessive diseases and can affect both boys and girls.
The defect is lack of an **enzyme (21-hydroxylase)** needed by the adrenal gland to make the major steroid hormones of the adrenal cortex: cortisol & aldosterone. Due to the block in synthesis of these hormones, there is abnormal 'feedback' & steroids are 'diverted' to becoming androgens, a form of male sex hormones
•An abnormal increase in the cortical cells results in **excessive androgen production;** during the **fetal period.**
•In females, it may lead to musculization of external genitalia & enlargement of clitoris resemble a penis , beard growth, deeper voice, masculine distribution of body hair,
•In males, it may remain undetected in early infancy but In pre-pubertal males it causes the rapid develop of secondary sexual characters
•Later in childhood, in both sexes, androgen excess may lead to rapid growth & accelerated skeletal maturation.

Physiology



Where do the Mineralocorticoids synthesize in the adrenal gland?
They are synthesized in zona glomerulosa of Adrenal cortex

What is the most important product of Mineralocorticoids?
Aldosterone (steroid hormone , essential for life)

Mention the pathway of Aldosterone synthesis.(see figure 1)

What is the level of Aldosterone during the day(diurnally rhythm)?
In parallel to cortisol rhythms, Highest conc. at 8 AM, lowest at 11 PM

list the actions of Aldosterone
1- Responsible for elevating Na+ reabsorption in Target cells are called "principal (P) cells in distal tubules and cortical collecting ducts.
2-It also affects Na+ reabsorption by sweat, salivary and intestinal cells. Stimulates synthesis of more Na/K-ATPase pumps.
3-Maintain extracellular volume.
3- Stimulates active secretion of potassium and hydrogen Ions from distal tubular cells into urine.
4- Essential for disposal of daily dietary potassium load at normal plasma potassium conc.

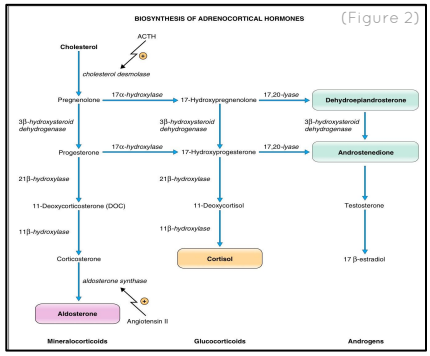
What is steroiodogenesis and the first and rate limiting step in synthesis of steriod hormone synthesis ?
Process by which cholesterol is converted to biologically active steroid hormones.
Pregnenolone

Q:How Aldosterone can be regulated?
stimulated by: #Direct: ⬆plasma potassium level. (Primary regulation) & -ACTH.
#Indirect: Angiotensin II (RAAS)[Renin-angiotensin II-aldosterone-system] (Primary regulation)
inhibited by:Atrial natriuretic peptide(ANP)-inhibits activity of the zona glomerulosa→⬇ Aldosterone

Renin-angiotensin-aldosterone axis
•Principal factor controlling Ang II levels is renin release.
•⬇circulating volume stimulates renin release via ⬇:
- BP (symp effects on JGA).
-[NaCl] at macula densa ("NaCl sensor")
-renal perfusion pressure ("renal" baroreceptor)

Role of AngII in Aldosterone synthesis
Angiotensin II acts on zona glomerulosa to stimulate aldosterone synthase enzyme leads to synthesis of aldosterone
Angiotensin II acts via ⬆ intracellular cAMP to stimulate aldosterone synthesis(see figure 2)

Role of ACTH in Aldosterone synthesis/release:
ACTH stimulates cholesteorol desmolase enzyme (cleaving cholesteorol to pregnenolone) first step of formation all steriod hormones so stimulates formation and secretion steriod homones including aldosterone.
However, ACTH stimulation is more transient than other stimuli & is diminished within several days.



What is the role of Angiotensin II in the regulation of Aldosterone?
Stimulate cholesterol desmolase and aldosterone synthase

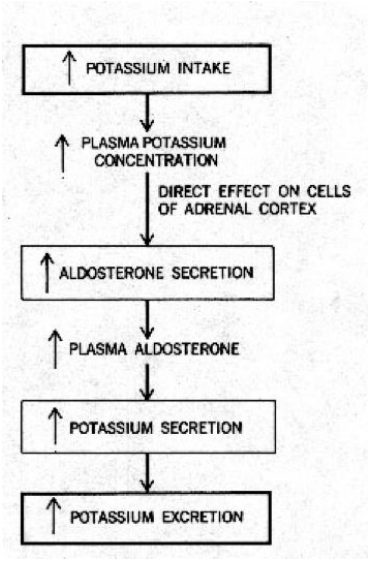
How does RAAS get activated?
Renal ischemia and low Na+ conc. at macula densa by the Juxtaglomerular apparatus (JGA)

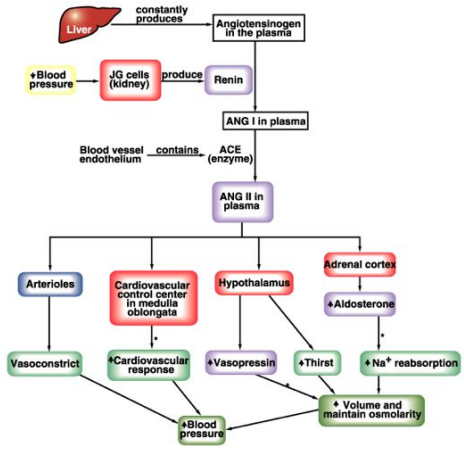
components of Juxtaglomerular apparatus

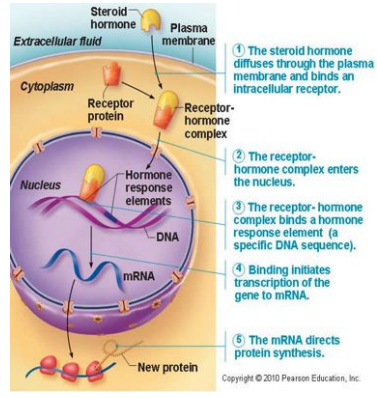
Macula densa cells:	Juxtaglomerular cells
Specialized **chemoreceptor** cells in the wall of the distal convoluted tubule	Specialized smooth muscle cells which act as **mechanoreceptors**
respond to changes in solute concentration (especially Na levels) in tubular fluid.	They are stretched in response to increases in the blood pressure of the afferent arteriole.
Information is conveyed to juxtaglomerular cells which will adjust their output of renin accordingly.	synthesize and secrete renin.

Clinical Features of

HYPERaldoseronism (Conn's syndrome)	HYPOaldosteronism
• Hypertenstion • Hypokalemia causing muscle weakness ↑ tubular (intercalated cells) H+ secretion, with resultant mild alkalosis. • Nocturnal polyuria & polydipsia • Neuromuscular manifestations: -weakness, paresthesia. -intermittent paralysis.	• ↑loss of Na, chloride, water. • ↓ECF volume. • Hyperkalemia. • Mild acidosis. • Plasma sodium ↓& may lead to circulatory collapse.↓cardiac output - shock - death within 4 days to 2 weeks if not treated. *Note:Complete failure to secrete aldosterone leads to death (dehydration, low blood volume).







Mechanism of action of steroid hormones

- Pathway by which an increased K intake induces greater K excretion mediated by aldosterone:
- K stimulates aldosterone synthesis by depolarizing zona glomerulosa cell membranes

Physiological effects of cortisol	
CHO metabolism	◆ ⬆blood glucose levels by: (+) gluconeogenesis in the liver. ◆ ⬇utilization of glucose by cells via direct inhibition of glucose transport into cells.
Protein metabolism	◆ ⬇protein formation in all tissues Except liver.Extrahepatic protein stores ⬇(catabolic). ◆ amino acids not transported into muscle cells ⬇protein synthesis & ⬆amino acid blood levels. ◆ These high blood amino acid levels are transported more rapidly to hepatic cells for gluconeogenesis & protein synthesis in liver.
Fat metabolism	◆ Lipolytic. ◆ ⬆appetite. ◆ Mobilizes fatty acids & glycerol from adipose tissue lead to ⬆their blood concentrations, so more glycerol available for gluconeogenesis. ◆ Fat broken down & less formed due to less glucose transported into fat cells. ◆ Redistribution of body fat: 1- ⬆formation of fat in trunk areas & face 2- ⬇fat (& muscle) from extremities.
Anti-inflammatory	◆ Stabilizes lysosomal membrane. ◆ ⬇ degree of vasodilatation. ◆ ⬇permeability of capillaries. ◆ ⬇migration of white blood cells. ◆ Suppresses immune system.
Blood Cells & Immunity	◆ ⬇ production of eosinophils and lymphocytes. ◆ Suppresses lymphoid tissue systemically → ⬇Tcell & antibody production ⬇ immunity. ◆ This effect is useful in transplantation surgery in reducing organ rejection.
circulation	◆ Maintains body fluid volumes & vascular integrity. ◆ Cortisol has mineralcorticoid effect, not as potent as aldosterone. ◆ BP regulation &CVfunction: sensitizes arterioles to action of noradrenaline(Permissive effect). ◆ ⬇ capillary permeability. ◆ Maintins normal renal function.
CNS	◆ Negative feedback control on release of ACTH. ◆ Modulates perception & emotion.
Mineral metabolism	◆ Anti-vitamin D effect.
GIT	◆ ⬆ HCl secretion.
Developmental Functions	◆ Permissive regulation of fetal organ maturation. ◆ Surfactant synthesis (phospholipid that maintains alveolar surface tension). ◆ Inhibition of linear growth in children due to direct effects on bone & connective tissue.

Cortisol excess Both exogenous & endogenous hyperfunction show manifestations of Cushing's disease.

Exogenous:	Endogenous
Most cortisol excess is induced by steroid therapy (prednisone): ✤ asthma ✤ rheumatoid arthritis ✤ lupus. ✤ immunosuppression after transplantation	Due to excessive production of cortisol: ✤ ACTH- independent: • 1ry adrenal defect (adenoma). ✤ ACTH-dependent: • Overproduction of ACTH by pituitary. • Overproduction of ACTH by ectopic ACTH-producing tumor.

What are the main glucocorticoids in humens? and which one is produced in higher rate?
Cortisol & corticosterone / Cortisol.

Explain glucocorticoids secretion rhythms, regulation, transport and metabolism?
❍ After stimulation by (stress, exersise infection, extreme heat and cold, truma & extreme mental anxity) glucocorticoids are secreted.
❍ Its secretion is controled by ACTH, after ACTH has been produced, cortisol will be secreted 15-20mins later´7-15 episodes per day.
❍ It has a major burst in the early morning.before awakening
❍ 90-95% bound to plasma protein.
❍ Importance: Binding to plasma proteins act as reservoirs & ensure a uniform distribution to all tissues.
❍ It is transported in blood bounded to plasma protein called Cortisol binding globulin (CBG) (transcortin) or albumin, To cross the target tissue membrane, the hormone must dissociate from its carrier protein.
❍ Only **un**bound steroid hormones are biologically active
❍ Metabolized in liver by reductases & conjugated to glucuronides & excreted via kidney as urine in the form of free cortisol.
❍ Aldosterone has a lower half-life than cortisol.

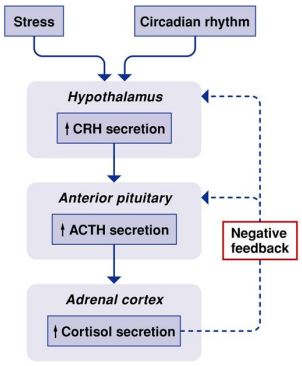
General Information about Androgens.
•Androgens are the hormones that exert masculinizing effects.
•They promote anabolism and growth.
•Testosterone from the testis is the major active, androgen.
•The adrenal androgens have less than 20% of its activity.
• A subset of androgens, includes :Dehydroepiandrosterone (DHEA) & androstenedione.
• The adrenal cortex produces both androgens i.e male sex hormones" & estrogens or "female sex hormones.
• The adrenal cortex in both sexes produces small amounts of sex hormone of the opposite sex
•Additional small amounts of sex hormones come from nonadrenal sources. Some testosterone in males is converted into estrogen by the enzyme aromatase found in adipose tissues.

What is the precursor of natural estrogens and the most abundant adrenal androgen?
Dehydroepiandrosterone (DHEA) (steroid hormone)

What are the functions of Androgens in the female ?
1- growth of pubic & axillary hair. 2- pubertal growth spurt. 3- development & maintenance of female sex drive.

What is the Androstenedione &the fate of it ?
❍ Androgenic steroid produced by the testes, adrenal cortex, and ovaries
❍ Converted metabolically to testosterone & to estrogens in the fat & other peripheral tissues. ·It is an important source of estrogen in men and postmenopausal women.

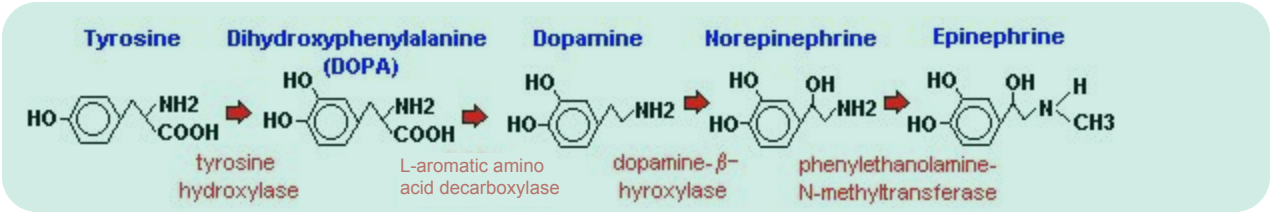
What controls androgen production & what is the Target tissue ? ACTH /General body cell.



Which part in the female produce androgen & why does it produce ?

- Ovaries. because of considred intermediate stepin estrogen production & little of this androgean is relased in the blood instead of being converted into estrogen.
- Ovarian thecal cells/stroma (Controlled by LH).
- Precursors DHEA and androstenedione are produced by the ovaries and adrenal cortices.
- The Adrenal cortex produces the majority of DHEA (80%) & its sulfate, DHEAS (> 90%).
- Direct ovarian secretion is thought to account for one third of testosterone production, whereas the remainder is accounted for by conversion of androstenedione in peripheral or extragonadal sites, including adipose tissue & skin.
- Dihydrotestosterone is produced mainly by target tissues.
- Most androgens in postmenopausal women, produced by the adrenal cortex. whereas testosterone is believed to originate primarily from the ovaries.

Mention the steps of catecholamines synthesis?



What are the Hormones that secreted by adrenal medulla?

1) Adrenaline (epinephrine) 80% 2) Noradrenaline (norepinephrine) 3) Dopamin

What is the mechanism of action: receptor mediated: α and β

1-norepinephrine α > β 2- epinephrine α = β

•Peripheral effects are dependent upon the type and ratio of receptors in target tissues.

Mention the effects of epinephrine in CVS, metabolism and respiartion ?

CVS : ↑ the heart rate, cardiac contractiluty & BP

matabolism : glycogenolysis in the liver and skeletal muscle,

Moblization of free fatty acids, ↑ metabolic rate & ↑ in O2 consumption

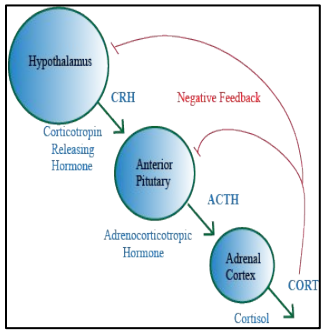
Respiration : ↑ in O2 consumption & respiratory rate

Differences between Epinephrine and Norepinephrine	
Epinephrine	**norepinephrine**
□ more in terms of cardiac stimulation leading to greater cardiac output (β stimulation). □ in terms of ↑ metabolism.	□ more in terms of constriction of blood vessels □ leading to ↑ peripheral resistance □ ↑ arterial pressure.

pheochromocytoma	
Definition	□ A catecholamine-secreting tumor of chromaffin cells of the adrenal medulla. □ Adrenal pheochromocytoma (90%) – Extra-adrenal pheochromocytoma.
Signs & Symptoms	classical triad : **1-resistant hypertension. (95%) 2-headache.3- sweating.** □ palpitations. □ chest pain. □ anxiety. □ glucose intolerance. □ ↑ metabolic rate.
Diagnosis	□ High plasma catecholamine. □ ↑ metabolites [VMA]* in urine. □ Imaging.
Treatment	Surgical resection.

What are the steps of Hypothalamic-pituitary-adrenal(HPA) Axis ?
1.hypothalamus secretes corticotrophinreleasing hormone (CRH) which stimulates the anterior pituitary gland to release ACTH.
2. ACTH acts on the zona fasiculata cells → release of glucocorticoids (Cortisol).

Talk about Regulation of HPA axis.
1. Negative feedback control.CRH → ↑ ACTH → ↑Cortisol → ↑[Cortisol] or synthetic steroid suppress CRH & ACTH secretion
2. Stress(e.g. major surgery, emotional stress). ↑↑CRH & ACTH → ↑↑Cortisol
3. The diurnal rhythm of plasma cortisol : Highest Cortisol level in the morning (8-9AM),Lowest Cortisol level in the late afternoon & evening (8-9PM)



What are the forms of glucocorticoids In the circulation?
1-protein-bound to cortisol-binding globulin (CBG) OR transcortin. (about90%)
2-unbound (free). The biologically active form (about10%)

What are the factors that alter the amount of CBG?
-CBG ↑ in pregnancy & estrogen treatment (e.g. oral contraceptives).
-CBG ↓ in hypoproteinemic states (e.g. nephrotic syndrome).

What are the laboratory tests that used to asses the Cortisol level?
1- Serum [cortisol] and plasma [ACTH] Serum measurement is preferred for cortisol & Plasma for ACTH. •Temporary↑-- in these hormones may be observed as a response to emotional stress.
2- Urinary cortisol excretion.
Urinary free cortisol (UFC)<250nmol/24hr ,Cortisol / Creatinine ratio<25µmol

What is the best time to take a sample?
Between 8 a.m. and 9 a.m. at morning and between 10 p.m. and 12 p.m. at night. (diurnal rhythm)

What is happen to cortisol after passing the liver ?
Cortisol is removed from plasma by the liver → metabolically inactive compounds → excreted in urine mainly as conjugated metabolites (e.g. glucuronides).

What are the Glucocorticoid functions?
- In liver: 1- ↑Gluconeogenesis 2-↑Amino acid uptake and degradation 3- ↑Ketogenesis
-In adipose tissue: - ↑Lipolysis through breakdown of fat
-In muscles: ↑proteolysis and amino acid release
-Conserving glucose: by inhibiting uptake into muscle and fat cells.

What are the Causes of elevated serum cortisol concentrations?
1. ↑ cortisol secretion: - Cushing's syndrome - Exercise- Stress, Anxiety, Depression- Obesity - Alcohol abuse - Chronic renal failure
2.↑cortisol binding globulin : Congenital , Estrogen theraby , Pregnancy

What are the symptoms Cushing's Syndrome?
- Weight gain (central obesity) - Buffalo's hump - Moon face - Excessive sweating - Atrophy of the skin - Purple striae - Proximal muscle weakness - Hirsuitism - ↓ libido ,menorrhoea & infertility - psychological disturbances (euphoria → psychosis)

What are the Signs Cushing's Syndrome?
- Loss of diurnal rhythm (The first sign to appear)
- Hypertension (due to the aldosterone - like effects) - Hyperglycemia or diabetes due to insulin resistance - Hypokalemic alkalosis- ↑protein metabolism- Impaired immunity

What are the causes of Pesudo-Cushing?
1-Depressed or extremely anxious patients 2-Severe intercurrent illness 3-Alcoholism

What are the Investigations used in case of suspected adrenocortical hyperfunction?

1- Screening tests. (to assess the clinical diagnosis of adrenocortical hyperfunction)
2- Confirmatory tests. (to confirm or exclude the provisional diagnosis)
3- Tests to determine the cause: to ascertain: (a) The site of the pathological lesion(adrenal cortex, pituitary or elsewhere?) b) The nature of the pathological lesion.

Explanation:

♣ Screening tests:

Low-dose dexamethasone suppression test .

- If cortisol is < 50 nmol/L = Supression → exclude Cushing's disease.
- If cortisol is > 50 nmol/L = No Supression→ Eather Pesudo-Cushing or True Cushing

24-hour urinary free cortisol(UFC).

If cortisol is < 250 nmol/day → exclude Cushing's disease > Disadvantage: incomplete collection of urine = a false-negative result → An alternative is to determine the urinary cortisol : creatinine ratio on an early morning specimen

♣ Confirmatory tests: (To distinguish true Cushing's syndrome from pseudo-Cushing's syndrome)

-Insulin-induced hypoglycemia (Hypoglycemia → ↑CRH → ↑ACTH → ↑cortisol)
- If the patient Show ↑ in cortisol, the patient have pseudo-Cushing
- If the patient Show no response, the patient have Cushing's syndrome

♣ Tests used to determine the cause of Cushing's syndrome: (Eather ACTH-dependent or ACTH-independent(Adrenal))

1- Plasma ACTH(diurnal rhythm)

-Undetectable: indicates functional adrenal tumor and confirmed by Abdminal CT scan
-High ACTH: Cushing's disease (pituitary-dependent)
-Extremly high ACTH: Ectopic (non-endocrine) origin of ACTH

2- High-dose dexamethasone suppression test. (It is used to distinguish Cushing's disease from ectopic ACTH secretion)

-90 % of patients with Cushing's disease show suppression
- patients with ectopic ACTH production will show no response or no suppression (Only 10% of them will DO!) note the supression is defined as fall to less than 50% of basal value

3- CRH stimulation test(measures the ACTH and cortisol levels)

-Cushing's disease: ↑ ACTH & cortisol above basal at 60 min. (10% of patients fail to respond.)
-Ectopic ACTH & adrenal tumors: No response

*Note: High-dose dexamethasone suppression test + the CRH test → 100 % specificity & sensitivity.

4-Radiological tests: MRI of pituitary & ultrasound or CT of adrenals

- Ultrasound or CT scanning of the adrenal glands
- MRI of the pituitary gland

Other blood tests:

Full blood count, Blood glucose, Blood electrolytes & pH ,Renal function tests ,Liver function tests

Test	Pseudo-Cushing	Cushing's disease	Adrenal tumor	Ectopic ACTH secreting tumor
S. cortisol	↑	↑	↑	↑
Dexamethasone Low dose test	Not suppressed	Not suppressed	Not suppressed	Not suppressed
Urinary cortisol	↑	↑	↑	↑
Diurnal rhythm	Lost	Lost	Lost	Lost
Insulin-induced hypoglycemia	Will ↑ CRH, ACTH and cortisol blood levels	No response	No response	No response
Plasma [ACTH]	-	Normal or ↑	Not detectable	↑↑↑
Dexamethasone High dose test	-	suppressed	Not suppressed	Not suppressed
CRH test	-	↑	No response	No response

Case..
A 24-year-old woman presentedin the ER with increasing darkening of the skin, dizziness, and easy fatigability ,There were no headaches, blurred vision, and neither loss of consciousness nor change in her bowel habit.
in biochemchal examination Na serum level 90mEq/L (normal 135-145 mEq/L) , K serum level 60 mEq/L (normal 3.5-5.0 mEq/L),glucose leve is low,
Main findings in the systemic examination that the blood pressure is 100/60 mmHg supine and 70/40mmHg sitting .. All other systems were essentially normal.

What is the likely diagnosis? Addison's disease

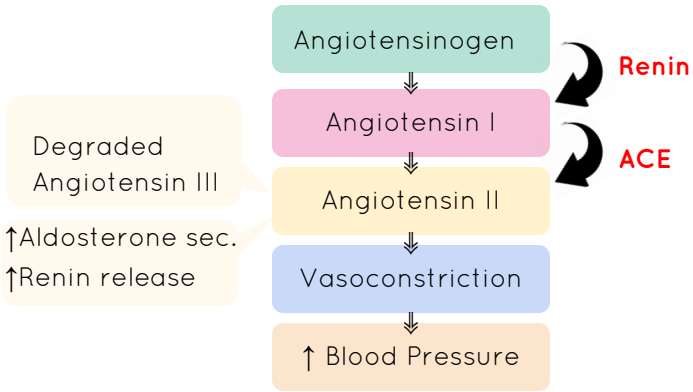
What does Aldosteron regulate? water , electrolytes & blood pressure

What is the mechanism of action of aldosteron AND where does it happen?
conserve Na+, mainly by facilitating Na+ reabsorption and reciprocal K+ or H+ secretion in the distal renal tubule. ↑ potassium excretion ↑ sodium and water reabsorption
note: The regulatory of cortisol is Hypothalamo-pituitary axis, while the regulatory of Aldosteron is Renin-Angiotensin system.

list situation that could stimulate Renin-Angiotensin system?
1-a fall in circulating blood volume.(Hypovolemia)
2-a fall in renal perfusion pressure.(Renal Ischima) for example stenosis.
3-loss of Na+.(hyponetremia)

where does Angiotensinogen synthesis ? α2-Globulin made in the liver

What will happen if there is decrease in BP ?(the mechanism of action Renin-Angiotensin system).
changes through baroreceptors



What are the causes of of AC hypofunction?
- 1ry(destruction of adrenal gland, Addison's disease:) autoimmune, infection: TB and infiltrative lesions eg: amylodosis
- 2ry :Pituitary tumors - Vascular lesions - Head trauma - Hypothalmic diseases, Iatrogenic (steroid therapy, surgery or radiotherapy)

Mention the symptoms of Primary adrenal failure?
- Lethargy, weakness, nausea & weight loss.
- Hypotension especially on standing (postural)
- Hyperpigmentation (buccal mucosa, skin creases, scars)
- Hypoglycemia, Na+, K+ & ↑ urea
- Deficiency of both glucocorticoids & mineralocorticoids
- Life threatening & need urgent care.

How does the pigmentation occur?

- The anterior pituitary POMC is cleaved into ACTH, γ-MSH, and β-lipotropin.
- The subunit ACTH undergoes further cleavage to produce α-MSH, the most important MSH for skin pigmentation.

What is the cause of hyperpegmintation in addison's disease?

Hyperpigmentation occurs because melanocyte-stimulating hormone (MSH) and (ACTH) share the same precursor molecule, Pro-opiomelanocortin
*POMC note: in secondary adrenal insufficiency ,skin darkening does not occur

Investigation for Addison's disease:

- Screening:Basal measurement of:Serum urea, Na+, K+ & glucose/Serum cortisol & plasma ACTH
- **confirmatory tests**

1. Short tetracosactrin (Synacthen) test (Short ACTH stimulation test) → Failure of S. cortisol to respond to stimulation, confirm AD.
Abnormal results: – emotional stress – glucocorticoid therapy – estrogen contraceptives
2. Adrenal antibodies
3. Imaging (Ultrasound/CT) * to identifying the cause of primary adrenal failure

Investigation for secondary Addison's disease insuffciency:

- Screening: Low ACTH and Low cortisol
- **confirmatory tests** Long ACTH stimulation test: Stepwise increase in S. cortisol

Depot Synacthen test (confirmatory test)
1. Measure basal S. cortisol
2. Stimulate with I.M. synthetic ACTH (1.0 mg) on each of three consecutive days
3. Measure S. cortisol at 5 hours after I.M. injection on each of the three days
Interpretation of results:
-Addison's disease: No rise of S. cortisol >600 nmol/L at 5 h after 3rd injection.
-Secondary AC: Stepwise increase in the S. cortisol after successive injections
-Limitations:

- Hypothyroidism: Thyroid deficiency must be corrected before testing of adrenocortical functions
- Prolonged steroid therapy

- Others : Insulin-induced hypoglycemia / MRI pituitary gland

Which type of GLUCOCORTICOIDS applied as creams on the face?
mild-moderate (Mometasone, Fluticasone and Hydrocortisone acetate)

What is the name of the drug used to treat emergency Adisonian crisis? parental cortisol

what is the advantage of inhalant drugs? Name one of them.
no systemic effects. (Fluticasone,budesonide)

What is the test witch used to diagnose Cushing's syndrome and what is the drug used after surgical removal of the tumor?
1-dexamethasone suppresion test. 2-cortisol.

What is the Drug of Choice in Replacement Therapy of Addison's disease? Fludrocortisone.

A patient came to you with Addison's Disease symptoms knowing that he has a peptic ulcer and osteoporosis what should you do?
treat him with glucocorticoids and treat peptic ulcer with (H2 blocker or proton pump inhibitors) and osteoporosis with Bisphosphonates.

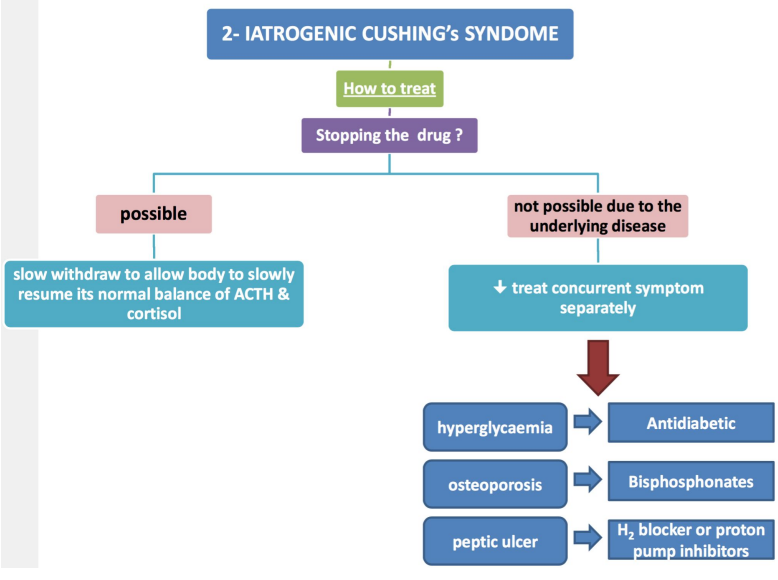
What are the drugs given to patient suffer from Addison's Disease? Cortisol and fludrocortisone.

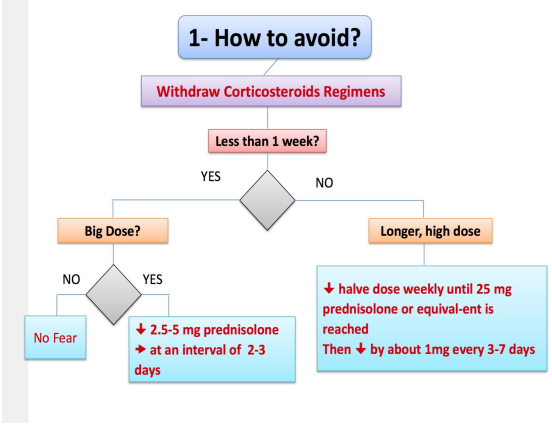
A patient treated with prednisolone for two weeks and you want to stop the medication, what should you do?
ß half-dose weekly until 25 mg then ß 1mg every 3-7 days.

A patient comes to you with Avascular necrosis of head of femur and Ocular toxicity . what is the type of drug he was treated with? glucocorticoids

Patients receiving GCs and he is subjected to stress. What should you do and why?
double the dose, to avoid Addisonian crisis.

pregnant women treated with fluorinated GCs, what will it cause to the fetus ? teratogenicity.





Pathology of Adrenal Cortex:

1- Hypercortisolism(Cushing Syndrome)(Hyperfunction)
A - exogenous(drugs for example) B- endogenous causes can be divided into:

ACTH-DEPENDENT(High ACTH)	ACTH-INDEPENDENT
1.Cushing disease (pituitary adenoma, rarely CRH-dependent pituitaryhyperplasia) **2.**Ectopic corticotropin syndrome (ACTH-secreting pulmonarysmallcell carcinoma (ParaneoplsamicSyndrome), bronchial carcinoid)	**1.**Adrenal adenoma, carcinoma **2.**Macronodularhyperplasia (ectopic expression of hormone receptors, including GIPR, LHR, vasopressin & serotonin receptors) **3.**Primary pigmented nodular adrenal disease (PRKARIA and PDE11 mutations) **4.**McCune-Albright syndrome (GNAS mutations)

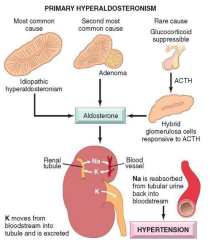
Clinical Features of Cushing Syndrome:
1-Obesity weight gain. 2-Facial plethora. 3-Rounded face (Moon face). 4-Hirsutism.
Morphology:
1.Cortical atrophy: results from exogenous glucocorticoids.
2.Diffuse hyperplasia: individuals with ACTH-dependent Cushing syndrome
3.Macronodular or micronodular hyperplasia. 4.Adenoma or carcinoma.

2-Hyperaldosteronism(Conn'sSyndrome) (Excess aldosterone secretion)(Hyperfunction)
1- 1ry aldosteronism:(overproduction of aldosterone)suppression the renin-angiotensin system
2-2ry hyperaldosteronism:aldosterone release occurs in response to activation of the renin-angiotensin system.
Clinical Features: 1-hypertension. 2-Hypokalemia.
Morphology: 1-Solitary . 2-Women>men. 3-Well-circumscribed lesions in the left>right.
Histogically: Vacuolated cytoplasm

3-Adrenocortical Insufficiency(Hypofunction)•Caused by-
1- 1ry adrenal disease: like (congenital adrenal hypoplasia)
2-Decreased stimulation of the adrenals due to a deficiency of ACTH(secondary hypoadrenalism).
Three patterns of adrenocortical insufficiency :
1- 1ry acute (Adrenal crisis). 2- 1ry chronic(Addison disease, an auto-immune disease)
3- 2ry (hemorrhage & infection → loss of function)or adrenalitis or long standing steroids.

Pathology of Adrenal Medulla:(the most important features Neuroblastoma in children & Pheochromocytoma in adults)
-Pheochromocytomas:(chromaffin cells) secrete catecholamines. some secrete other peptide hormones. Mau assioted with caushing syndrome
-Hypertensionis the most predominant clinical manifestation
-Majority of them are benign The only thing to say it's malignant if there is metastasis

Syndromes Components:
1-MEN, type 2A :Medullary thyroid carcinomas, Pheochromocytomas, Parathyroid hyperplasia.
2-MEN, type 2B :Medullary thyroid carcinomas, Pheochromocytomas, Mucosal neuromas.
3-Von Hippel-Lindau:Renal, hepatic, pancreatic, and epididymal cysts, Renal cell carcinomas, Cerebellar hemangioblastomas, Pheochromocytoma.
4-Von Recklinghausen's Neurofibromatosis Type I: Café au laitskin spots, Schwannomas, meningiomas, gliomas, Pheochromocytoma.
5-Sturge-Weber : Cavernous hemangiomasof fifth cranial nerve distribution



Morphology: 1-Polygonal to spindle shaped (chromaffin, chief cells)
2-Small to large hemorrhagic 3-Well demarcated
4-Sustentacularsmall cells 5-Together, Zellballennests

THANK YOU FOR CHECKING OUR TEAM..

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