

Endocrinology

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د. حازم اسماعيل غزالي

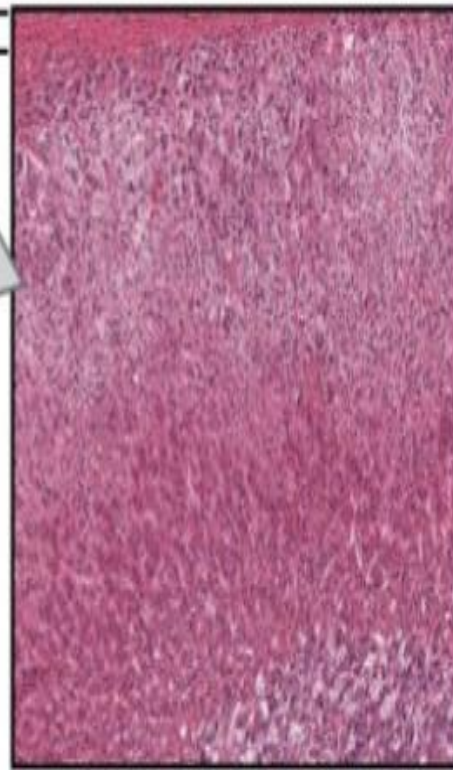
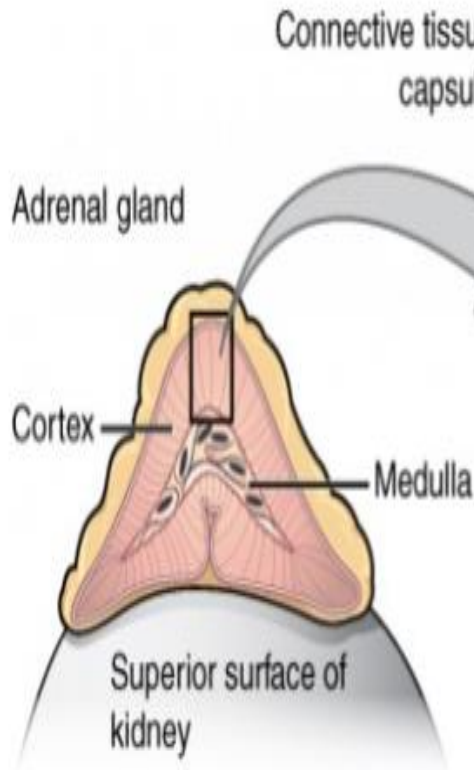
Consultant In Internal Medicine

Anbar Medical College

Medical Department

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Adrenal glands



Tissue area	Hormones released	Examples
Zona glomerulosa (adrenal cortex)	Mineralcorticoids (regulate mineral balance)	Aldosterone
Zona fasciculata (adrenal cortex)	Glucocorticoids (regulate glucose metabolism)	Cortisol Corticosterone Cortisone
Zona reticularis (adrenal cortex)	Androgens (stimulate masculinization)	Dehydroepian- drosterone
Adrenal medulla	Stress hormones (stimulate sympathetic ANS)	Epinephrine Norepinephrine

The adrenal glands

- ❖ The adrenals function as several separate endocrine glands within one anatomical structure.
- ❖ The **adrenal medulla** is an extension of the sympathetic nervous system which secretes catecholamines.
- ❖ Most of the **adrenal cortex** is made up of cells which secrete **cortisol** and adrenal **androgens**, and form part of the **hypothalamic-pituitary-adrenal axis**.
- ❖ The small outer **glomerulosa** of the cortex secretes **aldosterone** under the control of the **renin-angiotensin system**.
- ❖ Subtle alterations in adrenal function may be important in common diseases, including **hypertension**, **obesity** and type 2 **diabetes mellitus**.
- **classical syndromes** of adrenal hormone deficiency and excess are relatively rare

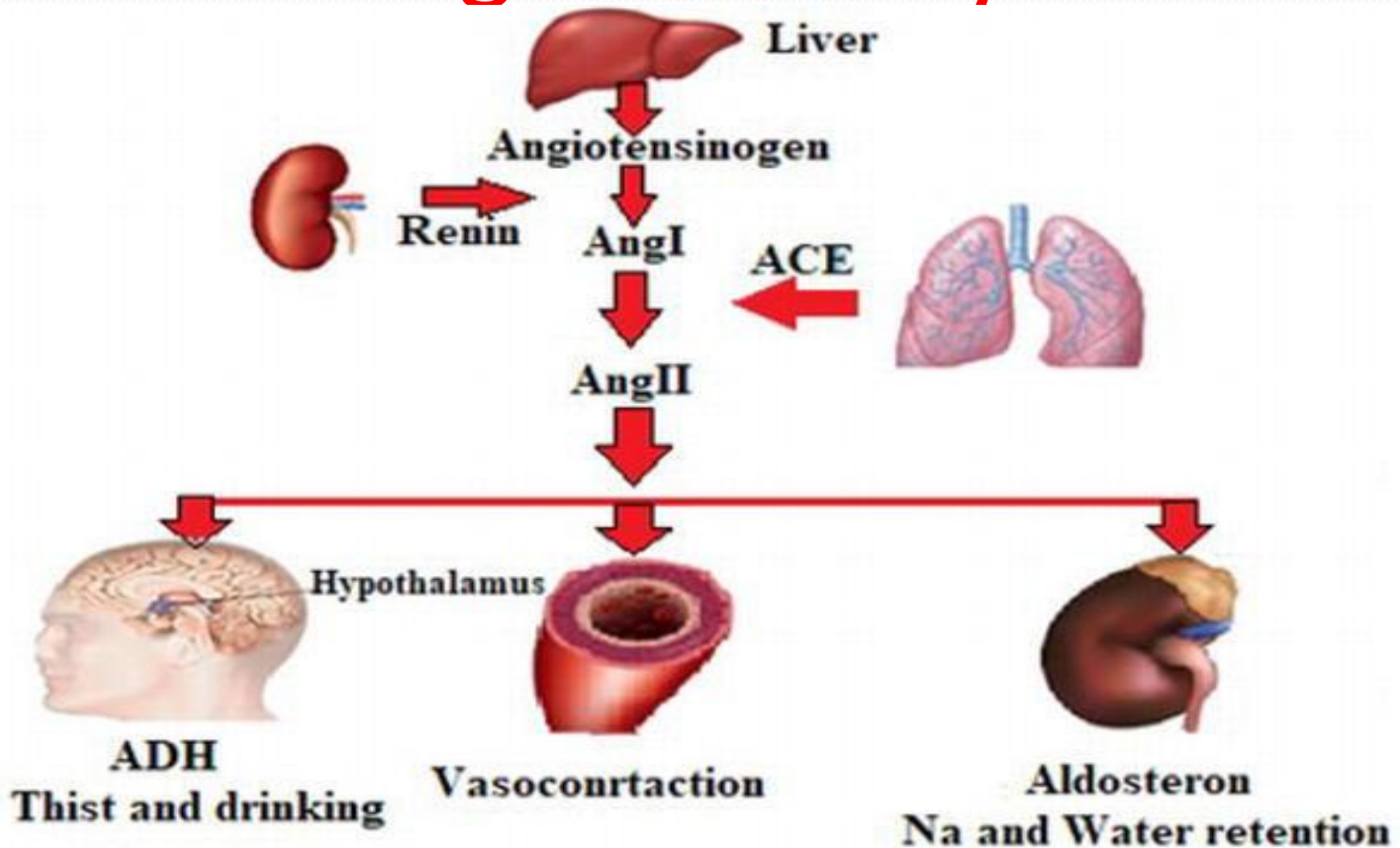
Glucocorticoids

- Cortisol is the major glucocorticoid in humans. Levels are highest in the **morning** on waking and lowest in the middle of the **night**.
- Cortisol rises dramatically during **stress**, including any illness. This elevation protects key metabolic functions (e.g. maintaining cerebral glucose supply during starvation) and puts an important '**brake**' on potentially damaging inflammatory responses to infection and injury.
- The clinical importance of cortisol deficiency is, therefore, most obvious at times of stress.
- In the circulation, more than **95% of cortisol** is bound to protein, principally **cortisol-binding globulin**. It is the free fraction which is biologically active via **glucocorticoid receptors**.
- Cortisol can also activate **mineralocorticoid receptors**, but it does not normally do so because most cells containing mineralocorticoid receptors also express an enzyme, **11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD₂)**, which converts cortisol to its inactive metabolite, cortisone.
- Loss of this protection of mineralocorticoid receptors by inhibition of 11 β -HSD₂ (e.g. by liquorice) results in cortisol acting like aldosterone as a potent sodium-retaining steroid

Mineralocorticoids

- **Aldosterone** is the most important sodium-retaining hormone, acting via mineralocorticoid receptors. Sodium is retained at the expense of increased excretion of potassium. Increased potassium in the lumen of the distal nephron also results in increased exchange with protons and metabolic alkalosis.
- The principal stimulus to aldosterone secretion is **angiotensin II**, a peptide produced by activation of **the renin-angiotensin system**.
- **Renin** secretion from the juxtaglomerular apparatus in the kidney is stimulated by low perfusion pressure in the afferent arteriole,.
- As a result, renin is increased in hypovolaemia and renal artery stenosis, and renin concentrations when standing are about double those when lying down.

Renin-angiotensin system



Catecholamines

- In humans, only a small proportion of circulating noradrenaline (norepinephrine) is derived from the **adrenal** medulla; much more is released from other **nerve endings**.
- The methyltransferase enzyme responsible for the conversion of noradrenaline to adrenaline (epinephrine) is induced by glucocorticoids.
- Blood flow in the adrenal is centripetal so that the medulla is bathed in high concentrations of cortisol so it is the major source of circulating adrenaline.

Adrenal androgens

- are secreted in response to ACTH and are the most abundant steroids in the blood stream.
- They are probably important in the initiation of puberty (the adrenarche).
- The adrenals are also the major source of androgens in adult females and may be important in female libido.

● **CUSHING'S SYNDROME**

- Cushing's syndrome is caused by excessive activation of glucocorticoid receptors.
- By far the most common cause is iatrogenic, due to prolonged administration of synthetic glucocorticoids such as prednisolone.
- -Non-iatrogenic Cushing's syndrome is rare, although it presents by many diverse routes and is often a 'spot diagnosis'.

Etiology

- Amongst endogenous causes, pituitary-dependent cortisol excess (called Cushing's disease) accounts for ~80% of cases.
- Both Cushing's disease and adrenal tumor are four times more common in women than men.
- In contrast, ectopic ACTH syndrome (often due to a small-cell carcinoma of the bronchus) is more common in men

Causes of Cushing's syndrome

❖ **ACTH-dependent**

- Pituitary adenoma secreting ACTH (i.e. Cushing's disease--)
- Ectopic ACTH syndrome (e.g. bronchial carcinoid, small-cell lung carcinoma, pancreatic neuro-endocrine tumour)
- Iatrogenic (ACTH therapy--)

❖ **Non-ACTH-dependent**

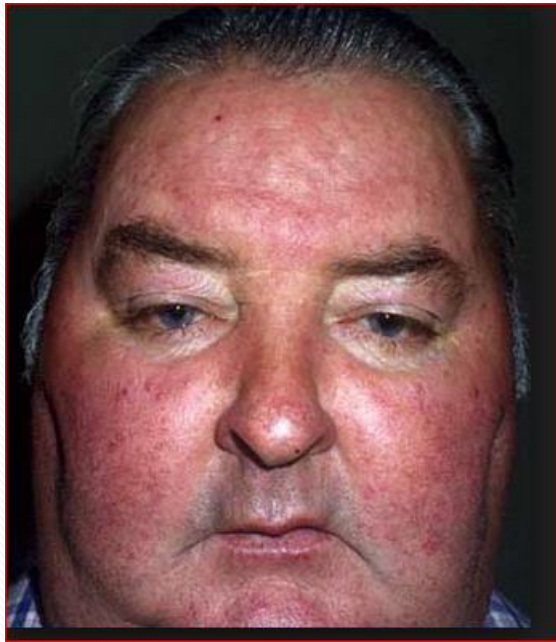
- Iatrogenic (chronic glucocorticoid therapy, e.g. for asthma)
- Adrenal adenoma
- Adrenal carcinoma

❖ **Pseudo-Cushing's syndrome**, i.e. cortisol excess as part of another illness

- Alcohol excess (biochemical and clinical features)
- Major depressive illness (biochemical features only, some clinical overlap)
- Primary obesity (mild biochemical features, some clinical overlap)

Cushing's syndrome :Clinical assessment

- Many of manifestations of glucocorticoid excess are not specific to Cushing's syndrome
- Some common disorders can be confused with Cushing's syndrome because they are associated with alterations in cortisol secretion: for example, **obesity and depression**. Features which have the best predictive value in favour of Cushing's syndrome in an obese patient are bruising, myopathy and hypertension.
- Any clinical suspicion of cortisol excess is best resolved by **further investigation**.
- Patients with features of Cushing's syndrome it is vital to exclude **iatrogenic causes**. **Even inhaled or topical** glucocorticoid administration can induce Cushing's syndrome in susceptible individuals.
- **A careful drug history** must be taken before embarking on complex investigations.
- Some clinical features are more common in **ectopic ACTH** syndrome. Unlike pituitary tumors secreting ACTH, ectopic tumours have no residual negative feedback sensitivity to cortisol, and both ACTH and cortisol levels are usually higher than with other causes.
- **Very high ACTH** levels are associated with marked pigmentation.
- Very high cortisol levels overcome the barrier of 11β -HSD₂ in the kidney and cause **hypokalaemic alkalosis**. Hypokalaemia aggravates both **myopathy** and **hyperglycaemia (by inhibiting insulin secretion)**.



● **Cushing's syndrome :Clinical assessment .cont.**

- When the tumor secreting ACTH is malignant (e.g. **small-cell lung carcinoma**), then the onset is usually rapid and may be associated with **cachexia**.
- For these reasons, the classical features of Cushing's syndrome are less common in ectopic ACTH syndrome, and if present suggest that a less aggressive tumor (e.g. **bronchial carcinoid**) is responsible.
- In Cushing's disease, the pituitary tumor is usually a micro adenoma (< **10 mm in diameter**); hence other features of a pituitary **macro adenoma** (hypopituitarism, visual failure or disconnection hyperprolactinemia **are rare**

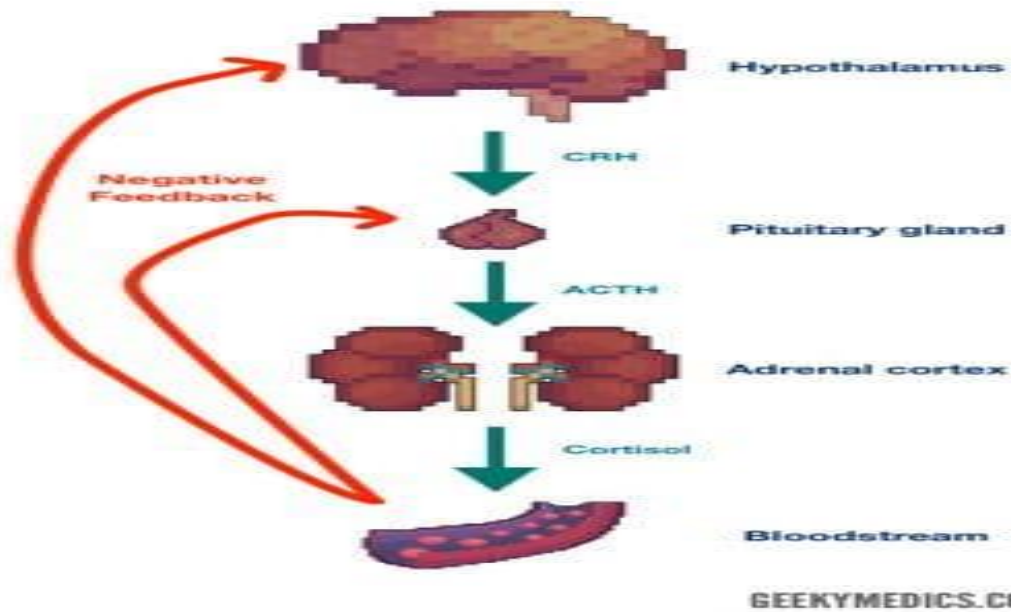
Investigations

- The large number of tests available for Cushing's syndrome reflects the fact that no single test is infallible and several are needed to establish the diagnosis.
- It is useful to divide investigations into those which establish whether the patient has Cushing's syndrome, and those which are used subsequently to elucidate the aetiology .

--Does the patient have Cushing's syndrome??

- Plasma cortisol levels are **highly variable in healthy** subjects so that patients with Cushing's syndrome often have daytime values within the normal range. For this reason, there is no place for a **random measurement of daytime** plasma cortisol in the clinic in either supporting or refuting the diagnosis.
- Cushing's syndrome is confirmed by the demonstration of increased secretion of **cortisol** (measured **in urine**) that fails to suppress with relatively **low doses of dexamethasone** (measured in plasma or urine).
- Loss of diurnal variation, with **elevated evening plasma** cortisol, is also characteristic of Cushing's syndrome, but samples are difficult to obtain .
- **Dexamethasone** is used for suppression testing because, unlike prednisolone, it does not cross-react in radioimmunoassays for cortisol.
- Also, the hypothalamic-pituitary-adrenal axis may 'escape' from suppression by dexamethasone if a more potent influence such as **psychological stress supervenes**.

Hypothalamic-Pituitary-Adrenal Axis



There is a rare syndrome of **cyclical Cushing's syndrome** in which the excessive secretion of cortisol is **episodic**. If there is a strong clinical suspicion of Cushing's syndrome but initial screening tests are normal, then weekly 24-hour urine cortisol measurements for up to 3 months are sometimes justified

What is the cause of the Cushing's syndrome??

- Once the presence of Cushing's syndrome is confirmed, measurement of plasma ACTH is the key to establishing the differential diagnosis.
- In the presence of excess cortisol secretion, an undetectable ACTH indicates an **adrenal tumor**, while any detectable ACTH is pathological.
- Tests to discriminate pituitary from ectopic sources of ACTH rely on the fact that pituitary tumors, but not ectopic tumors, **retain some features of normal regulation of ACTH secretion**. Thus, in Cushing's disease ACTH secretion is suppressed by dexamethasone, at a higher dose than in health, and ACTH is stimulated by corticotrophin-releasing hormone (CRH).
- Localisation of tumors secreting ACTH or cortisol by **MRI with gadolinium contrast enhancement** detects around **70% of pituitary microadenomas secreting ACTH**.
- **Venous catheterisation** with measurement of **inferior petrosal sinus** ACTH (i.e. draining directly from the pituitary) may be helpful in confirming **Cushing's disease** if the MRI does not show a microadenoma.
- **CT or MRI detects most adrenal adenomas. Adrenal carcinomas are usually large (> 5 cm).**

TESTS FOR CUSHING'S SYNDROME

Test

- **Protocol**
- **1 -does the patient have Cushing's syndrome?**
-
- Overnight dexamethasone suppression test-**A**
- 1 mg orally at midnight;
- measure plasma cortisol at 0800-0900 hrs
- Plasma cortisol < 60 nmol/l (< 2.2 µg/dl) excludes Cushing's
- Low-dose dexamethasone suppression test **B-**
- 0.5 mg 6-hourly for 48 hrs;
- sample 24-hr urine cortisol during second day and 0900-hr plasma cortisol after 48 hrs
- Urine cortisol < 100 nmol/day (36 µg/day) or plasma cortisol < 60 nmol/l (< 2.2 µg/dl) excludes Cushing's

2-what is the cause of crushing's syndrome •

A-High-dose dexamethasone suppression test

- 2 mg 6-hourly for 48 hrs;

sample 24-hr urine cortisol at baseline and during second day

- Urine cortisol < 50% of basal suggests pituitary-dependent A disease; > 50% of basal suggests ectopic ACTH syndrome

- **B-Corticotrophin-releasing hormone test**

100 µg ovine CRH i.v. and monitor plasma ACTH and cortisol for 2 hr

- Peak plasma cortisol > 120% and/or ACTH > 150% of basal values suggests pituitary-dependent disease; lesser responses suggest ectopic ACTH syndrome

Inferior petrosal sinus sampling C-

Catheters placed in both inferior petrosal sinuses and simultaneous sampling from these and peripheral blood for ACTH; may be repeated 10 minutes after peripheral CRH injection

ACTH concentration in either petrosal sinus > 200% peripheral ACTH suggests pituitary-dependent disease; < 150% suggests ectopic ACTH syndrome

Management •

- Untreated Cushing's syndrome has a 50% 5-year mortality.
- Most patients are treated surgically with medical therapy given for a few weeks prior to operation.
- A number of drugs are used to inhibit corticosteroid biosynthesis, including metyrapone, aminoglutethimide and ketoconazole. The dose of these agents is best titrated against 24-hour urine free cortisol

Cushing's disease

- Trans-sphenoidal surgery with selective removal of the adenoma is the treatment of choice. Experienced surgeons can identify microadenomas which were not detected by MRI and cure about 80% of patients.
- - If the operation is unsuccessful then bilateral adrenalectomy is an alternative.
- If bilateral adrenalectomy is used in patients with pituitary-dependent Cushing's syndrome, then there is a risk that the pituitary tumor will grow in the absence of the negative feedback suppression previously provided by elevated cortisol levels. This can result in Nelson's syndrome, with an aggressive pituitary macroadenoma and very high ACTH levels causing pigmentation. Nelson's syndrome can be prevented by **pituitary irradiation**

Adrenal tumors

- Adrenal adenomas are removed via laparoscopy or a loin incision. Adrenal carcinomas are resected if possible,
- - the tumor bed irradiated and the patient given the adrenolytic drug **mitotane**.
- -Cytotoxic chemotherapy may retard disease progression in patients with metastases.

Ectopic ACTH syndrome

- Localised tumors causing this syndrome (e.g. bronchial carcinoid) should be removed.
- During treatment or palliation of non-resectable malignancies, it is important to reduce the severity of the Cushing's syndrome using medical therapy