Session 8 , Lecture 2

Duration : 1 hr

Metabolism

Adrenal Glands

Disorders of the Adrenal Cortex

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1.Harper's Illustrated Biochemistry, Thirtieth Edition Copyright © 2015
2. Lehninger Principles of Biochemistry Sixth Edition (6th Edition)
3. Marks Essentials of Medical Biochemistry.

Learning outcomes (LO)

- List the hormones produced by the adrenal glands and their functions. LO1
- Describe the structure of the steroid hormones.LO2
- Explain how the steroid hormones affect their target tissues.LO3
- Explain how cortisol secretion is controlled by ACTH and CRH.LO4
- Describe the structure and functions of adrenaline.LO5

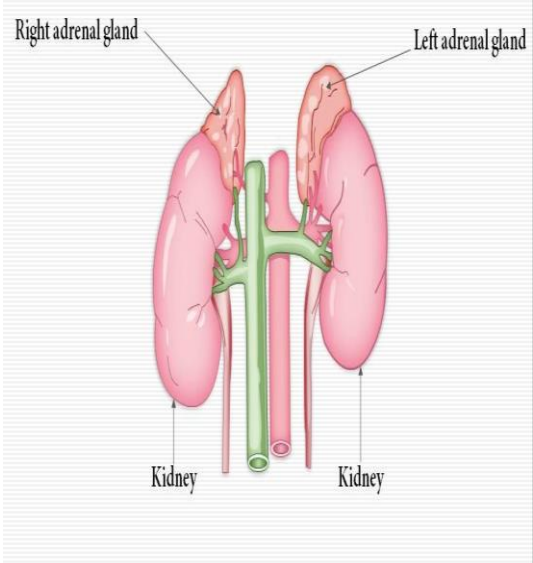
Learning outcomes (LO):

- Explain how ACTH can lead to increased pigmentation in certain areas of the body.LO6
- Effects of over-and under-secretion of cortisol. LO7
- Tests of adrenal cortical function.LO8
- Explain how cortisol can have weak mineralocorticoid & androgen effects. LO9

Adrenal glands

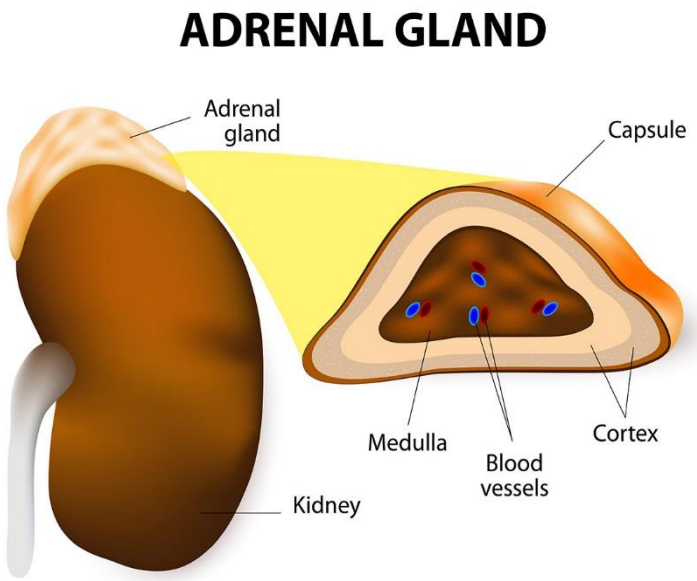
L01

- a **pair** of endocrine glands that cap the upper poles of the kidneys (suprarenal glands).



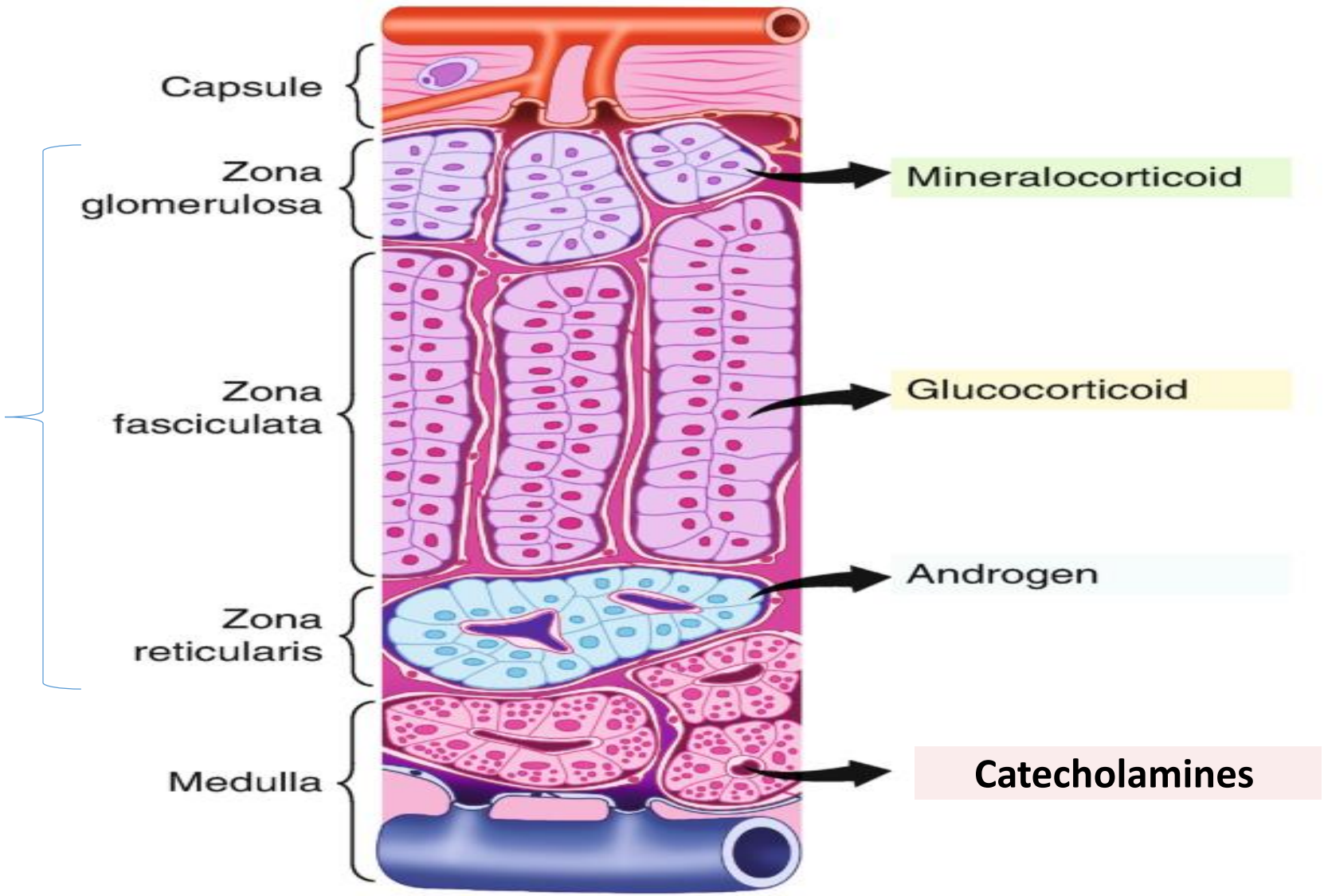
➢The gland consists of <u>two regions:</u>

- **Outer cortex**
- **Inner medulla**



L01

Cortex


Capsule
Zona glomerulosa
Zona fasciculata
Zona reticularis
Medulla
Mineralocorticoid
Glucocorticoid
Androgen
Catecholamines

L01

	Layer	Hormones	Regulation of secretion	Function
Cortex	**Zona Glomerulosa**	**Mineralocorticoid** Aldosterone (C21)	Renin-angiotensen system	❖ Reabsorption of **Na+ & Water** in exchange of **K+/H+** at DCT ❖ Excess aldosterone cause hypertension, hypokalemia
	Zona Fasciculata	**Glucocorticoid** Cortisol (C21)	HPA-axis ACTH	❖ Affect metabolism of (CHO, protein ,fat) ❖ Immunosuppression ,anti-inflammatory
	Zona Reticularis	**Androgens** Dehydroepiandrosterone Androstenedione (C19)	HPA-axis ACTH	Sexual development
	Medulla	**Catecholamine** Epinephrine	Sympathetic preganglionic neuron	Stress response

LO2

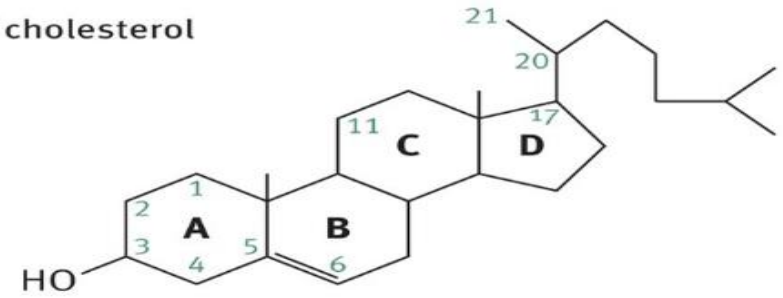
Steroid Hormones Structure

- Steroid hormones are **Lipophilic ,** synthesized from **cholesterol (C27) via progesterone** ,in a series of enzyme catalyzed reactions .

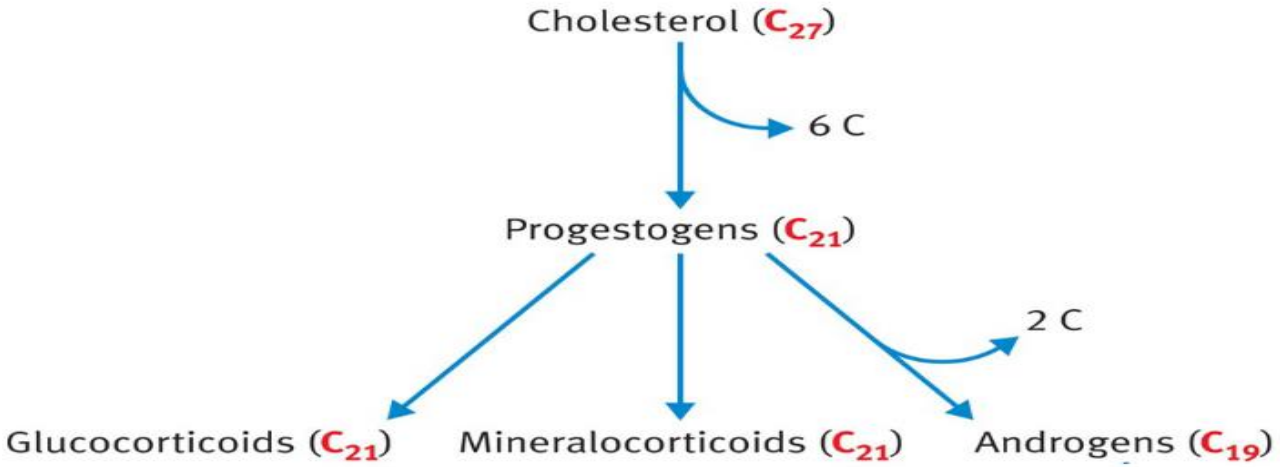
Structural differences :

1. The number of carbon atoms.
2. Functional groups, the side chain on C17 is the main determinant of the hormone activity .
3. Distribution of C=C double bonds.

A Structure of cholesterol



B Synthesis of steroid hormones from cholesterol



In part B of this figure, C = carbon atom

LO3

Transport in plasma

- Steroid hormones are lipophilic and must be transported **bound to plasma proteins.**
- 90 % **bound** to cortisol binding globulin (CBG; transcortin).
- 10% being **free** and **biologically active**.

Mechanism of action of steroids on target cells

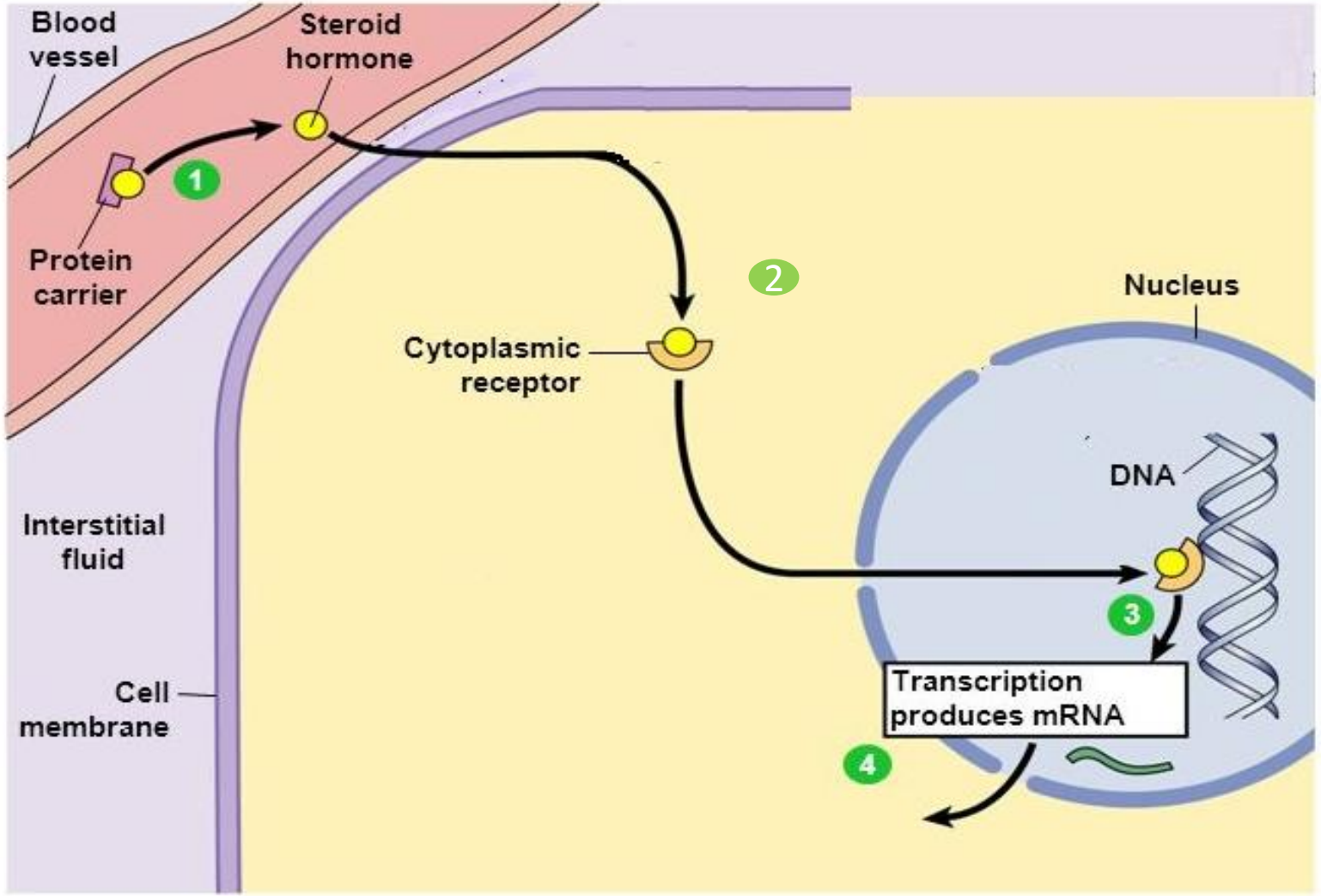
LO3

1. Only free hormone can diffuse into target cell

2. Steroid receptors typically in the cytoplasm

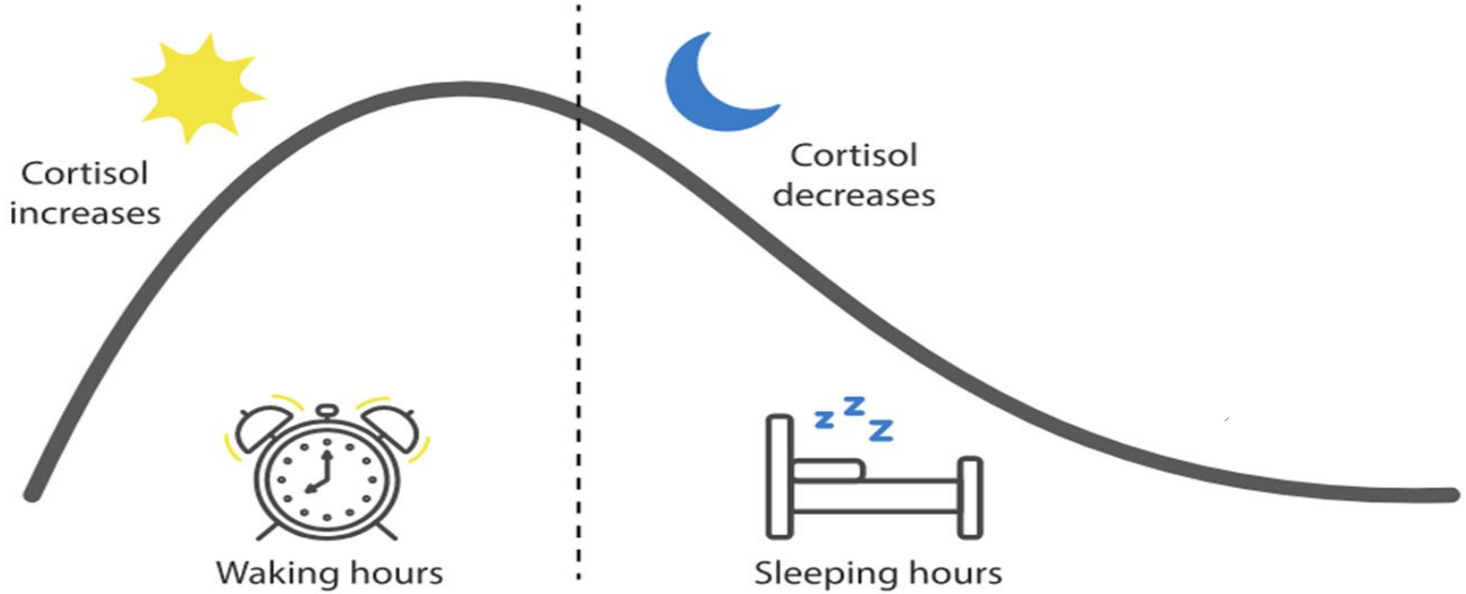
3. The hormone/receptor complex then enters the nucleus to interact with specific regions of DNA activating one or more genes .

4. Activated gene produce mRNA that move into the cytoplasm to be translated into specific protein at the ribosome, that alter the cell's activity



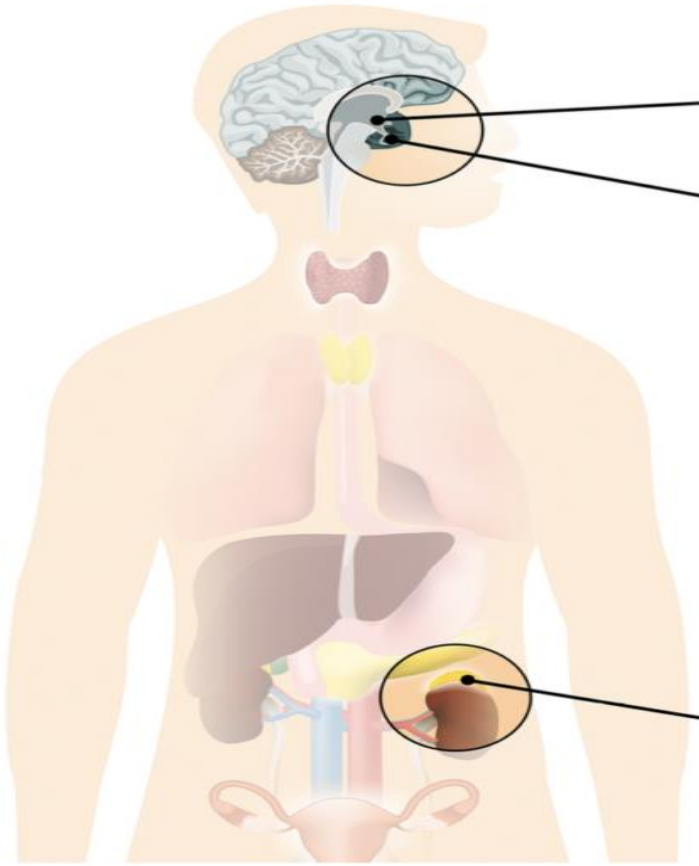
- Plasma cortisol concentrations are usually **highest** between about **07.00 - 09.00 a.m.** and lowest between **23.00 pm - 04.00 am .**

- Loss of circadian rhythm is one of the earliest features of Cushing's syndrome



Control of cortisol secretion

LO4



Circadian rhythm

Stress

Hypothalamus

CRH
(corticotropin releasing hormone)

Pituitary gland

ACTH
(adrenocorticotropic hormone)

Adrenal glands

Cortisol

Immunosuppression
Anti-inflammatory

lipolysis

Gluconeogenesis

Protein catabolism

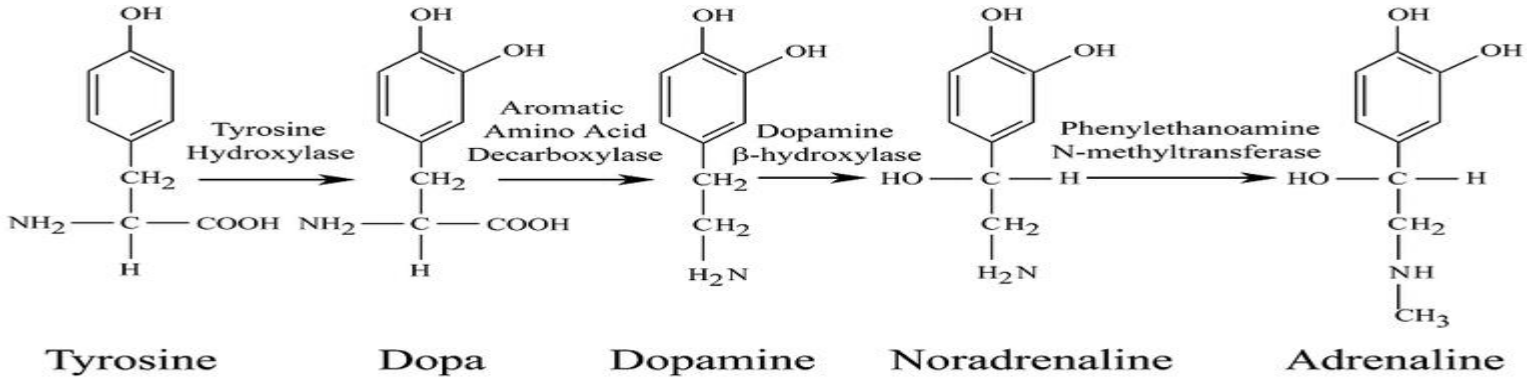
LO5

Adrenal Medulla

The adrenal medulla is a modified **sympathetic ganglion** that synthesizes **catecholamines** : adrenaline (epinephrine) , noradrenaline (norepinephrine) and dopamine.

Catecholamine synthesis

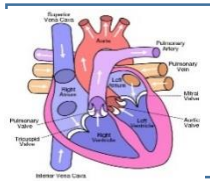
- The catecholamines are synthesized from amino acid **Tyrosine** by a series of enzyme-catalyzed steps
- The catecholamines are stored in the medullary cells in membrane-limited vesicles.



LO5

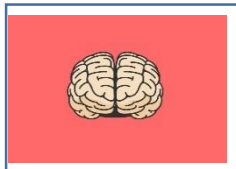
Actions of adrenaline

- Adrenaline is released as part of the fright, flight or fight response and it is secreted in response to **stressful situations**.



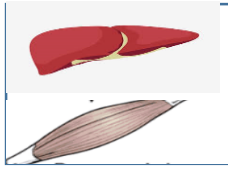
Cardiovascular system

Increase cardiac output, blood supply to muscle



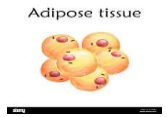
Central nervous system

(mental alertness)



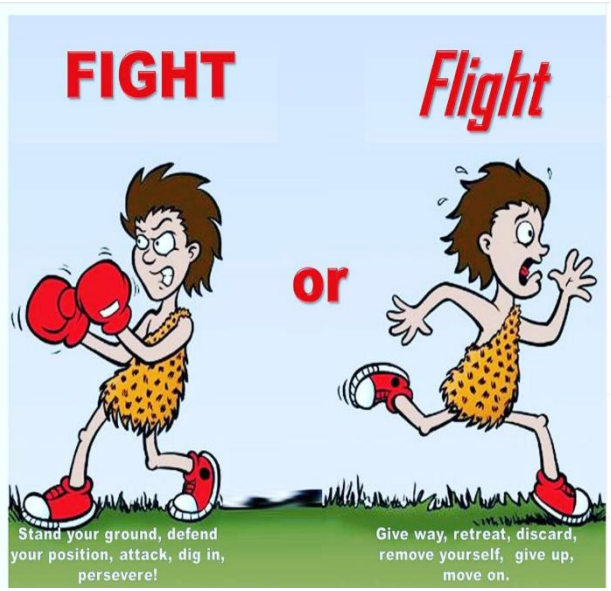
Carbohydrate metabolism

Increase glycogenolysis in liver and muscle



lipid metabolism

increase lipolysis in adipose tissue



LO6

ACTH associated hyperpigmentation

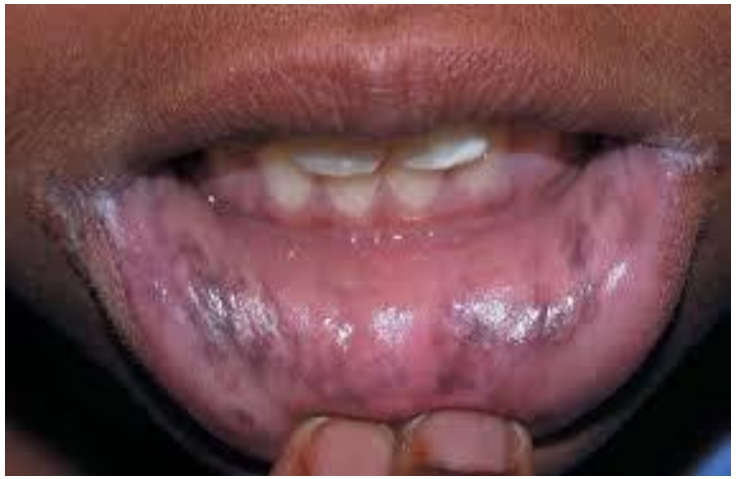
- ACTH is a single-chain polypeptide made up of 39 amino acids

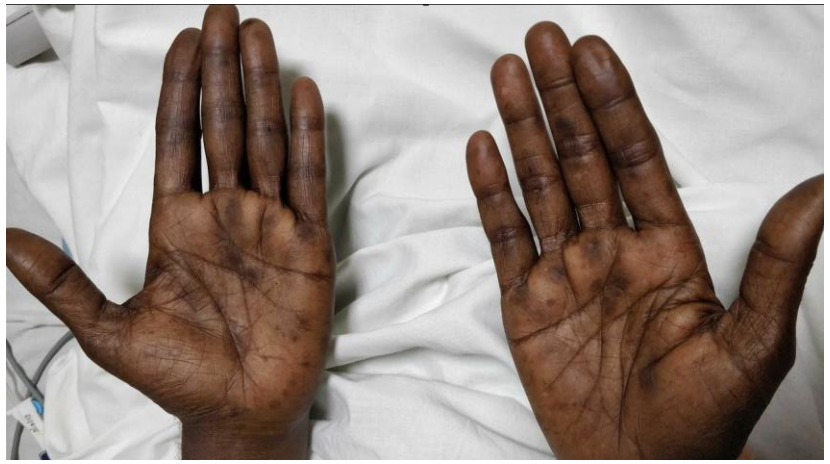
- The initial biosynthetic precursor is a large protein (~250 amino acids) **called proopiomelanocortin (POMC).**

- The MSH (melanocyte stimulating hormone) sequence of 13 amino acids is contained within the ACTH sequence in POMC giving **ACTH some MSH-like activity when present in excess.**

LO6

- **increased pigmentation due to partial MSH activity.**





LO7

Disorders of Adrenal Cortex

- Disease can result from **overproduction**, as well as **deficiency**, of adrenocortical hormones.

- Moreover, excess or deficiency of these hormones can be :

  Primary (resulting from adrenal gland dysfunction) ***or***

  Secondary (resulting from dysfunction of pituitary gland)

LO7

Cushing ‘s syndrome: Increased glucocorticoids due to:

1. Adrenal cortex tumor (↑cortisol , ↓ ACTH)

2. Increased the secretion of ACTH caused by pituitary tumor **(Cushing ‘s disease)** (↑cortisol , ↑ ACTH)

3. Iatrogenic : drug induced ex: steroid abuse (most common cause)

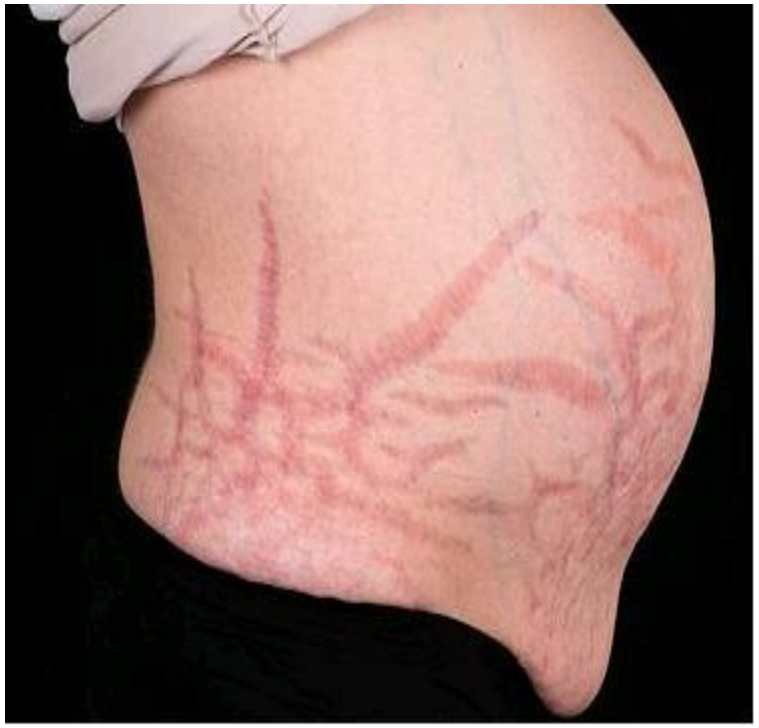
LO7

Effects of over-secretion of cortisol – clinical features of Cushing ‘s syndrome:

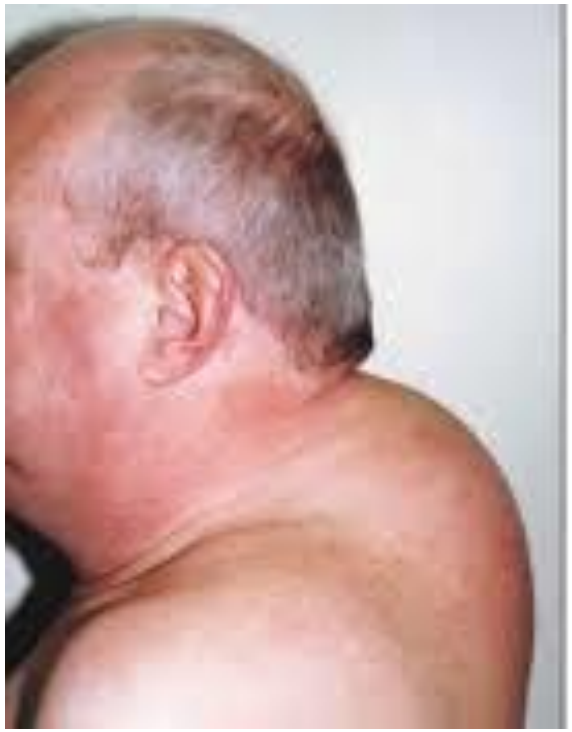
1. **Increased lipogenesis** in the trunk, face and neck leading to characteristic body shape & moon-shaped face.

2. Cortisol has the opposite action to that of insulin, causing **increased gluconeogenesis and hyperglycemia.**

3. **Increased protein catabolism** causing proximal muscle wasting with weakness, thinning of the skin and bone osteoporosis.



striae



buffalo hump

moon-shaped face

LO7

- **Skin thinning** increase the tendency to bruising and purple striae (most obvious on the abdominal wall) .

4. Increased susceptibility to infections

5.Hypertension due to sodium and fluid retention (Mineralocorticoid activity)

LO7

Decreased activity of the adrenal cortex may be due to:

1. Addison ‘s disease: diseases of the adrenal cortex (auto-immune destruction , infection) , all cortical zones will be involved reduces glucocorticoids and mineralocorticoids.(↓cortisol , ↓aldosterone, ↑ACTH)

2. Disorders in pituitary that lead to decreased secretion of ACTH **only affects glucocorticoids.** (↓cortisol , **normal** aldosterone, ↓ACTH)

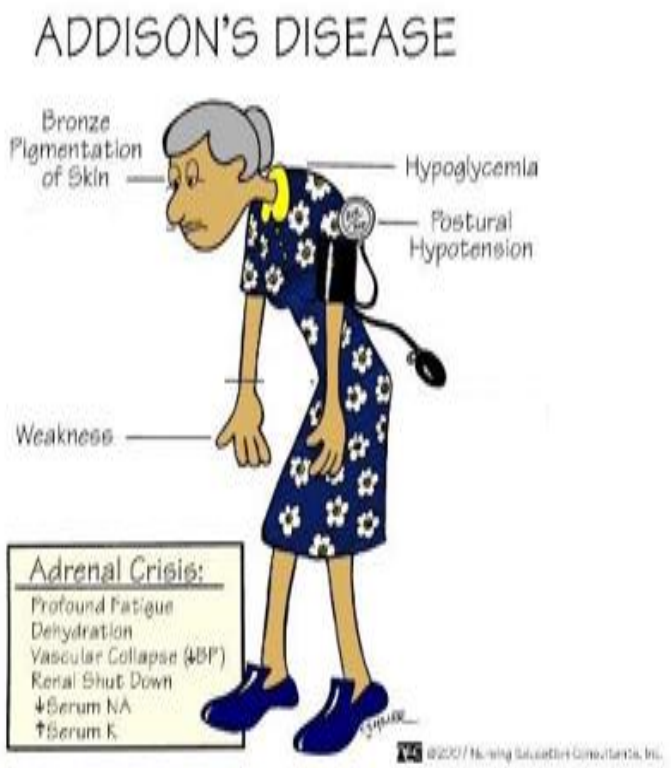
LO7

Effects of under-secretion – clinical features of Addison's disease

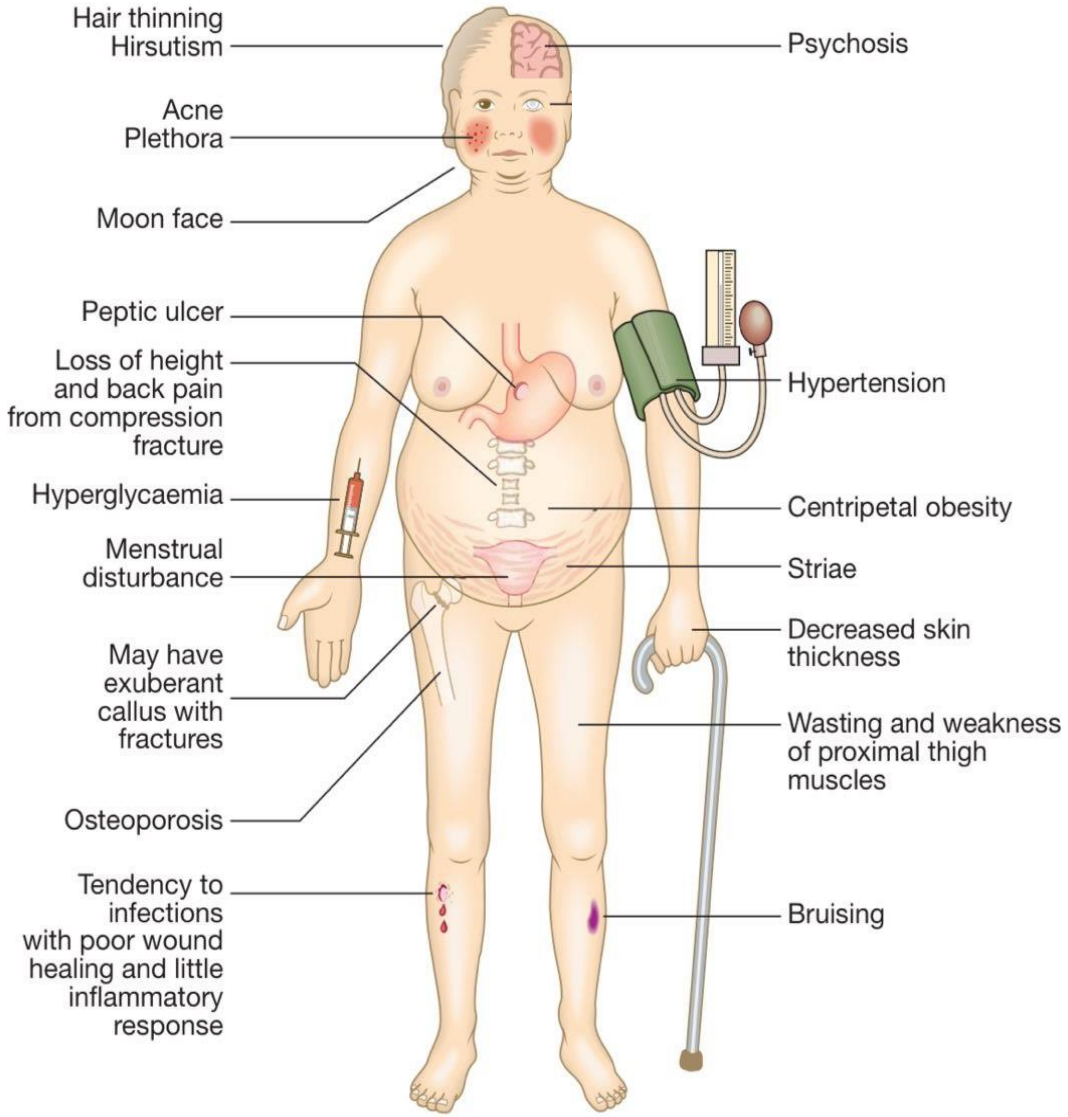
1. Tiredness, muscular weakness, occasional dizziness.
2. Decreased blood pressure and postural hypotension.
3. Hypoglycemic episodes especially on fasting
4. A more specific sign is the **increased pigmentation**, particularly on the exposed areas of the body, points of friction, buccal mucosa, scars and palmar creases due **to ACTH-mediated melanocyte stimulation.**

LO7

- These effects may be exacerbated by stress such as trauma or severe infection lead to extreme dehydration, hypotension, confusion, fever and even coma **(Addisonian crisis)**, this a clinical emergency that must be treated with intra-venous cortisol and fluid replacement to avoid death.



Cushing ‘s syndrome



LO8

Clinical tests of adrenocortical function

1. Early morning plasma cortisol.
2. ACTH.
3. 24 hour urinary cortisol.
4. Dynamic tests: dexamethasone suppression tests and ACTH stimulation test

- Dexamethasone is a potent synthetic steroid that, when given orally would normally suppress (by feedback inhibition) the secretion of ACTH and thus cortisol.
- Dexamethasone suppression **of plasma cortisol by >50%** is characteristic of **Cushing s disease** because for the diseased pituitary, even though it is relatively insensitive to cortisol, it does retain some sensitivity to potent synthetic steroids.
- Suppression does not occur in adrenal tumors.

LO9

Steroid hormone receptor homology

The steroid receptors have three main regions:

1. **Hydrophobic hormone-binding region.**
2. **DNA-binding region.**
3. **Variable region.**

LO9

- There is homology in the hormone binding regions of the receptors with the mineralocorticoid, androgen receptors.

- Cortisol will bind to the mineralocorticoid and androgen receptors with low affinity but the binding may become significant when high levels of the hormone are present