Introduction

- Among most important and vital endocrine organ

- Small bilateral yellowish retroperitoneal organ

- Lies just above kidney in gerota’s fascia
The Adrenal Gland

Anatomy was first described in 1563.

Is located above (or attached to) the upper pole of the kidney.

Is pyramidal in structure and weights about 4-5 grams.

Consists of the adrenal cortex and adrenal medulla

Activities are regulation of fluid volume and stress response
Anatomy

- Right adrenal is triangular, related to upper pole Right kidney
  - Left adrenal is crescent shaped, related to upper and medial part Left kidney
- Size : 3 - 6cm long, 0.9 – 3.6cm
- Weight : 3-5 gm app
- Width : 2-3 cm
Anatomy
Right adrenal:
  gland
  vein

Adrenal arteries

Left adrenal:
  gland
  vein

Right kidney

Inferior phrenic artery

Inferior vena cava

Aorta

Left kidney
Adrenal Histology

- Adrenal cortex
- Adrenal medulla
- Connective tissue capsule
- Zona glomerulosa
- Zona fasciculata
- Zona reticularis
- Medulla
Zona fasciculata
Adrenal Cortex

• Is divided into 3 zones in the adult gland:
  • Zona Glomerulosa,
  • Zona Fasciculata,
  • Zona Rericularis.

• Is divided onto 4 zones in the fetal gland.

• The three zones of the permanent cortex constitutes only 20% of the fetal gland’s size.

• The remaining zone (fetal cortex) comprises up to 80% of gland’s size during fetal life.
Adrenal Cortex: Steroid Hormone Production

- Aldosterone, sex hormones, cortisol
- Synthesized from cholesterol–steroid ring
Region of adrenal gland

- Adrenal medulla
  - Zona reticularis
- Adrenal cortex
  - Zona fasciculata
  - Zona glomerulosa
  - Capsule

Secretes

- Catecholamines
- Sex hormones
- Glucocorticoids
- Aldosterone
Adrenal gland
- Medulla
- Cortex

Kidney

(a) Adrenal gland:
- Capsule
- Zona glomerulosa
- Zona fasciculata
- Zona reticularis
- Adrenal medulla

(b) Micrograph of adrenal medulla
Adrenal Cortex

Zona Reticularis:
Androgens

Zona Fasiculata:
Glucocorticoids (Cortisone)

Zona Glomerulosa:
Aldosterone
Adrenal cortex and medulla

Cortex (from mesoderm)

Medulla (from neural crest)

GFR corresponds with Salt (Na⁺), Sugar (glucocorticoids), and Sex (androgens).

“The deeper you go, the sweeter it gets.”

Pheochromocytoma—most common tumor of the adrenal medulla in adults.

Neuroblastoma—most common in children.

Pheochromocytoma causes episodic hypertension; neuroblastoma does not.
ACTH  
Ketoconazole  

\[ \text{Desmolase} \]

\[ \begin{align*}
\text{Pregnenolone} & \quad \rightarrow \quad 17\text{-hydroxypregnenolone} \\
3\beta\text{-hydroxysteroid dehydrogenase} & \\
\text{Progesterone} & \quad \rightarrow \quad 17\alpha\text{-hydroxyprogesterone} \\
\text{11-deoxycorticosterone} & \quad \rightarrow \quad 11\text{-deoxycortisol} \\
\text{Corticosterone} & \quad \rightarrow \quad \text{Cortisol} \\
\text{Aldosterone synthase} & \\
\text{Aldosterone} & \\
\text{Angiotensin II} & \\
\end{align*} \]

\[ \begin{align*}
\text{Dehydroepiandrosterone (DHEA)} & \\
\text{Androstenedione} & \quad \rightarrow \quad \text{Estrone} \\
\text{Testosterone} & \quad \rightarrow \quad \text{Estradiol} \\
5\alpha\text{-reductase} & \\
\text{DHT} & \\
\end{align*} \]

\[ \begin{align*}
\text{Glomerulosa} & \quad \text{Mineralocorticoids} \\
\text{C21} & \\
\text{Fasciculata} & \quad \text{Glucocorticoids} \\
\text{C21} & \\
\text{Reticularis} & \quad \text{Androgens} \\
\text{C19} & \\
\text{Periphery} & \quad \text{Estrogens} \\
\text{C18} & \\
\end{align*} \]

\[ \begin{align*}
\text{A} = 17\alpha\text{-hydroxylase deficiency.} & \quad \downarrow \text{sex hormones}, \downarrow \text{cortisol}, \uparrow \text{mineralocorticoids. Cx = HYPERtension, hypokalemia; phenotypically female but no maturation.} \\
\text{B} = 21\alpha\text{-hydroxylase deficiency.} & \quad \downarrow \text{cortisol (increased ACTH)}, \downarrow \text{mineralocorticoids,} \\
& \quad \uparrow \text{sex hormones. Cx = masculinization, female pseudohermaphroditism, HYPOtension, hyperkalemia,} \\
& \quad \uparrow \text{plasma renin activity, and volume depletion. Salt wasting can lead to hypovolemic shock in the newborn.} \\
\text{C} = 11\beta\text{-hydroxylase deficiency.} & \quad \downarrow \text{cortisol,} \downarrow \text{aldosterone and corticosterone,} \uparrow \text{sex hormones.} \\
& \quad \text{Cx = masculinization, HYPERtension (11-deoxycorticosterone is a mineralocorticoid and is secreted in excess).} \\
\end{align*} \]
Hypothalamus: CRH

Pituitary: ACTH

Adrenal: Cortisol
Cholesterol

Pregnenolone → 17-Hydroxypregnenolone

Progesterone

Dehydroepiandrosterone

17-Hydroxyprogesterone → Androstenedione

11-Deoxycortisol

Cortisol

21-Hydroxylase
Figure 23-2: Synthesis pathways of steroid hormones
Adrenal Cortex

Cholesterol → Pregnenolone → 17α-Hydroxy-pregnenolone → 17α-Hydroxy-progesterone → Progesterone → 11-Deoxycorticosterone → Corticosterone → 18-Hydroxy cortisolistone → Aldosterone

Mineralocorticoid Pathway
Glucocorticoid Pathway
Androgen Pathway
**Adrenal Medulla**

phenylethanolamine-N-methyltransferase

Norepinephrine

Epinephrine
Physiology

• Adrenal cortex produces

  - Glucocorticoids (Zona Fasciculata)
  - Mineralocorticoids (Zona Glomerulosa)
  - Adrenal androgens (Zona Reticularis)
Physiology

- Adrenal medulla produces
  - Epinephrine (adrenaline)
  - Norepinephrine (noradrenaline)

- Help inc in cardiac output, vascular resistance and mediate stress response

- All are absolutely required for life
Functions

- Aldosterone helps in Na reabsorption & potassium excretion & preventing dehydration
- Cortisol stimulate protein breakdown, inhibition of tissue response in injury & antagonism to action of insulin
- Androgens helps in early development of male sex organ in childhood
Functions

Nerve signal

ACTH

Epinephrine

Glucocorticoids (Cortisol)

Increased heart rate, breathing rate, blood sugar

Liver releases glucose

Adrenal Glands

Medulla

Cortex

Kidney
Cortisol Effects: Body Responses to Stress

- Permissive effect on glucagon
- Memory, learning & mood
- Gluconeogenesis
- Skeletal muscle breakdown
- Lipolysis, calcium balance
- Immune depression
- Circadian rhythms
Cortisol Effects: Body Responses to Stress

Figure 23-4: Circadian rhythm of cortisol secretion
Control of Cortisol Secretion: Feedback Loops

- External stimuli
- Hypothalamic
- Anterior Pituitary
- Adrenal cortex
- Tissues
Cortisol: Role in Diseases and Medication

- Use as immunosuppressant
  - Hyperimmune reactions (bee stings)
  - Serious side effects
- Hypercortisolism (Cushing's syndrome)
  - Tumors (pituitary or adrenal)
  - Iatrogenic (physician caused)
- Hypocortisolism (Addison's disease)
Aldosterone

- Exclusively synthesized in Z. Glomerulosa
- Essential for life.
- Promotes sodium retention and Potassium elimination by the kidney.
- Expands ECF volume
Aldosterone acts mainly on the distal tubules and collecting ducts of the nephron, the functioning unit of the kidney, causing the:

- conservation of sodium,
- secretion of potassium,
- increased water retention,
- increased blood pressure.

The overall effect of aldosterone is to increase reabsorption of ions and water in the kidney – increasing blood volume and, therefore, increasing blood pressure.
Aldosterone

Its activity is

• reduced in Addison's disease
• increased in Conn's syndrome.
Stimulation

- Increase in the plasma concentration of Angiotensin III, a metabolite of Angiotensin II increase in plasma angiotensin II,
- ACTH, or potassium levels, which are present in proportion to plasma sodium deficiencies. (The increased potassium level works to regulate aldosterone synthesis by depolarizing the cells in the zona glomerulosa, which opens the voltage-dependent calcium channels.)
- Potassium levels are the most sensitive stimulator of aldosterone.

Plasma acidosis

- The stretch receptors located in the atria of the heart.

If decreased blood pressure is detected, the adrenal gland is stimulated by these stretch receptors to release aldosterone, which increases sodium reabsorption from the urine, sweat, and the gut.

The secretion of aldosterone has a diurnal rhythm
Regulation of Aldosterone Secretion

- Hemorrhage
- Upright posture
- Sodium deprivation
  - ↓ Extracellular fluid volume
  - Potassium load
  - ↑ Plasma potassium
  - Adrenal Zona glomerulosa
    - Angiotensin II
    - Angiotensin I
    - Renin
    - Liver
    - Converting enzyme
    - Lungs

Other modulators:
- Stimulation: ACTH, Plasma Na⁺, Serotonin, Acetyl choline, VIP, PACAP
- Inhibition: ANP, Dopamine
Aldosterone: Role in diseases

• Complete failure to secrete aldosterone leads to death (dehydration, low blood volume).

• Hyperaldosterone states: Contribute to hypertension associated with increased blood volume.
Adrenal Medulla: A Modified Sympathetic Ganglion

• Sympathetic stimulation
  ▫ Catecholamine release to blood
    • Epinephrine
    • Norepinephrine
  ▫ Travel to:
    • Multiple targets
    • Distant targets
Adrenal Medulla:
A Modified Sympathetic Ganglion

Figure 11-10: The adrenal medulla
Mechanism: Norepinephrine Release and Recycling

Figure 11-9: Norepinephrine release at a varicosity of a sympathetic neuron

1. Action potential arrives at the varicosity.
2. Depolarization opens voltage-gated Ca$^{2+}$ channels.
3. Ca$^{2+}$ entry triggers exocytosis of synaptic vesicles.
4. NE binds to adrenergic receptor on target.
5. Activity ceases when NE diffuses away from the synapse.
6. NE is transported back into the axon.
7. NE can be taken back into synaptic vesicles for re-release.
8. NE is metabolized by monoamine oxidase (MAO).
Review of Efferent Pathways: Motor & Autonomic

Figure 11-11: Summary of efferent pathways.
Catecholamines: Activity

- Stimulates the “fight or flight” reaction
- Increased plasma glucose levels
- Increased cardiovascular function
- Increased metabolic function
- Decreased gastrointestinal and genitourinary function
Activity of Epinephrine

- Insulin:
  - Stimulates glucose uptake by muscle.
  - Inhibits glycogen breakdown in liver.

- Glucose:
  - Stimulates glycogen synthesis in liver.
  - Stimulates lactate production in muscle.

- Glucose-P:
  - Stimulates glycogen breakdown in liver.
  - Stimulates pyruvate production in liver.

- Pyruvate:
  - Stimulates free fatty acids production in liver.

- Glycogen:
  - Stimulates glucose production in liver.

- Lactate:
  - Inhibits glucose production in liver.

- Free fatty acids:
  - Stimulates triglyceride synthesis in adipose tissue.

- Triglyceride:
  - Stimulates insulin production in pancreas.

- Insulin:
  - Stimulates glycogen synthesis in pancreas.
  - Stimulates glucose uptake by adipose tissue.

- Glucagon:
  - Stimulates glycogen breakdown in pancreas.

- Pancreatic islets:
  - Stimulates insulin production in pancreas.
  - Stimulates glucagon production in pancreas.
Aldosterone

**MOA:** transcription of enzymes and proteins

**Major actions:** \( \uparrow \) Na reabsorption in distal tubule

**Extrarenal effects:** Na reabsorption in saliva, sweat, stool
Hypersecretion of Aldosterone

1º aldosteronism – Conn’s syndrome

2º aldosteronism – liver/kidney disease

SXS: hypertension
hypokalemia
metabolic alkalosis
**Pathophysiology**

Primary Hyperaldosteronism

↑Aldosterone ➔ ↑Na retention ➔
↓Renin

↑ ECZ volume
+ 
↑ Renal perfusion
pressure

Secondary Hyperaldosteronism

retention ↓Renal perfusion ➔ ↑Renin ➔ ↑Aldosterone ➔
+ pressure
↑ Na
↑ ECF
volume
Pathophysiology

Hyposecretion of Aldosterone

1° hyposecretion – Addisons’ dse
2° hyposecretion – kidney damage

SXS: hypovolemicia
hyponatremia
hyperkalemia
Pathology

- pheochromocytoma
  - adrenal medulla tumor
  - increase BP due to release of catecholamines
- Addison’s disease - decrease cortisol
  - hyponatremia, dehydration
  - hyperkalemia
- Cushing’s disease - increase cortisol
  - moon face, hirsutism
Cushing's disease/syndrome
<table>
<thead>
<tr>
<th>METABOLIC EFFECT</th>
<th>SYMPTOM</th>
<th>SIGN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate metabolism:</td>
<td>• increased glycogenesis</td>
<td>Diabetes Mellitus:</td>
</tr>
<tr>
<td>• increased glucogenesis</td>
<td>• polydypsia</td>
<td>• impaired glucose use</td>
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<tr>
<td>Increased protein catabolism</td>
<td>• muscle weakness</td>
<td>• hyperglycaemia</td>
</tr>
<tr>
<td>• easily bruised thin skin*</td>
<td>• polyuria</td>
<td>• insulin resistance</td>
</tr>
<tr>
<td>• growth retardation</td>
<td></td>
<td></td>
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<tr>
<td>Increase and redistribution of body fat</td>
<td>• central obesity</td>
<td>• thin osteoporotic bone</td>
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<tr>
<td>Reduced inflammatory response</td>
<td></td>
<td>• pathological fractures*</td>
</tr>
<tr>
<td>Increased stomach acid production</td>
<td></td>
<td>• poor wound healing</td>
</tr>
<tr>
<td>Mineralcorticoid effects</td>
<td></td>
<td>• abdominal striae*</td>
</tr>
<tr>
<td>• sodium retention</td>
<td></td>
<td>• pathological muscle wasting and myopathy*</td>
</tr>
<tr>
<td>• redistribution of fluids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood</td>
<td>• depression</td>
<td>• hypertension*</td>
</tr>
<tr>
<td>Sex hormones</td>
<td>• acne</td>
<td>• oedema</td>
</tr>
<tr>
<td></td>
<td>• hirsutism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• amenorrhoea/oligomenorrhoea</td>
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</tr>
</tbody>
</table>
- Upper body obesity with thin arms and legs
- Buffalo Hump
- Rad, Round Face
- High Blood Sugar
- High Blood Pressure
- Vertigo
- Blurry Vision
- Acne
- Female Balding
- Water Retention
- Menstrual Irregularities
- Thin Skin and Bruising
- Purple Striae
- Poor Wound Healing
- Hirsutism
- Severe Depression
- Cognitive Difficulties
- Emotional Instability
- Sleep Disorders
- Fatigue
Addison's disease

Abdomen of [Elizabeth Lawrence], exhibiting general dinginess of the integumet, with several small circumscribed deposits of darker pigment.
Addison's disease:

- Note the generalised skin pigmentation (in a Caucasian patient) but especially the deposition in the palmer skin creases, nails and gums.

- She was treated many years ago for pulmonary TB. What are the other causes of this condition?
Anatomy

Smooth and cardiac muscles
Some endocrine and exocrine glands. Some adipose tissue

CNS

ACh
Ganglia
Sympathetic pathways

NE
b1
b2
E

Adrenal sympathetic pathway

Adrenal cortex
Adrenal medulla

Blood vessel

E
Conn's syndrome [adrenoma adrenal glands]
Biologic Actions-Glucocorticoids

- Stress response—increased vascular tone
- Immunosuppressive and anti-inflammatory actions
- Fat cells—Increased lipolysis
- Skeletal muscle and other tissues
- Liver
  - Increased gluconeogenesis, glycogenesis, glycogen storage, and enzyme activity (e.g., glucose 6-phosphate)
- Increased mobilization of amino acids
- Increased mobilization of glycerol and fatty acids
Pathophysiology

Secondary hypersecretion due to hypothalamic problem

HYPOTHALAMUS ➔ CRH

Anterior pituitary ➔ ACTH

Adrenal cortex ➔ Cortisol

Symptoms of excess

- CRH levels – high
- ACTH levels – high
- Cortisol levels – high
Pathophysiology

Secondary hypersecretion due to pituitary problem

- Hypothalamus → CRH → Anterior Pituitary
  - $\uparrow$ ACTH → Adrenal cortex
    - $\uparrow$ Cortisol
  - Symptoms of excess
    - CRH levels – low
    - ACTH levels – high
    - Cortisol levels – high
Pathophysiology

Primary hypersecretion due to problem with adrenal cortex

Hypothalamus → CRH

Anterior pituitary → ACTH

ADRENAL CORTEX → Cortisol

Symptoms of excess

CRH levels – low
ACTH levels – low
Cortisol levels – high
## Major Functions of Cortisol and Their Clinical Expression

<table>
<thead>
<tr>
<th>Effect</th>
<th>Cortisol Deficiency</th>
<th>Cortisol Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbohydrate metabolism</strong></td>
<td></td>
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</tr>
<tr>
<td>Increased gluconeogenesis</td>
<td>Hypoglycemia</td>
<td>Hyperglycemia</td>
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<tr>
<td>Decreased glucose utilization</td>
<td></td>
<td></td>
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<tr>
<td>Decreased sensitivity to insulin</td>
<td>Insulin sensitivity</td>
<td>Insulin resistance</td>
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<tr>
<td><strong>Protein metabolism</strong></td>
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<tr>
<td>Decreased extrahepatic amino acid utilization</td>
<td>Hypoglycemia</td>
<td>Decreased protein structure of bone, skin, muscle</td>
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<tr>
<td>Increased gluconeogenesis</td>
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<td>Poor wound healing</td>
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<tr>
<td><strong>Fat metabolism</strong></td>
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<tr>
<td>Increased lipolysis, decreased lipogenesis</td>
<td>Weight loss</td>
<td>Hyperlipemia</td>
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<td>Distribution of fat</td>
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<td>Redistribution of body fat, truncal obesity</td>
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<tr>
<td><strong>Circulatory</strong></td>
<td>Vasodilation</td>
<td>Hypertension</td>
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<tr>
<td>Maintain ECF volume</td>
<td>hypotension</td>
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<tr>
<td>Maintain capillary integrity</td>
<td></td>
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<tr>
<td><strong>Mineralocorticoid</strong></td>
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<tr>
<td>Sodium retention</td>
<td>Hypovolemia</td>
<td>Hypervolemia</td>
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<tr>
<td>Potassium excretion</td>
<td>Hyponatremia</td>
<td>Hypernatremia</td>
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<tr>
<td><strong>Inflammatory and immune responses</strong></td>
<td>Hyperkalemia</td>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Stabilize leukocytes</td>
<td>Propensity</td>
<td>Decreased inflammatory response</td>
</tr>
<tr>
<td>Suppress synthesis of antibodies</td>
<td>toward autoimmune disease</td>
<td>Increased susceptibility to infection</td>
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<tr>
<td>Decrease capillary permeability</td>
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<td>Decreased fibrous tissue formation</td>
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<td>Decrease phagocytosis</td>
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<tr>
<td><strong>Hematopoietic</strong></td>
<td>Anemia</td>
<td>Erythrocytosis</td>
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<td>Stimulate red cell production</td>
<td>Lymphocytosis</td>
<td>Lymphopenia</td>
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<tr>
<td>Lympholysis</td>
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<td>Leukocytosis</td>
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<td>Inhibit neutrophil accumulation at inflammatory sites</td>
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<td><strong>Central nervous system</strong></td>
<td>Anorexia</td>
<td>Euphoria</td>
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<td>Fatigue</td>
<td>Increased ACTH secretion</td>
<td>Depression</td>
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<td><strong>Hypothalamic-pituitary feedback control of ACTH</strong></td>
<td>Pigmentation</td>
<td>Decreased ACTH secretion</td>
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<td>If secondary to stimulation by hypothalamic-pituitary axis,</td>
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Pathophysiology