Physiology Team

ENDOCRINE BLOCK

LECTURE 10

MINERALOCORTICOIDS

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OBJECTIVES

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Not Given :\

MIND MAP

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Adrenal gland **histology and its hormones**

Aldosterone **action**

Regulation of aldosterone secretion

Adrenal insufficiency

Tests Confirming the Diagnosis of Primary Aldosteronism

Aldosterone and Body Fluid Balance

Renin Angiotensin Aldosterone System (RAAS): Pathway, Functions & Terms

Hyperaldosteronism: Causes, Dangers & Treatments

Adrenal (suprarenal) glands

Male's Slide

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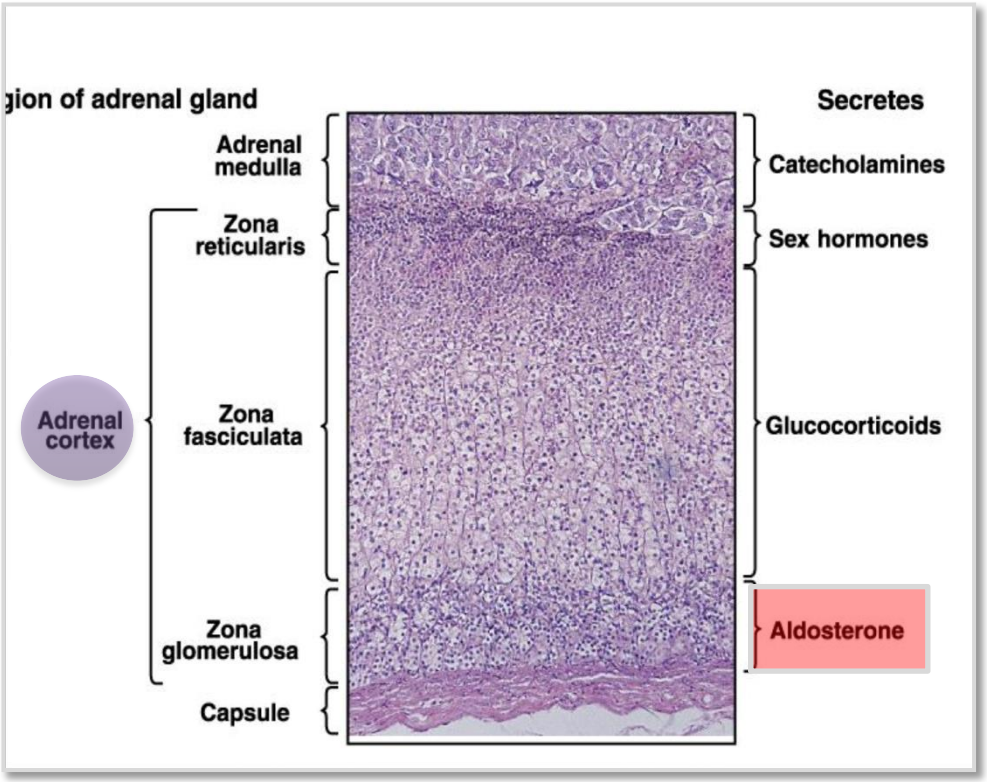
- Adrenal glands – paired, pyramid-shaped organs atop the kidneys
- Weigh 6-10 g.
- Structurally and functionally, they are two glands in one

Adrenal cortex

(80-90%)– glandular tissue derived from embryonic mesoderm

Adrenal medulla

(10-20%)– formed from neural ectoderm, can be considered a modified sympathetic ganglion



Hormones of adrenal gland

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Cortex	Medulla
(Secretes steroid hormones): • Glucocorticoids. • **Mineralocorticoids.** • Androgens	(Amino acid secretions) : • Catecholamines

Notes mentioned by the doctor

- if both adrenal glands are destroyed or damaged , deficiency of hormones will appear but if just one gland is damaged deficiency will not be very significant because the other gland will compensate
- Each layer of adrenal cortex synthesizes and secrete one type of steroid : Glucocorticoids ,Mineralocorticoids , Androgen . The basis for this specialization is the presence or absence of the enzymes that catalyze various modification of the **steroid nucleus .**
- Mineralocorticoids = are hormones that influence minerals metabolism
- We can block the action of aldosterone by blocking the enzymes required for its synthesis and its receptors in the target cells

Steroid Hormone Synthesis

Male's Slide

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- Steroids are derivatives of cholesterol.
- Cholesterol is from the lipid droplets in cortical cells (**cholesterol esters in LDL**)
- Removed cholesterol is replenished "تجديد" by cholesterol in LDL in blood or synthesized from acetate.
- Steroid hormones are synthesized and secreted on demand (not stored).
- The first and rate-limiting step in the synthesis of all steroid hormones is conversion of cholesterol to pregnenolone by the enzyme cholesterol dismolase (aka cholesterol side chain cleavage (SCC) enzyme.
- Newly synthesized steroid hormones are rapidly secreted from the cell.
- Following secretion, all steroids bind to some extent to plasma proteins: CBG "cortisol binding globulin" and albumin.

Genetic Defects in Adrenal Steroidogenesis

Congenital adrenal hyperplasia

Decresed cortisol → **Increase** ACTH → Adrenal hyperplasia

21-hydroxylase (P450c21) deficiency:

- cortisol, corticosterone, and aldosterone deficiency.
- **increse ACTH** leading to **Adrenal hypertrophy** and high amounts of androgen causing **Virilization** of female (masculanization)

Aldosterone

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- **A steroid** hormone.
- **Essential** for life.
- **Responsible** for regulating **Na+ reabsorption** in the distal tubule and the cortical collecting duct
- **Target cells** are called "principal (P) cell".
- **It also** affects Na+ reabsorption by sweat, salivary and intestinal cells. Stimulates synthesis of more Na/K- ATPase pumps.

- **Much of** secreted aldosterone is converted in the liver to tetrahydroglucuroind derivative. **(metabolism)**
  - **Liver disease = increase activity of the hormone leading to**
  - **Increase Na+ reabsorption ⇒ EDEMA**
- **Aldosterone** exerts the 90% of the mineralocorticoid activity.
- **Secreted** by Zona glomerulosa.
- **Cortisol also** have mineralocorticoid activity, but only 1/400th that of aldosterone. (appear at supraphysiological or therapeutically levels of the hormone)

Aldosterone Action

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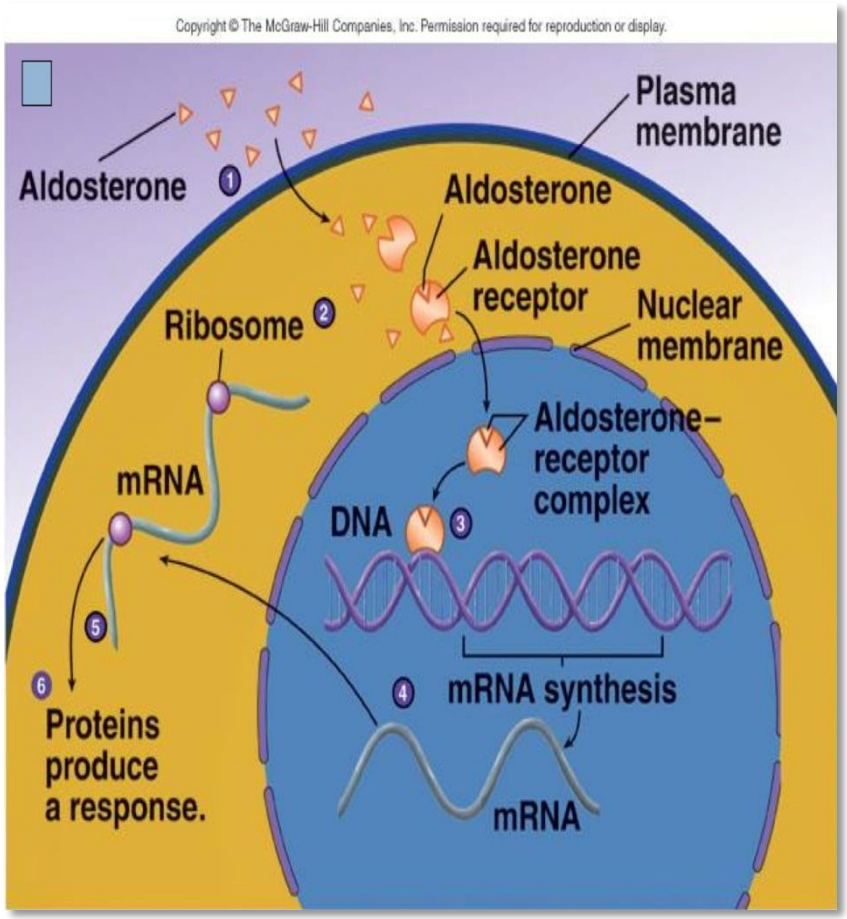
Aldosterone diffuses across the cell membrane and enter the target cell

Binds to a specific receptor protein that is located in the cytosol

The aldosterone receptor complex binds to a specific element of DNA and has now become a transcription factor

New mRNA is transcribed

The mRNA is translated to a new protein that have specific physiological action of the aldosterone hormone



Aldosterone Action

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1. Maintains extracellular fluid volume by conserving body sodium.
- If you were fasting or depleted of sodium , what is the role of aldosterone ?
- It will go to the distal convoluted tubes >> try to conserve Na+ that is left >> withdraw little amount of water.

2. Aldosterone stimulates sodium & potassium transport in sweat glands, salivary glands, & intestinal epithelial cells.
- Child with oral ulcer due to virus infection >> Increase salivation to buffer the inflammation >> Loss of sodium within the saliva (aldosterone is secreted but it can't compensate the loss) >> If severe , may lead to dehydration

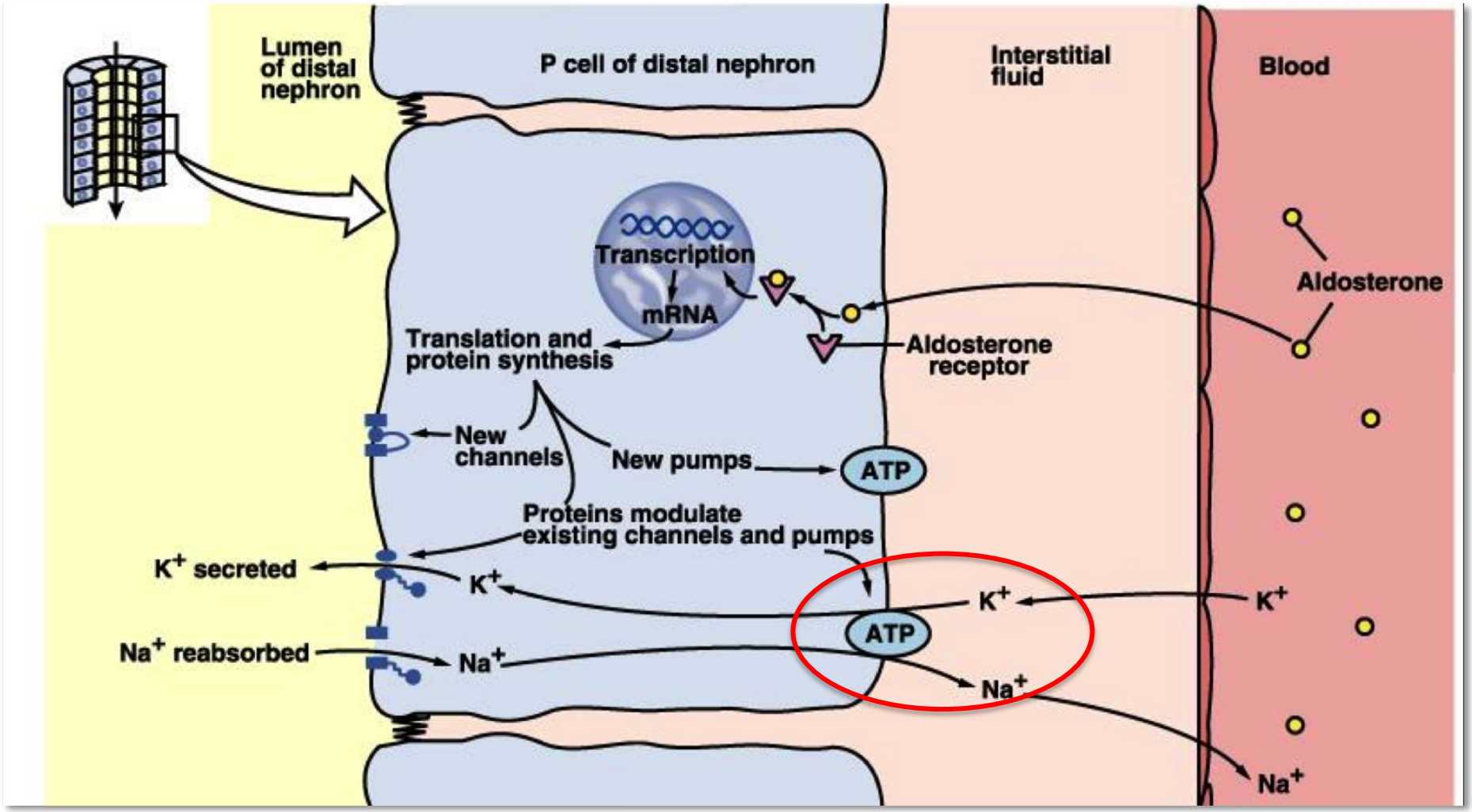
3. Aldosterone stimulates the active secretion of potassium from the distal tubular cell into the urine. (very important function because high levels of potassium affect heart and muscles)

4. Hence aldosterone is critical for disposal of daily dietary potassium load at normal plasma potassium concentrations
- normal range of potassium (3.5 – 5 mmol/L).

5. Stimulates synthesis of more Na/K-ATPase pumps.

6. Stimulates secretion of H+ by the kidney:
- Increase aldosterone ⟹ alkalosis
- Decrease aldosterone ⟹ acidosis

Summary of Aldosterone action



Regulation of aldosterone secretion

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Direct stimulators of release

- High plasma **potassium (k)** level

(strong stimuli)

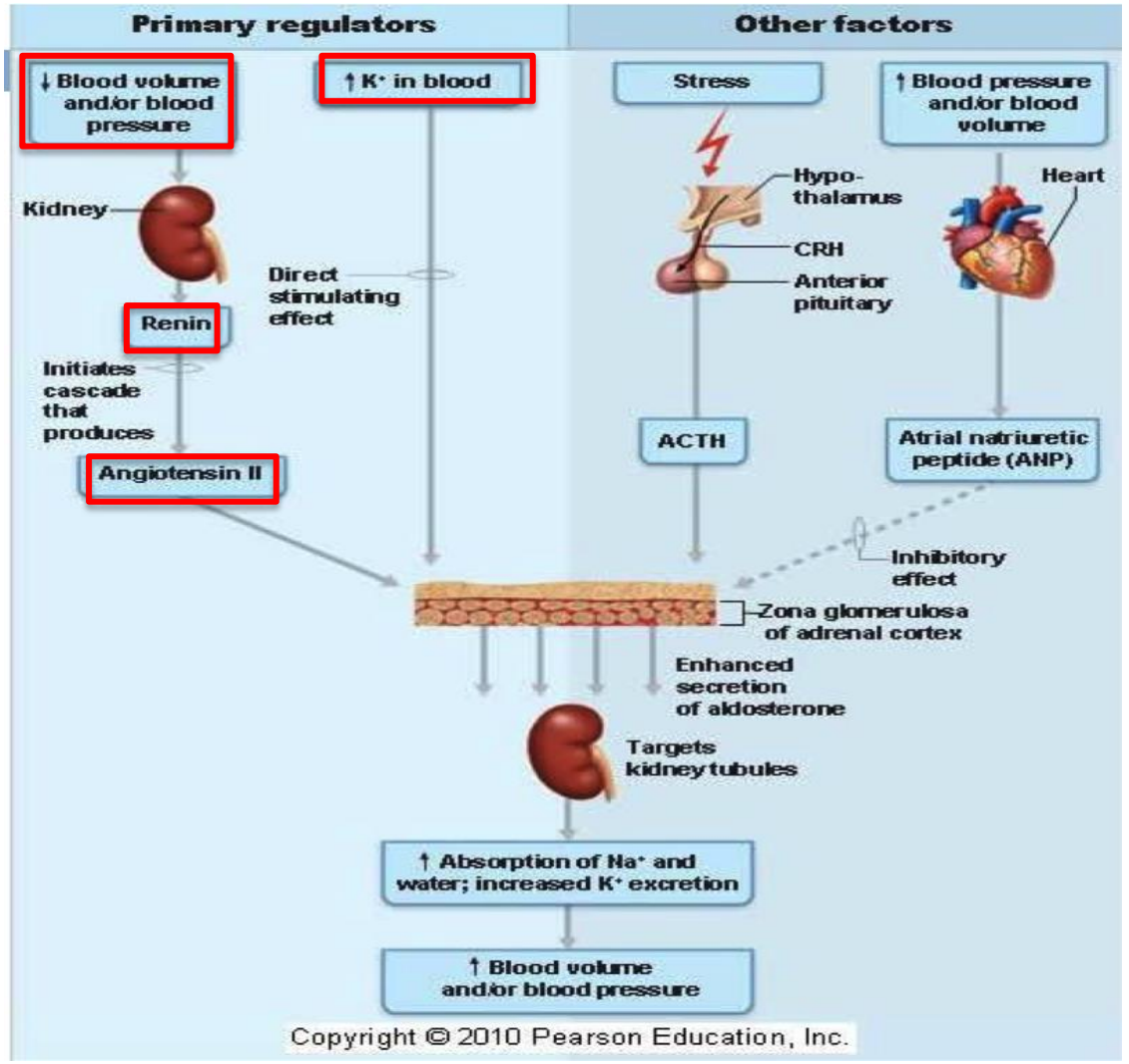
- **ACTH**

(the weakest one)

Indirect stimulators of release

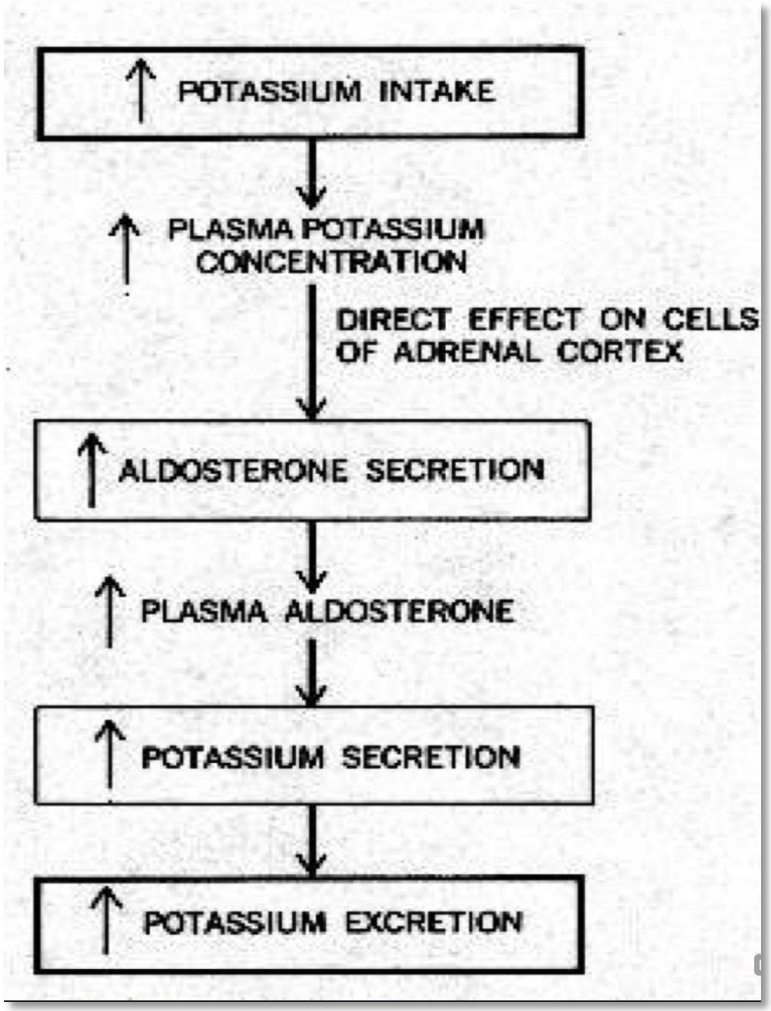
- **Ang II (RAAS)** strongest stimuli

this system is activated by renal ischemia and low Na+ concentration at macula densa.



Pathway by which an :

- **increased potassium intake**
- induces greater potassium excretion mediated by aldosterone
- Potassium stimulates aldosterone synthesis by depolarizing zona glomerulosa cell membranes



Role of ACTH in Aldosterone synthesis/release

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- ACTH also stimulates aldosterone synthesis.
- However the ACTH stimulation is more transient than the other stimuli and is diminished within several days.
- Aldosterone levels fluctuate diurnally—**highest concentration being at 8 AM, lowest at 11 PM**, in parallel to cortisol rhythms.

- ACTH is a weak stimulator "not that strong."
- ACTH is the hormone that is responsible for the circadian level of Aldosterone (Controlled by Hypothalamus "CRH")
- And **don't forget** that the **Hypothalamus** is the **center of the circadian rhythm.**

Juxtaglomerular apparatus (JGA):

- **A specialized collection of two cell types:**

1. Macula densa cells
2. Juxtaglomerular cells

located at the juncture of the afferent and efferent arterioles with a portion of the distal convoluted tubule of the nephron of the kidney

Juxtaglomerular apparatus (JGA)

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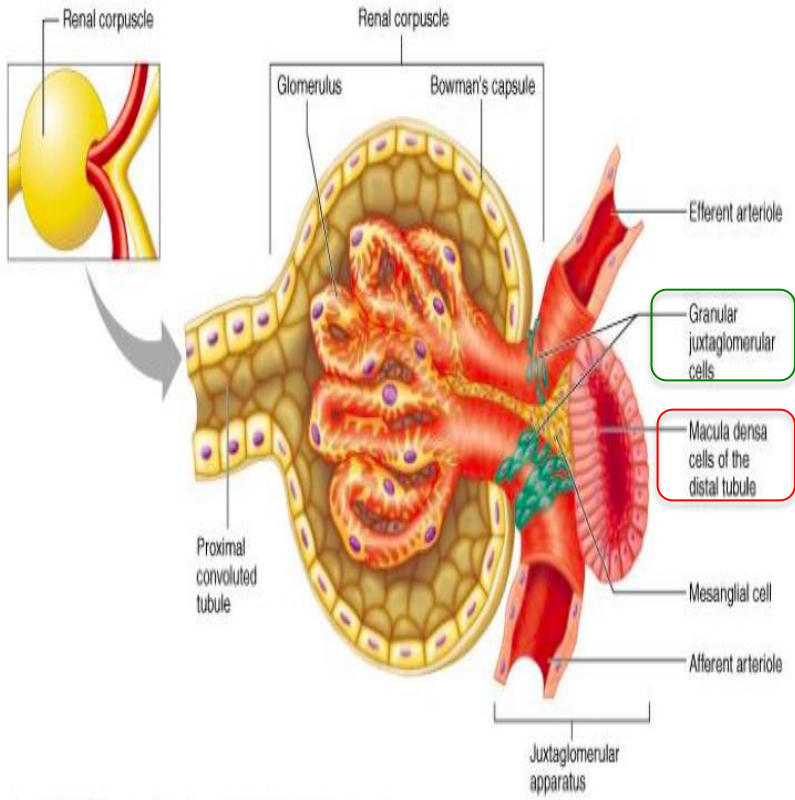
Macula densa cells

- Specialized chemoreceptor cells in the wall of the distal
- convoluted tubule
- respond to changes in solute concentration (especially sodium levels) in the tubular fluid.
- Information is conveyed to the juxtaglomerular cells which will adjust their output of renin accordingly.

Juxtaglomerular cells

- Specialized smooth muscle cells which act as mechanoreceptors which stretch in response to increases in the blood pressure of the afferent arteriole
- synthesize and secrete the enzyme renin



- Release of the aldosterone hormone in the indirect way which is the cascade of RAS system
- Affect the aldosterone directly by affecting the Zona glomerulosa

Renin – Angiotensin - Aldosterone Axis

Important

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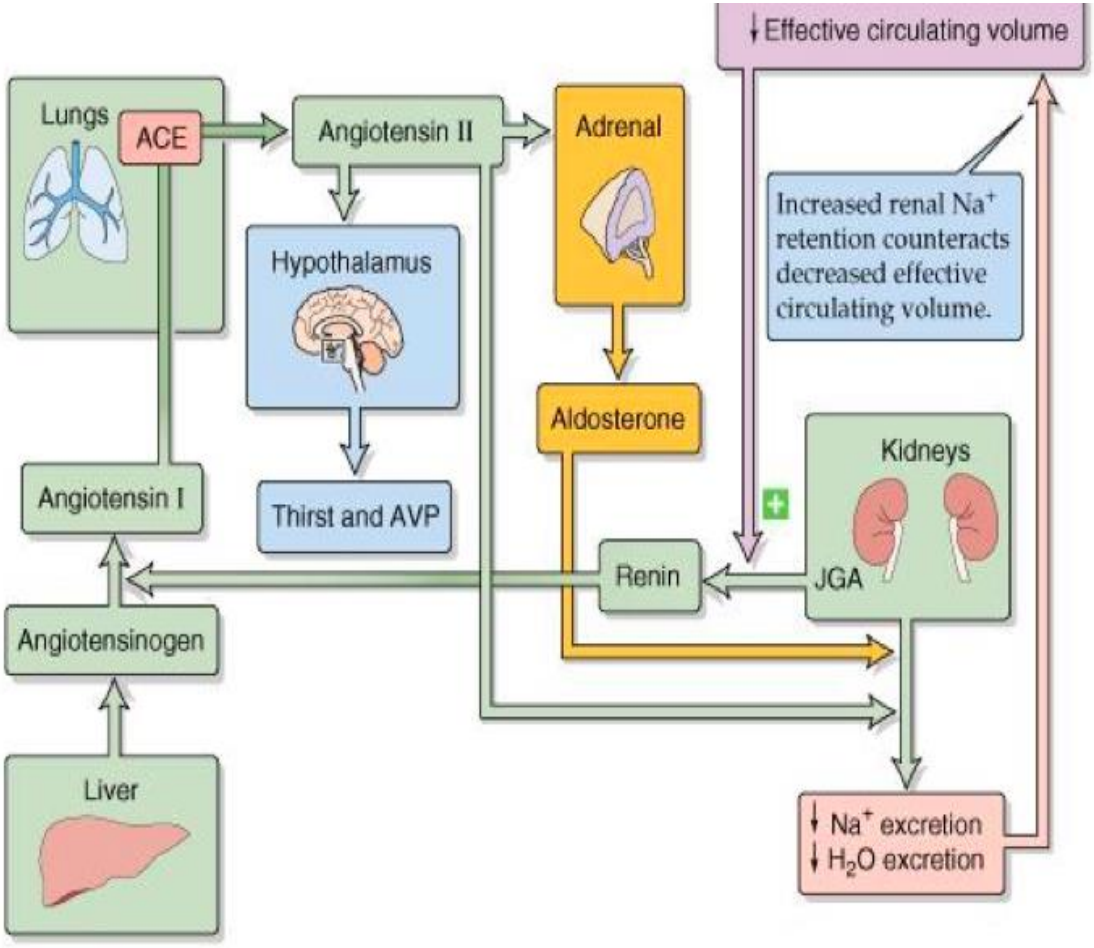
Principal factor controlling Ang II levels is renin release.

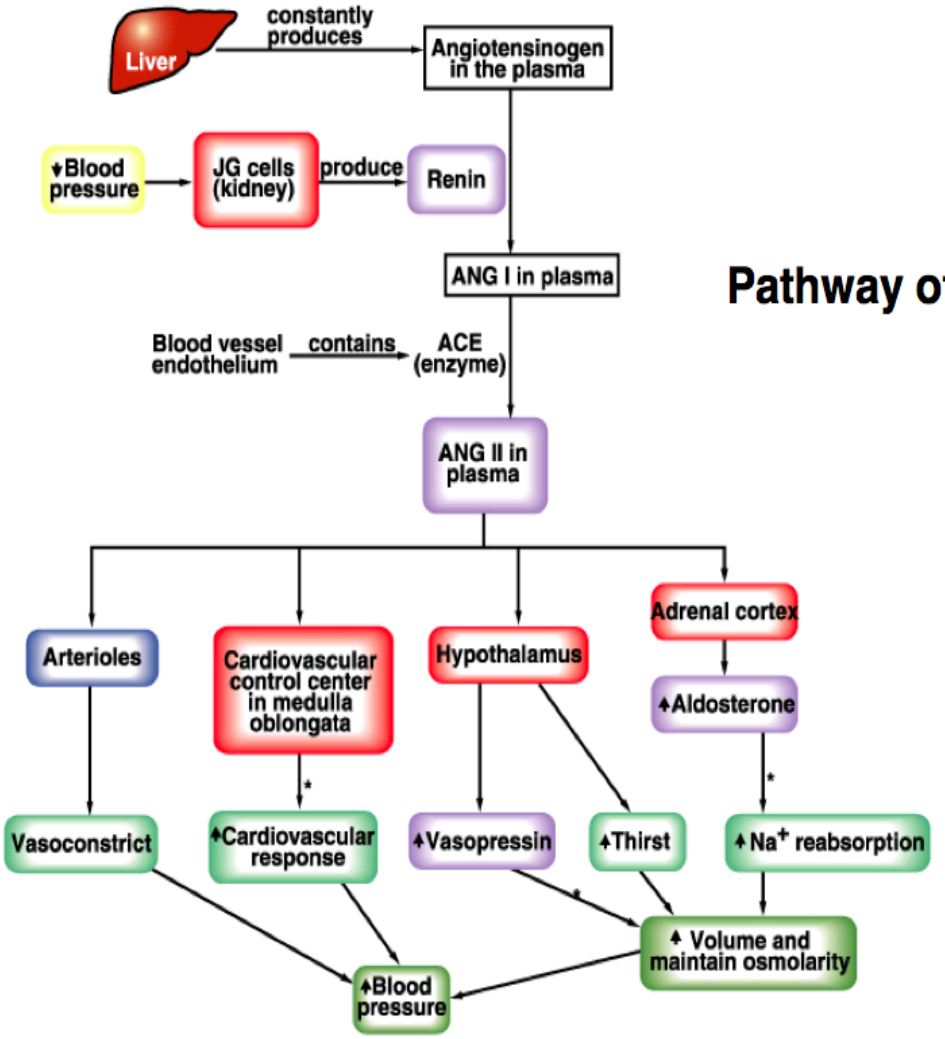
Decreased circulating volume stimulates renin release via:

- ✓ Decreased BP (symp effects on JGA).
- ✓ Decreased [NaCl] at macula densa ("NaCl sensor")
- ✓ Decreased renal perfusion pressure ("renal" baroreceptor)



Role of AngII in Aldosterone synthesis:

- Angiotensin II acts on the zona glomerulosa to stimulate aldosterone synthesis.
- Angiotensin II acts via increased intracellular cAMP to stimulate aldosterone synthesis.



Pathway of RAAS

Important

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Addison's Disease

Inadequate amounts of **adrenocortical** hormones due to bilateral destruction of adrenal cortices.

Causes:

- Autoimmunity.
- TB
- Radiation.
- Malignancy.

Addison's Disease !

- Deficiency **never** happens to **a single** hormone, instead it usually affects all adrenal hormones.
- Deficiency of the gland usually affects all hormones not just the mineralocorticoids because there will be (bilateral destruction of the gland) so it will not distinguish between the zones (it affects all the hormones of the gland regardless of the zones)

Mineralocorticoids Deficiency Vs. Hyperaldosteronism

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Mineralocorticoids Deficiency	Hyperaldosteronism
Lack of aldosterone	**Hyperaldosteronism can be caused by**

• Increased loss of sodium, chloride, water
• Decrease ECF volume
• Hyperkalemia
• Mild acidosis
• Plasma sodium decreases and may lead to circulatory collapse.
• **Decrease cardiac output** – shock - death within 4 days to a 2 weeks if not treated.
• **Arrhythmia** due to the K+ level
	Primary overproduction of aldosterone in conditions such as Conn's syndrome.
	Clinical Features of Primary Aldosteronism :
	• Hypertension associated with increased blood volume..
	• Hypokalemia
	• Nocturnal polyuria & polydipsia due to "mineralocorticoid escape" which is the escape from the sodium-retaining effects of excess aldosterone (or other mineralocorticoids).
	• Increased tubular (intercalated cells) hydrogen ion secretion, with resultant mild alkalosis.
	• **Neuromuscular manifestations :**
	  • Weakness, paresthesia
	  • Intermittent paralysis

Diagnosis of Primary Aldosteronism

Test Confirming the Diagnosis of Primary Aldosteronism	
• **Plasma supine aldosterone at 0800h**	> 15 ng/dl
• **Urinary aldosterone metabolites** ✓ 18-Monoglucuronide ✓ Tetrahydroaldosterone	 > 20 ug/24h > 65 ug/24h
• **NaCl infusion/ suppression test – PA** • If we infuse NaCl >> aldosterone will be decreased (normally) but if we find the aldosterone level more than 10 = it means it is not responsive = Diagnosis for PA is conformed	> 10 ng/dl

SUMMARY

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Aldesterone (Is essential for life) :

- It affects Na+ reabsorption by sweat, salivary and intestinal cells. Stimulates synthesis of more Na/K- ATPase pumps.
- Stimulates the active secretion of potassium from the distal tubular cell into the urine.
- Stimulates secretion of H+ by the kidney.
- Aldosterone exerts the 90% of the mineralocorticoid activity.
- Secreted by Zona glomerulosa.

Regulated by :

- Direct stimulators of release: **High plsama potassium level (major stimulator)** / ACTH
- Indirect stimulators of release: Ang II (RAAS)

Adrenal insufficiency

(Lack of aldosterone) **characterized by:**

- Increased loss of sodium, chloride, water ,Decrease ECF volume ,Hyperkalemia , Mild acidosis , Plasma sodium decreases

Hyperaldosteronism can be caused by: Conn's syndrome and **characterized by:**

- Hypertension, Hypokalemia, Nocturnal polyuria, polydipsia , mild alkalosis, Neuromuscular manifestation

Aldosterone secretion is stimulated by:

- Decreasing blood volume or pressure **(renin-angeotensin system)** is the major stimulant
- Rising blood levels of K^+
- Low blood Na^+
- ACTH

The Four Mechanisms of Aldosterone Secretion

1. Renin-angiotensin mechanism – kidneys release renin, which is converts and produces **angiotensin II** that in turn stimulates aldosterone release
2. Plasma concentration of potassium and sodium– directly influences the zona glomerulosa cells
3. ACTH – causes small increases of aldosterone during stress
4. Atrial natriuretic peptide (ANP) – inhibits activity of the zona glomerulosa

Over production of Aldosterone

- **primary causes**, ie. Conn's syndrome >> adenoma, nodular hyperplasia of zona glomerulosa
- **Secondary >>** cirrhosis, ascites, nephrotic syndrome
- **symptoms, signs (** headache, hypokalemia causing muscle weakness, hypernatremia, hypervolemia, nocturnal polyuria, hand cramping

Treatment (surgical for adenoma) – (Spironolactone)

QUESTIONS

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1. What is the major stimulator of aldosterone secretion:

A. Low plasma sodium level
B. High plasma potassium level
C. ACTH
D. Ang II

2. Aldosterone is :

A. Steroid hormone
B. Synthezied by the adrenal medulla
C. Is metabolized in the kidney
D. All above are correct

3. How can you explain the Nocturnal polyuria & polydipsia in Primary Aldosteronism :

A. Catecholamine escape
B. Uknow mechanism
C. Mineralocorticoid escape
D. Non of the above

4. Primary Aldosteronism is characterized by :

A. Acidosis
B. Hypotension
C. Hyperkalemia
D. Hypokalemia

5. Aldosterone can be increased in which one of the following conditions :

A. Conn's syndrome
B. Adrenal insufficiency
C. SIADH
D. Non of the above

1	b
2	a
3	C
4	D
5	A

THE END

Physiology Team

If there are any Problems or Suggestions,
Feel free to contact us:

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