# The Adrenal Medulla & Adrenal Cortex

# 20

## Second Part

**OBJECTIVES**

*After reading this chapter, you should be able to:*

- Name the three catecholamines secreted by the adrenal medulla and summarize their biosynthesis, metabolism, and function.
- List the stimuli that increase adrenal medullary secretion.
- Differentiate between $C_{18}$, $C_{19}$, and $C_{21}$ steroids and give examples of each.
- Outline the steps involved in steroid biosynthesis in the adrenal cortex.
- Name the plasma proteins that bind adrenocortical steroids and discuss their physiologic role.
- Name the major site of adrenocortical hormone metabolism and the principal metabolites produced from glucocorticoids, adrenal androgens, and aldosterone.
- Describe the mechanisms by which glucocorticoids and aldosterone produce changes in cellular function.
- List and briefly describe the physiologic and pharmacologic effects of glucocorticoids.
- Contrast the physiologic and pathologic effects of adrenal androgens.
- Describe the mechanisms that regulate secretion of glucocorticoids and adrenal sex hormones.
- List the actions of aldosterone and describe the mechanisms that regulate aldosterone secretion.
- Describe the main features of the diseases caused by excess or deficiency of each of the hormones of the adrenal gland.

| | |
|---|---|
| The Adrenal Medulla & Adrenal Cortex | • adrenal medulla: structure & function of medullary hormones<br>• regulation of adrenal medullary secretion<br>• adrenal cortex: structure & biosynthesis of adrenocortical hormones<br>• transport, metabolism, & excretion of adrenocortical hormones<br>• effects of adrenal androgens & estrogens<br>• physiologic effects of glucocorticoids<br>• pharmacologic & pathologic effects of glucocorticoids<br>• regulation of glucocorticoid secretion<br>• effects of mineralocorticoids<br>• regulation of aldosterone secretion<br>• role of mineralocorticoids in the regulation of salt balance |

# EFFECTS OF ADRENAL ANDROGENS & ESTROGENS

**Effects of Adrenal Androgens**

1. **Masculinizing effects**
2. **promoted protein anabolism and growth**

**Testosterone** is the most active androgen. DHEA and androstenedione has less than 20%testosterone activity

**Effect of secretion rate:**

- Normal secretion exerts very little musculizing effects
  *(Normal secretion is seen in normal males, castrated males and females)*
- Excessive secretion produce appreciable masculinization

**Excess adrenal androgens**

- **In adult male:** just expressing the existing characteristics
- **In prepubertal boys:** can cause precocious (early) development of the secondary sex characteristics without testicular growth

## ANDROGENS

Androgens are the hormones that exert masculinizing effects and they promote protein anabolism and growth

Testosterone from the testes is the most active androgen and the adrenal androgens have less than 20% of its activity. Secretion of the adrenal androgens is controlled acutely by ACTH and not by gonadotropins.

in normal males, castrated males and females these hormones exert very little masculinizing effect when secreted in normal amounts. However, they can produce appreciable masculinization when secreted in excessive amounts.

In adult males, excess adrenal androgens merely accentuate existing characteristics, but in prepubertal boys they can cause precocious development of the secondary sex characteristics without testicular growth

**Effects of Adrenal Estrogen**

**Androstenedione** is converted tin **fat** and other **peripheral tissues** into:

1. **Testosterone**
2. **Estrogens** (aromatization)

This represent an important **source** of **estrogen** in **men** and **postmenopausal women**

## ESTROGENS

The adrenal androgen androstenedione is converted to testosterone and to estrogens (aromatized) in fat and other peripheral tissues. This is an important source of estrogens in men and postmenopausal women .

**Mechanism of action**
**GC receptor:** Nuclear
**GC-GCR complex** act as transcription factor of certain genes

### EFFECT ON METABOLISM

**A. Rise in plasma glucose** by:

1. Enhance hepatic **gluconeogenesis** (and protein catabolism)
2. Enhance **glycogenolysis** (and increase G6PD activity)
3. **Antagonize insulin** action in peripheral tissues

- The rise in plasma glucose provides extra glucose to **brain** and **heart** (These **DO NOT** require insulin action)
- This effect make diabetes worse

B. **Rise in plasma lipids and an increase in ketone bodies** in diabetic patients

### EFFECTS ON ACTH SECRETION

- Inhibit ACTH secretion (-ve feedback response on the pituitary)

### EFFECTS ON THE NERVOUS SYSTEM

- **Adrenal insufficiency** causes **changes** in the **nervous** system
- **Slower β rhythm** than normal (seen in electroencephalography) reflecting poor concentration and lose of deep thinking
- **Personality changes** (**irritability**, **apprehension** "**anxiety**, fear", and **inability** to **concentrate**)
- These changes are **reversed** only by GCs

# PHYSIOLOGIC EFFECTS OF GLUCOCORTICOIDS

## MECHANISM OF ACTION

The multiple effects of glucocorticoids are triggered by binding to glucocorticoid receptors, and the steroid–receptor complexes act as transcription factors that promote the transcription of certain segments of DNA

## EFFECTS ON INTERMEDIARY METABOLISM

They include increased protein catabolism and increased hepatic glycogenesis and gluconeogenesis. Glucose-6-phosphatase activity is increased, and the plasma glucose level rises. Glucocorticoids exert an anti-insulin action in peripheral tissues and make diabetes worse. However, the brain and the heart are spared, so the increase in plasma glucose provides extra glucose to these vital organs. In diabetics, glucocorticoids raise plasma lipid levels and increase ketone body formation.

## EFFECT ON WATER METABOLISM

- **Adrenal insufficiency** characterized by **inability** to **excrete** a **water load**, causing the possibility of **water intoxication**.
- *Explanation*: Inadequate secretion of aldosterone and cortisol accompany by reduced reabsorption of sodium (and hyponatremia). On prolong time low sodium would be excreted by the kidney and hence low urine output. Excessive water drinking by adrenally insufficient patients then is retained and difficult to excrete (water intoxication)
- **Only GCs repair** this **deficit**.
- **In patients with adrenal insufficiency** who have not received GCs, **glucose infusion** may cause high fever ("glucose fever") followed by **collapse** and **death (water dilute glucose after metabolism making glucose infusion as hypotonic with subsequent swollen of thermoregulatory center cells)**

## EFFECTS ON THE BLOOD CELLS & LYMPHATIC ORGANS:

- **Lower** the number of circulating **eosinophils** by increasing their sequestration in the spleen and lungs.
- **Lower** the number of **basophils** in the circulation
- **Increase** the number of **neutrophils**, **platelets**, and **RBCs**

# EFFECTS ON THE BLOOD CELLS & LYMPHATIC ORGANS

Glucocorticoids decrease the number of circulating eosinophils by increasing their sequestration in the spleen and lungs. Glucocorticoids also lower the number of basophils in the circulation and increase the number of neutrophils, platelets, and red blood cells.

## RESISTANCE TO STRESS

- **Stress** : any **change** in the **environment** that **changes** or threatens to change an **existing optimal steady state**.
  - Stress activates processes at the molecular, cellular, or systemic level to restore the previous homeostatic reactions
  - Some stresses stimulate ACTH secretion.
  - Most stress stimulate both ACTH and sympathetic nervous system
- The **increase** in **ACTH** secretion is **essential** for **survival** when the **stress** is **severe**.
- The function of circulating **GCs** may be **maintenance** of **vascular reactivity** to **catecholamines**.
- **Short term** increase in ACTH is **beneficial**
- **Long term** increase in ACTH is **harmful** and **disruptive** causing **Cushing syndrome** and other abnormalities

# RESISTANCE TO STRESS

The term stress as used in biology has been defined as any change in the environment that changes or threatens to change an existing optimal steady state. Most, if not all, of these stresses activate processes at the molecular, cellular, or systemic level that tend to restore the previous state, that is, they are homeostatic reactions. Some, but not all, of the stresses stimulate ACTH secretion. The increase in ACTH secretion is essential for survival when the the stress is severe. Most of the stressful stimuli that increase ACTH secretion also activate the sympathetic nervous system, and part of the function of circulating glucocorticoids may be maintenance of vascular reactivity to catecholamines.

It should also be noted that the increase in ACTH, which is beneficial in the short term, becomes harmful and disruptive in the long term, causing among other things, the abnormalities of Cushing syndrome.

**Cushing syndrome**

**Cause:** Prolong increase in plasma GCs

**Metabolic effects:** excess protein catabolism cause protein-depletion

**Physical changes**:

- **Body Skin** & subcutaneous tissues: Thin
- **Muscle**: Poorly developed
- **Wound healing**: Poor (mild injuries cause bruises and ecchymosis)
- **Hair**: Thin and scraggy.
- **Face skin**: Increase in facial hair and acne causes by increase adrenal androgens secretion that accompany the increase in GCs
- **Body fats**: redistributed producing buffalo hump
  **Buffalo hump characterized by**: thin extremities; **fat collection in abdominal wall, face and upper back**

- **Electrolyte disturbance**: **Na**+ & **water retention** (produce rounded **moon-face** plethoric appearance), **K+ depletion**

- **Blood pressure**: 85% of patients are hypertensive
  - Hypertension may be due to:
    1. Increased **deoxycorticosterone** secretion
    2. Increased **angiotensinogen** secretion
    3. **Direct** GC **effect** on blood **vessels**

# PHARMACOLOGIC & PATHOLOGIC EFFECTS OF GLUCOCORTICOIDS

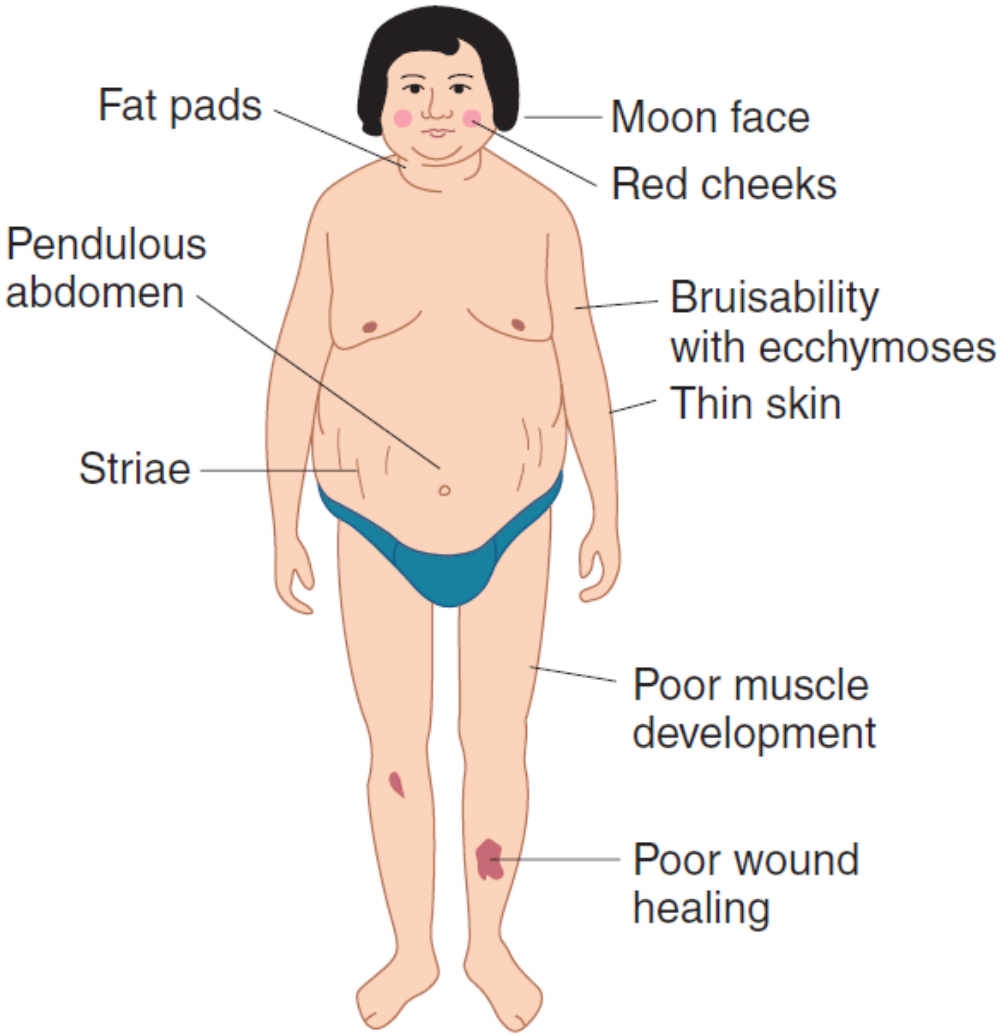
## CUSHING SYNDROME

The clinical picture produced by prolonged increases in plasma glucocorticoids was described by Harvey Cushing and is called **Cushing syndrome** (Figure).

Patients with Cushing syndrome are protein-depleted as a result of excess protein catabolism. The skin and subcutaneous tissues are therefore thin and the muscles are poorly developed. Wounds heal poorly, and minor injuries cause bruises and ecchymoses. The hair is thin and scraggly. Many patients with the disease have some increase in facial hair and acne, but this is caused by the increased secretion of adrenal androgens and often accompanies the increase in glucocorticoid secretion.

Body fat is redistributed in a characteristic way. The extremities are thin, but fat collects in the abdominal wall, face, and upper back, where it produces a "buffalo hump."

The salt and water retention plus the facial obesity cause the characteristic plethoric, rounded "moon-faced" appearance, and there may be significant $K^+$ depletion and weakness. About 85% of patients with Cushing syndrome are hypertensive. The hypertension may be due to increased deoxycorticosterone secretion, increased angiotensinogen secretion, or a direct glucocorticoid effect on blood vessels.




**Typical findings in Cushing syndrome.**

**In inflammatory reactions**
**GCs** **inhibits** the **inflammatory response** to tissue injury

**In allergic reactions**
**GCs** **suppress** the release of **histamine** from mast cells and basophils

**Both actions** require **high level** of circulating GCs but this produce GCs excess manifestations (side effects)

## ANTI-INFLAMMATORY & ANTI-ALLERGIC EFFECTS OF GLUCOCORTICOIDS

Glucocorticoids inhibit the inflammatory response to tissue injury. The glucocorticoids also suppress manifestations of allergic disease that are due to the release of histamine from mast cells and basophils. Both of these effects require high levels of circulating glucocorticoids and cannot be produced by administering steroids without producing the other manifestations of glucocorticoid excess. Furthermore, large doses

**Role of ACTH in GCs secretion**
**Effect**: **Basal** GCs secretion and GCs secretion in **stress** depend on ACTH from pituitary

**Half-life**: 10min in blood
**Adrenal responsiveness**: **increases** the **sensitivity** of **adrenal** to **subsequent doses** of **ACTH**

## REGULATION OF GLUCOCORTICOID SECRETION

### ROLE OF ACTH

Both basal secretion of glucocorticoids and the increased secretion provoked by stress depend on ACTH from the anterior pituitary. its half-life in the circulation in humans is about 10 min.

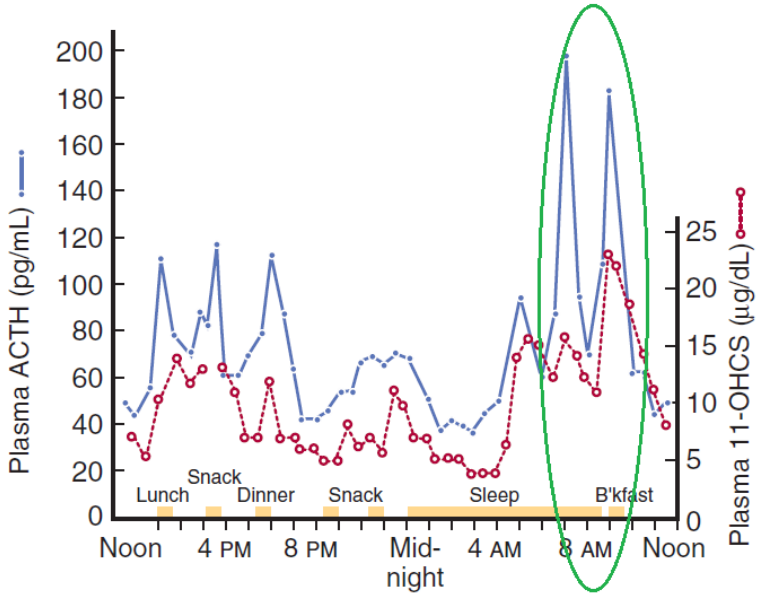
### ADRENAL RESPONSIVENESS

ACTH not only produces prompt increases in glucocorticoid secretion but also increases the sensitivity of the adrenal to subsequent doses of ACTH.

**Pattern of ACTH secretion: Irregular bursts**:

**Bursts frequency:**
**Early morning: Most frequent - 75%** of **cortisol** production occurs between **4:00AM** and **10:00** AM
**Evening: Least frequent**

**In adrenal insufficiency: Diurnal (circadian) rhythm** in ACTH secretion is **present** in patients receiving **constant doses** of **GCs**




**Fluctuations in plasma ACTH and glucocorticoids throughout the day in a normal girl (age 16)**

# CIRCADIAN RHYTHM

ACTH is secreted in irregular bursts throughout the day and plasma cortisol tends to rise and fall in response to these bursts (Figure ). In humans, the bursts are most frequent in the early morning, and about 75% of the daily production of cortisol occurs between 4:00 AM and 10:00 AM. The bursts are least frequent in the evening. This **diurnal (circadian) rhythm** in ACTH secretion is present in patients with adrenal insufficiency receiving constant doses of glucocorticoids.

# GLUCOCORTICOID FEEDBACK

Free glucocorticoids inhibit ACTH secretion, and the degree of pituitary inhibition is proportional to the circulating glucocorticoid level. The inhibitory effect is exerted at both the pituitary and the hypothalamic levels.

A drop in resting corticoid levels stimulates ACTH secretion, and in chronic adrenal insufficiency the rate of ACTH synthesis and secretion is markedly increased.

**-ve feedback:** Free GCs inhibits ACTH secretion at pituitary and hypothalamic levels.
**The degree of inhibition**: **proportional** to **GCs** plasma **level**
**Drop in resting GC levels**: **stimulates ACTH** secretion
**In adrenal insufficiency**: **ACTH** secretion rate **markedly increase** (**absence of -ve feedback**)

**Aldosterone action: Na+ retention** (from urine, saliva, sweat, colon), **expands ECF volume**, **K+ excretion** (Kaluresis; K diuresis), H+ excretion (acidic urine)
**Renal site of action**: Principles cells (P cells) of the collecting ducts

**Aldosterone mechanism of action:**
**Receptors (MR): in the cytoplasm**
Aldosterone-MR complex move to the nucleus and cause gene transcription
**Action of synthesized proteins**:
Increase ENaC insertion into the cell membrane from a cytoplasmic pool (Increase ENaC activity) – Rapid effect
Increase synthesis of ENaC – Slower effect

# EFFECTS OF MINERALOCORTICOIDS

## ACTIONS

Aldosterone and other steroids with mineralocorticoid activity increase the reabsorption of $Na^+$ from the urine, sweat, saliva, and the contents of the colon. Thus, mineralocorticoids cause retention of $Na^+$ in the ECF. This expands ECF volume. In the kidneys, they act primarily on the **principal cells (P cells)** of the collecting ducts Under the influence of aldosterone, increased amounts of $Na^+$ are in effect exchanged for $K^+$ and $H^+$ in the renal tubules, producing a $K^+$ diuresis and an increase in urine acidity.

## MECHANISM OF ACTION

Like many other steroids, aldosterone binds to a cytoplasmic receptor, and the receptor–hormone complex moves to the nucleus where it alters the transcription of mRNAs.

The aldosterone-stimulated proteins have two effects—a rapid effect, to increase the activity of epithelial sodium channels (ENaCs) by increasing the insertion of these channels into the cell membrane from a cytoplasmic pool; and a slower effect to increase the synthesis of ENaCs.

## EFFECT OF ACTH

- When first administered, **ACTH stimulates** the output of **aldosterone** as well as that of **glucocorticoids** and **sex hormones**.
- The **amount** of ACTH **required** to increase aldosterone output is somewhat **greater** than the amount **that stimulates maximal glucocorticoid secretion**.

## EFFECTS OF ANGIOTENSIN II & RENIN

- Injections of **angiotensin II** stimulate **adrenocortical secretion and**, **in small doses**, affect **primarily the secretion of aldosterone**.
- **Hemorrhage** stimulates **ACTH** and **renin** secretion.
- **Standing** and **constriction** of the thoracic **inferior vena cava decrease intrarenal arterial pressure** also stimulate **ACTH** and **renin** secretion.
- Dietary **$Na^+$ restriction (reduce** ECF volume**)** also **increases aldosterone** secretion via the **RAAS** . However; **aldosterone** and **renin** secretion are **increased before any** consistent **decrease** in **blood pressure** takes place (hemostatic control)

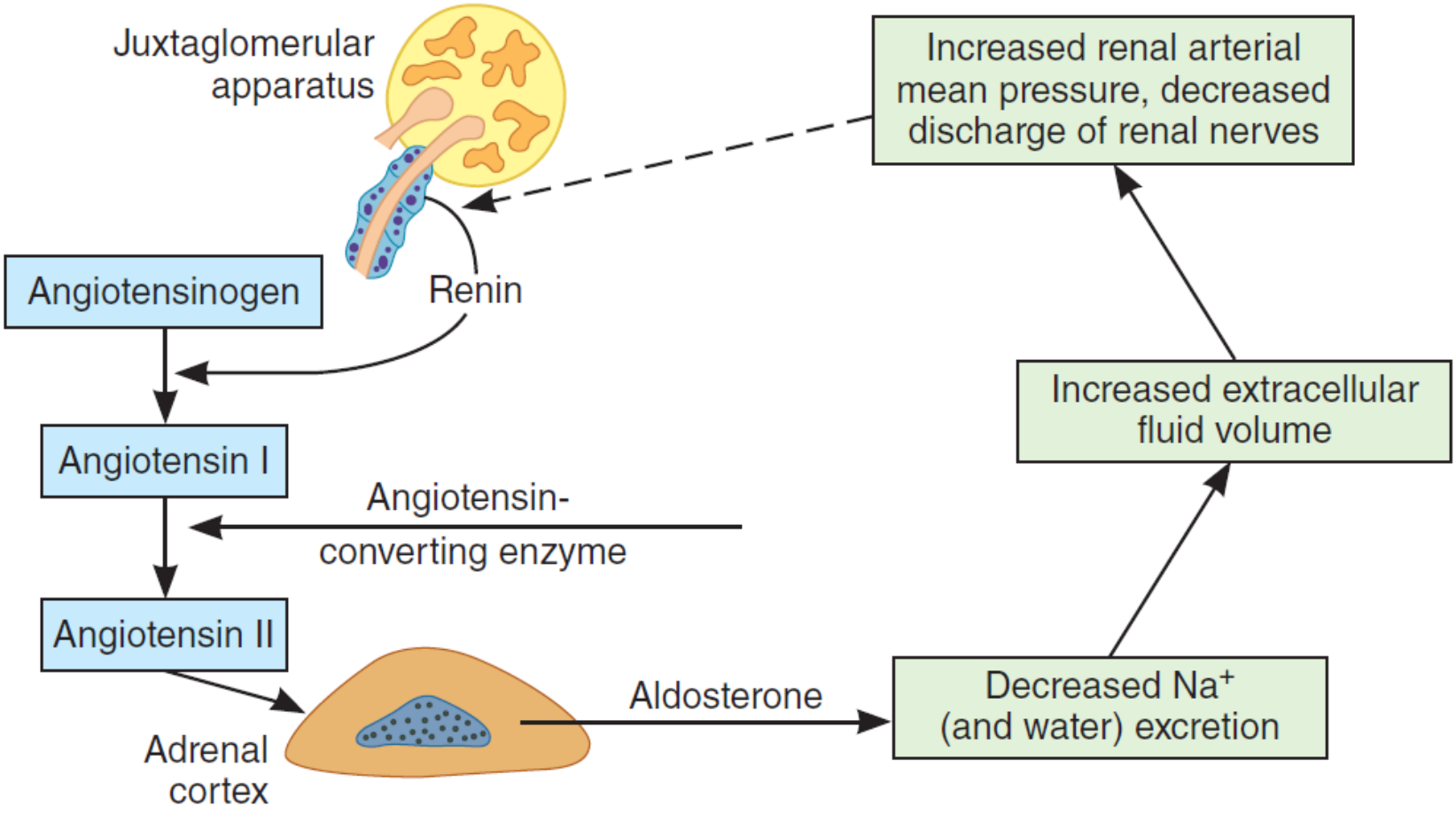
# REGULATION OF ALDOSTERONE SECRETION

## STIMULI

The principal conditions that increase aldosterone secretion are summarized in Table below Some of them also increase glucocorticoid secretion; others selectively affect the output of aldosterone. The primary regulatory factors involved are ACTH from the pituitary, renin from the kidney via angiotensin II, and a direct stimulatory effect on the adrenal cortex of a rise in plasma $K^+$ concentration.

**TABLE Conditions that increase aldosterone secretion.**

| |
|---|
| **Glucocorticoid secretion also increased** |
| Surgery |
| Anxiety |
| Physical trauma |
| Hemorrhage |
| **Glucocorticoid secretion unaffected** |
| High potassium intake |
| Low sodium intake |
| Constriction of inferior vena cava in thorax |
| Standing |
| Secondary hyperaldosteronism (in some cases of heart failure, cirrhosis, and nephrosis) |




**Feedback mechanism regulating aldosterone secretion.** The dashed arrow indicates inhibition.

## Factors in the regulation of Na+ excretion

1. Aldosterone
2. GFR
3. Atrial natriuretic peptide (ANP)
4. Presence or absence of osmotic diuresis
5. Change in tubular reabsorption of Na+ independent of aldosterone

### Change in position

- When one rises **from supine** to the **standing position** **aldosterone secretion increase**; this **increase Na+ retention** from urine
- The decrease in Na+ excretion (urine content) developed too rapidly and can not explained by the sole effect of aldosterone secretion (**Aldosterone take some time to act**)
- The primary function of aldosterone secretion is to **restore intravascular volume** (plasma volume, ECF) BUT it is **only one of the hemostatic mechanisms** involved in this regulation (i.e.; **Baroreflexes** also **operated**)

# ROLE OF MINERALOCORTICOIDS IN THE REGULATION OF SALT BALANCE

Variations in aldosterone secretion is only one of many factors affecting $Na^+$ excretion. Other major factors include the glomerular filtration rate, ANP, the presence or absence of osmotic diuresis, and changes in tubular reabsorption of $Na^+$ independent of aldosterone. It takes some time for aldosterone to act. When one rises from the supine to the standing position, aldosterone secretion increases and $Na^+$ is retained from the urine. However, the decrease in $Na^+$ excretion develops too rapidly to be explained solely by increased aldosterone secretion. The primary function of the aldosterone-secreting mechanism is the defense of intravascular volume, but it is only one of the homeostatic mechanisms involved in this regulation.

MCQ: The secretion of which of the following would be least affected by a decrease in extracellular fluid volume?

A. CRH
**B. AVP**
C. DHEA
D. Estrogens
E. Aldosterone

MCQ: Which of the following is produced only by large amounts of glucocorticoids?

A. Normal responsiveness of fat depots to norepinephrine
B. Maintenance of normal vascular reactivity
C. Increased excretion of a water load
**D. Inhibition of the inflammatory response**
E. Inhibition of ACTH secretion

MCQ: Which of the following has the greatest effect on Na+ excretion?

A. Progesterone
B. Cortisol
C. AVP
**D. Aldosterone**
E. DHEA

MCQ: Which of the following has the greatest effect on plasma osmolality?

A. Progesterone
B. Cortisol
**C. AVP**
D. Aldosterone

MCQ: Which of the followings is an effect of aldosterone?

**A. Promotes excretion of K+ in DCT and CD**
B. Causes Na+ reabsorption in the PCT
C. Secretion is controlled by plasma free fatty acid level
D. Is secreted from the placenta
E. Produces hair growth in females

MCQ: In women, Cushing's syndrome is manifested by all the following EXCEPT

A. Moon face
B. Buffalo hump
C. Muscle weakness
**D. Facial hair growth**
E. Purplish skin striae

MCQ: Cortisol hormone is considered as

A. A hypoglycemic hormone
B. Mainly an anabolic hormone
C. Inhibited by ACTH
**D. Mainly a lipolytic hormone**
E. Stimulated by angiotensin II

MCQ: Excess glucocorticoids (cortisol) lead to which of the followings effects?

A. Lack of gluconeogesis
**B. Hyperlipidemia and ketosis**
C. Reduce protein catabolism
D. Reduce fat mobilization
E. Increase susceptibility to stress

MCQ: The most important regulator of aldosterone secretion is

A. Renin angiotensin system
B. Atrial pressure
C. Plasma concentration of K+
D. ACTH
E. Plasma concentration of Na+

MCQ: The most important regulator of aldosterone secretion is

A. Atrial pressure
**B. Plasma concentration of K+**
C. ACTH
D. Plasma concentration of Na+
E. All options are involved

MCQ: All the followings are true about cortisol EXCEPT

A. Released by zona fasciculata
**B. Is an example of mineralocorticoid steroid**
C. Is highly bound to plasm protein
D. Has comparable affinity to MR receptors
E. Has low obvious Na+ absorptive ability (mineralocorticoid)

MCQ: Cushing's disease results in the followings EXCEPT

A. Increased fat deposition (buffalo hump) secondary to fat redistribution
B. Hypertension secondary to over mineralocorticoid activity
C. Hyperglycemia secondary to increased hepatic gluconeogesis
D. Increased skin pigmentation secondary to over stimulation of melanocytes by elevated ACTH
**E. Infertility**