Adrenal Gland Medullary and cortical hormones I

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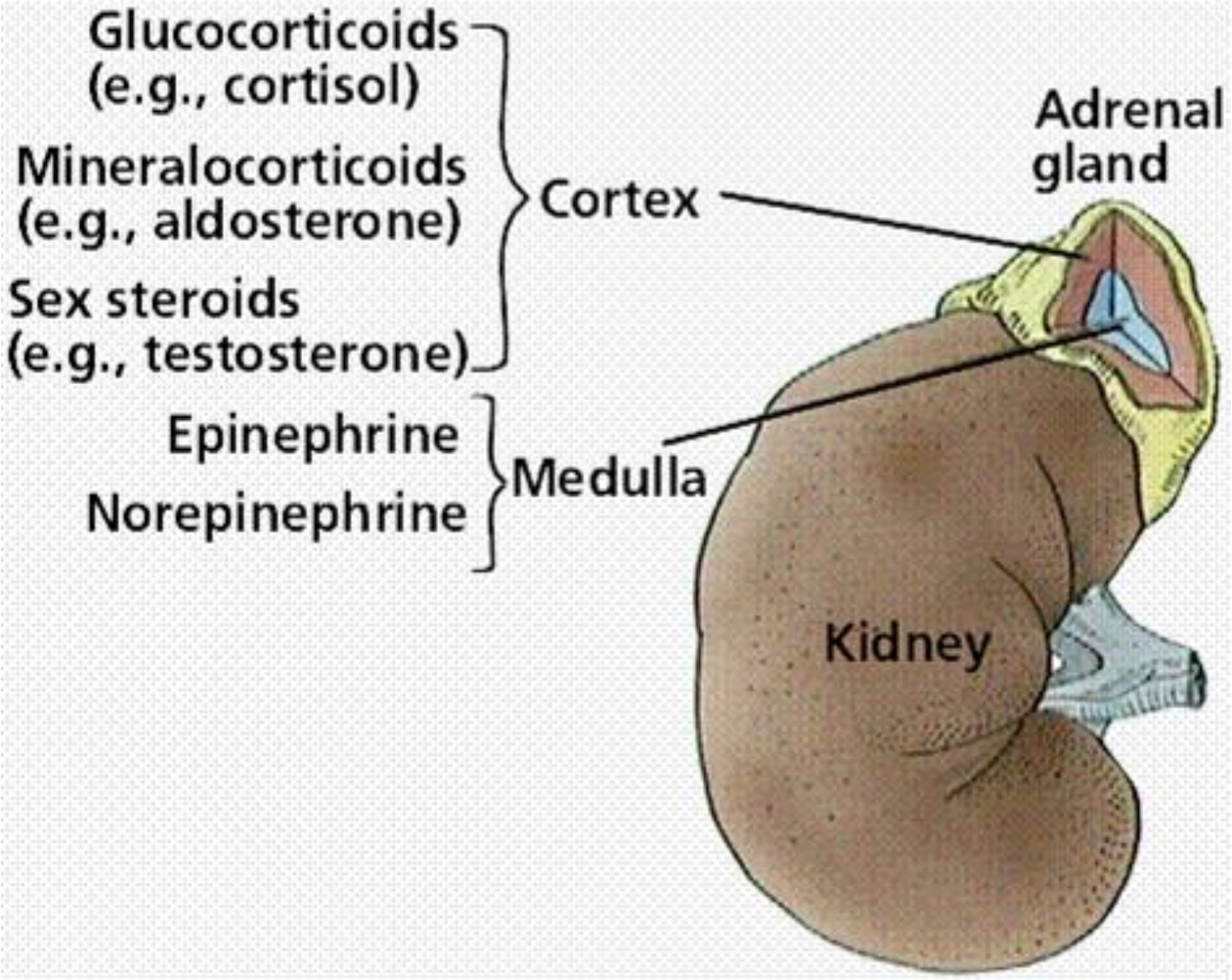
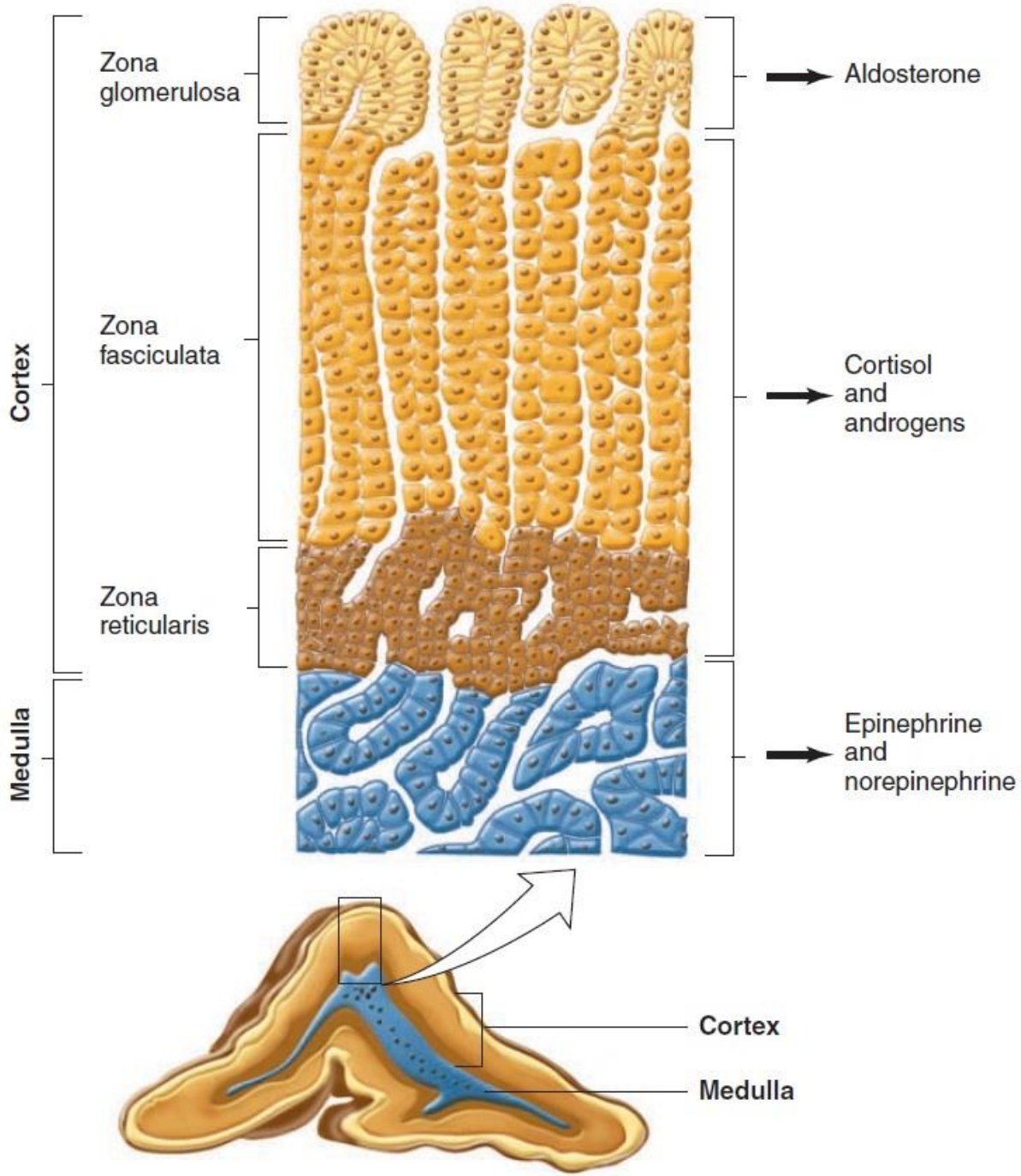
Lecture Objectives:

1. Describe the role of adrenal in preparing the body to face stress.
2. List the catecholamines secreted by the adrenal medulla.
3. Describe the actions of catecholamines in human body.
4. List the factors that regulate adrenal medullary secretion.
5. Describe the hypothalamic pituitary adrenal axis.
6. Describe the role of the adrenal cortex in regulation of plasma sodium, potassium, and blood volume.
7. Describe the major physiological effects of mineralococorticoids.
8. Describe the regulation of mineraloocorticoids secretion.

Introduction

- The adrenal gland is composed of the adrenal medulla (the central 20%) and the adrenal cortex (80% of the gland).
- The medulla is functionally related to the sympathetic nervous system. It is derived from a subpopulation of neural crest cells. It synthesizes and secretes **epinephrine**, **norepinephrine**, and **dopamine** (function?) in response to direct sympathetic stimulation. These hormones cause almost the same effects as direct stimulation of the sympathetic nerves.
- The adrenal cortex is derived from mesodermal tissue and secretes **corticosteroids**. These hormones are synthesized from the cholesterol.


Glucocorticoids
(e.g., cortisol)
Mineralocorticoids
(e.g., aldosterone)
Sex steroids
(e.g., testosterone)
Cortex
Epinephrine
Norepinephrine
Medulla
Adrenal gland
Kidney


Cortex
Medulla
Zona glomerulosa
Zona fasciculata
Zona reticularis
Aldosterone
Cortisol and androgens
Epinephrine and norepinephrine
Cortex
Medulla

The adrenal medullary hormones

- Catecholamines are amino acid-derived hormones, synthesized from the amino acid tyrosine by the medullary pheochromocytes in response to nicotinic cholinergic receptors stimulation. The type of cell that secretes dopamine is unknown.
- The half-life of circulating catecholamines is short (2-3 minutes). Most (>50%) of the catecholamines released circulate bound to albumin with low affinity.
- Catecholamines do not cross the blood-brain barrier easily, therefore they exert their effects almost exclusively in peripheral tissues and not in the brain.
- About 80% of the secretion is epinephrine (E) and 20% is norepinephrine (NE). These proportions can change under different physiological conditions.
- Humoral catecholamines have the same effects caused by direct sympathetic stimulation, except that the effects last 5-10 times longer. Postganglionic sympathetic neurons also produce and secrete NE but do not produce epinephrine.

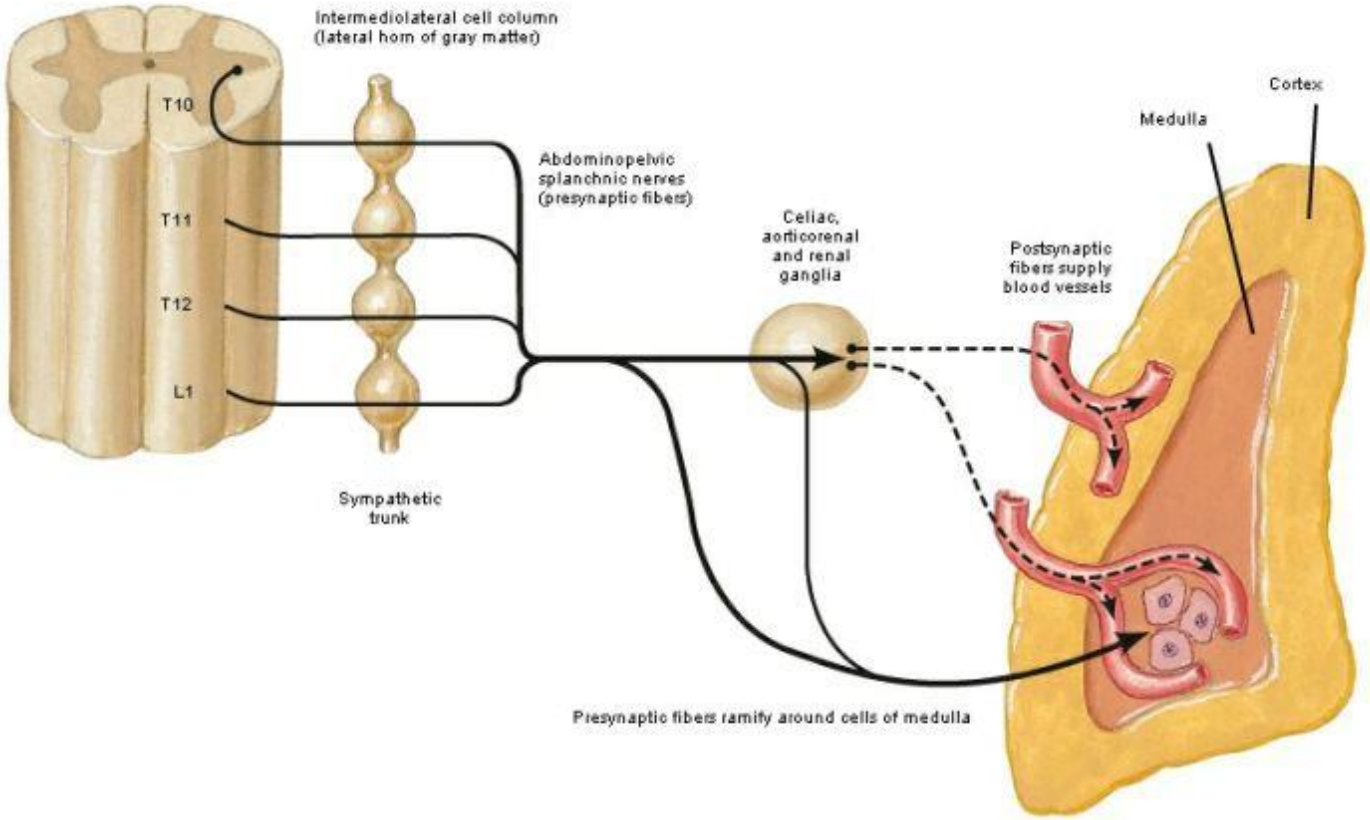
The adrenal medullary hormones (Cont.)

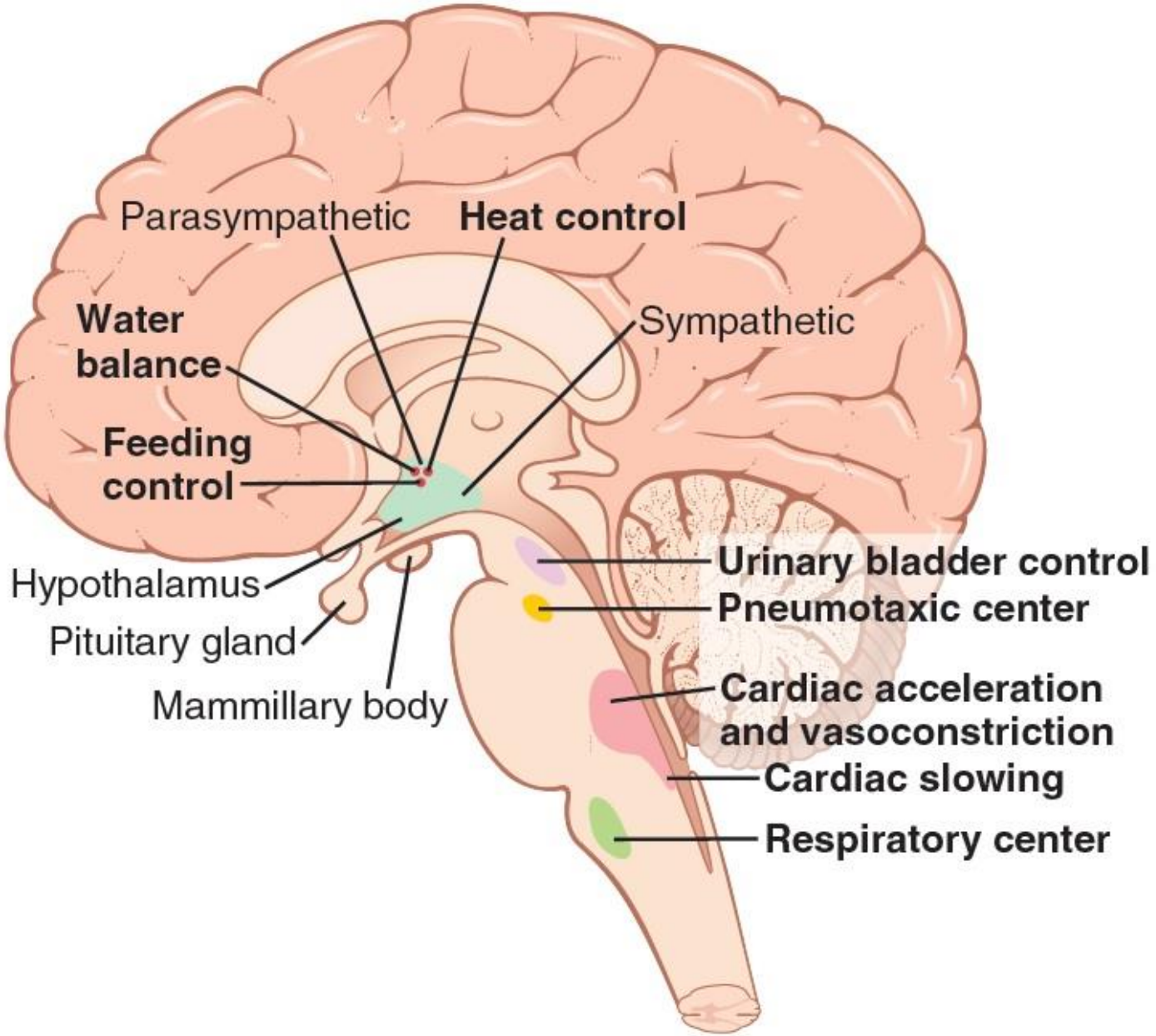
- Two hormones are known to produce upregulation of adrenergic receptors: the glucocorticoids and thyroid hormone. Receptor upregulation by thyroid hormone is critical in hyperthyroid patients because the combined effects of thyroid hormone and catecholamines can exacerbate cardiovascular manifestations of disease.
- Chronic exposure to adrenergic receptor agonists can reduce the number of receptors in the plasma membrane because of decreased synthesis of the receptor (downregulation). Examples include β-agonist-promoted desensitization in asthma and α-agonist-stimulated tachyphylaxis (a rapid and short-term onset of drug tolerance) in patients receiving sympathomimetic nasal decongestants.
- Epinephrine is a universal adrenergic receptor stimulator; and since it stimulates β receptors it causes powerful cardiac stimulation, mild rise in blood pressure, and grater metabolic effect (5-10 times) compared to that of norepinephrine
- The metabolic effects include an increase in BMR, ↑ glycogenolysis and gluconeogenesis (β2) in the liver and muscles, ↑ lipolysis (β1), and ↑ glucose and lactate release into the blood (hyperglycemia and hyperlactatemia). The metabolic effect of humoral catecholamine cannot be substituted by direct sympathetic stimulation as small proportion of all the cells in the body are innervated directly by sympathetic fibers.

The adrenal medullary hormones (Cont.)

- Most of the increase in fat utilization occurs during heavy exercise. This results almost entirely from release of E and NE by the adrenal medulla. Both hormones activate triglyceride lipase in fat cells → liberation of free fatty acids.
- There is basal secretion of E and NE by the adrenal medulla (0.2 µg/kg/min for E and about 0.05 µg/kg/min for NE). This basal rate of secretion maintains the blood pressure. The gland increases its secretion rate in **alarm** or **stress response** (= mass discharge of sympathetic system) such as during physical exercise, mental stress (anger, anxiety, pain), cold, hypoglycemia, hypoxia, bleeding, injury, etc.
- The overall reaction to the sudden release of catecholamines is known as the "**fight-or-flight**" response
- The regulatory sympathetic centers are mainly present in the brain stem reticular substance. However, signals from the hypothalamus and even from the cerebrum can modulate activities of all autonomic control centers.
- Pheochromocytomas are adrenal medullary tumors that mostly secrete NE. They cause episodic or sustained hypertension.
- Dopamine has positive inotropic effect (↑ systolic blood pressure but has no effect on diastolic blood pressure). Therefore, moderate doses are useful in treatment of traumatic and cardiogenic shock

Nerves of Suprarenal Glands
Schema





Autonomic control areas in the brain stem and hypothalamus.

A list of some major effects mediated by epinephrine and norepinephrine

- **Increase alertness:** E and NE are equally potent in this regard, although in humans epinephrine usually evokes more anxiety and fear.
- **Increased rate and force of contraction of the heart muscle:** this is predominantly an effect of epinephrine acting through beta receptors.
- **Constriction of blood vessels:** norepinephrine, in particular, causes widespread vasoconstriction, resulting in increased resistance and hence arterial blood pressure.
- **Dilation of bronchioles:** assists in pulmonary ventilation.
- **Stimulation of lipolysis in fat cells:** this provides fatty acids for energy production in many tissues and aids in conservation of dwindling reserves of blood glucose.
- **Increased metabolic rate:** oxygen consumption and heat production increase throughout the body in response to epinephrine. Medullary hormones also promote breakdown of glycogen in skeletal muscle to provide glucose for energy production.
- **Dilation of the pupils:** particularly important in situations where human or animal are surrounded by conditions of low ambient light.
- **Inhibition of certain "non-essential" processes:** an example is inhibition of gastrointestinal secretion and motor activity.

The adrenal cortical hormones

- The adrenal cortex synthesizes and secretes mainly **mineralocorticoids, glucocorticoids,** and **androgens (male sex hormones)** in response to hypothalamic-pituitary-adrenal hormone stimulation.
- The mineralocorticoids are those hormones in which effects on Na^+ and K^+ excretion predominate. Glucocorticoids are those hormones in which effects on glucose and protein metabolism predominate.
- **Aldosterone** hormone is the principal mineralocorticoid secreted by the zona glomerulosa, whereas, **cortisol** is the principal glucocorticoid secreted by the zona fasciculata. This latter zone secretes **Corticosterone** and small amounts of adrenal **androgens** (Dehydroepiandrosterone, DHEA) as well.
- The zona reticularis develops postnatally and is recognizable at approximately age 3 years; it also produces androgens, as well as small amounts of estrogens and some glucocorticoids.
- All steroids have some degree of mineralocorticoids activities, i.e. they cause salt and water retention.

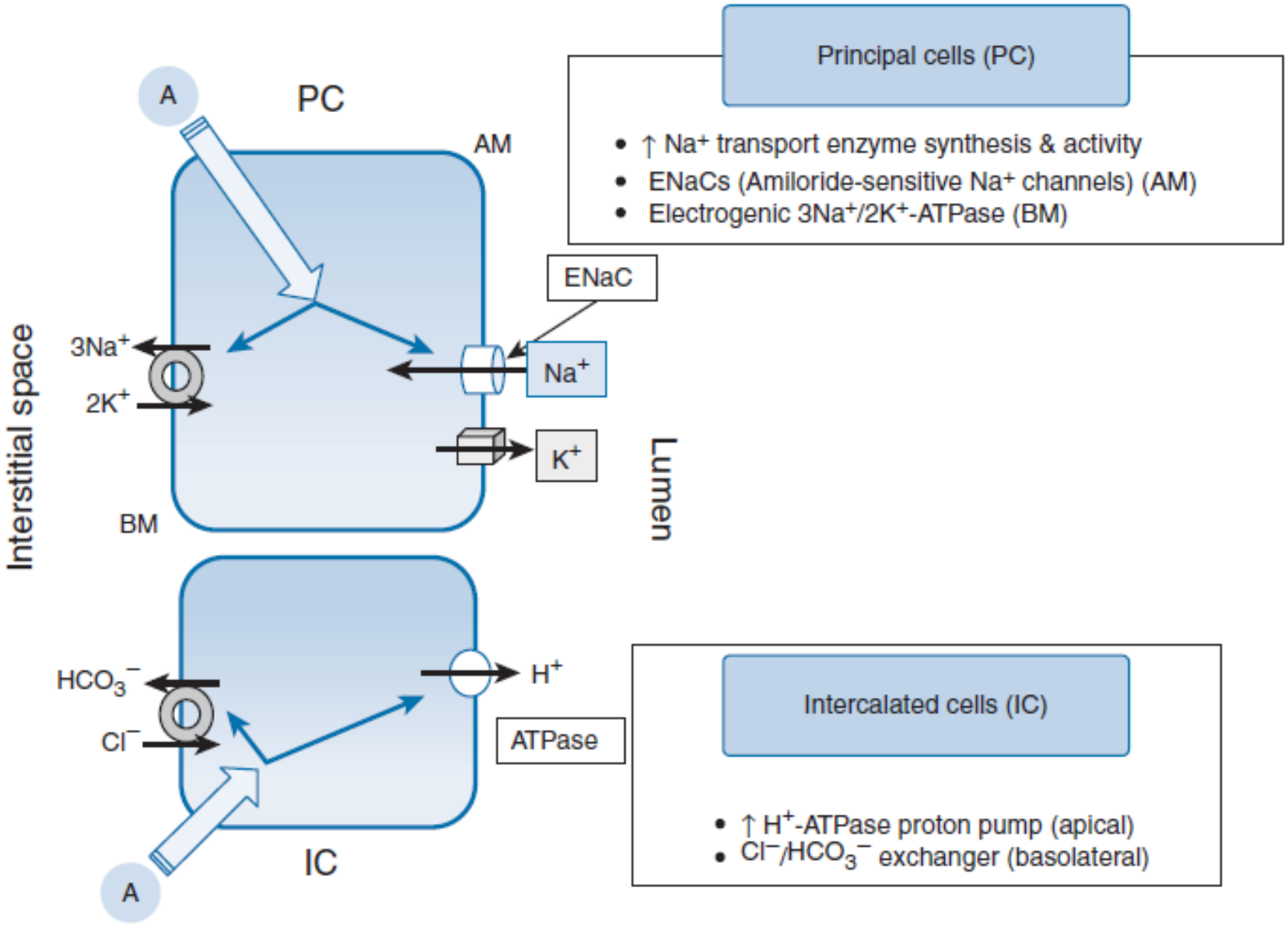
Adrenal cortex- outer layer

Zone layer	Production	Principal steroid
zona glomerulosa	Mineralocorticoids	Aldosterone
zona fasciculata	Glucocorticoids	Cortisol
zona reticularis	Androgens	Dihydroepiandrosterone & Androstenedione (and Corticosterone)

Note: **Angiotensin II** increase the output of aldosterone and cause hypertrophy of the zona glomerulosa, and has no effect on the other two zones. **ACTH** increase secretion of cortisol and adrenal androgens and cause hypertrophy of the zona fasciculata and zona reticularis. ACTH has little effect on the zona glomerulosa.

The Aldosterone

- It is **essential for life**. Its main function is to:
  1. Regulates sodium and potassium ions
  2. Promotes secretion of H^+ so helps control pH
  3. Regulates BP and blood volume
- Aldosterone binds to a cytoplasmic receptor, and the receptor-hormone complex moves to the nucleus where it alters the transcription of mRNAs.
- Aldosterone ↑ absorption of Na^+ and ↑ secretion of K^+ especially by the principal cells of the collecting tubules and to a lesser extent in the distal tubules and collecting ducts → conserve Na^+ in the extracellular compartment → expansion of the extracellular fluid volume.
- The epithelium of the second half of renal distal tubule and collecting tubule has two types of cells, the ***principal*** and ***intercalated* cells**. Principal cells (express more aldosterone receptors) are responsible for Na^+ and water reabsorption and secretion of K^+. This function is controlled by aldosterone and K^+ concentration in blood.

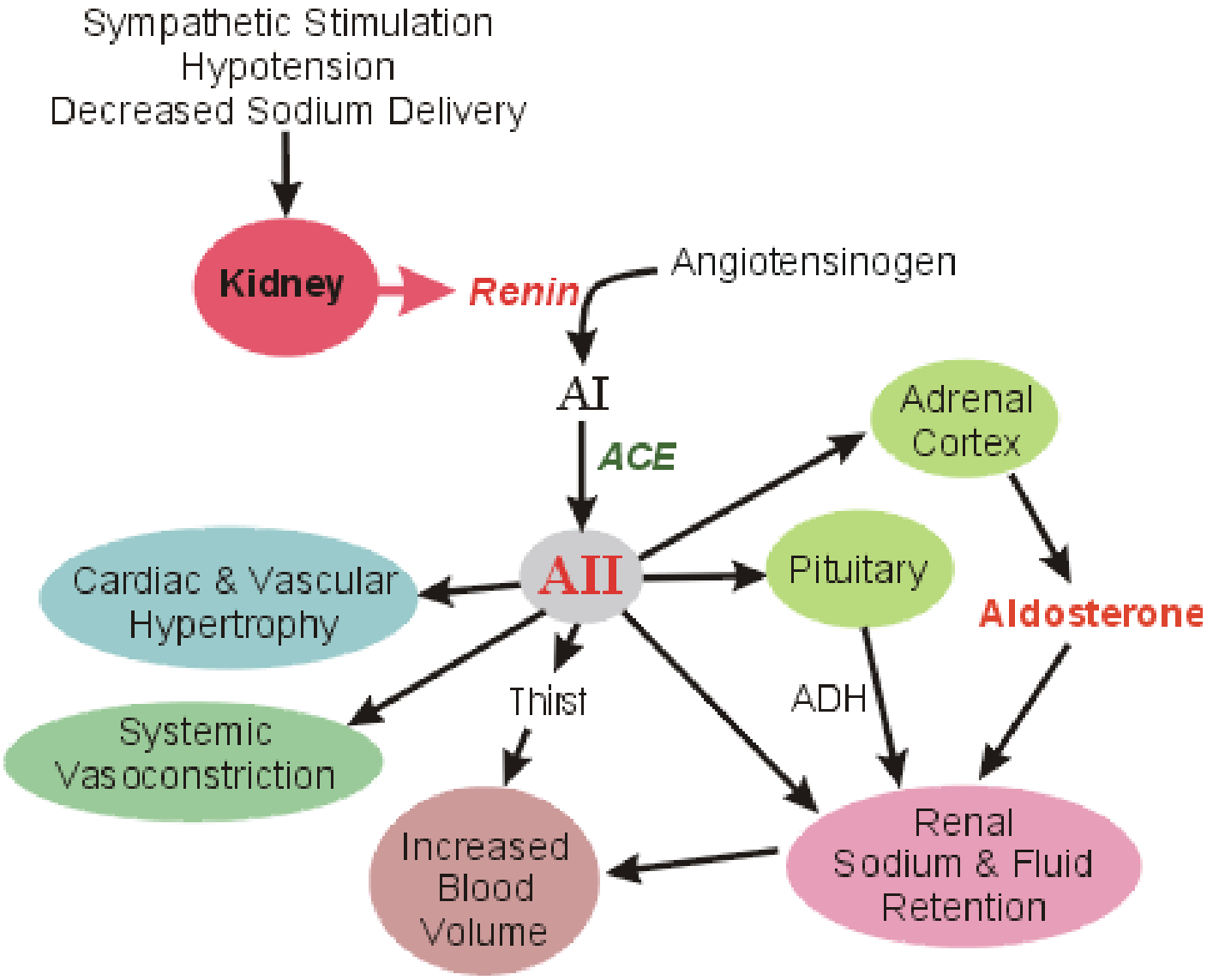


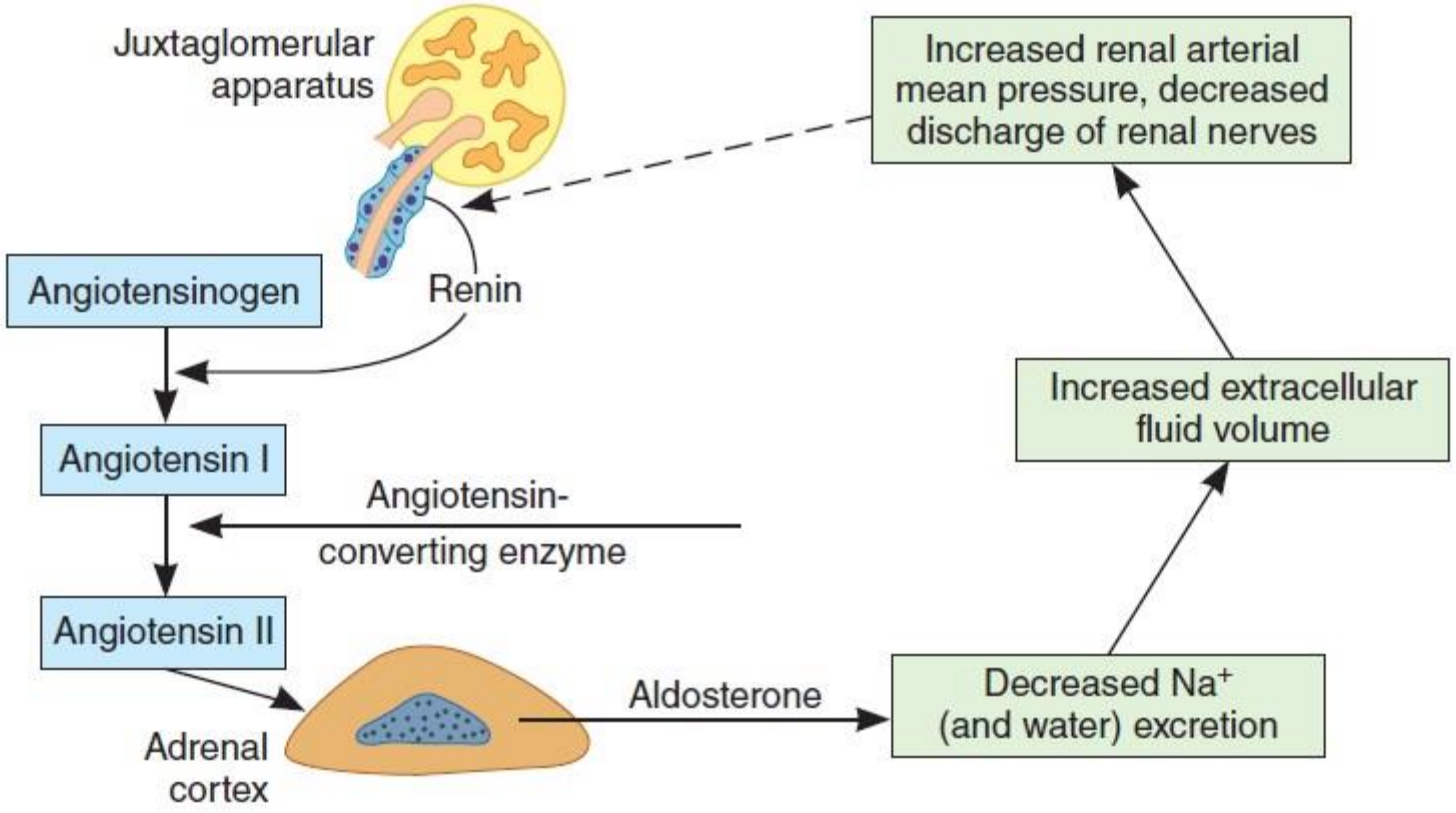
A, aldosterone; AM, apical membrane; BM, basolateral membrane;
ENaC: epithelial sodium channel

The Aldosterone (Cont.)

- Intercalated cells reabsorb K^+ and secrete H^+, a process that requires H^+-ATPase (i.e. responsible for acidification of urine). This mechanism is similar to that in stomach and can create $[H^+]$ gradient of 1/1000. Cellular H^+ ion is obtained from the carbonic acid synthesized in these cells by the enzyme carbonic anhydrase.
- Aldosterone has almost the same effects on sweat glands, salivary gland, and content of the GIT as it has on the renal tubules.
- The regulation of aldosterone is multifactorial and secretion is achieved by the following mechanisms:
  1. ↑ in plasma K^+ concentration → ↑ aldosterone secretion
  2. ↑ in angiotensin II level → ↑ aldosterone secretion
  3. ACTH from anterior pituitary gland is necessary for basal aldosterone secretion. Great ↑ in ACTH → ↑ secretion of all cortical hormones including the aldosterone

Note: Factors that suppress aldosterone secretion include atrial naturetic hormone, high sodium concentration and potassium deficiency


Sympathetic Stimulation
Hypotension
Decreased Sodium Delivery
Kidney
Renin
Angiotensinogen
AI
ACE
Adrenal Cortex
Cardiac & Vascular Hypertrophy
AII
Pituitary
Aldosterone
Thirst
ADH
Systemic Vasoconstriction
Increased Blood Volume
Renal Sodium & Fluid Retention



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

Test Question:

Q. Which autonomic receptor mediates secretion of epinephrine by the adrenal medulla?

A. Adrenergic α receptors

B. Adrenergic β_1 receptors

C. Adrenergic β_2 receptors

D. Cholinergic muscarinic receptors

E. Cholinergic nicotinic receptors

Test Question:

Q. A 60-year-old man suffers from elevated blood pressure (185/130 mmHg). Lab tests reveal an increase in plasma renin activity, plasma aldosterone level, and left renal vein renin level. His right renal vein renin level is decreased. What is the most likely cause of the patient's hypertension?

A. Aldosterone-secreting tumor

B. Adrenal adenoma secreting aldosterone and cortisol

C. Pheochromocytoma

D. Left renal artery stenosis

E. Right renal artery stenosis