HYPOTHALAMUS – PITUITARY-ADRENAL AXIS

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Learning objectives

- Describe the structural and functional organization of the adrenal gland.
- Describe the synthesis and secretion of cortical adrenal hormones.
- Describe the mechanism of action and physiologic effects of adrenal hormones.
- Explain the control of adrenal hormone synthesis and secretion. Describe the major feedback loops that integrate the hypothalamic axis and body homeostasis.
- Explain the physiologic roles of the adrenal hormones in normal physiology.

OVERVIEW

The adrenal glands maintain homeostasis in response to stress. Three major classes of hormones are secreted by these glands: aldosterone (mineralocorticoid), cortisol (glucocorticoid), DHEA (weak androgen), and catecholamines (epinephrine and norepinephrine).

FUNCTIONAL ANATOMY

The adrenal gland is located on top of the kidney. Like the pituitary, two distinct tissues merge during development to form the adrenal cortex (glandular tissue) and medulla (modified neuronal tissue) (Fig 1).

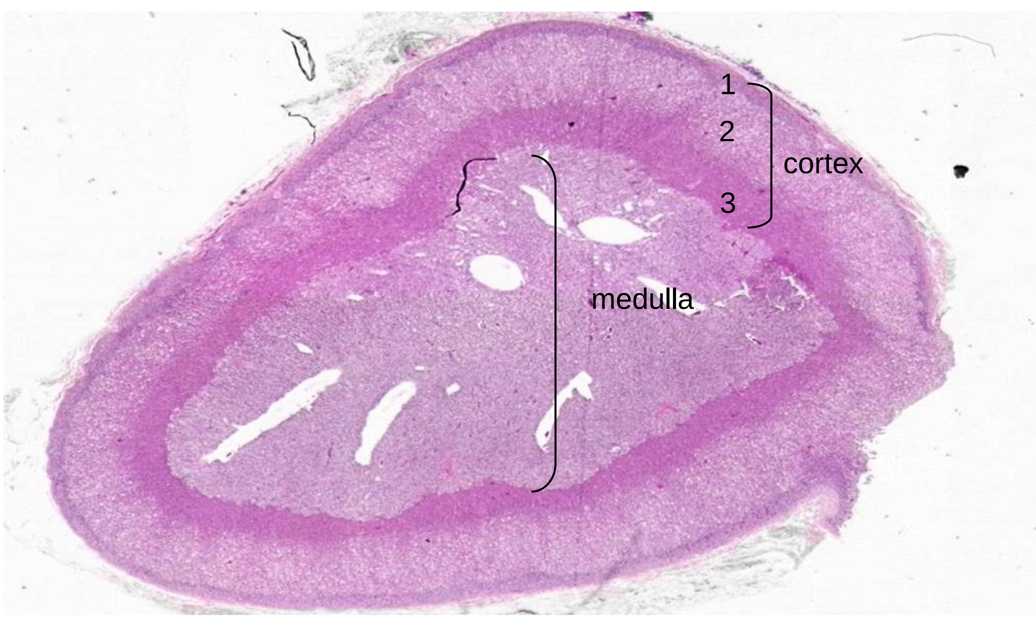

Figure 1. Structure of the adrenal gland. The cortex secretes three steroid hormones: 1. aldosterone, 2. cortisol, 3. a weak androgen, DHEA. The medulla secretes epinephrine (Epi) and norepinephrine (NorEpi).

MINERALOCORTICOIDS

The major mineralocorticoid in humans is **aldosterone**. **Aldosterone is NOT under the hypothalamus-pituitary control and does not mediate a negative feedback to this axis.** Aldosterone secretion is increased by the vasoconstrictor, angiotensin II, and by elevated plasma K+ concentration. Elevated plasma Na+ inhibits the secretion of aldosterone.

Aldosterone, acts in the kidney to promote secretion of K+ into the urine from the blood and the reabsorption of Na+ from the urine into the blood. Water follows the sodium thereby increasing blood volume (Fig. 2). The loss of the adrenal glands can be life threatening due to reduced ECF volume, reduced cardiac output, and elevated blood K+ levels.

Aldosterone also acts in acid-base balance. We will consider this action when we discuss the urinary system.

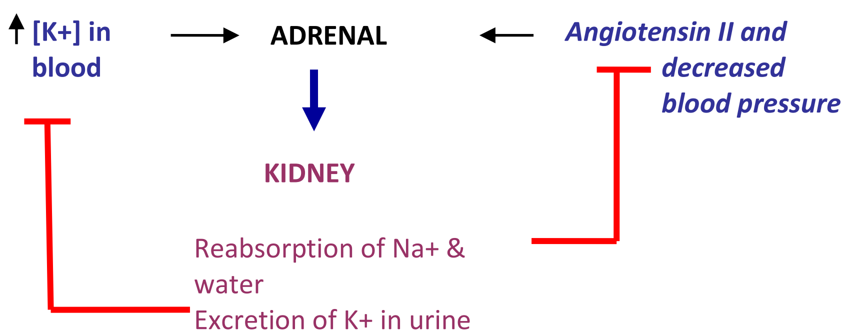

Figure 2. Mechanism of aldosterone action. Aldosterone acts in the kidney to stimulate Na+ reabsorption from the urine and to move K+ from blood into the urine (excretion).

GLUCOCORTICOIDS

In response to stress, the glucocorticoid, **cortisol**, maintains blood glucose levels for "fight or flight". Cortisol mobilizes energy stores. It changes metabolism in the body to degrade protein and fat and to synthesize glucose. These are **catabolic** actions that elevate blood glucose levels. Cortisol also suppresses the immune system.

Regulation of cortisol is governed by the hypothalamus-pituitary –adrenal axis in response to stress and sleep-wake cycles (Fig 3). Cortisol level is highest in the circulation in early morning just before waking.

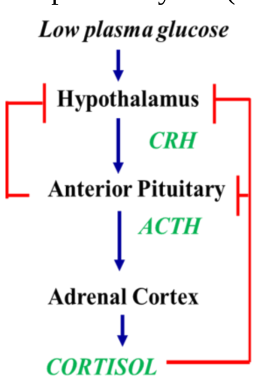

Figure 3. Hypothalamic-pituitary-adrenal axis.

Cortisol is a steroid derivative. It follows the typical steroid hormone pattern for synthesis, release, transport, and action. Upon synthesis, cortisol diffuses into the blood, where it binds to a **carrier** for delivery. A small fraction of the hormone is free. The free hormone diffuses into cells where it binds to the **intracellular glucocorticoid receptor** and changes **transcription**.

In general the response to glucocorticoids is 60-90 minutes because cortisol is synthesized on demand.

All nucleated cells of the body have glucocorticoid receptors. However cortisol is inactivated in tissues that express the minearlocorticoid receptor to prevent inappropriate activation.

PATHOLOGY

Too much: Cushing's disease is caused by over-secretion of ACTH leading to an excess of circulating **cortisol**. These patients develop hyperglycemia (high blood glucose levels) which is not corrected by insulin from the pancreas. Elevated levels of cortisol cause wasting of the muscle, bone and fat depots in the legs and arms of these individuals but also increased deposition of fat in the trunk ('beer belly"), face ("moon face") and at the back of the neck ("buffalo hump").

Too little: Addison's disease is caused by the destruction of the adrenal gland. This is a life threatening condition due to the loss *of **aldosterone and cortisol***. These patients exhibit lowered serum Na+ concentration, elevated serum K+ concentration, and low blood pressure. Why do these patients have low blood pressure? Would someone with Addison's disease have normal, low or high levels of ACTH in the blood?

ADRENAL MEDULLA HORMONES

Cells in the adrenal medulla synthesize and secrete norepinephrine (NorEPI) and epinephrine (EPI). The ratio of the two catecholamines differs considerably among species but in humans roughly **80 % of the catecholamine output is epinephrine**.

EPI and Nor EPI are stored in granules. Their secretion is stimulated by the sympathetic nervous system in response to heavy exercise, hypoglycemia, and trauma (Fig 5).

The physiologic effects of EPI and NorEPI are mediated by **adrenergic receptors** on target cells. The physiologic consequences of increased medullary catecholamine include:

- Increased heart rate and force of contraction of heart muscle.
- Constriction of blood vessels (increased blood pressure).
- Dilation of bronchioles to assist in pulmonary ventilation.
- Increased metabolic rate, oxygen consumption, and heat production.
- Stimulation of lipolysis in adipose cells to provide additional sources of energy (free fatty acids) for "fight or flight" response.
- Inhibition of insulin release from the pancreas to help maintain elevated blood glucose levels (Fig 4).

The adrenal hormones, cortisol and epinephrine work in concert in stress conditions with a third hormone, glucagon which is secreted by the pancreas. All three hormones act to raise blood glucose levels in a synergistic manner (Fig 4).

SYNERGY

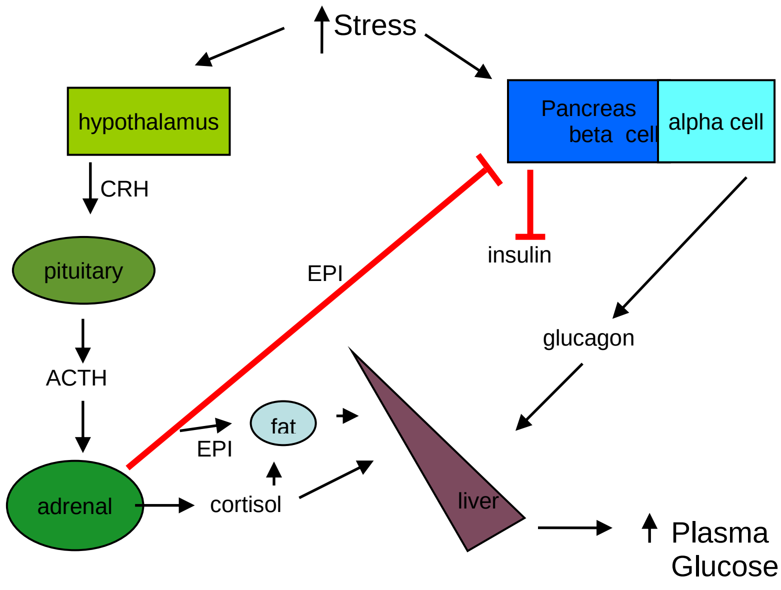

Figure 4. Synergistic actions of cortisol, epinephrine (EPI), and glucagon raise blood glucose.

KEY CONCEPTS

1. Adrenal gland contains two distinct glands that are regulated separately and produce different hormone products.
2. Adrenal cortex produces steroid hormones.
   a. Aldosterone acts on the kidneys and influences Na+ and K+ balance in the body.
   b. Cortisol affects metabolism, resulting in release of stored fuels.
   c. DHEA, a weak androgen, affects secondary sex traits.
3. Adrenal medulla functions as part of the sympathetic nervous system and secretes primarily epinephrine (EPI). EPI acts on the cardiovascular and respiratory systems to increase delivery of oxygen to tissues and on the pancreas to inhibit insulin secretion to help raise plasma glucose levels. Combined effects of cortisol, EPI and glucagon (from the pancreas) act synergistically to raise blood glucose for "fight or flight response".

QUESTIONS

1. When compared to the resting state, which of the following is increased in the blood during strenuous exercise?
   A. glucagon
   B. epinephrine
   C. insulin
   D. A and B
   E. A, B and C

2. Excess secretion of aldosterone would lead to:
   A. Increased loss of K+ in the urine
   B. Increased ECF volume
   C. Increased loss of Na+ in the urine
   D. A and B
   E. B and C

ANSWERS

1. D
2. D