Adrenal gland disorders

Background

The adrenal glands are important in the synthesis and regulation of key human hormones. They play a crucial role in water and electrolyte homeostasis, as well as regulation of blood pressure, carbohydrate and fat metabolism, physiologic response to stress, and sexual development and differentiation.

The adrenal gland is located on the upper segment of the kidney. It consists of an outer cortex and an inner medulla.

The adrenal medulla secretes the catecholamines epinephrine (also called adrenaline) and norepinephrine (also called noradrenaline), which are involved in the regulation of the sympathetic nervous system.

The adrenal cortex consists of three histologically distinct zones:

1. the outer zona glomerulosa
2. the zona fasciculata
3. an innermost layer called the zona reticularis

Each zone is responsible for production of different hormones

The **zona glomerulosa** is responsible for the production of:

1. the mineralocorticoids aldosterone
2. 18-hydroxy-corticosterone
3. Corticosterone
4. Deoxycorticosterone

Aldosterone promotes renal sodium retention and potassium excretion. Its synthesis and release are regulated by renin in response to decreased vascular volume and renal perfusion. Adrenal aldosterone production is regulated by the renin-angiotensin-aldosterone system.

- The zona fasciculata is the middle layer and produces the glucocorticoid hormone cortisol.
- Cortisol is responsible for maintaining homeostasis of carbohydrate, protein, and fat metabolism.

Its secretion follows a **circadian rhythm**:

1. generally beginning to rise at approximately 3 to 4 am
2. peaking around 6 to 8 am
3. cortisol levels decrease throughout the day, approach 50% of the peak value by 4 pm
4. reach their **nadir** around midnight

Cortisol plays a key role in the body's response to stress. Cortisol is converted in the liver to an inactive metabolite known as **cortisone**.

The zona reticularis produces the androgens androstenedione, dehydroepiandrosterone (DHEA), and the sulfated form of dehydroepiandrosterone (DHEA-S). Only a small amount of testosterone and estrogen is produced in the adrenal glands. Androstenedione and DHEA are converted in the periphery, largely to testosterone and estrogen.

Adrenal hormone production is controlled by the ***hypothalamus and pituitary***. Corticotropin-releasing hormone (CRH) is secreted by the hypothalamus and stimulates secretion of adrenocorticotropic hormone (ACTH; also known as corticotropin) from the anterior pituitary. ACTH in turn stimulates the adrenal cortex to produce cortisol. When sufficient or excessive cortisol levels are reached, a negative feedback is exerted on the secretion of CRH and ACTH, thereby decreasing overall cortisol production. The control of adrenal androgen synthesis also follows a similar negative feedback mechanism.

Adrenal insufficiency

Adrenal insufficiency generally refers to the inability of the adrenal glands to produce adequate amounts of cortisol for normal physiologic functioning or in times of stress. The condition is usually classified as primary, secondary, or tertiary, depending on the etiology.

Primary adrenal insufficiency, also known as Addison disease, occurs when the adrenal glands are unable to produce cortisol. It occurs from destruction of the adrenal cortex, usually from an autoimmune process.

Acute adrenal insufficiency (ie, adrenal crisis) results from the body's inability to sufficiently increase endogenous cortisol during periods of excessive physiologic stress.

Adrenal crisis can occur when patients with chronic adrenal insufficiency do not receive adequate glucocorticoid replacement during stressful conditions such as those experienced during surgery, infection, fever, acute illness, invasive medical procedures, or trauma.

Abrupt discontinuation or rapid tapering of glucocorticoids, given chronically in supraphysiologic doses, may lead to adrenal crisis.

Treatment and Outcome Evaluation

Chronic Adrenal Insufficiency

The general goals of treatment are to manage symptoms and prevent development of adrenal crisis.

Lifelong glucocorticoid replacement therapy may be necessary for patients with adrenal insufficiency, and mineralocorticoid replacement therapy is usually required for those with Addison disease.

Glucocorticoids with sufficient mineralocorticoid activity are generally required. However, the addition of a potent mineralocorticoid such as fludrocortisone, along with adequate salt intake, is sometimes needed to prevent sodium loss, hyperkalemia, and intravascular volume depletion.

Mineralocorticoid supplementation typically is not indicated for the treatment of secondary or tertiary adrenal insufficiency because aldosterone production is often unaffected.

Hydrocortisone is often prescribed because it most closely resembles endogenous cortisol with its relatively high mineralocorticoid activity and short half-life and allows the design of regimens that simulate the normal circadian cycle.

For the treatment of primary adrenal insufficiency (Addison disease) in adults, 15–25 mg/day of oral hydrocortisone is typically administered in two divided doses, with **two-thirds** of the dose given in the morning upon awakening to mimic the early morning rise in endogenous cortisol, and the remaining **one-third** of the dose given in the late afternoon to avoid insomnia and allow for the lowest concentration in the blood at around midnight.

Acute Adrenal Insufficiency

During an acute adrenal crisis, the immediate treatment goals are to:

1. correct volume depletion
2. manage hypoglycemia
3. provide glucocorticoid replacement.

Volume depletion and hypoglycemia can be corrected by giving large volumes (~ 2–3 L) of IV normal saline and 5% dextrose solution.

Glucocorticoid replacement can be accomplished by administering IV hydrocortisone, starting at a dose of 100 mg every 6 hours for 24 hours, decreasing to 50 mg every 6 hours on the second day after achieving hemodynamic stability, and thereafter be tapered to a lower maintenance dose by the fourth or fifth day and fludrocortisone can be added if needed.

HYPERCORTISOLISM (CUSHING SYNDROME)

Cushing syndrome refers to the pathophysiologic changes associated with exposure to supraphysiologic cortisol concentrations (endogenous hypercortisolism) or pharmacologic doses of glucocorticoids (exogenous hypercortisolism).

Treatment

The goal of treatment in patients with Cushing syndrome is reversal of hypercortisolism and management of the associated comorbidities, including the potential for long-term sequelae such as cardiac hypertrophy.

Surgical resection is considered the treatment of choice for Cushing syndrome from endogenous causes if the tumor can be localized and if there are no contraindications.

The **treatment of choice** for Cushing syndrome from exogenous causes is gradual discontinuation of the offending agent.

In drug-induced Cushing syndrome, discontinuation of the offending agent is the best management option. However, abrupt withdrawal of the glucocorticoid can result in adrenal insufficiency or exacerbation of the underlying disease.

Glucocorticoid doses less than 7.5 mg/day of prednisone or its equivalent for less than 3 weeks generally would not be expected to lead to suppression of the HPA axis.

However, in patients receiving pharmacologic doses of glucocorticoids for prolonged periods, gradual tapering to near physiologic levels (5–7.5 mg/ day of prednisone or its equivalent) should precede drug discontinuation.

Administration of a short-acting glucocorticoid in the morning and use of alternate-day dosing may reduce the risk of adrenal suppression.