Academia Open
Vol. 10 No. 1 (2025): June (In Progress)
DOI: 10.21070/acopen.10.2025.10797

Review of Adrenal Gland Dysfunction and Its Link to Endocrine Disorders: Tinjauan Disfungsi Kelenjar Adrenal dan Kaitannya dengan Gangguan Endokrin

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General Background: The adrenal glands, also known as suprarenal glands, are vital endocrine organs located above each kidney. **Specific Background:** Comprising the cortex and medulla, these glands produce a variety of hormones essential for metabolic regulation, immune response, stress adaptation, and cardiovascular function. **Knowledge Gap:** Despite extensive research on adrenal hormone synthesis, a comprehensive understanding of how structural and functional alterations in these glands contribute to various endocrine disorders remains limited. **Aims:** This study aims to elucidate the correlation between adrenal gland composition, hormone secretion, and the manifestation of adrenal-related diseases. **Results:** Findings demonstrate that the adrenal cortex synthesizes steroid hormones—mineralocorticoids, adrenal androgens, and glucocorticoids—while the medulla produces catecholamines such as epinephrine and norepinephrine. Dysregulation in hormonal output is linked to disorders including Addison's disease, Cushing's syndrome, congenital adrenal hyperplasia, primary aldosteronism, and adrenal cancers. **Novelty:** This study provides an integrated perspective on the structural-functional relationship of the adrenal gland and its role in disease etiology. **Implications:** Understanding these mechanisms enhances diagnostic and therapeutic strategies for managing endocrine disorders associated with adrenal dysfunction.

Highlights:

1. Adrenal glands regulate vital hormones for body homeostasis.
2. Dysfunction causes Addison's, Cushing's, and adrenal-related diseases.
3. Insights aid diagnosis and treatment of endocrine disorders.

Key words: Adrenal gland structure , Corticosteroids, Catecholamines, Adrenal gland disorder

Introduction

The two adrenal glands, which weigh roughly 4 grams each, The upper ends of the two kidneys are home to the adrenal gland[(1)] It is invented of an inner medulla and an external cortex. There are

three histologically separate zones in the adrenal cortex. The generation of various hormones is the responsibility of each zone. The mineralocorticoids aldosterone, 18-hydroxy-corticosterone, corticosterone, and deoxycorticosterone stay produced by the outer zona glomerulosa; the glucocorticoid hormone cortisol is produced by the middle layer, zona fasciculate; and the androgens androstenedione dehydroepiandrosterone(DHEA),and the sulfated formula of dehydroepiandrosterone (DHEA-S)stay formed via the innermost layer, known as the zona reticularis. In the adrenal glands, very little estrogen and testosterone are generated. The periphery converts androstenedione and DHEA mostly to estrogen and testosterone.The catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline), which are created through the adrenal medulla, are important in the sympathetic nervous system's control[(2)(3)]

The pituitary and hypothalamus that control the production of adrenal hormones. The hypothalamus secretes corticotropin-releasing hormone (CRH),which reasons the frontal pituitary to relief adrenocorticotropic hormone (ACTH), normally mentioned to as corticotropin. The adrenal cortex is then stimulated to create cortisol by ACTH. When cortisol levels are either too high or too low, CRH and ACTH secretion is negatively impacted, which lowers total cortisol output. Additionally, a similar negative feedback system governs the regulation of adrenal androgen production[(4)(5)]

Adrenal gland structure

In the retroperitoneum on both sides of the body, the adrenal glands remain situated above and slightly medial to the kidneys. The left adrenal gland in humans remains semilunar or arc-shaped and is marginally bigger than the right, which has a pyramidal form. [(6)]. About 5 cm in extent, 3 cm in thickness, and up to 1 cm in width are the dimensions of the adrenal glands [(7)] . In an adult person, they weigh between 7 and 10 grams[(8)]. The fatty capsule that envelops the adrenal glands is part of the renal fascia, which envelops the kidneys as well. The kidneys are separated from the glands by a weak connective tissue wall called the septum. The renal fascia connects the adrenal glands, which are situated just beneath the diaphragm, to the diaphragmatic crura[(9)].

Each adrenal gland is poised of two discrete portions: the adrenal cortex and the adrenal medulla. The cortex is separated into three regions. These run from the outside to the inside and are called the zona fasciculata, zona glomerulosa, and zona reticularis. [(10)]. Just inside the capsule, the zona glomerulosa, which comprises 15 percent of the cortex, is composed of closely spaced, round or arched cords of columnar or pyramidal cells with numerous capillaries. [(11)]. These cells produce a class of steroids known as mineralocorticoids, which effect the uptake of water, K+, and Na+ through renal tubule cells . Aldosterone, a crucial regulator of salt balance that encourages Na+ reabsorption in the distal convoluted tubules, is the main product. Angiotensin II and an augment in plasma K+ content are the main factors that motivate aldosterone secretion; ACTH has very little effect. [(12)(13)].

The cortex's central zona fasciculata makes about 80% of it.It is made up of lengthy cords of big, one- or two-cell thick polyhedral cells that are divided by sinusoidal capillaries with fenestration. The cells appear vacuolated in standard histologic preparations and are packed with lipid droplets[(11)]. These cells release tiny amounts of adrenal androgens and estrogens in addition to glucocorticoids like cortisol and corticosterone. Adrenocorticotropic hormone (ACTH), which is a key constituent of the hypothalamic-pituitary axis, regulates the secretion of these cells[(14)]. A network of asymmetrical cords with broad capillaries and smaller cells scattered throughout comprise the innermost zona reticularis, which involves approximately 10% of the cortex. Due to the presence of additional lipofuscin coloring and less lipid droplets, the cells in this zone are often additional rigorously stained than those in the further regions. [(11)] In addition to producing cortisol, the zona reticularis cells secrete weak androgens like dehydroepiandrosterone (DHEA), which is transformed to testosterone in mutually males and females. Furthermore, these cells' secretion is motivated via ACTH with regulatory feedback. [(14)]. Each adrenal gland has an adrenal medulla at its core, which is encircled by the adrenal cortex. The body gets its catecholamines, including

noradrenaline and adrenaline, primarily from the chromaffin cells of the medulla. 80% adrenaline (epinephrine) and 20% noradrenaline (norepinephrine)[14]

The adrenal medulla is made up of great, pale-staining polyhedral cells that are prepared in cords or clusters and maintained via a system of reticular fibers. There are a few parasympathetic ganglion cells and a large network of sinusoidal capillaries that bridge the gap between neighboring cords. Neural crest cells give rise to postganglionic neurons of sympathetic and parasympathetic ganglia as well as medullary parenchymal cells called chromaffin cells. Since chromaffin cells are secretory cells with no axons or dendrites, they might be thought of as modified sympathetic postganglionic neurons[15][16].

Supplying the adrenal glands with blood

The adrenal glands stay highly vascularized and need a substantial blood supply since they produce a number of hormones that are vital to the body. Neuroendocrine and paracrine processes tightly regulate the blood supply, which is one way to control the systemic ranks of adrenal hormones[17] The arterial blood supply originates from three origins: the inferior adrenal artery as of the renal arteries, the middle adrenal as of straight off the abdominal aorta, and the superior adrenal arteries as of the inferior phrenic arteries. Most of the time, a single central vein drains the gland, releasing its blood into the left renal vein and the right vena cava. Blood flows from the outer cortex to the inner medulla[18]

The adrenal arteries can have many different origins. Rarely, the intestinal aorta, the celiac axis, or an intercostal artery may emerge as the superior adrenal artery. The superior adrenal artery stays frequently found in various arteries. The medium adrenal artery can originate from the renal, superior mesenteric, inferior phrenic, or celiac axis arteries. The lower adrenal arteries may likewise create as of the abdominal aorta or the lower phrenic artery [19][20]. The venous drainage as of the adrenal gland is determined by its side. Because the left adrenal gland is anatomically farther away from the inferior vena cava ., the left adrenal vein empties into the left renal vein. The right adrenal vein empties straight into this sizable vessel, while the inferior vena cava is much closer. Distinctions in adrenal venous drainage are mutual, especially on the left adjacent. There have been descriptions of venous associates between the left vaginal vein, the left adrenal vein, and the lower phrenic vein. Additionally, it is common to have double left adrenal veins. [21]

Development of Adrenal gland

The adrenal glands are poised of two distinct tissue kinds. The sympathetic nervous system's adrenal medulla, which yields and releases noradrenaline and adrenaline into the bloodstream, is situated in the center. The cortex, which generates a range of steroid hormones, surrounds the medulla. These tissues grow differently during pregnancy and are derived from various embryological precursors. The medulla originates as of the neural crest, which is of ectodermal source, whereas the adrenal gland's cortex is made of mesoderm. [22].

A newborn baby's adrenal glands are significantly bigger than an adult's in relation to body size. (23). At three months of age, for example, the glands stay four intervals bigger than the kidneys. After birth, the glands' size comparatively diminishes, primarily due to the cortex's atrophy. The cortex redevelops between the ages of 4 and 5, having nearly vanished by the age of 1. At birth, the glands weigh around 1 gram, and by adulthood, they weigh roughly 4 grams each. The glands of a fetus are initially visible next the sixth week of progress [22] The intermediate mesoderm is the source of the tissue found in the adrenal cortex. It emerges 33 days after fertilization, begins to produce steroid hormones by the eighth week, and grows quickly throughout the initial trimester of pregnancy. Unlike its adult counterpart, the fetal adrenal cortex is separated into two separate regions: the external "definitive" region, which is in a proliferative stage, and the inner "fetal" region, which contains the majority of the hormone-producing action. The placenta uses the huge quantities of adrenal androgens (manly sex hormones) produced in the fetal zone for the

manufacture of estrogen[24]. ACTH hormone generated by the pituitary gland that promotes the manufacture of cortisol, primarily controls the cortical development of the adrenal gland[25]. The majority of the cortical volume is occupied by the fetal zone at midgestation, The daily production of DHEA-S, an androgen and ancestor to mutually estrogens and androgens (feminine sex hormones), ranges from 100 to 200 mg [26]. The progress of organs during pregnancy, particularly the maturation of the lungs, depends on adrenal hormones, mainly glucocorticoids like cortisol. As a result of the fetal zone's quick departure after birth, the adrenal gland shrinks in size and secretes less testosterone[24] Androgen synthesis and secretion are modest in early childhood, but changes in the morphological and purposeful elements of cortical androgen manufacture take place between the ages of 6 and 8 years before puberty, which results in augmented excretion of the steroids DHEA and DHEA-S. Adrenarche is a process that has only been reported in humans and a few other primates, and these alterations are a part of it. Adrenarche is autonomous of gonadotropins and ACTH and is associated with a developing condensing of the cortex's zona reticularis layer. In terms of function, adrenarche supplies androgens for the growth of pubic and axillary hair prior to adolescence [27][28]. Neural crest cells, which originate in the embryo's ectoderm layer, give rise to the adrenal medulla. These cells move from their starting location and gather around the dorsal aorta, a primeval blood vessel, which triggers the cells' distinction by releasing proteins called BMPs. The adrenal medulla and additional sympathetic nervous system organs are formed by these cells migrating again from the dorsal aorta[29]. Since they have granules that dye with chromium salts—a feature not found in entirely sympathetic organs—the cells of the adrenal medulla are known as chromaffin cells. It used to be believed that the differentiation of chromaffin cells was caused by glucocorticoids generated in the adrenal cortex. According to more recent studies, this is mostly caused by BMP-4 released in adrenal tissue, with glucocorticoids only being involved in the cells' subsequent development[29] .

Adrenal gland hormones

Numerous hormones that are involved in several vital biological processes are secreted by the adrenal gland [22].

Corticosteroids

corticosteroids, are secreted by the adrenal cortex. Their chemical formulae are similar, and they are all produced from the steroid cholesterol. Nonetheless, they perform a number of distinct yet crucial roles due to minor variations in their molecular architectures[30]The adrenal cortex secretes two chief categories of adrenocortical hormones: mineralocorticoids and glucocorticoids. Small levels of sex hormones are also released, particularly androgenic hormones, which have physiological effects similar to those of the male sex hormone testosterone[31].

Mineralocorticoids

Sodium and potassium in particular are the electrolytes (minerals) of the extracellular fluids that are particularly impacted by the mineralocorticoids, hence their name. The construction of aldosterone, a mineralocorticoid, through the adrenal gland is crucial for controlling blood volume and salt (mineral) balance. By helping the re-absorption of sodium and the emission of together hydrogen and potassium ions, aldosterone affects the kidneys' distal complicated tubules and gathering ducts[32]. Around 2% of the clarified glomerular filtrate stays reabsorbed due to aldosterone. Sweat glands and the distal colon both react to aldosterone receptor stimulation by retaining sodium. The two primary factors that control the synthesis of aldosterone stay angiotensin II and extra-cellular potassium. Blood pressure is influenced by the extra-cellular volume, which is influenced by the body's sodium content. Thus, aldosterone's effects on salt retention are crucial for blood pressure management[33][34]. The renin-angiotensin-aldosterone system (RAAS) is the main trigger for aldosterone release[35] The greatest significant physiological apparatus for medium- to long-term blood pressure management is the RAAS, which is based on the liver-produced plasma protein angiotensinogen[36].

The kidneys create the renin enzyme in reaction to a reduction in blood pressure, which changes angiotensinogen into the inert protein known as angiotensin I. Angiotensin-converting enzymes (ACE) transform this into physiologically vigorous angiotensin II as it travels through the plasma till it spreads the lung tissue. This mostly acts as a vasoconstrictor, promoting the relief of aldosterone as of the adrenal cortex and assisting in lowering blood pressure. Aldosterone increases plasma Na+ concentration by encouraging the kidneys to reabsorb Na+. This promotes osmosis, which moves water from the tissues into the blood arteries, raising blood pressure and volume[34] .

Glucocorticoids

The glucocorticoid hormones are secreted by the zona fasciculata. Cortisol, a long-term stress hormone, is the most significant glucocorticoid in humans. The hypothalamic-pituitary-adrenal (HPA) axis is activated by chronic stressors such physical harm, malnutrition, or mental strain, which results in the relief of cortisol

As their term suggests, glucocorticoid hormones affect blood glucose levels; they cooperate with numerous additional hormones, counting as glucagon and insulin, to preserve glucose homeostasis [37]. The release of cortisol encourages an increase in blood-glucose levels. This happens since cortisol promotes the cessation of protein and fat, turning the glycerol component of fat and amino acid residues into glucose. This biochemical method is known as gluconeogenesis, which translates to "the creation of new glucose." When food supplies are scarce, gluconeogenesis is able to maintain blood-glucose concentrations, and elevated blood glucose offers a useful energy source for tissue regeneration following physical trauma. In addition, cortisol has a number of immunosuppressive qualities and affects mood, behavior, and the sleep/wake regulation[38] . It is a potent usual anti-inflammatory chemical that aids in reducing and managing the inflammatory reaction in terms of immunological regulation. Strong steroidal anti-inflammatory drugs that replicate the effects of cortisol include hydrocortisone creams, which are frequently used to treat inflammatory skin problems[39].

Androgens

Small levels of hormones known as androgens, which structurally resemble the male sex hormone testosterone, are produced by cells in the adrenal glands' zona reticularis. similar to testosterone, These hormones, which work as anabolic steroids with different levels of effectiveness, encourage the formation of masculine physical traits like deeper voice, more muscle mass, and facial and body hair. The libido, musculoskeletal system, and the formation of mediates for the production of oestrogens are all significantly impacted by androgens in females[40]. People who are physically changing from female to transgender can benefit from androgens, such as synthetic testosterone, as they help assure gender congruence, or a match between gender identity and physical appearance. Often referred to as gender-affirming hormone therapy, masculinizing hormone therapy helps suppress the regular menstrual cycle and limit the action of female sex hormones like oestrogens. Both men and women emit adrenal androgens, however in men, the presence of testosterone generated by the testes tends to lessen the physiological effects of these hormones. Hyperandrogenism, or excessive androgen secretion, can cause early-life premature (precocious) puberty in boys and possibly undesired masculine hair growth patterns and irregular menstruation cycles in cisgender females[41].

Catecholamines

Epinephrine (adrenaline) and norepinephrine (noradrenaline) are the two primary catecholamine hormones. They are water-soluble substances with a construction composed of group an amine and a catechol . The majority of the adrenaline that flows in the body is produced by the adrenal glands, but very little noradrenaline is produced by them [42]. The thick network of blood arteries in the adrenal medulla releases these hormones, Through its interactions with adrenoreceptors located throughout the body, adrenaline and noradrenaline produce effects for instance elevated heart

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Vol. 10 No. 1 (2025): June (In Progress)
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degree and blood pressure. The struggle or flight reaction, which is characterized by an augment in blood pressure, a contraction of blood vessels in numerous areas of the body, and a hastening of respiration and heart ratio, stays carried on by the actions of adrenaline and noradrenaline[43]. .

Adrenal gland disorder

- Cushing's syndrome

A pituitary adenoma that produce too abundant adrenocorticotropic hormone (ACTH) foundations Cushing's syndrome, a rare hormonal illness. The symptoms of Cushing's syndrome stay brought on via the adrenal glands producing too much cortisol [44][45]. Both the unsuppressed cortisol hypersecretion and the pituitary adenoma that secretes ACTH cause bilateral adrenocortical hyperplasia[46]. Anatomopathological analysis typically reveals a chromophobe or basophilic pituitary adenoma (particularly the larger ones). 40:1,000,000 people have Cushing's disease, and women are more likely to get it than men (9:1 in favor of women) [44] . Among the many symptoms and indicators of the condition are: central weight increase, primarily in the abdomen, skin that is thin and bruised, elevated blood sugar and blood pressure, Weakness in muscles, usually in the back of the legs , In women may experience irritability, anxiety, depression, or irregular or stopped menstrual cycles. Men may be less fertile and have little to no desire to have sex. hair thinning and absence of fresh hair development. Nonetheless, women may have an overabundance of hair on their thighs, chest, neck, and face[47][48] . High rates of morbidity and mortality are linked to Cushing's disease because it increases the risk of cardiovascular and metabolic symptoms, as well as respiratory issues, mental health issues, osteoporosis, and infections [45].

Primary aldosteronism

Over-production of aldosterone via the zona glomerulosa results in primary aldosteronism. Conn's syndrome is produced via either aldosterone-producing adenomas or bilateral hyperplasia (extreme tissue growing) of the glands respectively, Hypertension and electrolyte imbalance are caused by primary aldosteronism, which also increases salt retention and potassium depletion [48]

Adrenal deficiency

The letdown of the adrenal glands to generate enough cortisol for regular physiological processes or during stressful situations is known as adrenal insufficiency, Depending on its cause, the circumstance is categorized as prime, secondary, or tertiary. [49]. The inability of the adrenal glands to yield cortisol, aldosterone, and androgen is known as primary adrenal insufficiency, or Addison disease. It could be brought on by an infarction, infection, or autoimmune disease. Pituitary gland failure results in secondary adrenal insufficiency, whereby a reduction in ACTH production and secretion lowers cortisol and androgen synthesis. It could be brought on by surgery, trauma, infection, infarction, or exogenous steroid use (from long-term suppression). A hypothalamic condition known as tertiary adrenal insufficiency causes a reduction in CRH construction and relief, which in turn reduces pituitary ACTH construction and relief. The secondary and tertiary types of the condition do not influence aldosterone production, unlike Addison's illness [50].

Addison's illness

Initial hypoadrenalism, or a lack of mineralocorticoid and glucocorticoid creation via the adrenal gland, is the term used to describe Addison's disease [51]. The most prevalent autoimmune disorder in the Western world is Addison's illness, where the body creates antibodies Attacks adrenal cortex cells. Globally, infection particularly from tuberculosisis the primary cause of the illness. Hyperpigmentation of the skin, which manifests with additional vague indications like exhaustion, is a characteristic of Addison's disease[49]. The majority of symptoms are brought on by reduced amounts of hormones that the adrenal glands would typically generate. Fatigue, malaise, joint and muscle discomfort, decreased appetite, weight loss, and heightened sensitivity to cold are just a

few of the symptoms that can result from low blood cortisol [52][53]. Particularly prevalent digestive symptoms include nausea, stomach pain, and vomiting [52][54]. Low aldosterone can make a person seek salty foods and create low blood pressure, which makes standing up lightheaded [54]. Little mineralocorticoid and glucocorticoid ranks that result in hypovolemic shudder and indications like fever and vomiting are hallmarks of an adrenal crisis, a medical emergency that can arise from crude Addison's syndrome and additional kinds of prime adrenal inefficiency. A prolonged adrenal crisis can cause stupor and coma [49].

Congenital adrenal hyperplasia

Congenital hyperplasia of the adrenal gland is a grouping of congenital disorders where glucocorticoid insufficiency and disruption of the HPA axis' negative feedback loop are caused by abnormalities in the enzymes that generate steroid hormones. The glucocorticoid cortisol in the HPA axis prevents the relief of the hormones CRH and ACTH, which in try promote the production of corticosteroid hormones. Due to the inability to synthesis cortisol, these hormones are released in large amounts, which in turn promotes the production of additional adrenal steroids. Congenital adrenal hyperplasia triggered by 21-hydroxylase insufficiency is the furthermost prevalent kind. 21-hydroxylase stays required for the synthesis of glucocorticoids and mineralocorticoids, but not androgens. Consequently, the production of excessive levels of adrenal androgens due to ACTH stimulus of the adrenal cortex might result in the development of secondary sex traits and ambiguous genitalia [55].

Adrenal cancers

Adrenal cancers are frequently discovered as incidentalomas, which are unanticipated, asymptomatic cancers discovered throughout medicinal imaging. About 3.4% of CT scans show them, and they stay typically benign adenomas. With only one case per million annually, adrenal carcinomas are extremely uncommon[49][56]. Pheochromocytomas are chromaffin cell-derived malignancies of the adrenal medulla. They can cause headaches, sweating, anxiety, and palpitations, among other nonspecific symptoms. Tachycardia and hypertension are typical symptoms. For tiny pheochromocytomas, surgery is the most usual treatment, particularly adrenal laparoscopy [57].

Conclusion

This study leads us to the conclusion that the adrenal gland secretes a diversity of hormones that stay essential to the body's vital functions and that any alteration in the gland's composition impacts both its function and hormone secretion, which can result in a number of diseases, such as Cushing's disorder, prime aldosteronism, Addison's sickness, congenital adrenal hyperplasia, and adrenal cancers.

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