Adrenal Anatomy and Physiology

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KEYWORDS

• Adrenal glands • Anatomy • Physiology • Hormones • Cortex • Medulla • Stress response

KEY POINTS

- The adrenal glands are paired endocrine organs that regulate blood pressure, stress response, metabolism, and electrolyte balance.
- Each gland consists of 2 regions: the cortex (produces steroid hormones) and the medulla (produces catecholamines).
- The adrenal cortex is divided into 3 zones: the zona glomerulosa (produces mineralocorticoids like aldosterone), the zona fasciculata (produces glucocorticoids like cortisol), and the zona reticularis (produces adrenal androgens).
- The adrenal medulla synthesizes catecholamines (adrenaline, noradrenaline, and dopamine) under sympathetic control, playing a crucial role in the stress response.
- The adrenal glands are highly vascularized and receive innervation from the sympathetic nervous system.

INTRODUCTION

The adrenal glands have a rich historical background, with their discovery and understanding evolving over centuries. The adrenal gland was first described by Italian anatomist, Bartolomeo Eustachio, who described the adrenals as "glandulae quae renibus incumbent" (glands lying on the kidney) in his book *Opuscola Anatomica*, published in 1564.[1]

The physiological significance of the adrenal glands remained largely a mystery until the 19th century. Thomas Addison first discovered the relationship between adrenal dysfunction and what became known as Addison's disease (Pearce). Around the same period, Charles-Édouard Brown-Séquard performed adrenalectomies in animals, providing their critical role in survival.[2]

Significant changes occurred in the 20th century, with the isolation and identification of adrenal hormones. Adrenaline was first isolated by Napoleon Cybulski in 1895 and later synthesized in 1901 by Jokichi Takamine.[3,4] Cortisol was discovered by Tadeusz Reichstein in 1930 and Edward Kendall laid the foundation for understanding glucocorticoid physiology, earning them the Nobel Prize in 1950.[5]

Advancements in molecular biology have since revealed the genetic and enzymatic basis of adrenal function, elucidating its critical role in

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Abbreviations	
ACE	Angiotensin converting enzyme
ACTH	Adrenocorticotropic hormone
ATPase	Adenosine triphosphatase
cAMP	Cyclic adenosine monophosphate
CBG	Corticosteroid-binding globulin
CRH	Corticotropin releasing hormone
DHEA	Dehydroepiandrosterone
ECF	Extracellular Fluid
ENaCs	Epithelial sodium channels
GR	Glucocorticoid receptor
HPA	Hypothalamic-pituitary-adrenal
IVC	Inferior vena cava
PKA	Protein kinase A
PLC	Phospholipase C
RAAS	Renin-angiotensin-aldosterone system

regulating critical processes like blood pressure, stress response, metabolism, and electrolyte balance, reflecting their intricate integration into the body's homeostatic systems. Today, the adrenal glands are recognized as essential components of the endocrine system, with ongoing research focusing on adrenal disorders and their treatments.

ANATOMY

Embryology

The adrenal gland comprises 2 different parts, the cortex and the medulla. These parts arise from the urogenital ridge of mesoderm and neural crest cells respectively.[6,7] These separate embryologic precursors converge to the same location during development and explain the varying functions of the cortex and medulla.[8]

Microscopic Anatomy

The cortex is the outer part of the adrenal, and the medulla is the inner part.[9] The cortex comprises 85% of the gland and is made of the outer zona glomerulosa, the inner zona fasciculata, and the innermost zona reticularis.[9]

Location

The adrenal glands are a pair, each located above its corresponding kidney; the triangular-shaped right gland is primarily suprarenal, whilst the crescent-shaped left is predominately prerenal in location (**Fig. 1**).[9,10] Each gland weighs approximately 2g–6g, independent of sex.[11] They are approximately 5 cm vertically, 2 cm–3 cm transversely, and 1 cm in the anteroposterior plane.[9,12] The right adrenal gland is located in front of the 12th rib.[10] The left gland lies in front of the 11th and 12th ribs, as well as the left sided lateral aspect of the vertebral column.[10] They are yellow-greyish in color and have a firm consistency.[12] Thick connective tissue encapsulates each adrenal.[9] Both adrenal glands are surrounded by perirenal fat.[11,13] They are further bounded by Gerota's (renal) fascia, except for in the plane between the gland and the kidney.[11,13] As the renal fascia attaches to the diaphragm, the adrenals are connected to the abdominal wall and move with respiration.[10]

Ectopic adrenal cortex tissue can be found in the ovaries, spermatic cord and testes.[14] Extra-adrenal medullary tissue may also be found in the path of neural cell migration but also may also be found in the neck, bladder, and para-aortic regions.[14] Adrenal tissue is not limited to these locations, with the pathogeneses likely to differ from location to location.[15]

Anatomic Relations

Right adrenal gland

The Inferior vena cava (IVC) is situated medially and partially anteriorly to the right adrenal gland, however, occasionally it covers the gland completely anteriorly (**Fig. 2**).[11,13] The bare area of the liver is usually in contact with the superolateral aspect of the gland.[12] Peritoneum, the liver, and hepatic flexure overlie the inferolateral aspect.[12] Further anterior to the IVC are the foramen of Winslow, second part of the duodenum, and head of the pancreas.[12,13] The inferior surface of the right adrenal gland is in contact with the upper pole of the right kidney.[16]

Left adrenal gland

The anterior surface of the adrenal gland is in relation to the omental bursa (superiorly), as well as the splenic vessels, body/tail of the pancreas and the medial edge of the spleen (inferiorly).[11,12] Further anterior to these structures lie the stomach and transverse mesocolon (see **Fig. 2**).[12,13] The medial aspect of the upper pole of the left kidney is directly in contact with the lateral portion of the adrenal gland.[11] The left adrenal gland is close to the renal vessels (inferiorly) and the aorta and celiac trunk (medially).[17]

Both adrenal glands

The posterior surfaces of each adrenal are bounded by the diaphragm and the corresponding left or right crus.[11,13,16] Medial to both adrenals are the inferior phrenic artery and vein, as well as the corresponding left or right celiac ganglion.[12,16]

Arterial Supply

The adrenals are highly vascularized, with blood flow rates of up to 10 mL per minute.[13] The superior, middle, and inferior adrenal arteries arise from

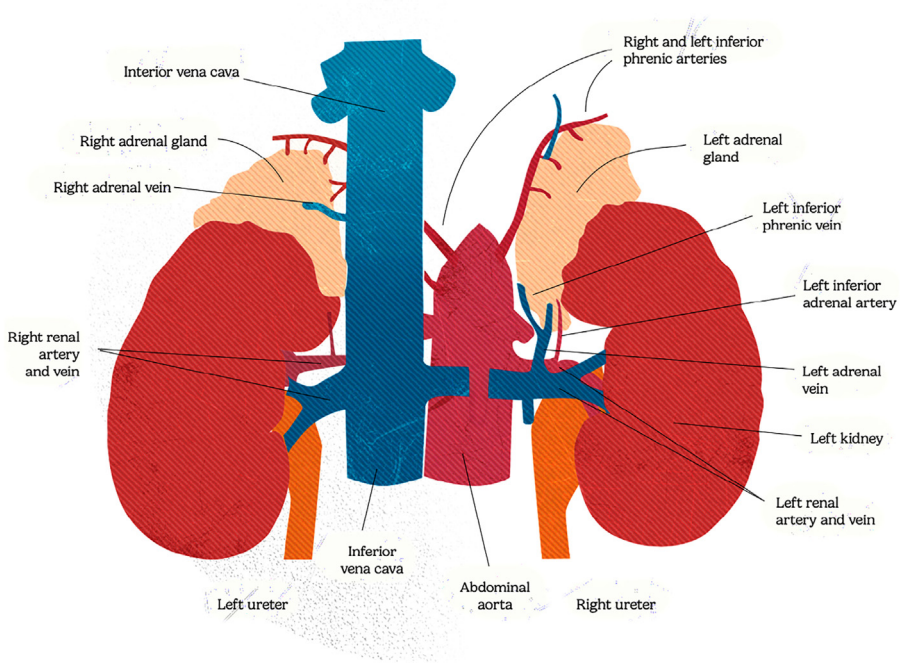

Fig. 1. Coronal section of adrenal gland and relation to kidneys, major vascular structures, and ureters. (*Adapted from* Townsend CM, Beauchamp RD, Evers BM, et al. Sabiston textbook of surgery: the biological basis of modern surgical practice. Elsevier Health Sciences; 2016, with permission.)

the inferior phrenic artery, aorta, and renal artery respectively.[16] It is not uncommon for there to be anatomical variations in the supply of the 3 major adrenal arteries. The superior adrenal artery may also arise from the aorta or the celiac trunk, and may exist as more than 1 branch.[18–20] The inferior phrenic, renal, superior mesenteric, or celiac trunk arteries are possible origins of the middle adrenal artery.[18–20] The inferior adrenal artery can come off the aorta, gonadal artery, or inferior phrenic artery.[18–20] In addition to the 3 main adrenal arteries, the adrenals may also receive blood supply from gonadal and subcostal arteries.[12]

The branches of these arteries further subdivide and form a plexus made up of 10 to 50 arterioles.[12] Within the adrenal gland, there are 3 types of arterial distribution; capsular arterioles only exist within the capsule, fenestrated cortical sinusoid capillaries

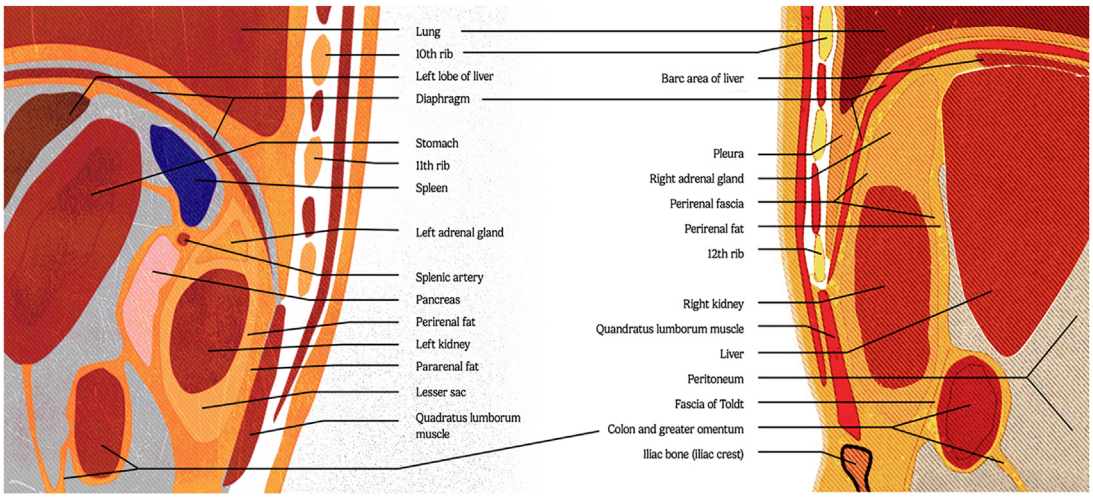

Fig. 2. Sagittal section showing relations of adrenal gland—left sided gland on left, right sided gland on right (*Adapted from* Caroço T.V., Costa Almeida C.E. (2023). Anatomy of the Adrenal Gland. In: Eduardo Costa Almeida, C. (eds) Posterior Retroperitoneoscopic Adrenalectomy. Springer.)

travel from the cortex to the medulla, and the medullary arterioles supply medullary sinusoids directly.[11] Therefore, there is dual supply of medullary sinusoids.[11]

Venous Drainage

Even though each adrenal commonly only has one central exiting hilar vein, their drainage is not same on both sides nor do they correspond to the pattern of arterial supply.[11,12] The left adrenal vein is longer than the right, and it joins the inferior phrenic vein to feed into the left renal vein 3 to 5 cm away from the IVC.[9,21] The right adrenal vein is extremely short and exits directly into the IVC, 3 to 5 cm above the right renal vein.[21] The left adrenal vein may occasionally be duplicated (whilst the right rarely is), and the right adrenal vein commonly has anatomic variations (whilst the left rarely does).[12,21] Collateral vessels may occur in cases of tumor development.[10]

Anatomic variations in the right adrenal vein exist in up to 12.8% of people.[22] The right adrenal vein can drain into an accessory right hepatic vein, right renal vein, or close to the confluence these veins with the IVC.[21]

Lymphatic Drainage

There are 2 lymphatic plexuses within each adrenal gland, one within the capsule and one within the medulla.[10] Lymphatic vessels that emerge from the adrenal often accompany vasculature; they usually end in lateral aortic nodes near the confluence of the renal veins with the IVC, or in para-aortic nodes near the origin of the renal arteries.[10] Some lymphatic vessels can drain into the mediastinum.[12]

Nerve Distribution

Whilst adrenocorticotropic hormone (ACTH) mediates the function of the adrenal cortex, the adrenal medulla is mediated by synaptic stimulation from the sympathetic visceral nervous system.[9,10] Preganglionic fibers from the spinal cord travel via the sympathetic chain to a nerve plexus at each capsule, which then directly innervate the medulla.[11] Cortical blood vessels are innervated by postganglionic fibers, which exist in much smaller proportion to the preganglionic fibers.[13]

PHYSIOLOGY OF THE ADRENAL CORTEX

The adrenal cortex secretes 3 predominant steroid hormones: Glucocorticoids (cortisol), mineralocorticoids (aldosterone) and adrenal androgens, which are dehydroepiandrosterone (DHEA), DHEA-sulfate and androstenedione.[23,24] Mineralocorticoids are produced in the zona glomerulosa while glucocorticoids and adrenal androgens are produced in the zona fasciculata and zona reticularis, respectively.[24] These hormones are all derivatives of cholesterol, supplied to the adrenal gland in the form of low-density lipoprotein.[23]

The 3 zones of the adrenal cortex produce different hormones because each zone expresses specific enzymes and regulatory factors that determine the biosynthetic pathway of steroid hormones. This functional differentiation is dictated by the unique gene expression profiles of the cells in each zone. The zona glomerulosa expresses the enzyme aldosterone synthase (CYP11B2), which is crucial for aldosterone synthesis.[24] It lacks the enzyme 17α-hydroxylase (CYP17A1), so it cannot produce glucocorticoids or androgens.[24] The zona fasciculata expresses CYP17A1, which enables the production of 17-hydroxyprogesterone, a precursor for cortisol. It lacks significant activity of aldosterone synthase (CYP11B2), so it does not produce aldosterone.[24] The zona reticularis expresses 17,20-lyase activity of CYP17A1, which converts precursors into androgens. It lacks significant activity of enzymes necessary for cortisol or aldosterone synthesis.[24]

Zona Glomerulosa

Mineralocorticoids: synthesis, circulation, action and inhibition

Aldosterone is the main mineralocorticoid synthesized in the zona glomerulosa. Its production is stimulated by activation of the renin-angiotensin-aldosterone system (RAAS), hyperkalaemia, and ACTH.[24,25] A decrease in afferent renal arteriole pressure, low serum sodium detected by the macula densa cells located in the distal convoluted tubule, as well as direct sympathetic stimulation to the macula densa cells, triggers the release of renin from the renal juxtaglomerular cells.[26] Renin catalyzes the conversion of angiotensinogen to angiotensin 1.[25] Angiotensin 1 is then cleaved to angiotensin 2 by angiotensin converting enzyme (ACE) located in the pulmonary vasculature.[26] Angiotensin 2 binds to G-protein-coupled receptors on zona glomerulosa cells, activating phospholipase C (PLC) pathway.[27] This increases intracellular calcium levels, which stimulates the transcription of CYP11B2, promoting aldosterone synthesis.[28] Elevated serum potassium levels depolarize zona glomerulosa cells, opening voltage-gated calcium channels.[29] This leads to an influx of calcium, which further enhances the transcription of CYP11B2 and aldosterone production.[30] ACTH, primarily involved in the glucocorticoid production, has transient effect on aldosterone synthesis by increasing intracellular cyclic adenosine monophosphate (cAMP).[24] Its

influence is minor and short-lived compared to angiotensin II and potassium.

Aldosterone modulates activity in the aldosterone-sensitive distal renal nephron (late distal convoluted tubule, connecting tubule, and collecting ducts). It therefore regulates the final stages of water absorption and electrolyte homeostasis.[31] Its effects are exerted within 1 hour of secretion.[32] It acts to increase extracellular fluid (ECF) volume by increasing sodium reabsorption.[24] It acts on the principal cells of the distal nephrons to increase sodium reabsorption by stimulating the insertion of epithelial sodium channels (ENaCs) into the apical membrane and enhancing the activity of Na/K adenosine triphosphatase, ATPasewhich pumps sodium into the ECF.[24] This process promotes water reabsorption via osmosis, increasing blood volume and pressure. Aldosterone increases potassium excretion by acting on principal cells of the distal nephron to stimulate the expression of renal outer medullary potassium channels in the apical membrane, excreting potassium into the tubular lumen.[33] Aldosterone also increases activity of Na^+/K^+-ATPase which drives potassium influx into the cell from the bloodstream, while increasing potassium secretion into the urine.[33] Aldosterone also increases activity of the H^+-ATPase in intercalated cells of the collecting duct, enhancing hydrogen ion secretion into the tubular.[27] This contributes to maintaining acid-base homeostasis by correcting metabolic acidosis.[27] Aldosterone also stimulates release of adrenaline and noradrenaline from the adrenal medulla and increases the release of vasopressin, an antidiuretic hormone, from the anterior pituitary gland, increasing vascular tone by increasing smooth muscle contraction in arterioles, as well as water reabsorption in the collecting duct.[27] The net effect of aldosterone, therefore, is to increase blood pressure through sodium and water reabsorption, increase vascular tone, and increase potassium and hydrogen ion excretion.

Aldosterone is transported in the blood bound to proteins and in a free form. Around half binds weakly to albumin, with a smaller portion attached to corticosteroid-binding globulin (CBG). The remaining 40% to 50% circulates as free aldosterone, which is biologically active and able to act on target tissues.[34]

Aldosterone is inhibited by multiple factors. Dopamine directly inhibits aldosterone at the adrenal gland.[35] Hypokalemia decreases aldosterone secretion by limiting the depolarization of zona glomerulosa cells.[36] Atrial natriuretic factor reduces intracellular calcium in the zona glomerulosa cells, thereby blocking the stimulatory effects of angiotensin 2, potassium, and ACTH.[35] Somatostatin inhibits aldosterone indirectly by inhibiting angiotensin 2.[32] Pharmacologic agents such as ACE inhibitors, angiotensin receptor blockers, and mineralocorticoid receptor antagonists (eg, spironolactone) can inhibit RAAS pathway or block aldosterone action.[37]

Metabolism and excretion

Aldosterone undergoes hepatic metabolism, where it is converted into inactive metabolites such as tetrahydroaldosterone.[38] These metabolites are conjugated with glucuronic acid to enhance solubility and are excreted in the urine.[38]

Zona Fasciculata

Cortisol's release from the zona fasciculata of the adrenal cortex initially begins at the medial paraventricular nucleus of the hypothalamus.[39] Its release is governed by the hypothalamic-pituitary-adrenal (HPA) axis, a feedback system designed to regulate stress responses, metabolic balance, and immune activity.[39]

Glucocorticoids: synthesis, circulation, action and inhibition

The hypothalamus samples signals from both the internal and external environment. When a stressor is perceived—be it physical, emotional, or metabolic—the hypothalamus releases corticotropin-releasing hormone (CRH) into the hypophyseal portal system, which carries it to the anterior pituitary gland, where it binds to CRH receptors on corticotroph cells, which subsequently stimulates the synthesis of ACTH.[40,41] ACTH is a polypeptide hormone, composed of 39 amino acids. It is cleaved from a larger precursor molecule known as pro-opiomelanocortin.[40] ACTH is then released into the systemic circulation.[40]

Its secretion is pulsatile and governed by circadian rhythms.[24] Bursts of secretion, stimulated by CRH and ACTH, occur between 0400 and 1000 hours, with the frequency reducing in the evening.[24] ACTH rises as the body awakens leading to an increase in cortisol during daytime.[42] ACTH release is increased during starvation, exercise, critical illness, psychiatric and psychological conditions such as anxiety and depression.[24,32]

ACTH's binds to melanocortin 2 receptors on the surface of zona fasciculata cells.[40] This activates a G-protein-coupled receptor system that stimulates adenylate cyclase, increasing intracellular levels of cAMP.[40] Elevated cAMP activates protein kinase A (PKA), which phosphorylates target proteins involved in steroidogenesis.[43]

One of the critical effects of ACTH stimulation is the mobilization of cholesterol.[27] Cholesterol is

transported to the mitochondria via the steroidogenic acute regulatory protein, where it undergoes enzymatic cleavage by CYP11A1, a cholesterol side-chain cleavage enzyme, to form pregnenolone, the first intermediate in cortisol synthesis.[40] A series of additional enzymatic steps, catalyzed by enzymes such as CYP17A1 and 11β-hydroxylase (CYP11B1), convert pregnenolone into cortisol.[44] The zona fasciculata is uniquely equipped for cortisol synthesis, as it expresses the full complement of enzymes required for this pathway.[44]

Most of the cortisol in circulation—approximately 80 to 90%—is bound to CBG, also known as transcortin.[27] This high-affinity transport protein is synthesized primarily in the liver and acts as a protective carrier, shielding cortisol from rapid degradation and inactivation. CBG's binding capacity can be influenced by various factors, including pregnancy, liver function, and the presence of estrogens, which can increase its synthesis.[45] Another fraction of cortisol, around 10% to 15%, is loosely bound to albumin.[45] While albumin has a lower affinity for cortisol than CBG, it plays a significant role in maintaining the hormone's transport, especially when CBG is saturated or levels are altered due to illness or hormonal fluctuations. A small but critical portion of cortisol—about 5 to 10%—circulates in its free form.[45] This unbound cortisol is the biologically active fraction.[46] Because only the free cortisol can interact directly with target cells, its concentration serves as a key indicator of functional cortisol levels in clinical assessments.

Cortisol exerts its effects by binding to intracellular glucocorticoid receptors (GRs) present in almost all cells.[47] After diffusing into cells, cortisol binds to the inactive GR in the cytoplasm, causing a conformational change that releases stabilizing proteins like heat shock proteins.[47] The activated cortisol-GR complex is transported into the nucleus, where it binds to specific DNA sequences called glucocorticoid response elements. This modulates gene expression through transactivation (upregulating antiinflammatory and metabolic genes) or transrepression (downregulating inflammatory pathways by interfering with transcription factors like NF-κB).[48] In addition to these genomic effects, cortisol can act via rapid nongenomic pathways, influencing cellular signaling directly.[49] These mechanisms are still not fully understood.

One of cortisol's most prominent roles is the regulation of metabolism, particularly during stress or fasting, to ensure adequate energy supply. Cortisol stimulates gluconeogenesis in the liver, increasing the production of glucose from non-carbohydrate sources like amino acids and glycerol.[50] Cortisol also inhibits glucose uptake and utilization in peripheral tissues, such as muscle and adipose tissue.[27,50] This ensures an adequate glucose supply for critical organs, especially the brain, during periods of low dietary intake or increased energy demand. In muscle and other tissues, cortisol stimulates protein catabolism, breaking down proteins into amino acids that are then used as substrates for gluconeogenesis. Prolonged elevation of cortisol can lead to muscle wasting and weakness. Cortisol also facilitates lipolysis, the breakdown of triglycerides into free fatty acids and glycerol in adipose tissue. These free fatty acids serve as an alternative energy source.[32] Paradoxically, prolonged cortisol exposure can lead to fat redistribution, often manifesting as central obesity, with fat accumulation in the abdomen, face, and back of the neck. Lastly, by countering the effects of insulin in peripheral tissues, cortisol can contribute to insulin resistance, particularly during chronic stress or hypercortisolemia.

Cortisol plays an essential role in maintaining cardiovascular stability, particularly under stress.[50] Cortisol enhances the sensitivity of blood vessels to vasoconstrictors such as catecholamines and angiotensin II, sustaining blood pressure during stress.[51] Without cortisol, vascular responsiveness diminishes, leading to potential hypotension. Cortisol also indirectly influences sodium and water retention by upregulating angiotensinogen in the RAAS, thereby supporting intravascular volume during stress.[52] In the kidneys, cortisol has a mild mineralocorticoid effect, contributing to sodium retention and potassium excretion.[32]

Cortisol exerts potent immunosuppressive and antiinflammatory effects, which are critical for controlling excessive immune responses but can impair immunity when prolonged. Cortisol inhibits the production of proinflammatory cytokines like interleukin-1 (IL-1), IL-6, and tumor necrosis factor-alpha.[53] It also suppresses the activation of inflammatory cells such as macrophages, neutrophils, and lymphocytes.[32] Cortisol reduces T-lymphocyte proliferation and shifts the balance toward antiinflammatory T-regulatory cells.[32] This can decrease the body's ability to fight infections or form robust immune responses. Cortisol reduces mast cell degranulation, lowering histamine release, and dampening allergic reactions.[32]

Cortisol influences brain function and behavior, with varying effects depending on levels and duration of exposure. Cortisol is central to the stress response by increasing arousal, focus, and energy availability. However, chronic stress and excessive cortisol can exacerbate anxiety, and contribute to mood disorders.[32] While short-term cortisol elevation can enhance memory

consolidation, prolonged exposure is neurotoxic, leading to hippocampal shrinkage and impaired memory. Cortisol follows a circadian rhythm and therefore plays a role in promoting wakefulness and regulating energy levels throughout the day.[32]

In prenatal and early life, cortisol influences growth and development. Cortisol is essential for fetal organ maturation, particularly the lungs, where it stimulates surfactant production.[32] Chronically elevated cortisol inhibits growth hormone secretion and impairs bone formation by reducing osteoblast activity, potentially leading to growth retardation in children and osteoporosis in adults.[32] Cortisol supports gastrointestinal integrity and motility. However, chronic elevations can increase gastric acid secretion, predisposing to peptic ulcers.[54]

Cortisol production and action are tightly regulated, with several mechanisms and factors inhibiting its synthesis, release, or activity. The most important regulator of cortisol is the HPA axis, which uses a negative feedback mechanism.[32] Elevated cortisol levels inhibit the secretion of CRH from the hypothalamus and ACTH from the anterior pituitary. This withdraws adrenal cortex stimulation, thereby decreasing cortisol synthesis and release.[32] Chronic exogenous glucocorticoid suppresses ACTH levels, leading to atrophy of the adrenal cortex.[32] With prolonged HPA axis suppression, the adrenal glands may fail to produce sufficient cortisol in response to physiologic stressors, such as illness, surgery, or trauma. This may result in an adrenal crisis if exogenous glucocorticoids are abruptly withdrawn, or stress is not managed with supplemental glucocorticoids.[27] In specific tissues, the enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) inactivates cortisol by converting it to cortisone, which has minimal glucocorticoid activity.[55] Certain medications such as ketoconazole and metyrapone block cytochrome P450 necessary in cortisol synthesis.

Glucocorticoids: metabolism and excretion

Cortisol is metabolized primarily in the liver, where it is converted to inactive cortisone by 11β-HSD2 or reduced to tetrahydrocortisol.[32] These metabolites are conjugated with glucuronic acid or sulfate for increased solubility and excreted via the kidneys in urine as free cortisol or metabolites.[32]

Zona Reticularis

Adrenal androgens: synthesis, circulation, action and inhibition

Adrenal androgens, primarily DHEA, DHEA sulfate, and androstenedione, are synthesized in the zona reticularis of the adrenal cortex.[24] Their synthesis is regulated by ACTH and involves the conversion of cholesterol into pregnenolone via cholesterol side-chain cleavage enzyme (CYP11A1).[27] Pregnenolone is then converted into 17α-hydroxypregnenolone by CYP17A1.[56] In the presence of CYP17A1's 17,20-lyase activity, 17α-hydroxypregnenolone is converted into DHEA. DHEA can be sulfated by sulfotransferase (SULT2A1) to form DHEA-S, a more stable and water-soluble form.[44] The synthesis of adrenal androgens increases at adrenarche during puberty, playing key roles in secondary sexual characteristics such as axillary and pubic hair development, libido and supporting gonadal steroidogenesis.[26]

Adrenal androgens, including DHEA, DHEA-S, and androstenedione, circulate bound to albumin and sex hormone-binding globulin, with DHEA-S being the most abundant.[57] These weak androgens serve as precursors for potent androgens like androstenedione, testosterone, and estrogens through enzymatic pathways in peripheral tissues.[32,57]

Adrenal androgens bind to androgen receptors or are converted to estrogens to act on estrogen receptors.[57] They are especially important in women, contributing to androgen levels after menopause. Their production is regulated by ACTH but is independent of gonadotropins. Cortisol feedback inhibition on ACTH indirectly affects adrenal androgen synthesis.[58]

Adrenal androgens: metabolism and excretion

DHEA is metabolized primarily in the liver and peripheral tissues. It undergoes conjugation reactions, including sulfation by sulfotransferase (SULT2A1) to form DHEA-S, which is more stable and water-soluble. DHEA and its metabolites are excreted predominantly in the urine after conjugation to water-soluble forms, such as glucuronides or sulfates.[32]

Adrenal Medulla

The adrenal medulla is a key component of the sympathetic nervous system.[32] Unlike typical sympathetic pathways, the adrenal medulla is innervated by preganglionic fibers predominantly from the thoracic spinal cord.[24,27] These fibers bypass ganglia and release acetylcholine directly onto chromaffin cells, which act as modified postganglionic neurons.[24] There are no traditional postganglionic fibers associated with the adrenal medulla, as it directly releases hormones into circulation, bypassing the need for downstream neurons.[27]

Catecholamines: synthesis, circulation, action and inhibition

Catecholamines (adrenaline, noradrenaline, and dopamine) are synthesized from tyrosine, which is

converted to L-DOPA by tyrosine hydroxylase (rate-limiting step) and then to dopamine by aromatic L-amino acid decarboxylase.[27] Dopamine is transported into vesicles, where dopamine β-hydroxylase converts it to noradrenaline.[24] In the adrenal medulla, noradrenaline is converted to adrenaline by phenylethanolamine N-methyltransferase, which is stimulated by cortisol.[24] The release of catecholamines is triggered by stress such as hypoglycemia, exercise, fear, or trauma. Preganglionic sympathetic neurons release acetylcholine, which binds to nicotinic receptors on chromaffin cells, causing calcium influx and catecholamine release into the bloodstream.[59] Once released from the adrenal medulla, catecholamines enter the bloodstream, where they circulate bound weakly to plasma proteins or in free form.

Noradrenaline and adrenaline exert their effects by binding to adrenergic receptors, which are distributed across various organs, activating intracellular signaling pathways.[27] These receptors are G-protein-coupled and trigger specific cascades based on their subtype.[27] There are alpha and beta-adrenergic receptors which are further classified into α1, α2, β1, β2, and β3 subtypes. α 1 receptors activate the Gq protein, stimulating PLC, which increases intracellular calcium and triggers smooth muscle contraction.[60] α2 receptors are linked to the Gi protein, which inhibits adenylate cyclase, reducing cAMP, and decreasing neurotransmitter release.[61] β1, β2, and β3 receptors are coupled to the Gs protein, stimulating adenylate cyclase, increasing cAMP levels, and activating PKA, leading to effects such as enhanced heart contractility, bronchodilation, and lipolysis.[61]

Adrenaline and noradrenaline exhibit receptor-specific affinities. Noradrenaline primarily binds to α1, α2, and β1 receptors, making it more effective in vasoconstriction and increasing cardiac output.[32] Adrenaline has a higher affinity for β2 receptors, allowing it to strongly induce bronchodilation and skeletal muscle vasodilation. Both catecholamines act on β1 receptors to enhance cardiac function but differ in their dominance at peripheral vascular and respiratory targets. This selective affinity underpins their distinct physiologic roles during stress and homeostasis.

α1 and α2 subtypes have distinct functions. α1 receptors are in arteriole smooth muscle, the iris, and the bladder and mainly cause contraction. Its action in arteriole smooth muscle stimulates vasoconstriction, which increases blood pressure.[32] In the eyes, α1 receptor activation causes pupil dilation (mydriasis), while in the bladder, it stimulates the contraction of the internal urethral sphincter, tightening the bladder outlet and inhibiting micturition.[27] These effects are mediated by the Gq protein, which activates phospholipase C, leading to an increase in intracellular calcium.[27] In contrast, α2 receptors are found presynaptically in the central nervous system and pancreas.[27] They function as part of a negative feedback loop, inhibiting the release of noradrenaline and reducing sympathetic outflow. In the pancreas, α2 activation decreases insulin secretion.[27] These actions are mediated through the Gi protein, which inhibits adenylate cyclase and reduces cAMP levels.[27]

β1, β2, and β3 subtypes also have distinct functions. β1 receptors are predominantly found in the heart and kidneys and play a crucial role in cardiovascular regulation.[32] In the heart, β1 activation increases chronotropy (heart rate), enhances the inotropy (force of cardiac contraction), and improves dromotropy (cardiac conduction velocity).[62] In the kidneys, it stimulates the release of renin from macula densa cells, regulates blood pressure and fluid balance through the RAAS activation.[62] These effects are mediated by the Gs protein activation, which increases cAMP levels.27 β2 receptors are in bronchioles, vascular smooth muscle, and skeletal muscle, and are particularly responsive to adrenaline.[32] Activation of β2 receptors induces bronchodilation, facilitating airflow during stress, and vasodilation in skeletal muscles, improving blood flow and substrate delivery.[32] Additionally, β2 stimulation promotes glycogenolysis in the liver and muscles, increasing glucose availability.[32] Like β1 receptors, β2 effects are mediated through cAMP. β3 receptors are found in adipose tissue and the bladder. They stimulate lipolysis, mobilizing stored energy, and relax the detrusor muscle of the bladder, aiding in urine storage.[32]

Dopamine also plays a significant role through its specific receptors, particularly D1 and D2 receptors. D1 receptors are located in the renal and mesenteric vasculature and promote vasodilation by increasing cAMP levels via Gs protein activation.[32] This enhances renal perfusion and promotes diuresis, particularly during states of stress or hypovolemia. D2 receptors are found in the central nervous system and presynaptic autonomic nerves and inhibit neurotransmitter release, including dopamine and noradrenaline. They act by reducing cAMP levels via Gi protein activation.[32] Additional dopamine receptors, such as D3, D4, and D5, are primarily involved in modulating central nervous system functions, including mood, cognition, and behavior.[27]

Catecholamines: metabolism and excretion

Catecholamines are rapidly metabolized and excreted to terminate their effects and maintain homeostasis.[27] Their breakdown begins with monoamine oxidase in neurons and peripheral

tissues, which deaminates them into intermediates like 3,4-dihydroxyphenylglycol.[63] Simultaneously, catechol-O-methyltransferase in the liver methylates catecholamines to form metanephrine and normetanephrine. Phenol-sulfotransferase in the liver and kidneys further sulfates catecholamines, enhancing water solubility.[63] These processes lead to the formation of vanillylmandelic acid, the primary metabolite excreted in urine.[27]

Other: chromogranin A, adrenomedullin, enkephalins

Chromogranin A is a glycoprotein co-released with catecholamines from chromaffin cells.[24] It regulates catecholamine storage and release, and its cleavage products, such as vasostatin and pancreastatin, modulate vascular tone and metabolic processes.[64]

Adrenomedullin is a vasodilatory peptide secreted by chromaffin cells and other tissues.[65] It helps maintain cardiovascular homeostasis by reducing vascular resistance and enhancing blood flow.[66] Adrenomedullin also exerts antiinflammatory and antioxidative effects, underscoring its protective role in stress responses mediated by the adrenal medulla.[65]

Enkephalin chromaffin cells secrete met-enkephalin and leu-enkephalin, which are endogenous opioid peptides synthesized in the adrenal medulla and co-stored with catecholamines.[23] They bind to opioid receptors, modulating pain perception and stress response.[23] Enkephalins also regulate catecholamine release and interact with other adrenal medullary hormones, playing a key role in maintaining homeostasis during acute stress.[23]

SUMMARY

The adrenal glands are paired organs that are intimately related to the superior aspect of the kidneys and other structures within the retroperitoneum. The adrenal glands are characterized by multiple separate zones and compartments, each with its unique function. The adrenal glands produce hormones that are critical to the regulation of metabolism, immune system, cardiovascular system as well as the body's response to stress and other essential functions. Understanding their anatomy and specific function is key to the medical and surgical management of adrenal gland dysfunction, including hormonal insufficiencies as well as benign and malignant diseases affecting the glands.

DISCLOSURE

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