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Module : 22 Adrenocorticomedullary Hormone



ज्ञान विज्ञान विमुक्तये







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Table of Contents

1. Learning Outcomes
2. Introduction
3. Structure and anatomy of adrenal gland
 - 3.1. Adrenal cortex
 - 3.2. Adrenal medulla
 - 3.3. Blood Supply
4. Corticosteroids
 - 4.1. Biosynthesis
 - 4.2. Transport
 - 4.3. Mechanism of action
 - 4.3.1. Genomic Action
 - 4.3.2. Non-genomic Action
5. Mineralocorticoids – Aldosterone
 - 5.1. Function of aldosterone
 - 5.2. Genomic effects of aldosterone
 - 5.3. Non-genomic effects of aldosterone
 - 5.4. Regulation of aldosterone secretion
6. Glucocorticoids - Cortisol
 - 6.1. Function of cortisol
 - 6.2. Regulation of cortisol secretion
7. Adrenal androgens
8. Medullary hormones
 - 8.1. Synthesis of catecholamines
 - 8.2. Release of catecholamines

- 8.3. Mechanism of action
- 8.4. Functions of epinephrine (EP) and norepinephrine (NE)
- 8.5. Functions of dopamine
- 9. Pathophysiology of adrenal gland
 - 9.1. Adrenal insufficiency
 - 9.1.1. Primary adrenocortical insufficiency/ Addison's disease
 - 9.1.2. Secondary adrenocortical insufficiency
 - 9.1.3. Congenital adrenal hyperplasia (CAH)
 - 9.2. Hyperadrenalism
 - 9.2.1. Cushing's Syndrome
 - 9.2.2. Primary hyperaldosteronism/Conn's syndrome
 - 9.2.3. Adrenal androgen hypersecretion/Adrenogenital Syndrome
 - 9.3. Pheochromocytomas
- 10. Summary

1. Learning Outcomes

After studying this module, you shall be able to understand the,

- Location, structure, and anatomy of the adrenal glands.
- Structure of the cortical and medullary hormones.
- Synthesis, regulation, mechanism, and function of the adrenal hormones.
- Disorders associated with any impairment in the functioning of the gland.
- Causes, symptoms and treatment for various disorders.

2. Introduction

Adrenal glands (Ad = Upon + Renal = Kidney) are pyramid shaped paired endocrine glands located at the superior poles of the two kidneys. Also known as suprarenal glands, they lie beneath the peritoneum (retroperitoneal), and are enclosed in a capsule made up of dense irregular connective tissue.

Adrenal glands are composed of two structurally and functionally distinct endocrine zones: an outer adrenal cortex (20%) and an inner adrenal medulla (80%). Adrenal cortex and medulla are present in the same organ and receive a common blood supply, but they have different embryological precursors, structure, and function.

Adrenal cortex is derived from mesoderm and divided into three anatomically distinct layers, each secreting different hormones (mineralocorticoids, glucocorticoids, and androgens) under the influence of ACTH from anterior pituitary. Hormones of adrenal cortex are collectively called **corticosteroids**, synthesized from steroid cholesterol, and have almost same basic chemical formulas. However, slight differences in their molecular structure give them different but very important functions. Corticosteroids are essential for life and depletion in the level of hormones leads to several pathological conditions due to dehydration and electrolyte imbalances.

Adrenal medulla is derived from ectoderm and source of three catecholamine hormones (norepinephrine, epinephrine, and dopamine) in response to stress. Hormones are secreted in

response to sympathetic stimulation and functionally give same effects as related to the sympathetic nervous system (SNS).

Collectively the hormones from adrenal gland regulate metabolism, immune system, and the salt-water balance in the bloodstream; they also play instrumental role in preparing the body for any kind of stress.

3. Structure and anatomy of adrenal gland

Each adrenal gland is composed of two distinct anatomic tissues: outer cortex and the inner medulla.

3.1. Adrenal cortex

Multiple layers of lipid-storing cells subdivide the adrenal cortex into three concentric zones called zona glomerulosa, zona fasciculata, and zona reticularis.

- **Zona glomerulosa** is the outmost region of the adrenal cortex, composed of irregular ovoid clumps of cells containing few lipid droplets and surrounded by sinusoidal capillaries. The cells of the zona glomerulosa are the site of mineralocorticoid production, mainly **aldosterone** and helps in regulation in the concentration of electrolytes (sodium and potassium), blood pressure and blood volume.
- **Zona fasciculata** is the largest zone of cortex exhibiting cells arranged in vertical columns or bundles between which are found capillaries and fine connective tissue fibres. Cells are light stained and secrete glucocorticoids (cortisol and cortisone) to augment stress and stimulate protein, fat and carbohydrate metabolism to maintain glucose homeostasis. Suppress inflammatory response by reducing the number of circulating lymphocytes and decreasing antibody production.
- **Zona reticularis** is the innermost zone, made up of small cells arranged in the form of cords and clumps surrounded by sinusoidal capillaries. Cells of zona reticularis are believed to secrete sex steroids which are weak androgens (dehydroepiandrosterone) and have little physiological significance.

3.2. Adrenal Medulla

Central part of the adrenal gland, composed of special cells called chromaffin cells, which are organized in clusters around blood vessels. Medulla is a modified neuroendocrine tissue and cells are modified postganglionic sympathetic neurons that have lost their axons and dendrites during development. The preganglionic fibre innervates the cells and medullary cells under the influence of impulses from hypothalamus synthesize and secrete catecholamines (epinephrine - 80% and norepinephrine – 20%). As a result, the release of amine hormones is under direct control of the sympathetic nervous system.

3.3. Blood Supply

The adrenal glands like thyroid glands have rich supply of blood capillaries, and are highly vascularized gland of the body and supplied by three arteries:

- The superior suprarenal arteries - multiple small branches from the inferior phrenic artery.
- Middle suprarenal artery - direct branch from the abdominal aorta.
- An inferior suprarenal artery - from the renal artery on each side.

The direction of blood flow in the arteries is from cortex to medulla so that each zone is encountering increasing levels of steroids especially medulla, which requires high cortisol levels to stimulate enzymes required for epinephrine biosynthesis.

Adrenal hormones are released into the circulation via the left and right suprarenal veins to the left renal vein or directly to the inferior vena cava on the right side.

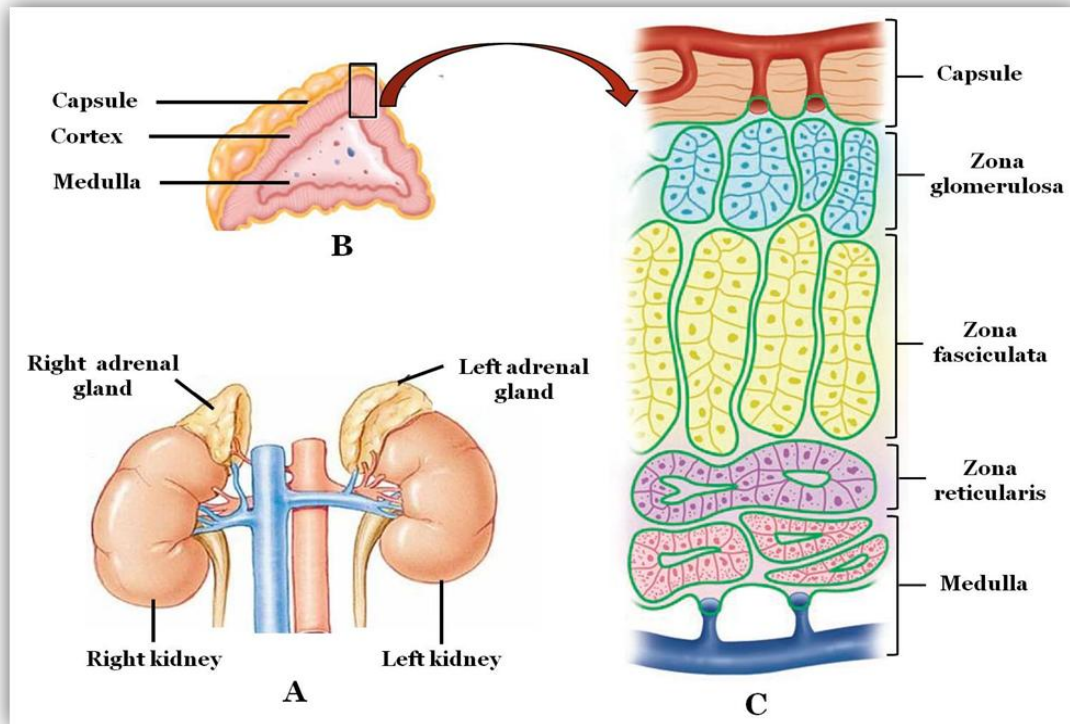


Figure 1. Location of adrenal glands on the superior poles of the kidney (A), Section through adrenal gland (B), Histological details of adrenal gland (C)

4. Corticosteroids

4.1. Biosynthesis

All the steroid hormones including corticosteroids are synthesized from common precursor cholesterol and have in common the 17-carbon cyclopentaoperhydrophenanthrene nucleus.

1. **Uptake of Cholesterol** - Low density lipoproteins (LDLs) from blood are transported into cells by receptor mediated endocytosis and provide a significant source for cholesterol. Most of the cholesterol is esterified to cholesteryl esters (CE) by cholesteryl ester hydrolase (CEH) and stored in cytoplasmic lipid droplets for subsequent hydrolysis and mobilization.
2. **Transport of cholesterol to mitochondria and synthesis of pregnenolone** – Under the stimulation of ACTH or cAMP, free cholesterol formed is transported

from the outer mitochondrial membrane to the inner mitochondrial membrane with the help of steroidogenic acute regulatory protein (StAR). In the mitochondria, a cytochrome P450 side chain cleavage enzyme ($P450_{SCC}$) converts cholesterol to pregnenolone. The fate of pregnenolone depends on the enzymes that are present in that tissue.

3. **Synthesis of DHEA and androstenedione** - Pregnenolone is converted to progesterone or 17α -hydroxypregnenolone by 3β -HSD enzyme and $P450_{c17}$ /Cyp17 respectively. Cyp17 or **P450c17** (17α -hydroxylase/c 17-20 lyase) is a single bi-functional enzyme and has two activities. First it converts pregnenolone and progesterone to 17α -hydroxypregnenolone and 17α -hydroxyprogesterone respectively. Secondly, 17α -hydroxypregnenolone and 17α -hydroxyprogesterone again acted on by $P450_{c17}$ (c 17-20 lyase) to yield dehydroepiandrosterone (**DHEA**) and androstenedione, respectively.
4. **Synthesis of cortisol and aldosterone** - Progesterone and 17α -hydroxyprogesterone are converted to 11-deoxycorticosterone and 11-deoxycortisol, respectively via hydroxylation catalyzed by **P450c21** (21α -hydroxylase). **P450c11** (11β -hydroxylase) catalyzes the final step in the synthesis of mineralocorticoids and glucocorticoids and bring about conversion of 11-deoxycorticosterone and 11-deoxycortisol to corticosterone and **cortisol** respectively. Corticosterone is finally converted to aldosterone by enzyme **aldosterone synthase**.
5. **Synthesis of testosterone and estradiol** - **17β -HSD** uses androstenedione as substrate to produce testosterone. Testosterone is further metabolized to 17β -estradiol (E_2) and dehydrotestosterone (DHT) by aromatase (Cyp19) and 5α -reductase respectively.

$P450_{SCC}$, $P450_{c11}$ (11β -hydroxylase), and aldosterone synthase are mitochondrial enzyme.

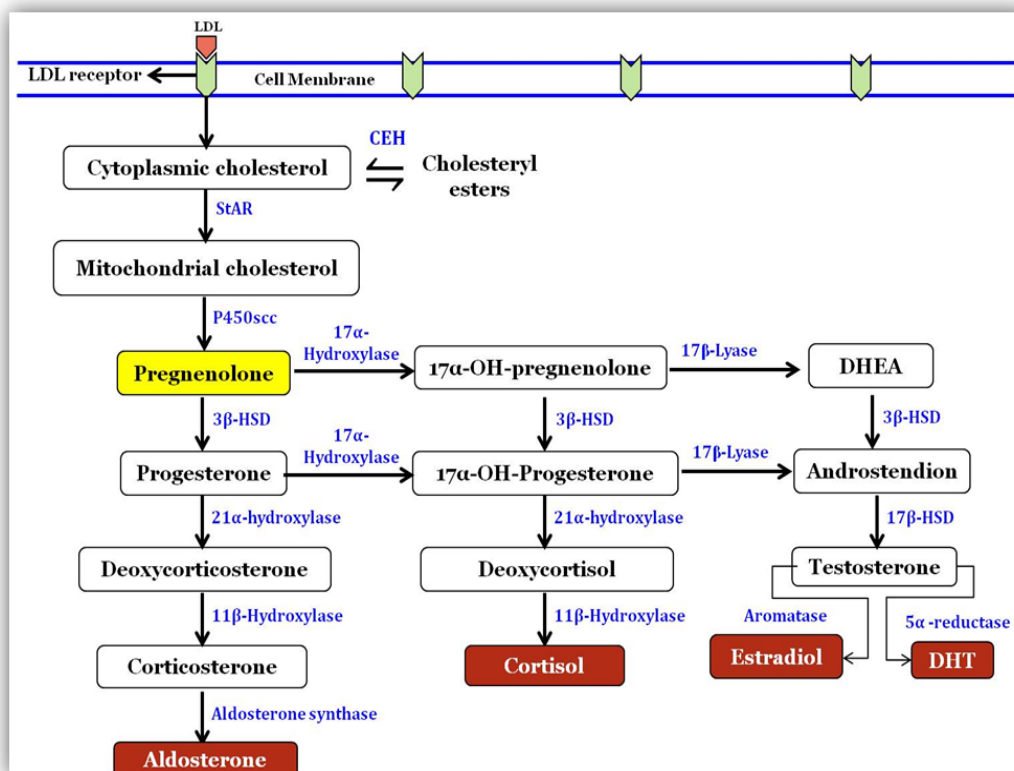


Figure 2. Pathway for the synthesis of corticosteroids

(Source: Authors)

Gene for enzyme	Enzyme Name	Action
StAR	Steroidogenic acute regulatory protein	Transport of cholesterol from outer mitochondrial membrane to inner mitochondrial membrane
CYP11A1	Cholesterol side chain cleavage enzyme/ desmolase (P450 _{scc})	Converts cholesterol to pregnenolone
3b-HSD II	3β-Hydroxylase dehydrogenase	Converts pregnenolone to progesterone
CYP21A2	21α-Hydroxylase (P450 _{c21})	Converts progesterone and 17-hydroxyprogesterone to 11-deoxycorticosterone and 11-deoxycortisol
CYP11B1	11β-Hydroxylase (P450 _{c11})	Converts deoxycorticosterone and 11-deoxycortisol to corticosterone and cortisol respectively.

CYP11B2	Aldosterone synthase	Corticosterone converted to aldosterone
CYP17	17 α -Hydroxylase/17, 20 lyase (P450c17)	<ul style="list-style-type: none"> Converts pregnenolone and progesterone to 17α-hydroxypregnenolone and 17α-hydroxyprogesterone respectively. 17α-hydroxypregnenolone and 17α-hydroxyprogesterone are converted to dehydroepiandrosterone (DHEA) and androstenedione
17b-HSD	17 β -Hydroxysteroid dehydrogenase	Converts androstenedione to testosterone
CYP19	Aromatase	Converts testosterone to estradiol

Table 1. Details of enzymes involved in biosynthesis of corticosteroids

4.2. Transport

Approximately 5% of cortisol and 40% of aldosterone circulate in the free form; the remainder is bound to corticosteroid-binding globulin (CBG) called **transcortin** and albumin. Transcortin along with the hormone binds to the target cell, and facilitates the entry of hormone to the target cell. Most of the aldosterone is present in a free state in the blood and therefore metabolized faster. Cortisol has longer half-life of 60-90 minutes as compared to aldosterone having 20 minutes. Corticosteroids are metabolized in liver by forming soluble salts of sulphates and glucuronic acid and then excreted via urine, bile, or feces. Pathological conditions where liver and kidney functions are impaired leads to decreased rate of corticosteroids inactivation and excretion of metabolized products

4.3. Mechanism of action

On the basis of receptor localization, the mechanism of hormone action is categorized into two categories:

- Hormones that binds to intracellular receptors follow genomic pathway of action
- Hormone that binds to cell surface receptors follow non genomic pathway of action

4.3.1. Genomic pathway

Corticosteroid receptors belong to the thyroid/steroid hormone receptor superfamily. Corticosteroids being lipid soluble directly diffuse to cell cytoplasm of the target cells. Then hormones interact with intracellular cytoplasmic receptor, termed as glucocorticoid and

mineralocorticoid receptors (GR and MR) forming a hormone-receptor complex. Unoccupied receptors have chaperone proteins bound to them and inhibit the cellular response. Dissociation of chaperons (HSP 90 and HSP 70) from receptors leads to activation of hormone-receptor complex. After translocation to the nucleus, dimerized hormone-receptor complex interact with specific DNA sequences in the promoter regions of target genes called hormone response element (HRE). This association induces the expression of respective genes to synthesize RNA and protein.

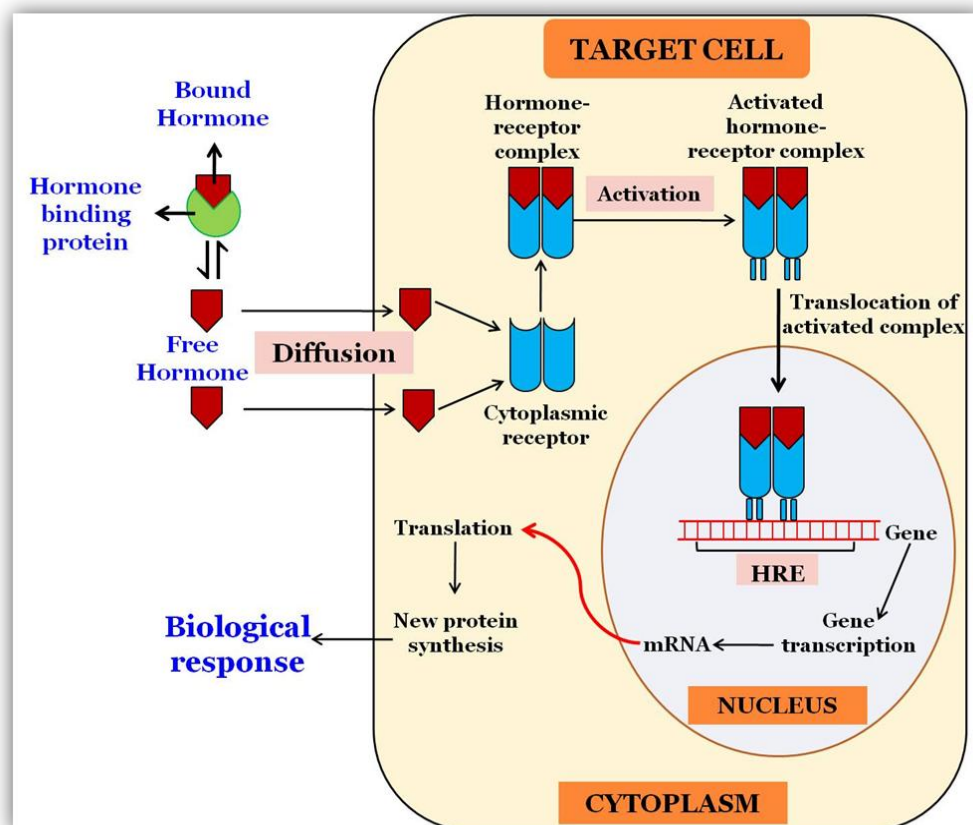


Figure 3. Genomic pathway for action of corticosteroids

(Source: Authors)

4.3.2. Non-genomic action

Besides having genomic action (60-90 minutes) corticosteroids have rapid non-genomic (seconds to few minutes) action on the target cell without any requirement for the synthesis of new proteins. These non-genomic actions are insensitivity towards inhibitors of

transcription & translation and are mediated by high affinity cell membrane receptors coupled to rise in second messenger concentration and activation of protein kinase cascades with subsequent phosphorylation and activation of target proteins.

5. Mineralocorticoids - Aldosterone

Aldosterone was first isolated by **Simpson and Tait (1953)**, is a very potent mineralocorticoid and accounts for about 90 percent of all mineralocorticoid activity.

5.1. Function of aldosterone

The name mineralocorticoid is derived from its role in regulating concentrations of minerals, particularly sodium and potassium in extracellular fluids.

- Aldosterone, the principle mineralocorticoid acts on cells of distal tubule, collecting tubule and collecting duct of the kidney, to stimulate the Na^+ retention accompanied by corresponding excretion of K^+ , H^+ and NH_4^+ ions.
- Increased retention of sodium ion leads to obligatory absorption of water to maintain osmotic balance thus controlling extracellular fluid volume as well. Thus, maintaining blood pressure indirectly.
- Aldosterone assists in attaining acid-base balance by controlling the level of hydrogen ion.
- Aldosterone has related effects on sweat glands, salivary glands and the colon where it helps in conservation of sodium chloride and water.

Mineralocorticoids are life saving corticosteroids and reduced rate of secretion leads to fatal consequences if remain untreated with salt therapy or hormone administration. Absence of mineralocorticoid causes retention of potassium ion and depletion in the level of sodium and chloride ions thus decreasing extracellular volume and blood volume. Decrease in blood volume further reduces cardiac output and blood pressure, producing a shock like state. Also increases level of potassium causes serious cardiac toxicity, including weakness of heart contraction and development of arrhythmia

High level of aldosterone causes **hypokalemia**, a condition of decrease in potassium ion concentration affecting normal electrical excitability of nerve and muscle fibers, preventing

action potential propagation. Increased excretion of hydrogen ion along with hypokalemia cause pH to increase, a condition called **mild alkalosis**.

Aldosterone secretion follows a cyclical pattern having peak secretion occurs in morning and lowest point at night.

5.2. Genomic actions of aldosterone

Aldosterone regulates gene transcription on the target cell following two steps:

1. In the first phase, regulatory proteins of pre-existing ion channels and transporters are modulated.
2. In the second phase, new pumps, transporters and ion channels are synthesized primarily in the cells of distal convoluted tubules (DCT), collecting duct and collecting tubules as explained:
 - The association of aldosterone with mineralocorticoid receptors (MR) presents in the tubular cells up regulates the gene transcription of sodium-potassium ATPase. Thus, number of "sodium pumps" in the basolateral membranes of tubular epithelial cells increases to facilitate reabsorption of three sodium ions at the cost of secretion of two potassium ions.
 - Expressions of sodium channel for uptake of sodium ions in the tubular lumen get enhanced thus increasing the permeability of apical membrane for Na^+ absorption.
 - Increase rate of ATP-synthase gene transcription for meeting energy demands.
 - Expression of genes coding for Na^+/Cl^- cotransporter increases to sustain the electrochemical balance.
 - Expression of Na^+/H^+ exchanger in the proximal colon, have also been reported to be controlled by aldosterone.

Overall all these, causes increase in renal and colonic sodium and water reabsorption and an increased potassium excretion.

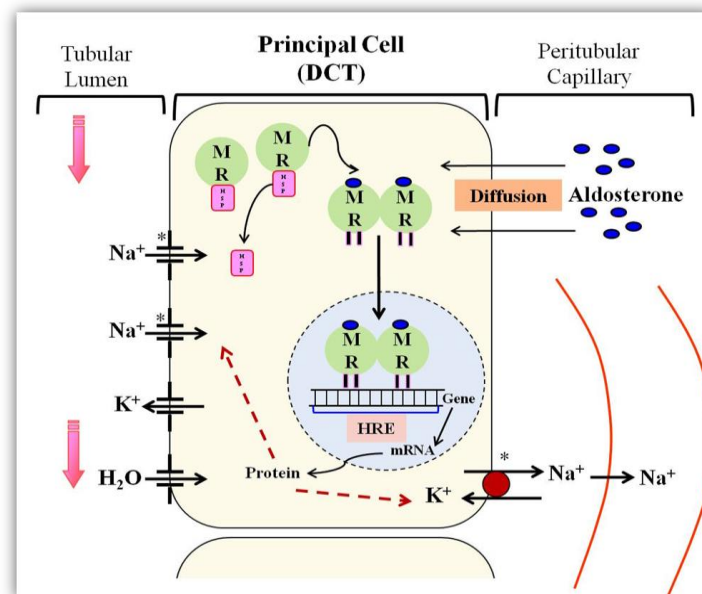


Figure 4. Genomic action of aldosterone
(Source: Authors)

5.3. Non-genomic effects of aldosterone

Aldosterone has been shown to increase formation of cAMP via second messenger system in vascular smooth muscle cells and in epithelial cells of the renal tubules rapidly. Aldosterone stimulation increases intracellular calcium ion concentration along with rapid stimulation of proton conductance of plasma membrane and increase pH of cytosol. Cumulatively all these factors enhance the number of Na^+/H^+ exchanger. In medullary thick ascending limb, there is a decrease in HCO_3^- absorption by increase in aldosterone stimulation. The other non-genomic effects of aldosterone are arterial vasodilation mediated by increase in NO level.

5.4. Regulation of aldosterone secretion

Aldosterone secretion by the zona glomerulosa is regulated by five major factors as follows:

1. **The major stimulus for aldosterone synthesis is angiotensin II or renin-angiotensin-aldosterone system (RAAS)** - The renin-angiotensin-aldosterone system is the major regulator of aldosterone secretion and stimuli for RAAS activation is Na^+ deficiency, dehydration or haemorrhage resulting in low blood volume and thus low blood pressure. These factors stimulate juxtaglomerular cells to secrete the enzyme renin, a very specific

protease synthesized by the juxtaglomerular apparatus (JGA) in the kidney. Renin converts the angiotensinogen (a precursor glycoprotein synthesized and released by the liver) to the bioinactive decapeptide angiotensin I. Angiotensin I is acted on by angiotensin-converting enzyme (ACE) in the lungs and other tissues to angiotensin II (octapeptide). Angiotensin II stimulate aldosterone synthesis by increasing the activity of P450_{11β} activity. Long-lasting stimulation up regulates the level of all the enzymes of glomerulosa required for aldosterone synthesis.

Binding of aldosterone to the cytosolic mineralocorticoid receptor and further molecular changes results in increased Na⁺ absorption and K⁺ & H⁺ secretion by the renal tubules. Angiotensin II and aldosterone also stimulates contraction of smooth muscle of arterioles. The resulting vasoconstriction of the arterioles increases blood pressure.

The resultant increase in plasma Na⁺, decrease in plasma K⁺ and elevated blood pressure provide a feedback mechanism for suppressing renin and, subsequently, aldosterone secretion (Fig. 5).

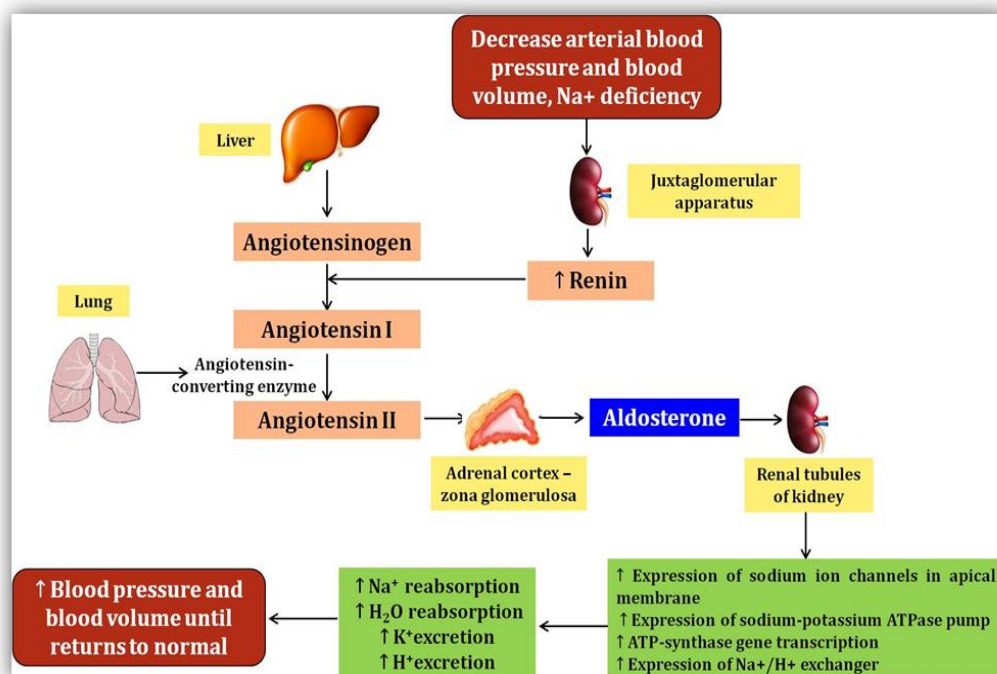


Figure 5. Control of aldosterone secretion by renin-angiotensin-aldosterone system (RAAS)

(Source: Authors)

2. **Increased potassium ion concentration in the extracellular fluid significantly augments aldosterone secretion** - Increase in potassium ion concentration sends positive signal for the synthesis of aldosterone mediated by increased intra-adrenal production of angiotensin II. Resultant increase in aldosterone acts on renal tubules to excrete the surplus potassium ions and bringing the RAAS system to normal.
3. **Decreased sodium ion concentration stimulates aldosterone slightly** - With 10 to 20 percent decreases in extracellular fluid sodium ion concentration can double the rate of aldosterone synthesis. The effect of sodium is mediated primarily by increased angiotensin II and secondary by increased renin release from the kidney.
4. **ACTH from the anterior pituitary gland is necessary for aldosterone secretion but has little effect in controlling the rate of secretion** - The role of ACTH (adrenocorticotrophic hormone, a polypeptide tropic hormone secreted by anterior pituitary gland) in controlling the secretion of aldosterone is minor. Maintained high levels of ACTH are required to stimulate the aldosterone production. Total absence of ACTH reduces aldosterone secretion and causes atrophy of the tissue.
5. **Atrial natriuretic peptide (ANP) is the only inhibitor for the synthesis of aldosterone** - Atrial natriuretic peptide (ANP) is a peptide hormone secreted by cells of atria in response to elevated blood pressure and volume. Increased ANP inhibits release of renin by the JGA and aldosterone synthesis by adrenal gland. ANP being a vasodilator is known to reduce blood pressure.

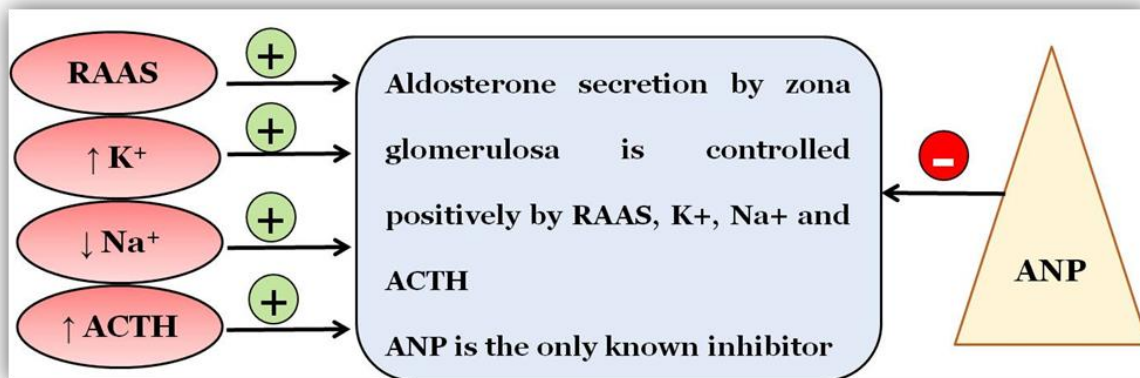


Figure 6. Factors controlling aldosterone secretion

(Source: Authors)

6. Glucocorticoids - Cortisol

The major glucocorticoids, secreted by zona fasciculata are cortisol (hydrocortisone), corticosterone, and cortisone. Cortisol is the most abundant hormone secreted by the zona fasciculata and account for 95% of glucocorticoid activity. The circulating glucocorticoids affect the entire body including the CNS via binding to glucocorticoid receptors (GR), and induce gene transcription that alter protein expression and structure along with the functioning of target cells.

6.1. Function of cortisol

Long-term exposure to stress, stimulate the release of cortisol which in turn promote increase in concentration of blood glucose at the expense of fat and proteins. Glucocorticoids are also instrumental in counteracting increased stress, inflammatory response and immune response.

- **Effect on carbohydrate metabolism** – Cortisol has dual role in carbohydrate metabolism and stimulates both gluconeogenesis and glycogenolysis in liver depending on the need. In hepatic cells cortisol facilitates synthesis of carbohydrates from non-carbohydrate precursors like amino acids and increase the level of stored glycogen which acts as a reservoir for glucose. The cortisol further stimulates glycogenolysis (stimulates glucose-6-phosphatase) as well, to augment energy requirement during low nutrient supply during

fasting or in the conditions of stress. Cortisol controls these processes by acting on the hepatic cells to increase the level of enzymes required for gluconeogenesis. It also ensures sufficient supply of extra hepatic amino acids (mainly muscles) to liver for gluconeogenesis and further promotes glucose formation.

Stored glycogen inside the liver cells allows glycolytic hormones, epinephrine and glucagon to make glucose available in need.

Cortisol inhibits glucose uptake by most cells of the body except brain. Increase gluconeogenesis and reduced uptake by cells increases blood glucose level upto 50%, causing **adrenal diabetes**. Increased circulating glucose causes increase in the level of plasma insulin as well to promote glycogen synthesis. But it has been observed that exposure to high level of glucocorticoids reduce the sensitivity of many tissues, especially skeletal muscle and adipose tissue, to the insulin. However, exogenous insulin administration has been effective in lowering the blood glucose level marginally in adrenal diabetes.

- **Effect on protein metabolism** – Cortisol increases the rate of protein metabolism to liberate extra amino acids from extra hepatic tissues, especially from muscles. The increased amount of amino acids acts as a raw material for gluconeogenesis in the hepatocytes. The cortisol essentially decreases the rate of protein synthesis enzymes in almost all the tissues except liver and increases the same in liver, thereby, increasing the level of proteins in liver and plasma.
- **Effect on lipid metabolism** – Cortisol are known to exert their effect on adipose tissue in same manner as in muscles but in adipose tissues they enhance the lipolysis to increase the level of free fatty acids in blood. The increased fatty acids in the blood act as energy fuel in case of starvation. Thus, glucose is used by the brain cells exclusively.

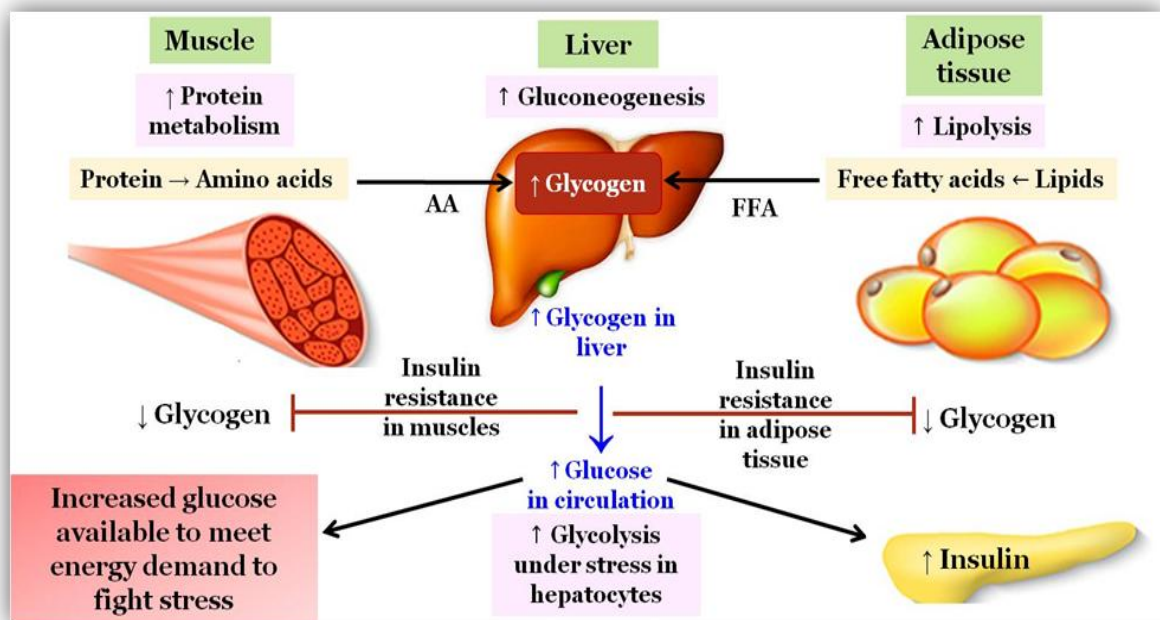


Figure 7. Effects of cortisol on carbohydrate, protein, and fat metabolism

(Source: Authors)

- **Resistance to stress** – Exposure to any kind of stress (physical, emotional, chemical, physiological or social) causes a steep rise in cortisol level. The increased cortisol provides excess glucose required to combat stress. It also helps in mobilization of amino acids and fats to meet excess demand of glucose to the brain and energy as discussed above. The other possible effects of cortisol are to modulate immune response, heart rate, blood pressure, and response of nervous system to overcome stress. Cortisol also has permissive effects on the action of catecholamines thereby, causing vasoconstriction and increasing blood pressure.
- **Anti-inflammatory effects** – Glucocorticoids inhibit almost all the steps of inflammatory response in any tissue damage or infection to increase the rate of healing. They decrease the number, migration and phagocytosis phenomena of white blood cells participate in inflammatory response. Cortisol stabilizes the lysosomal membranes, decreases the permeability of the capillaries, inhibit the immune system, causing lymphocyte reproduction to decrease markedly and attenuate fever.

- Although, high doses are known to retard tissue repair, slow down the process of healing and cause mental disturbances. Glucocorticoids are very useful in the treatment of chronic inflammatory disorders such as rheumatoid arthritis.
- **Depression of immune responses** - Cortisol suppresses the immune response by affecting most of the cells (cellular and humoral immunity) that participate in immune reactions. The rate of lymphocyte proliferation goes down along with increase in rate of apoptosis. The effectiveness of glucocorticoids (prednisone, prednisolone, etc.) in suppressing immune system makes them an ideal drug to be prescribed during organ transplant surgeries to limit the chances of tissue rejection.
- **Effects on cardiovascular system:** Cortisol is a known vasoconstrictor and by contracting smooth muscles of blood vessels it increases blood pressure. Strength of cardiac muscle is increased by virtue of the direct effect of cortisol in regulating sodium and potassium concentration in heart cells.
- **Effects on central nervous system:** Cortisol affects the behavior, mood, and electrical excitability of the neurons. It has been studied that any imbalance in the levels of cortisol causes symptoms of adrenal fatigue leading to moodiness, decreased tolerance, decreased clarity of thought and decreased memory. Hippocampus of temporal lobe is responsible for memory formation and has many glucocorticoid receptors and sensitive to stress, thus glucocorticoids play an important role in memory as well.
- **Effects on water and electrolyte metabolism:** Deficiency causes increased production of ADH which can decrease in glomerular filtration rate causing water retention in the body.

Thus, the overall effect of cortisol is to inhibit tissue building while stimulating the breakdown of stored nutrients to maintain adequate fuel supplies.

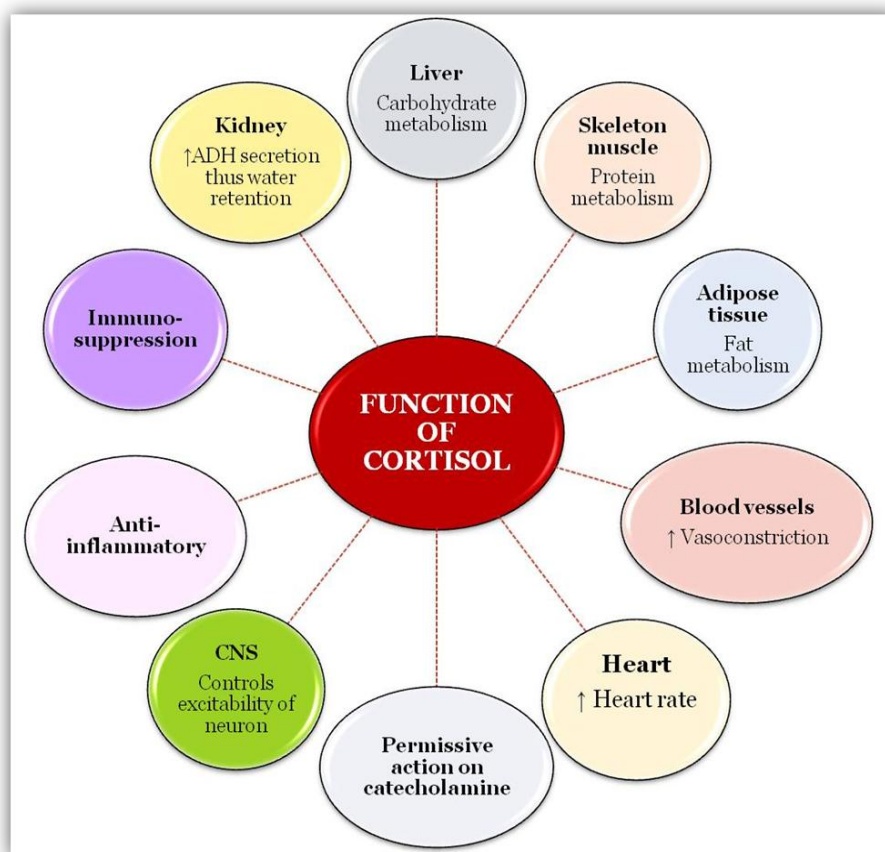


Figure 8. Functions of cortisol
(Source: Authors)

6.2. Regulation of cortisol secretion

The hypothalamus-pituitary-adrenal axis (HPA) is a negative feedback system responsible for controlling cortisol level according to the needs of the body under normal and stressed conditions. Long term exposure to stress stimulates corticotropin-releasing hormone (CRH) secretion, a peptide hormone from the hypothalamus. CRH *via* G-protein coupled receptors present in the cells of anterior pituitary triggers the release of ACTH. The association of ligand with receptor thus activates adenylyl cyclase-cAMP-PKA pathway to increase the level of calcium ion and then ACTH.

The cells of zona fasciculata and reticularis express cell surface receptor for ACTH. The coupling of ligand with receptors activates second messenger system causing elevation in cAMP level and thereby, increased cAMP-dependent protein kinase activity. This kinase then

phosphorylates other proteins and synthesis of glucocorticoids take place. The effects of ACTH on adrenal gland are intensity and duration dependent:

- **Rapid effects due to transient increases in ACTH (for minutes):**

ACTH leads to activation of cholesterol esterase and StAR, responsible for release of cholesterol from the lipid droplet and proteins responsible for cholesterol transport into the mitochondria.

- **Medium term effects due to prolonged increases in ACTH (6 - 36 hours):**

Increased synthesis of all of the steroidogenic enzymes, especially of P450_{scc}, and increased uptake of cholesterol from circulation by increasing the number of LDL receptors.

- **Chronic stimulation of the adrenal by ACTH results in adrenal hyperplasia (weeks-months):**

Long term exposure to ACTH up regulates the expression of genes responsible for synthesis of all steroidogenic enzymes. Genes responsible for steroidogenic enzyme synthesis contains cAMP response element, and therefore their transcription is controlled in part by CREB (cAMP Response Element Binding Protein). ACTH is responsible for adrenal hyperplasia mediated by cAMP.

- **ACTH-stimulation is required to prevent adrenal atrophy (lifetime):** The adrenal requires a constant low level of ACTH to maintain normal responsiveness to hormonal stimuli and prevent atrophy of the tissue.

The increased level of cortisol has direct negative feedback effects on (1) the hypothalamus to decrease the formation of CRH and (2) the anterior pituitary gland to decrease the formation of ACTH. Both of these feedbacks help regulate the plasma concentration of cortisol.

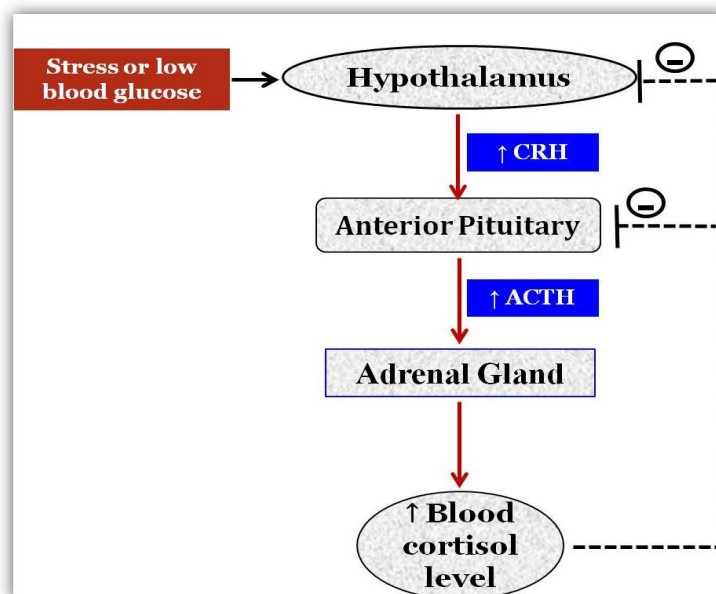


Figure 9. Regulation of cortisol secretion - The hypothalamus-pituitary-adrenal axis (HPA)

(Source: Authors)

7. Adrenal androgens

Adrenal androgens are weak androgens, synthesized by zona reticularis of adrenal cortex. The major androgens secreted are dehydroepiandrosterone (DHEA) and androstenedione. Adrenal androgens are produced in response to ACTH and converted to testosterone or estrogen in peripheral tissues. During prepubertal phase, androgens stimulate growth of axillary and pubic hair in boys and girls. After puberty the major sources of androgens are from gonads thus, the role of adrenal androgen is not very significant. However, in adult females adrenal androgens promote sex drive. After menopause, when ovarian secretion of estrogens ceases, adrenal androgens become the major source of all the estrogen required by the system.

8. Medullary hormones

8.1. Synthesis of catecholamines

As discussed earlier adrenal medulla is neuroendocrine tissue composed of postganglionic sympathetic nervous system (SNS) neurons and under the influence of stimulus from

hypothalamus synthesize and secrete catecholamines. They are commonly named as catecholamines due to presence of catechol nucleus and an amine group in their structures. Chromaffin cells of adrenal medulla synthesize catecholamines from amino acid tyrosine catalyzed by various enzymes using following steps:

Step 1: Tyrosine hydroxylase (TH) catalyzes the rate-limiting step in catecholamine synthesis and catalyzes the addition of a hydroxyl group to the tyrosine, thus forming 3, 4-dihydroxy-l-phenylalanine (l-DOPA). (TH can also hydroxylate phenylalanine to form tyrosine, which is then converted to l-DOPA; this alternative synthetic route may be of significance in patients affected with phenylketonuria, a condition in which phenylalanine hydroxylase activity is depressed).

Step 2: DOPA decarboxylase, a pyridoxine-dependent enzyme catalyzes the synthesis of first catecholamine i.e. **dopamine** from l-DOPA by decarboxylation.

Step 3: Dopamine β -hydroxylase (DBH) further catalyzes the addition of hydroxyl group to the β carbon on the side chain of dopamine to synthesize **norepinephrine** and use copper as cofactor.

Step 4: NE synthesized in the granules of chromaffin cells diffuse to cytoplasm and methylated by phenylethanolamine N-methyltransferase (PNMT). PNMT catalyzes the addition of methyl group to the nitrogen of norepinephrine (NE) forming a third amine, **epinephrine**.

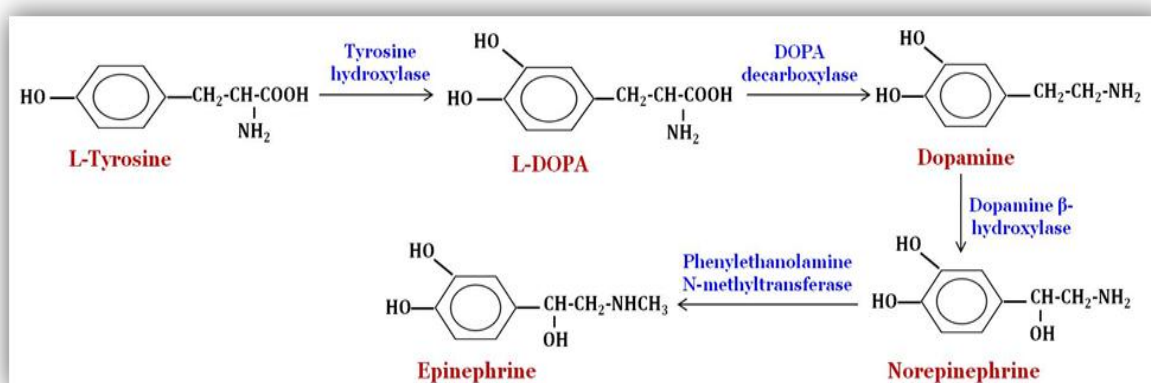


Figure 10. Pathway for catecholamine synthesis in adrenal medulla

(Source: Authors)

8.2. Release of catecholamines

Once synthesized, catecholamines are stored in secretory granules of chromaffin cells. Acetylcholine released from preganglionic sympathetic fibers as a result of stress (physical or psychological or both) stimulates nicotinic cholinergic receptors and causes depolarization of the adrenomedullary chromaffin cell. Depolarization leads to activation of voltage-gated Ca^{2+} channels resulting in exocytosis of secretory vesicle contents. A Ca^{2+} -sensing receptor appears to be involved in the process of exocytosis causing release of catecholamines to the circulation where they circulate in the bound form with albumin or other serum proteins. The half-life of catecholamine is very short (~ 2 minutes) and thereafter degraded by catechol-O-methyltransferases (COMT) or by deamination by monoamine oxidases (MAO) *via* methylation or deamination respectively.

8.3. Mechanism of action

Catecholamines interact with transmembrane adrenergic receptors present on the plasma membrane of target cells. The adrenergic receptors have seven transmembrane domains with associated G proteins (trimeric). The binding of ligand activates the receptors which causes G protein activation ($\text{GDP} \rightarrow \text{GTP}$). Further $\text{G}\alpha$ domain of activated G protein, dissociates from $\text{G}\beta$ - $\text{G}\gamma$ domain and binds to another transmembrane protein called adenylyl cyclase. The association of $\text{G}\alpha$ with adenylyl cyclase stimulates the cAMP mediated second messenger system which later induces protein kinase and leads to phosphorylation of proteins required for the desired effect in the target cells.

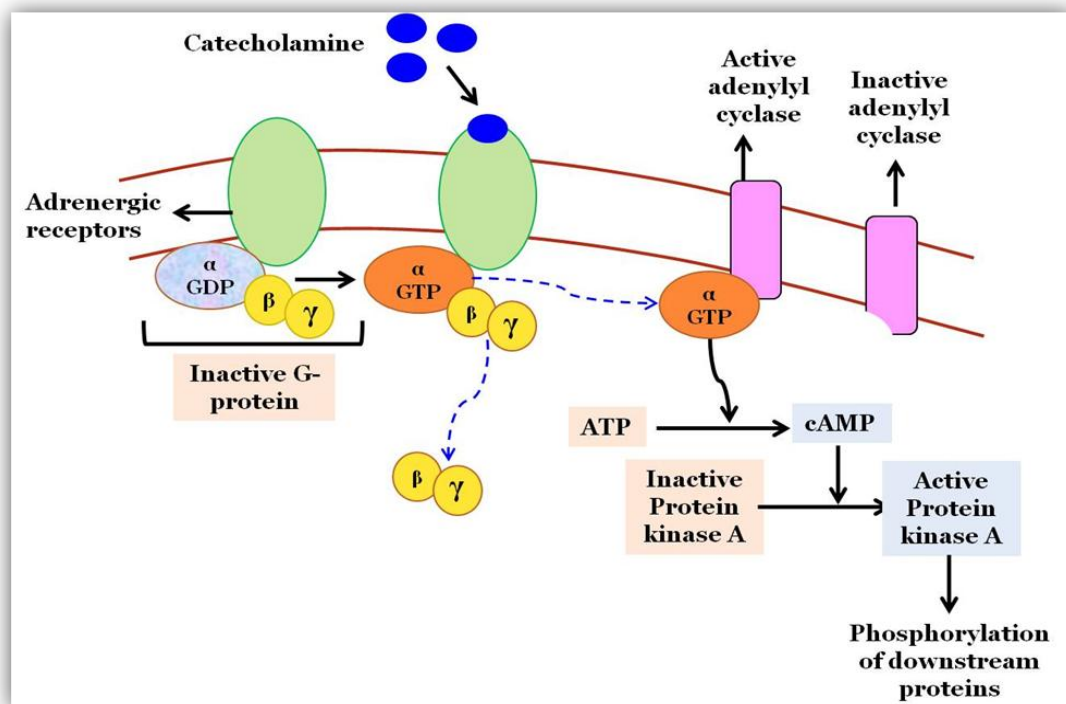


Figure 11. Cyclic AMP mediated pathway of action for catecholamine on target cell having adrenergic receptors
(Source: Authors)

It has been reported that there are two major types of adrenergic receptors, alpha receptors (α_1 , α_2) and beta receptors (β_1 , β_2). They are differentially expressed in different type of tissues and cells and have differential binding affinity to various ligands.

Norepinephrine stimulates both the receptors but has more pronounced effect on alpha receptors. On the contrary, epinephrine acts on both the receptors equally. Therefore, the response in target cell is depends on the type of receptor as well as on the ligand.

Receptor	Effectively Binds	Effect of Ligand Binding
Alpha₁	Epinephrine, Norepinphrine	Increase free calcium (operate through the phosphoinositide second messenger system, which leads to an increased calcium (Ca^{2+}))
Alpha₂	Epinephrine, Norepinphrine	Decreased cyclic AMP
Beta₁	Epinephrine, Norepinphrine	Increased cyclic AMP
Beta₂	Epinephrine	Increased cyclic AMP

Table 2. Different type of adrenergic receptors

8.4. Functions of epinephrine (EP) and norepinephrine (NE)

Epinephrine and norepinephrine synthesized and released by adrenal medulla under the influence of impulses from hypothalamus through sympathomedullary (SAM) pathway. These amines have long lasting effect, and prepare the body to fight any kind of stress as done by SNS. Advantage of having these hormones along with SNS is that they circulate in the blood and can send the signals to the cells that are not directly innervated by nerve fibers. The following are the effects of EP and NE:

- **Increased rate and force of contraction of the heart muscle:** catecholamines have both positive inotropic affect (cardiac contraction) and chronotropic effects (heart rate) on heart. Predominantly these effects are controlled by epinephrine through beta receptors. Epinephrine directly stimulates myocardial cells to increase the strength of ventricular contraction thus increased heart rate. Also causes vasoconstriction in the vessels of the skin, mucosa, and kidney.
- **Constriction of blood vessels:** norepinephrine causes vasoconstriction, resulting in increased arterial blood pressure and therefore blood flow to the skeletal muscles and central nervous system is increased. The action of vasoconstriction is counter balanced by vasodilator action of alpha 2 receptors to some extent.
- **Dilation of bronchioles:** epinephrine is a powerful bronchio-dilator and thus assists in pulmonary ventilation.
- **Stimulation of lipolysis in adipose tissues:** 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 to increase the rate of metabolism. Medullary hormones also promote glycogenolysis in skeletal muscle and liver to provide glucose for supplementing energy requirement.
- **Dilation of the pupils:** important in low intensity of light.

- **Inhibition of certain "non-essential" processes:** an example is inhibition of gastrointestinal secretion and motor activity.

8.5. Functions of dopamine

In the brain, dopamine functions as a neurotransmitter, activating dopamine receptors. Dopamine has important role in cognition, movement, flow of information to frontal lobes from other areas of brain, and regulation prolactin secretion. Besides this, dopamine is associated with the pleasure system of the brain, providing us feelings of enjoyment and motivation. Dopamine system has also been strongly linked to parkinson's disease, psychosis and schizophrenia.

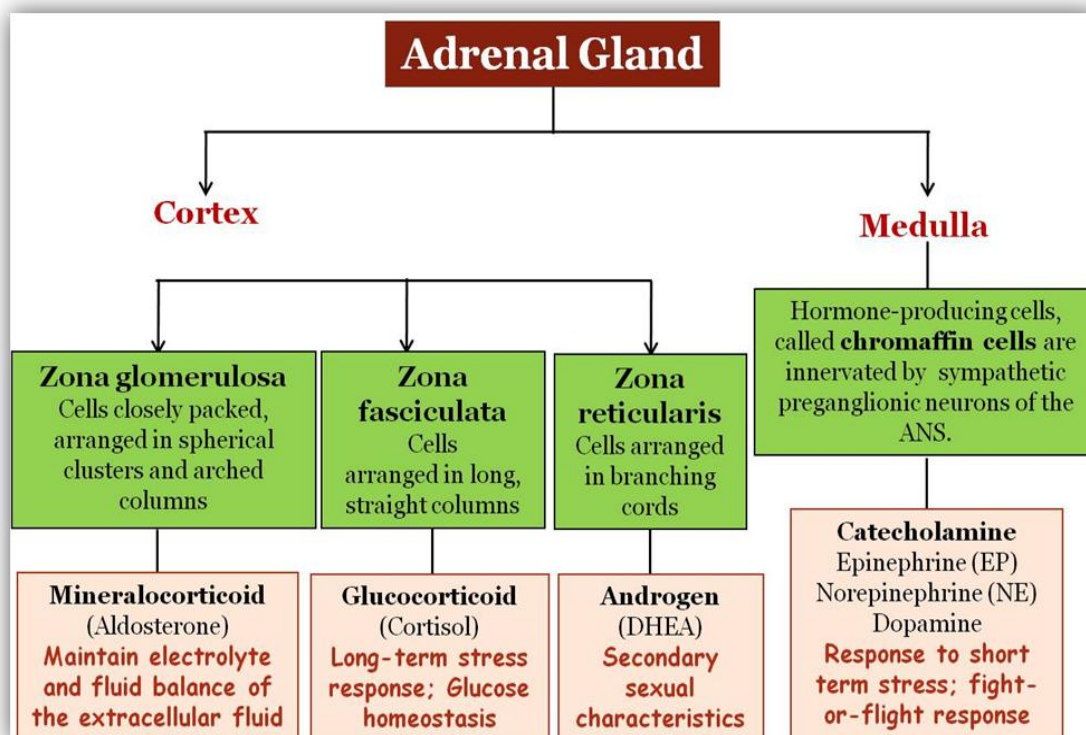


Figure 12. Overview of adrenal gland
(Source: Authors)

9. Pathophysiology of adrenal gland

Several disorders are caused by the dysregulation of the hormones produced by the adrenal glands. Hypersecretion of corticosteroids causes Cushing's disease characterized by high blood glucose levels and the accumulation of lipid deposits on the face and neck. In contrast, the hyposecretion of corticosteroids can result in adrenal insufficiency, characterized by low blood glucose levels and low blood sodium levels.

9.1. Adrenal insufficiency

Corticoid insufficiency arises from three main reasons:

1. Primary - destruction or dysfunction of the adrenal cortex known as Addison's disease
2. Secondary - dysfunction of HPA axis causing low levels of ACTH
3. Congenital adrenal hyperplasia

9.1.1. Primary adrenocortical insufficiency/ Addison's disease

Addison's disease is named after **Thomas Addison**, the British physician who first described the condition in 1855. A life-threatening condition caused by atrophy or dysgenesis of the adrenal gland. The primary cause of Addison's disease leading to hyposecretion of corticoids is due to autoimmune attack on the adrenal. Antibodies cause adrenal cortex destruction or block binding of ACTH to its receptors. Besides this, tuberculosis, and cancer are other possible causes for Addison's disease.

The signs and symptoms of Addison's disease appear until 90% of the adrenal cortex has been destroyed. Symptoms include mental lethargy, anorexia, nausea and vomiting, weight loss, hypoglycemia, muscular weakness, and cravings for salty food. The Addison's disease is manifested by various disturbances as follows:

Mineralocorticoid deficiency/ hypoaldosteronism

Low levels of aldosterone inhibit the sodium ion and water absorption from renal tubules with concomitant excretion of potassium and hydrogen ions. All these factors cause decrease in blood volume and pressure manifesting three conditions:

- Hypotension – low blood pressure due to overall decrease in blood volume

- Hyponatremia - low level of sodium in the blood
- Hyperkalemia – high level of potassium in the blood

Also there is decrease in cardiac output, fluid volume and increase in red blood cell count (polycythemia).

Glucocorticoid deficiency

The deficiency of glucocorticoids is characterized by difficulty in mobilization of energy stores, rapid fatigue, and inability to fight stress. Loss of cortisol levels causes hypoglycemia, weakness of muscle, weight loss, hyponatremia, increased pigmentation, abnormal metabolic functions, irritability and mental sluggishness. Lack of adequate glucocorticoid secretion also makes a person with Addison's disease highly incapable of fighting any kind of stress and a small bacterial or viral infection can cause death of the individual. If remain untreated patient with Addison's disease die in few days to few weeks. Treatment consists of administering glucocorticoids and mineralocorticoids and increasing sodium in the diet.

9.1.2. Secondary adrenocortical insufficiency

Low levels of corticosteroid secretion caused by disorder of HPA axis leading to diminished level of ACTH and ultimately low stimulation of adrenal cortex. Besides disturbance in HPA axis infection, pituitary tumors and irradiation also affect the synthesis of ACTH by anterior pituitary gland.

9.1.3. Congenital adrenal hyperplasia (CAH)

Congenital adrenal hyperplasia as the name suggests is a congenital disorder caused by mutation in the genes for the enzymes (especially 21-hydroxylase catalyze the final steps of mineralocorticoids and glucocorticoids synthesis, but not androgens) required for synthesis of steroid hormone. This causes decreased synthesis of glucocorticoid and lead to malfunctioning of HPA axis. Due to low levels of cortisol negative feedback is interrupted and therefore, compensatory high levels of CRH and ACTH are synthesized by hypothalamus and anterior pituitary respectively. The increased ACTH causes hyperplasia of the adrenal and (usually) elevated levels of other adrenal steroid products. The most common enzyme mutated in CAH is 21-hydroxylase, catalyses the final steps of mineralocorticoids and glucocorticoids synthesis, but not androgens. Therefore, ACTH stimulation of the adrenal

cortex induces the release of excessive amounts of adrenal androgens, which can lead to the development of ambiguous genitalia and secondary sex characteristics.

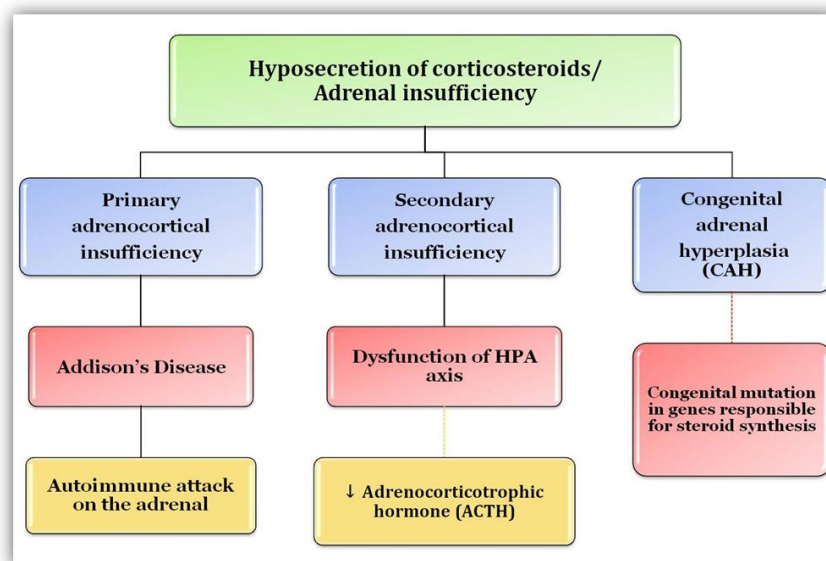


Figure 13. Disorders Associated with hyposecretion of corticosteroids

(Source: Authors)

9.2. Hyperadrenalism

9.2.1. Cushing's Syndrome

Cushing's syndrome is associated with hypersecretion of cortisol caused by adenoma of the adrenal gland, or anterior pituitary responsible for secretion of ACTH, which in turn stimulates excessive secretion of cortisol. The condition is characterized by breakdown of muscle proteins and redistribution of body fat i.e. mobilization of fat from the lower part of the body, with concomitant extra deposition of fat in the thoracic and upper abdominal regions giving rise to a buffalo torso. Exposure to higher level of glucocorticoids also affects the appearance of face described as a "moon face". Acne, excess facial hair (hirsutism) is other symptoms of the Cushing's syndrome. The elevated level of cortisol also causes hyperglycemia (risk of developing type 2 diabetes), osteoporosis, weakness, hypertension, increased susceptibility to infection (low immunity), decreased resistance to stress, and mood swings. People who need long-term glucocorticoid therapy—for instance, to prevent rejection of a transplanted organ—may develop a Cushingoid appearance.

Treatment of Cushing's syndrome consists of removing an adrenal tumor surgically or destroyed by radiation, followed by administration of adrenal steroids to supplement for decrease level of hormones. Drugs that block steroidogenesis, such as metyrapone, ketoconazole, and aminoglutethimide, or that inhibits ACTH secretion (serotonin antagonists and GABA-transaminase inhibitors) are prescribed to avoid surgery.

9.2.2. Primary hyperaldosteronism/ Conn's syndrome

Excess aldosterone secretion, due to bilateral idiopathic cortical hyperplasia or tumor of zona glomerulosa is associated with sodium retention and potassium depletion. High rate of sodium ion (Hypernatremia) and water retention causes high blood pressure (hypertension) associated with hypokalemia. Low extracellular potassium concentration causes muscle paralysis due to depressive effect on action potential transmission by the nerve fibers. Due to negative feedback of increased aldosterone level renin secretion is inhibited by JGA. (85%) Hyperaldosteronism treatment includes surgery and administration of aldosterone antagonists.

9.2.3. Adrenal androgen hypersecretion/Adrenogenital Syndrome

Adrenocortical tumor also causes excess androgen secretion by adrenal gland causing intense masculinising effects throughout the body. In females over production of testosterone leads to overdeveloped male characteristics such as hirsutism, deepening voice and more muscular arms and legs. Increases androgen levels before puberty manifested by development of premature secondary sex characteristics such as deep voice, beard, enlarged penis and a sex drive although gonads are not functioning and there is no sperm production.

9.3. Pheochromocytomas

Tumor of the chromaffin cells of adrenal medulla is known as pheochromocytomas and leads to hypersecretion of catecholamines causing rapid heart rate (cardiac arrhythmias), high blood pressure (hypertension), high levels of glucose in blood and urine, an elevated basal metabolic rate (BMR), flushed face, nervousness, sweating, and decreased gastrointestinal motility. Surgical removal of the gland is practiced if the lesions are localized. α -Methyl-p-tyrosine (an inhibitor of tyrosine hydroxylase, the rate-limiting enzyme in catecholamine biosynthesis) may be used to decrease catecholamine secretion from the tumor.

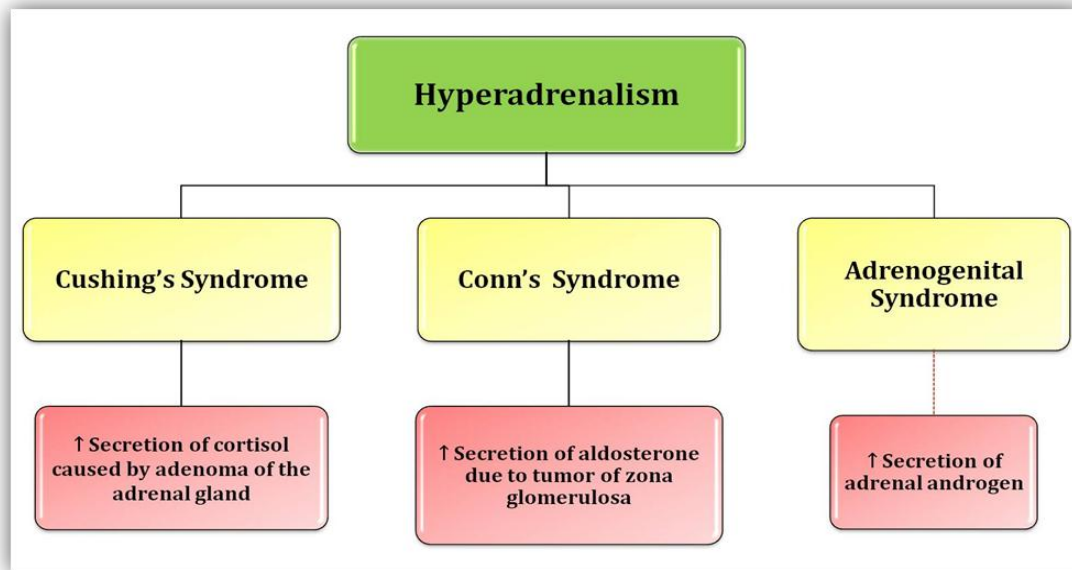


Figure 14. Disorders Associated with hypersecretion of corticosteroids

(Source: Authors)

10. Summary

- Adrenal glands are paired endocrine gland located in the abdominal cavity above the kidney, in retroperitoneal position.
- Anatomically they are divided into two zones; outer cortex and inner medulla.
- The main function of gland is to secrete corticosteroids (mineralocorticoid, glucocorticoids, and androgens) and catecholamines (norepinephrine, epinephrine, and dopamine).
- Corticosteroids are synthesized from common precursor cholesterol by the cells of adrenal cortex under the influence of ACTH released from anterior pituitary and circulate in bound as well as in free form.
- Aldosterone, the main mineralocorticoid acts primarily on renal tubules, sweat glands, salivary glands and colon to maintain electrolyte and fluid balance of the extracellular fluid, and follows a cyclical pattern of secretion.

- Cortisol helps in fight against long term stress through its direct control on carbohydrate, protein, and fat metabolism. Besides this cortisol depress immune system and inflammatory responses of the body.
- The HPA axis is a negative feedback system, responsible for controlling cortisol level according to the needs of the body under normal and stressed conditions.
- Catecholamines are synthesized from tyrosine in the chromaffin cells of adrenal medulla following specific pathway and released in the circulation under the influence of stimulus from preganglionic fibers.
- Catecholamines have specific adrenergic receptors on the target cells and prepare the body to fight against short term stress.
- Several disorders are associated with dysregulation of the hormones produced by adrenal glands. Hypersecretion of corticosteroids causes Cushing's disease characterized by high blood glucose levels and the accumulation of lipid deposits on the face and neck. In contrast, the hyposecretion of corticosteroids can result in adrenal insufficiency, characterized by low blood glucose levels and low blood sodium levels.
- Low levels of catecholamines do not show much effect as their role is counter balanced by sympathetic nervous system however, hypersecretion causes cardiac arrhythmias, hypertension, high levels of glucose in blood and urine, an elevated basal metabolic rate etc.