Adrenal Gland

**Adrenal medulla:**
Adrenal medulla structure and function of medullary hormones:

1. **Catecholamines:**
   Norepinephrine, epinephrine, and dopamine are secreted by the adrenal medulla.

![Chemical Reaction Diagram]

Most of the catecholamine output in the adrenal vein is epinephrine.
Norepinephrine enters the circulation from noradrenergic nerve endings
Sulfate conjugates are inactive and their function is unsettled.
In recumbent مستلقي نائم humans, the normal plasma level of free norepinephrine is less than standing.
On standing, the level increases 50–100%.
The plasma norepinephrine level is generally unchanged after adrenalectomy, but the free epinephrine level, falls to essentially zero.
The epinephrine found in tissues other than the adrenal medulla and the brain is for the most part absorbed from the bloodstream rather than synthesized in situ.
Interestingly, low levels of epinephrine reappear in the blood sometime after bilateral adrenalectomy, and these levels are regulated like those secreted by the adrenal medulla. They may come from cells such as the intrinsic cardiac adrenergic (ICA) cells (Intrinsic cardiac adrenergic (ICA) cells are present in mammalian hearts (atria more than ventricle) and contain catecholamine-synthesizing enzymes sufficient to produce biologically active norepinephrine levels), but their exact source is unknown.
Half the plasma dopamine comes from the adrenal medulla, whereas the remaining half presumably comes from the sympathetic ganglia or other components of the autonomic nervous system.
The catecholamines have a half-life of about 2 min in the circulation.
For the most part, they are methoxylated and then oxidized to 3-methoxy-4-hydroxymandelic acid (vanillylmandelic acid [VMA]).

2. **Chromogranin A:**
Chromogranin A is major soluble protein of chromaffin granules.
In the medulla, norepinephrine and epinephrine are synthesized by adrenal medulla secretory cell (chromaffin cell or post-ganglionic cell) and stored in chromaffin granules along with ⓀATP,
 أصحاب chromogranin A
Chromogranin A released from the adrenal medulla together with catecholamines upon stimulation of the splanchnic nerve, and also present in various neuro-endocritical tissues.
Chromogranin A widely used tumor marker (Pheochromocytoma and neuro-endocritical such as carcinoid tumor and neuroblastoma).

3. **Adrenomedullin**
Adrenomedullin was initially isolated from a pheochromocytoma, a tumor of the adrenal medulla. Adrenomedullin is a 52 amino acid peptide found in the adrenal medulla and in other tissues, heart, kidney, and intestine. Adrenomedullin is structurally similar to CGRP (calcitonin-gene related peptide) with a 27% homologue.

Adrenomedullin was

1. has vasodilator and natriuretic effects.
2. up-regulating angiogenesis
3. increasing the tolerance of cells to oxidative stress and hypoxic injury

**Effects of epinephrine and nor-epinephrine:**

1. Catecholamines (norepinephrine and epinephrine) mimicking the effects of noradrenergic nervous discharge.

   Catecholamines potentiate and sustain the effects of sympathetic stimulation.

2. Catecholamines (norepinephrine and epinephrine) exert metabolic effects that include:
   a. mobilization of free fatty acids (FFA),
   b. increased plasma lactate,
   c. stimulation of the metabolic rate.

3. Catecholamines (norepinephrine and epinephrine) effects on CVS system:

   ![](chart.png)

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<tr>
<th>Features</th>
<th>Adrenaline</th>
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   a. norepinephrine and epinephrine increase the force and rate of contraction of the isolated heart. These responses are mediated by β 1 receptors.
   b. norepinephrine and epinephrine increase myocardial excitability, causing extra-systoles and, occasionally, more serious cardiac arrhythmias.
c. Norepinephrine produces vasoconstriction in most if not all organs via α1 receptors, but epinephrine dilates the blood vessels in skeletal muscle and the liver via β2 receptors. This usually overbalances the vasoconstriction produced by epinephrine elsewhere, and the total peripheral resistance drops.

d. When norepinephrine is infused slowly in normal animals or humans, the systolic and diastolic blood pressures rise.

e. The hypertension stimulates the carotid and aortic baroreceptors, producing reflex bradycardia that overrides the direct cardio-acceleratory effect of norepinephrine. Consequently, cardiac output per minute falls.

f. Epinephrine causes a widening of the pulse pressure, but because baroreceptor stimulation is insufficient to obscure the direct effect of the hormone on the heart, cardiac rate and output increase. Most adrenal medullary tumors (pheochromocytomas) secrete norepinephrine, or epinephrine, or both, and produce sustained hypertension. However, 15% of epinephrine-secreting tumors secrete this catecholamine episodically, producing intermittent bouts of palpitations, headache, glycosuria, and extreme systolic hypertension. These same symptoms are produced by intravenous injection of a large dose of epinephrine.

4. Catecholamines increase alertness.

Epinephrine and norepinephrine are equally potent in increase alertness.

Epinephrine usually evokes more anxiety and fear.

5. The catecholamines have several different actions that affect blood glucose.

a. Epinephrine and norepinephrine both cause glycogenolysis.

Epinephrine and norepinephrine produce this effect via β-adrenergic receptors that increase cyclic adenosine monophosphate (cAMP), with activation of phosphorylase, and via α-adrenergic receptors that increase intracellular Ca 2+

b. Epinephrine and norepinephrine increase the secretion of insulin and glucagon via β-adrenergic mechanisms and inhibit the secretion of these hormones via α-adrenergic mechanisms.

c. Epinephrine and norepinephrine produce a prompt rise in the metabolic rate that is independent of the liver and a smaller, delayed rise that is abolished by hepatectomy and coincides with the rise in blood lactate concentration.

The initial rise in metabolic rate may be due to cutaneous vasoconstriction, which decreases heat loss and leads to a rise in body temperature, or to increased muscular activity, or both.

The second rise is probably due to oxidation of lactate in the liver.

6. When injected, epinephrine and norepinephrine cause an initial rise in plasma K+ because of release of K+ from the liver and then a prolonged fall in plasma K+ because of an increased entry of K+ into skeletal muscle that is mediated by β2-adrenergic receptors. Some evidence suggests that activation of α receptors opposes this effect.

Effects of dopamine:

The physiologic function of the dopamine in the circulation is unknown.

 Injected dopamine produces

a. renal vasodilation and the mesentery.

b. vasoconstriction, probably by releasing norepinephrine

c. positively inotropic effect on the heart by an action on β1-adrenergic receptors.

The net effect of moderate doses of dopamine is
① an increase in systolic pressure
② no change in diastolic pressure.
Because of these actions, dopamine is useful in the treatment of traumatic and cardiogenic shock. Dopamine is made in the renal cortex. Dopamine causes natriuresis and may exert this effect by inhibiting renal Na\(^+\)–K\(^+\) ATPase.

**Adrenal Cortex**

The adrenal cortex three distinct layers secretions:
1. The zona glomerulosa, secreting significant amounts of aldosterone
2. The zona fasciculata secretes the glucocorticoids (cortisol and corticosterone) as well as small amounts of adrenal androgens and estrogens.
3. The zona reticularis secretes the adrenal androgens, small amounts of estrogens and some glucocorticoids.

Factors such as angiotensin II that specifically increase the output of aldosterone and cause hypertrophy of the zona glomerulosa have no effect on the other two zones. Similarly, factors such as ACTH that increase secretion of cortisol and adrenal androgens and cause hypertrophy of the zona fasciculata and zona reticularis have little effect on the zona glomerulosa.

All human steroid hormones, including those produced by the adrenal cortex, are synthesized from cholesterol provided by low-density lipoprotein (LDL) in the circulating plasma. Adrenocortical hormones are bound to plasma proteins. Approximately 90 to 95 percent of the cortisol in the plasma binds to plasma proteins, especially a globulin called cortisol-binding globulin or transcortin and, to a lesser extent, to albumin. This high degree of binding to plasma proteins slows the elimination of cortisol from the plasma; therefore, cortisol has a relatively long half-life of 60 to 90 minutes. Only about 60 percent of circulating aldosterone combines with the plasma proteins, so about 40 percent is in the free form; as a result, aldosterone has a relatively short half-life of about 20 minutes.

**Mineralocorticoid:**
In humans, aldosterone exerts nearly 90 percent of the mineralocorticoid activity of the adrenocortical secretions, but cortisol, the major glucocorticoid secreted by the adrenal cortex, also provides a significant amount of mineralocorticoid activity. The mineralocorticoid activity of aldosterone is about
3000 times greater than that of cortisol, but the plasma concentration of cortisol is nearly 2000 times that of aldosterone.

The receptor is activated by mineralocorticoids such as **aldosterone** and its precursor deoxycorticosterone as well as glucocorticoids, like **cortisol**. In intact animals, the mineralocorticoid receptor is "protected" from glucocorticoids by co-localization of an enzyme, Corticosteroid 11-beta-dehydrogenase isozyme 2 (11β-hydroxysteroid dehydrogenase 2; 11β-HSD2), that converts cortisol to inactive cortisone thus allowing **aldosterone** to bind to its receptor

The intense glucocorticoid activity of the synthetic hormone dexamethasone, which has almost zero mineralocorticoid activity, makes it an especially important drug for stimulating specific glucocorticoid activity.

**Functions of aldosterone:**

1. Aldosterone reabsorb Na+ and H2O and secrete K+ especially in the principal cells of the collecting tubules and, to a lesser extent, in the distal tubules and collecting ducts.

Aldosterone binds the mineralocorticoid receptor (MR) inside the cell. Mineralocorticoid receptor (MR) are found in high concentration in:

A. Epithelial sites:
   1. renal collecting duct (Principle cell)
   2. colon
   3. ducts of sweat and salivary glands

B. Non-epithelial sites:
   1. heart
   2. brain
   3. vascular smooth muscle
   4. liver
   5. peripheral blood leukocytes.

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Aldosterone (A) binds the mineralocorticoid receptor (MR) inside the cell forming MR-A complex. MR-A Complex join DNA forming aldosterone-induced protein (AIP). AIP will have the following effects:

A. Affects mitochondria to increase energy production

B. Open epithelium Na channels (ENaC) ⇒ increase Na inside the cell ⇒ Na pushed out by Na-K ATPase
The efflux of sodium from the epithelial cells is an energy-dependent process that is mediated by sodium-potassium ATPase (Na.K-ATPase) in the basolateral membrane. C. Na-K ATPase (the energy supply (ATP) will be form mitochondria) will increase K concentration\(\Rightarrow\)K will be secretion to urine by opening K antagonist channels-ROMK. The Renal Outer Medullary potassium channel (ROMK) is an ATP-dependent potassium channel that transports potassium out of cells.

Epithelium Na channels (ENaC) or amiloride-sensitive epithelial sodium channel (ENaC) is the major determinant of renal sodium re-absorption. About 45 minutes is required before the rate of sodium transport begins to increase; the effect reaches maximum only after several hours.

Epithelium Na channels availability in open conformation at the apical membrane of the cell is increased by: 1) aldosterone 2) vasopressin, 3) glucocorticoids, and 4) insulin.

Down-regulate by elevated intracellular levels of: 1) calcium and 2) sodium

About 2% of overall Na\(^+\) re-absorption are affected by aldosterone.

When sodium is reabsorbed by the tubules, simultaneous osmotic absorption of almost equivalent amounts of water occurs.

**Aldosterone escape**

Continuous increase of aldosterone will increase Na and water retention but this effect will continue only for few days and after that the effect of Na and water retention will stop and water and Na levels return to normal.

Aldosterone escape is a protective mechanism during abnormal elevation of aldosterone or Na retention.

### Aldosterone Escape

![Aldosterone Escape Graph](image)

The term "aldosterone escape" has been used to refer to 2 distinct phenomena that are exactly opposite each other:

1. **Primary hyper-aldosteronism** either idiopathic or tumor (conn syndrome) or familial

   The escape of the kidney from salt and water retention effect of aldosterone

   **Aldosterone escape explanation**

   Primary hyper-aldosteronism ► Na and water retention ► increase blood pressure ►

   a. Pressure natriuresis (increase Na secretion)

   b. Pressure diuresis (increase water secretion secretion)
NO edema is found
(2) Refractory (or secondary) hyperaldosteronism
The escape of aldosterone from suppression secretory effect of ACE inhibitor or angiotensin receptor blocker during the treatment of heart failure and these represent about one third of patients
The possible explanation:
a. Aldosterone is produced by tissues other than adrenal cortex (as heart and blood vessels) and by a system other than Renin-Angiotensin-aldosterone system
b. ACE inhibitor or angiotensin receptor blocker therapy causes hyperkalemia that stimulate aldosterone secretion
Aldosterone escape explanation
1. Secondary hyper-aldosteronism ► Na and water retention ► ANP release ► natriuresis + diuresis
2. Secondary hyper-aldosteronism ► Na retention ► increase plasma osmolarity
   i. Increase thirst ► water intake ► decrease plasma osmolarity
   ii. Increase vasopressin ► water retention ► decrease plasma osmolarity
This why it is preferred to use aldosterone antagonist to avoid aldosterone elevation during hear failure treatment
2. Excess aldosterone increases tubular hydrogen ion secretion and causes alkalosis.
Aldosterone causes secretion of hydrogen ions in exchange for potassium in the intercalated cells of the cortical collecting tubules. This decreases the hydrogen ion concentration in the extracellular fluid, causing metabolic alkalosis.
3. Effect of aldosterone on sweat and salivary glands and intestinal epithelial cells:
A. Sweat and salivary glands:
The sweat and salivary gland secretions which contain the same quantity of Na and Cl as plasma pass the duct. In the duct Na and Cl will be absorbed and K and HCO3 will be secreted. This process will be enhanced by aldosterone. Causing a decrease of Na and Cl secretion by these glands.

B. Colon epithelium:
Aldosterone stimulates Na reabsorption which means enhance water reabsorption (osmotic gradient), and Cl reabsorption (electrical gradient).

Regulation of aldosterone secretion:
Regulation of aldosterone secretion by the zona glomerulosa cells is almost entirely independent of regulation of cortisol and androgens by the zona fasciculata and zona reticularis.

The following four factors are known to play essential roles in regulation of aldosterone:
1. Increased potassium ion concentration in the extracellular fluid greatly increases aldosterone secretion.
2. Increased angiotensin II concentration in the extracellular fluid greatly increases aldosterone secretion.

The factors affecting the secretion of aldosterone through angiotensin:

i) A drop in ECF volume or intra-arterial volume:
They lead to a reflex increase in renal nerve discharge and decrease renal arterial pressure. Both changes increase renin secretion, and the angiotensin II formed by the action of renin increase the rate of secretion of aldosterone. The aldosterone causes Na and, secondarily, water retention, expanding ECF volume and shutting off the stimulus that initiated increase renin secretion.

ii) Hemorrhage:
Hemorrhage stimulates ACTH and renin secretion.

iii) Standing and constriction of the thoracic inferior vena cava:
Those two conditions associate with a decrease in intra-arterial volume.

iv) Dietary sodium restriction:
Dietary sodium restriction causes:
First: reflex increases in the activity of the renal nerves.
Second: up-regulation of the angiotensin II receptors in the adrenal cortex and hence increase the response to angiotensin II, whereas it down-regulates the angiotensin receptors in the blood vessels.

3. Increased sodium ion concentration in the extracellular fluid very slightly decreases aldosterone secretion. An acute decline in plasma Na about 20 meq/L stimulates aldosterone secretion but changes of this magnitude are rare. 4. ACTH from the anterior pituitary gland is necessary for aldosterone secretion but has little effect in controlling the rate of secretion in most physiological conditions. ACTH appears to play a “permissive” role in regulation of aldosterone. Of these factors, potassium ion concentration and the renin-angiotensin system are by far the most potent in regulating aldosterone secretion.

5. Effect of other factors:
   ◊ Aldosterone secretion increase in the individuals carrying on activities in the upright position due to a decrease in the rate of the removal of aldosterone from the circulation by the liver.
   ◊ Atrial natriuretic peptide (ANP) inhibits renin secretion and decrease the responsiveness of the zona glomerulosa to angiotensin II.
   ◊ Individuals who are confined to bed show a circadian rhythm of Aldosterone and Renin secretion, with the highest values in the early morning before awakening.

The factors control the Na levels are:
Aldosterone, ANP, Osmotic diuresis.

Changes in tubular re-absorption of Na independent of Aldosterone.

Relation of mineralo-corticoid to gluco-corticoid:
It is intriguing that in vitro, the mineralo-corticoid receptors have an appreciably higher affinity for gluco-corticoid receptors does, and gluco-corticoid are present in large amount in vivo. This raises the question of why gluco-corticoid does not bind to the mineralo-corticoid receptors in the kidney and other location and produce mineralo-corticoid effects. At least in part, the answer is that the kidney and other mineralo-corticoid-sensitive tissues also contain the enzyme (11β-hydroxy-steroid dehydrogenase type 2). This enzyme leaves, aldosterone untouched, but it converts cortisol to cortisone and corticosterone to its 11-oxy derivative. Those derivatives do not bind to the receptor.

Mineralocorticoid deficiency causes
Hypoaldosteronism associated with Hyperkalemia, hypotension, hyponatremia, metabolic acidosis
A. Hyperkalemia ► serious cardiac toxicity, including weakness of heart contraction and development of arrhythmia, becomes evident, and progressively higher concentrations of potassium lead inevitably to heart failure.
B. Severe renal sodium chloride and water exertion ► the total extracellular fluid volume and blood volume become greatly reduced ► circulatory shock
Total loss of adrenocortical secretion may cause death within 3 days to 2 weeks unless the person receives extensive salt therapy or injection of mineralocorticoids.

Excess Mineralocorticoid causes
Hyperaldosteronism associated with Hypokalemia, hypertension, hypernatremia, metabolic alkalosis
A. Hypokalemia ► severe muscle weakness often develops. This muscle weakness is caused by alteration of the electrical excitability of the nerve and muscle fiber membranes, which prevents transmission of normal action potentials.
B. Severe renal sodium chloride and water retention ► hypertension
Glucocorticoid
At least 95 percent of the glucocorticoid activity of the adrenocortical secretions results from the
secretion of cortisol, known also as hydrocortisone. In addition, a small but significant amount of
glucocorticoid activity is provided by corticosterone

Effects of cortisol in physiological level
1. Effect of cortisol on carbohydrate metabolism
A. Stimulation of Gluconeogenesis.
Glucocorticoid stimulates gluconeogenesis (i.e., the formation of carbohydrate from proteins and some
other substances) by the liver, often increasing the rate of gluconeogenesis as much as 6- to 10-fold.
i. Cortisol increases the enzymes required to convert amino acids into glucose in liver cells.
ii. Cortisol causes mobilization of amino acids from the extra-hepatic tissues, mainly from muscle.
iii. Cortisol antagonizes insulin’s effects to inhibit gluconeogenesis in the liver
The net effect of cortisol is to increase glucose production by the liver.
B. Cortisol causes a moderate decrease in glucose utilization by most cells in the body
Although the precise cause of this decrease is unclear,
   i. Glucocorticoids decrease translocation of the glucose transporters GLUT 4 to the cell membrane,
especially in skeletal muscle cells, leading to insulin resistance.
   ii. Glucocorticoids may also depress the expression and phosphorylation of other signaling cascades
   that influence glucose utilization directly or indirectly by affecting protein and lipid metabolism.
   High level of growth hormone causes pituitary diabetes.
   High level of glucocorticoid hormone causes adrenal diabetes (due to high glucose level & insulin
   resistance).
   Low level of insulin causes pancreatic diabetes.
2. Effect of cortisol on protein metabolism:
   A. Effect of glucocorticoids on extra hepatic tissues:
      i. Increase protein catabolism and decrease amino acid transport to extra-hepatic cell ➤ increase
         protein catabolism
      ii. Increase amino acid transport from cell to plasma ➤ increase plasma amino acid concentration
   B. A. Effect of glucocorticoids on hepatic tissues:
Cortisol mobilizes amino acids from the non-hepatic tissues and in doing so diminishes the tissue
stores of protein.
The increased plasma concentration of amino acids and enhanced transport of amino acids into the
hepatic cells by cortisol could also account for enhanced utilization of amino acids by the liver to cause
such effects as
   i. increased rate of deamination of amino acids by the liver,
   ii. increased protein synthesis in the liver,
   iii. increased formation of plasma proteins by the liver
   iv. increased gluconeogenesis.
3. Effect of cortisol on fat metabolism:
   A. Cortisol promotes mobilization of fatty acids from adipose tissue.
   B. This increases the concentration of free fatty acids in the plasma.
   C. Increase fat utilization for energy.
D. Cortisol has a direct effect to enhance the oxidation of fatty acids in the cells.
The mechanism by which cortisol promotes fatty acid mobilization:
$$\downarrow$$
- diminished transport of glucose into the fat cells
- diminished $\alpha$-glycerophosphate, which is derived from glucose, is required for both deposition and maintenance of triglycerides in these cells.
The cortisol mechanism that
- increased mobilization of fats by cortisol, combined with increased oxidation of fatty acids in the cells, helps shift the metabolic systems of the cells from utilization of glucose for energy to utilization of fatty acids in times of starvation or other stresses.
The cortisol mechanism, requires several hours to become fully developed (not nearly so rapid or so powerful an effect as a similar shift elicited by a decrease in insulin).
The cortisol mechanism that increases use of fatty acids for metabolic energy is an important factor for long-term conservation of body glucose and glycogen.

In pathological and pharmacological quantities glucocorticoids have other effects including:

1. Anti-inflammatory effects of high levels of cortisol

Five main stages of inflammation occur:
- release from the damaged tissue cells of chemicals such as histamine, bradykinin, proteolytic enzymes, prostaglandins, and leukotrienes that activate the inflammation process;
- an increase in blood flow in the inflamed area caused by some of the released products from the tissues, an effect called erythema;
- leakage of large quantities of almost pure plasma out of the capillaries into the damaged areas because of increased capillary permeability, followed by clotting of the tissue fluid, thus causing a non-pitting type of edema;
- infiltration of the area by leukocytes; and
- after days or weeks, ingrowth of fibrous tissue that often helps in the healing process.

When large amounts of cortisol are secreted or injected into a person, the glucocorticoid has two basic anti-inflammatory effects:

1. it can block the early stages of the inflammation process before noticeable inflammation even begins
   - Cortisol has the following effects in preventing inflammation:
     - Cortisol stabilizes lysosomal membranes
     - Cortisol decreases permeability of the capillaries, probably as a secondary effect of the reduced release of proteolytic enzymes. This decrease in permeability prevents loss of plasma into the tissues.
     - Cortisol decreases both migration of white blood cells into the inflamed area and phagocytosis of the damaged cells.
     - Cortisol suppresses the immune system, causing lymphocyte reproduction to decrease markedly.
     - Cortisol attenuates fever mainly because it reduces release of interleukin-1 from white blood cells,
2. if inflammation has already begun, it causes rapid resolution of the inflammation and increased rapidity of healing. These effects are explained further in the following sections.

Perhaps this results from
- the mobilization of amino acids and use of these acids to repair the damaged tissues;
- the increased glucogen synthesis that makes extra glucose available in critical metabolic systems;
increased amounts of fatty acids available for cellular energy; or
some effect of cortisol for inactivating or removing inflammatory products.

Administration of large amounts of cortisol can usually block inflammation or even reverse many of its
effects once it has begun this is why it is beneficial in some conditions such as rheumatoid arthritis,
rheumatic fever, and acute glomerulonephritis. All these diseases are characterized by severe local
inflammation, and the harmful effects on the body are caused mainly by the inflammation and not by
other aspects of the disease.

When cortisol or other glucocorticoids are administered to patients with these diseases, almost
invariably the inflammation begins to subside within 24 hours. Even though the cortisol does not correct
the basic disease condition, preventing the damaging effects of the inflammatory response can often be
a lifesaving measure.

2. Effect on blood cells and on immunity in infectious diseases.
(i) Decreased the number of circulating eosinophils by increasing their sequestration in the spleen and lungs.
(ii) Lower the number of basophile in circulation and increase the number of neutrophils, platelets, and RBC.
(iii) Decreased the circulating lymphocytes count and the size of the lymph node and thymus by inhibiting
lymphocytes mitotic activity. The reduce secretion of the cytokine IL-2 leads to reduced proliferation of
lymphocytes, and these cells undergo apoptosis.

**Cortisol blocks the inflammatory response to allergic reactions.**
The basic allergic reaction between antigen and anti-body is not affected by cortisol, and even some of
the secondary effects of the allergic reaction still occur. Glucocorticoids are anti-allergic because they
protect against the release of secretion products of granulocytes, mast cells, and macrophages, which
have vesicles containing serotonin, histamine, and hydrolases that contribute to the inflammatory
response. Glucocorticoids inhibit cellular de-granulation, inhibit histamine synthesis, and stabilize the
lysosomal membranes.

3. Permissive action:
Small amount of cortisol must be present for a number of metabolic reactions to occur, although the cortisol
does not produce the reaction by themselves. This effect is called their (permissive action).
Permissive effects means requirement for cortisol to:
1. for glucagon and catecholamine to exert their calorigenic effects,
2. for catecholamine to exert their lipolytic effects
3. for catecholamine to produce presser response and broncho-dilation.

4. Delayed wound healing.
**Effects of cortisol insufficiency:**
- The vascular smooth muscle becomes unresponsive to nor-epinephrine and epinephrine so the
capillary dilated.
- EEG waves slower than normal
- Personality abnormality (irritability, apprehension, and inability to concentrate).
- an inability to excrete a water load, causing the possibility of water intoxication
- Glucose infusion may cause high fever (glucose fever).

**The cortisol control system:**
The key to this control is the excitation of the hypothalamus by different types of stress. Stress stimuli activate
the entire system to cause rapid release of cortisol, through release of CRF (Corticotropin releasing factor)
which by itself stimulate anterior hypothalamus to release ACTH (adreno-corticotrophin hormone). The ACTH will cause the release of cortisol from adrenal gland.

Cortisol has direct negative feedback effects on:
1. The hypothalamus to decrease the formation of CRF.
2. The anterior pituitary gland to decrease the formation of ACTH.

The factors affects the release of cortisol includes:

A. Stress:

**Stress**: any change in the environment that changes or threatens to change an existing optimal steady state.

Almost any type of stress, whether physical or neurogenic, causes an immediate and marked increase in ACTH and cortisol.

The different types of stress that increase cortisol release:
- Trauma, Infection, Intense heat or cold, Injection of norepinephrine and other sympathomimetic drugs,
- Surgery, Injection of necrotizing substances beneath the skin, Restraining an animal so it cannot move,
- Debilitating diseases, prolonged heavy exercise, decreased oxygen supply, sleep deprivation, pain, fright, and other emotional stresses.

The reason an elevated circulating ACTH, and hence glucocorticoid level, is essential for resisting stress remains for the most part unknown.

Most of the stressful stimulants:

A. ACTH secretion and steroid

The possible benefit of increase steroid in stress is glucocorticoids cause rapid mobilization of amino acids and fats from their cellular stores, making them immediately available both for energy and for synthesis of other compounds, including glucose, needed by the different tissues of the body.
B. activate the sympathetic nervous system
1. part of the function of circulating glucocorticoids may be maintenance of vascular reactivity to catecholamines.
2. Glucocorticoids are also necessary for the catecholamines to exert their full FFA-mobilizing action, and the FFAs are an important emergency energy supply

B. Emotion and Mental stress: This is believed to result from increased activity in the limbic system, especially in the region of the amygdala and hippocampus.

C. Circadian (diurnal) rhythm:
CRF, ACTH is secreted in irregular throughout the day and plasma cortisol tends to rise and fall in response to these bursts.

In human the burst are most frequent in the early morning, and about 75% of the daily production of cortisol occurs between 4 AM and 10 AM. The burst are least frequent in the evening. If the day is lengthened experimentally to more than 24 hours (i.e. if the individual is isolated and day’s activities are spread over more than 24 hours) the adrenal cycle also lengthened, but the increase in ACTH secretion still occurs during the period of sleep. The biological clock responsible for the diurnal ACTH rhythm is located in the suprachiasmatic nuclei of the hypothalamus.

Impulses ascending to the hypothalamus via the nociceptive pathways and the reticular formation trigger increased ACTH secretion in response to injury.

The baroreceptors exert an inhibitory input via the nucleus of the tractus solitarius.

Adrenal androgens:
Several moderately active male sex hormones called adrenal androgen are continually secreted by the adrenal cortex especially during fetal life.
Secretion of the adrenal androgens is controlled acutely by ACTH and not by gonadotropins

In Male:
Testosterone from the testes is the most active androgen and the adrenal androgens have less than 20% of its activity.
It is possible that part of the early development of the male sex organs results from childhood secretion of adrenal androgens also exert mild effects in the female, not before puberty but also throughout life. Androgens are the hormones that exert masculinizing effects and they promote protein anabolism and growth.
Some of the adrenal androgens are converted to testosterone, the major male sex hormone, in the extra-adrenal tissue, which probably accounts for much of their androgenic activity.

The secretion of adrenal androgens is nearly as great in castrated males and females as it is in normal males, so it is clear that these hormones exert very little masculinizing effect when secreted in normal amounts. However, they can produce appreciable masculinization when secreted in excessive amounts.

In adult males, excess adrenal androgens merely accentuate existing characteristics, but in Pre-pubertal boys they can cause precocious development of the secondary sex characteristics without testicular growth (precocious pseudopuberty).

In Female

Much of the growth of the pubic and axillary’s hair in the female results from the action of these hormones.

Excess adrenal androgens in females cause female pseudo-hermaphroditism and the Congenital adrenal hyperplasia, also called adrenogenital syndrome

Some health practitioners recommend injections of dehydroepiandrosterone to combat the effects of aging, but results to date are controversial at best.

Estrogen

Also, progesterone and estrogen, which are female sex hormones, are secreted from adrenal cortex in minute quantities.

The adrenal androgen androstenedione is converted to testosterone and to estrogens (aromatized) in fat and other peripheral tissues. This is an important source of estrogens in men and postmenopausal women

Pathophysiology of the adrenal cortex

a. Adreno-cortical insufficiency:

Primary adreno-cortical insufficiency (Addison's disease):

It is the most commonly caused by autoimmune destruction of adrenal cortex and causes acute adrenal crisis.

• is characterized by the following:
  (a) ↓adrenal glucocorticoid, androgen, and mineralocorticoid
  (b) ↑ ACTH (Low cortisol levels stimulate ACTH secretion by negative feedback.)
  (c) Hypoglycemia (caused by cortisol deficiency)
  (d) Weight loss, weakness, nausea, and vomiting
  (e) Hyperpigmentation (Low cortisol levels stimulate ACTH secretion; ACTH contains the MSH fragment.)
  (f) ↓ pubic and axillary hair in women (caused by the deficiency of adrenal androgens)
  (g) ECF volume contraction, hypotension, hyperkalemia, and metabolic acidosis (caused by aldosterone deficiency)

b. Adrenocortical excess-Cushing's syndrome

• is most commonly caused by the administration of pharmacologic doses of glucocorticoids.
  • is also caused by primary hyperplasia of the adrenal glands.
  • is called Cushing's disease when it is caused by overproduction of ACTH.
  • is characterized by the following:
(1) ↑ cortisol and androgen levels
(2) ↓ ACTH (if caused by primary adrenal hyperplasia or pharmacologic doses of glucocorticosteroids); increase ACTH (if caused by overproduction of ACTH)
(3) Hyperglycemia (caused by elevated cortisol levels)
(4) ↑ protein catabolism and muscle wasting
(5) Central obesity: Excess cortisol secretion, causes excess deposition of fat in the chest “a buffalo-like torso” and head “moon face” this obesity results from ① excess stimulation of food intake, ② fat being generated in some tissues of the body more rapidly than it is mobilized and oxidized
(6) Poor wound healing
(7) Virilization of women (caused by elevated levels of adrenal androgens)
(8) Hypertension (caused by elevated levels of cortisol and aldosterone)
(9) Osteoporosis (elevated cortisol levels causes increased bone resorption)
(10) Striae.
• Ketoconazole, an inhibitor of steroid hormone synthesis, can be used to treat Cushing's disease.