Suprarenal gland

The suprarenal gland is located at the upper pole of the kidney and consists of:

1. The suprarenal cortex which develops from the mesoderm.
2. The suprarenal medulla which develops from the neural crest.

Suprarenal cortex

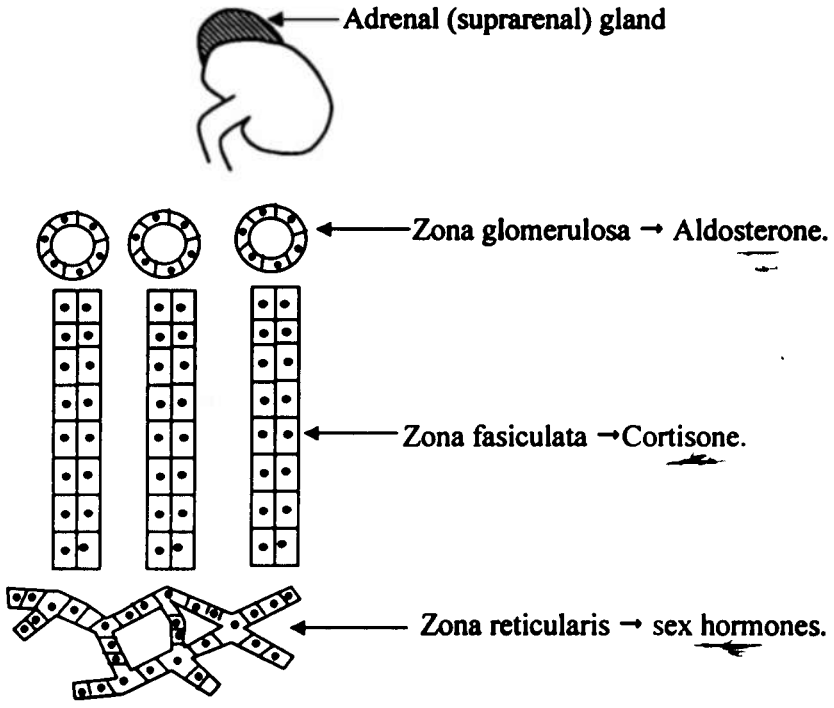
The adrenal cortex is divided into 3 zones:

1. **Zona glomerulosa:-** Cells are arranged in circular pattern. It secretes mineralocorticoids mainly aldosterone. They regulate Na^+, K+ and H_2O metabolism. They have weak glucocorticoids like activity.
2. **Zona fasiculata:** Cells are arranged in columns. It secretes glucocorticoids mainly cortisol. They regulate CHO, fat and protein metabolism. They have weak mineralocorticoids like activity. This zone is the widest of the 3 zones.
3. **Zona reticularis:** Cells are arranged in a network. It secretes sex hormones mainly androgens (dehydroepiandrosterone)(DHEA) and very small amount of estrogens.

Notes:-

1- The suprarenal gland is larger in female than in males.

2- Cortisol and aldosterone are essential for life.



Metabolism of adrenal steroids (corticosteroids):-

- The major organ for inactivation of adrenal steroids is the liver.

1) **Transformation to tetrahydrosteriod derivatives:-** Aldosteron and 90% of cortisone are reduced by liver enzymes to dihydrosteroid derivative, then to tetrahydroderivative which, in trun, is conjugated mainly with glucoronic acid.

- Cortisol is excreted as tetrahydrocortisol glucoronide.
- Aldosterone is excreted as tetrahydroaldosterone glucoronide.

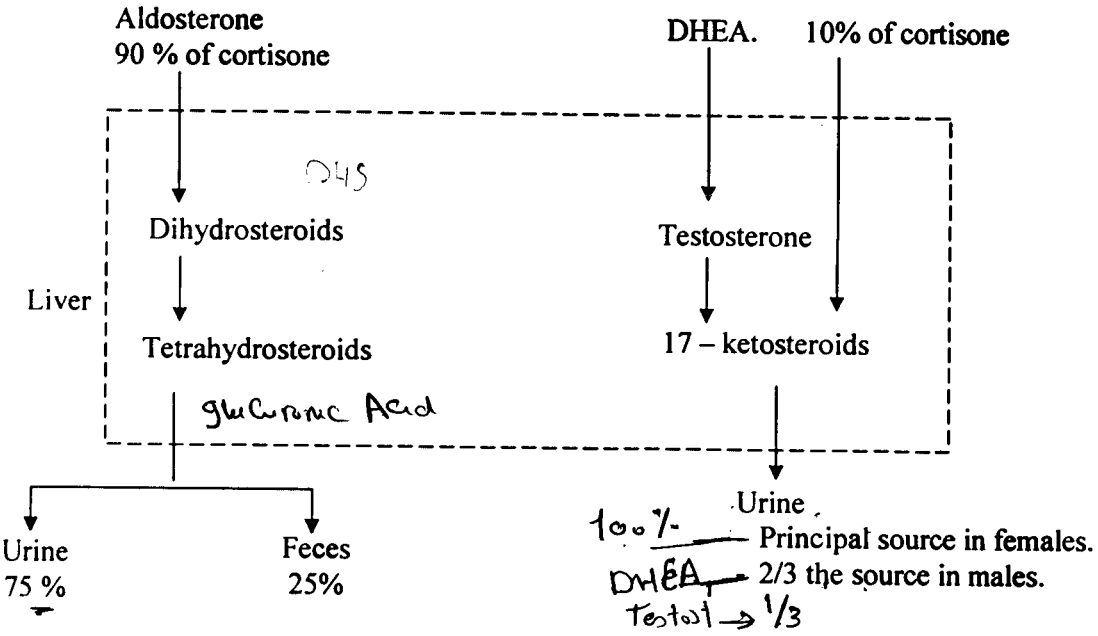
- Tetrahydroderivtives are excreted as follows:-

1- In urine 75%.
2- In faces 25%, they reach feces through bile.

2) **Transformation to 17 – ketosteroids:-**

- 10 % of secreted cortisol is excreted in urine as 17 keotsteroids.
- DHEA is metabolized to testosterone, then to 17- ketosteroid which is:-

1- The principle source of urinary 17 keotosteroids in females.
2- 2/3 of the urinary 17 keotsteroids in males. (the remaining 1/3 comes from metabolism of testosterone of the testes).



Transport of adrenal steroids:-

1- Glucocorticoids (Cortisone):-

A- Bound form:- **96%**

1- 90% are bound to **cotisol binding globulin (CBG)**, also called transcortin which is an alpha globulin.
2- 6% are bound to albumin.

B- Free form:- **4%** unbound (free in plasma), it is the active form.

2- Mineralocorticoids (aldosterone) :-

A- Bound form:- **60%**

Most of it is bound to albumin and small amount to transcortin.

B- Free form:- **40%**

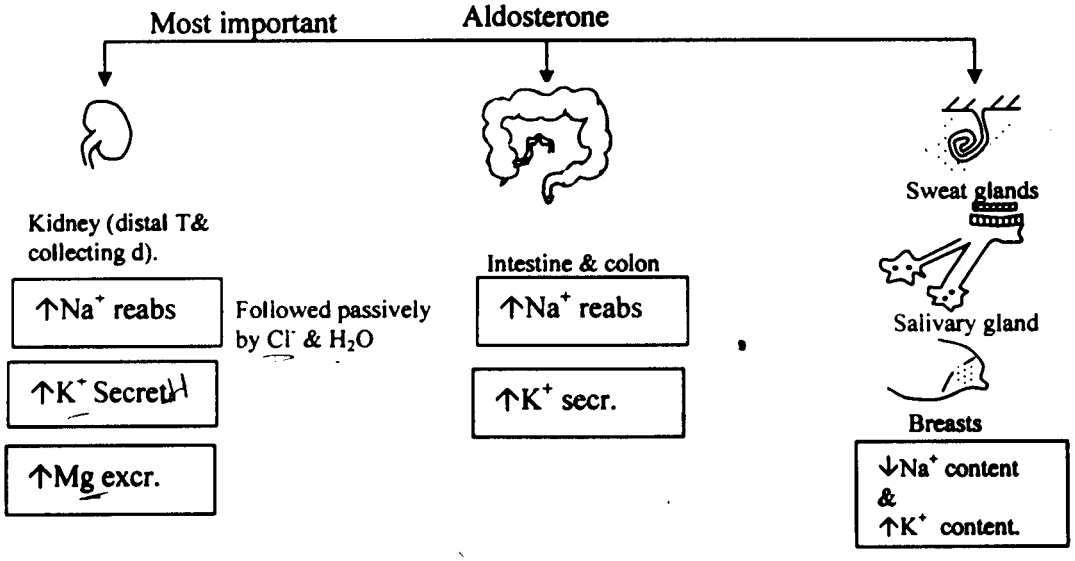
Because of high free form of aldosterone, it has a relatively short half life.

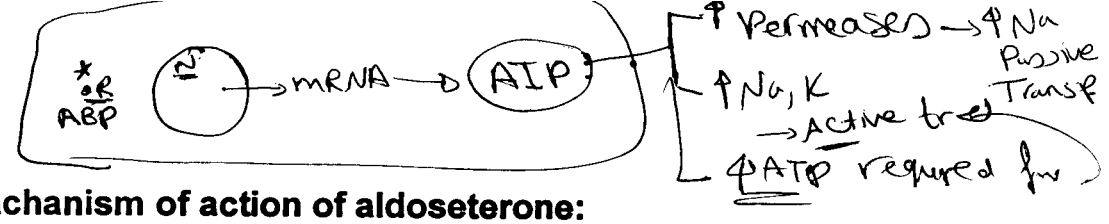
Mineralocorticoids (aldosterone)

Actions of mineralocorticoids:

1. **On kidney:** most important.
   a. Increases sodium reabsorption.
      - Aldosterone acts mainly on the distal and collecting tubules i.e., the distal half of the nephron.
      - The increased Na ion in the extracellular fluid in turn, causes increased water reabsorption. Thus, the exteraceelular fluid volume is increased.
   b. Increases potassium and H^+ secretion and excretion in two ways.
      1. Secondary to Na+ absorption the lumen becomes electronegative. K+ and H+ are attracted by the negative charges in the lumen.
      2. Direct stimulation of K^+ and H^+ secretion, independent on Na^+ reabsorption.
   c. Increases Mg excretion.
2. **On intestine and colon:** Aldosterone incrases Na reabsorption and K^+ secretion.
3. **Aldosterone decreases the Na^+ contents of:-** Sweat, saliva milk and other secretions and increases the K^+ content.

All these actions tends to elevate the Na^+ content and reduce K^+ content of the extracellular fluid and to promote water retention.





Machanism of action of aldoseterone:

- Aldosterone, being steroid, binds to a specific cytoplasmic receptor known as aldosterone binding protein (ABP) present in kidney and intestine.
- Aldosterone leads to the synthesis of Aldosterone induced protein (AIP), which increases Na transport in these ways.
  1. At luminal border:- AIP induces the formation of a permease, which increases the rate of passive entry of Na^+ into the cell.
  2. At basal border:- AIP increases the efficiency of Na^+ - K^+ pump.
  3. At mitochondria:- AIP increases the amount of ATP required for the Na^+ K^+ pump.

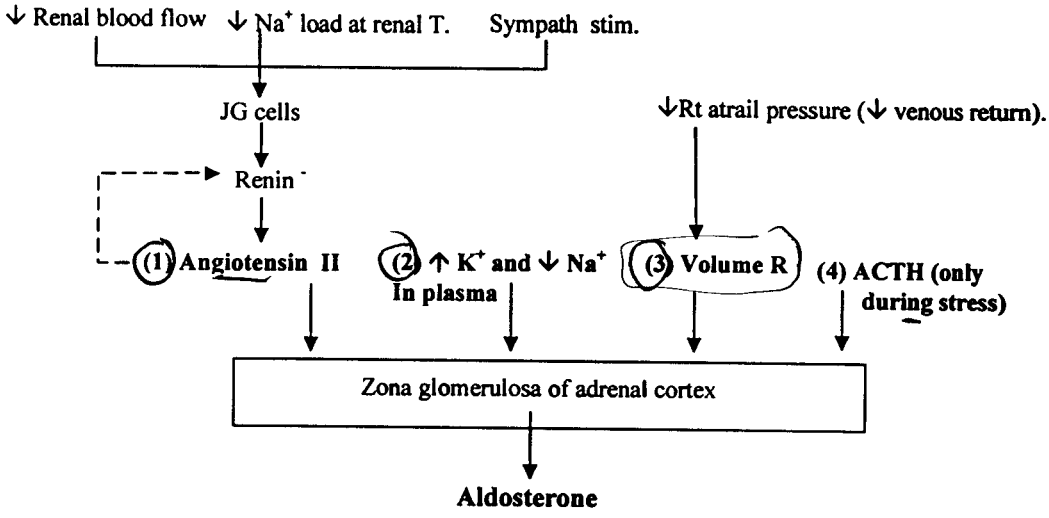
Regulation of mineralocorticoids (aldosterone) secretion:

1. **Renin angiotensin system:** — ve feed back —

renin → ↓ Angiogen ↓ AngI ↓ ACE ↓ AngII ↓ Aldosteron

- Angiotensin II stimulates aldosterone formation and secretion within minutes.
- Angiotensin II is formed as a result of renin production.
- Renin is released in the following conditions:
  a. Decreased blood flow to the kidney.
  b. Decreased sodium load to the renal tubules at the region of JG apparatus.
  c. Increased beta adrenergic activity (sympathetic stimulation).
- Angiotensin II has a direct inhibitory effect on renin secretion (short loop feed back).

2. **Role of changes in Na+ and K+ concentration:**
   Aldosterone secretion is stimulated by:
   - Increased K^+ ions concentration in plasma (more important).
   - Decreased Na^+ ions concentration in plasma.
3. **Role of volume receptors:** A drop in pressure in atria and large neck veins leads to stimulation of the secretion of both ADH & aldosterone.



4. **Role of ACTH:**
   - Only during stresses ACTH stimulates aldosterone secretion: i.e., ACTH does not effect the basal level of aldosterone.
   - However ACTH has permissive effect on aldosterone i.e. the function of zona glomerulosa depends on minimal amount of ACTH.

Glucocorticoids (cortisol)

Actions of glucocorticoids:

1. **Metabolic actions:-**
   a. **Protein metabolism:**
      1- In extraheptaic tissue:- **Catabolic**
      - Cortisol increases extraheptaic protein catabolism.
      - Cortisol inhibits amino acids uptake by extrahepatic tissue.
      - Cortisol inhibits extrahepatic protein synthesis.

      2- In liver:- **Anabolic**
      Cortisol increases amino acid transport into the liver cells, thus liver proteins and plasma proteins formed by the liver are increased.

   b. **CHO metabolism: Hyperglycemic** (diabetogenic)
      - Cortisol stimulates gluconeogenesis from the amino acids of broken proteins of extrahepatic tissues.
      - Cortisol inhibits glucose utilization by the cell (anti-insullin effect). Thus, excess cortisol elevates the blood glucose level leading to adrenal (steroid) diabetes.

   c. **Fat metabolism: Lipolytic.**
      - Cortisol causes lypolysis → increased fatty acids delivary to the liver leading to ketosis.
      - Excess cortisol promotes deposition of fat (lipogenesis) in abnormal sites as face → buffalo neck and trunk → buffalo hump.

[redacted]:

2. **Aldosterone like action** → salt and water retention.
3. **Anti inflammatory effects:**
   a. Stabilizes the membrane of the lysosomes, thus prevents action of their hydrolytic enzymes which cause damage to nearby cells .
   b. ↓ Capillary permeability.
   c. Inhibits diapedesis of leukocytes across the capillary wall and their migration through tissues.
   d. Inhibit lymphocytes specially T lymphocytes.
   e. Inhibits fibrous tissue (granuloma) formation.

4. **Anti- allergic effects:**
   a. Cortisol blocks the inflammatory response to allergic reaction, but it does not prevent allergic reaction (antigen antibody reaction).
   b. Cortisol may inhibit antibody formation.
5. **Anti – shock and anti- stress:**
   Gluccorticoids allow mammals to adapt to various stresses whether physical or mental as trauma, surgery, infection, debilitating diseases etc.
6. **Lymphoid tissue and blood cells(anti-immunity effect):**
   - Cortisol increases circulating RBCs, and platelets.
   - Cortisol decreases eosinophils and lymphocytes.
   - Cortisol decreases the size of lymph nodes, spleen and thymus (thymus involution).
7. **Inhibiton of growth (anti-growth effect):-** Cortisol inhibits growth and ↓ growth hormone secretion.
8. **On skin and connective tissue:-** ↓ collagen synthesis → thin skin and poor wound healing.
9. **On bone:-** Leads to osteoporosis due to:-
   a. ↓ Collagen synthesis.
   b. ↓ Ca^{2+} in bone by :-
      1. ↓Intestinal absorption of Ca^{2+} by antagonizing vitamin D.
      2. ↑Parathormone secretion.
10. **Permissive action on catecholamines:** Cortisol is essential for catecholamines to produce their actions.

Regulation of glucocorticoids secretion:

1) **Pituitary control:-** glucorticoids are regulated by ACTH of the anterior pituitary(ACTH:-
   a. Is a polypeptide.
   b. Is secreted by the basophil cells of ant. pituitary.
   c. Acts through cAMP.
   d. Maintains structures, size and vascularity of the adrenal cortex and stimulates secretion of adrenocortical hormones mainly glucocorticoids and sex hormones.

2) **Hypothalamic control:-**

Hypothalamus stimulate the release of glucocorticoids through release of corticotropin releasing hormone (CRH), which in turn stimulate synthesis and release of ACTH.

- CRH acts through cAMP.

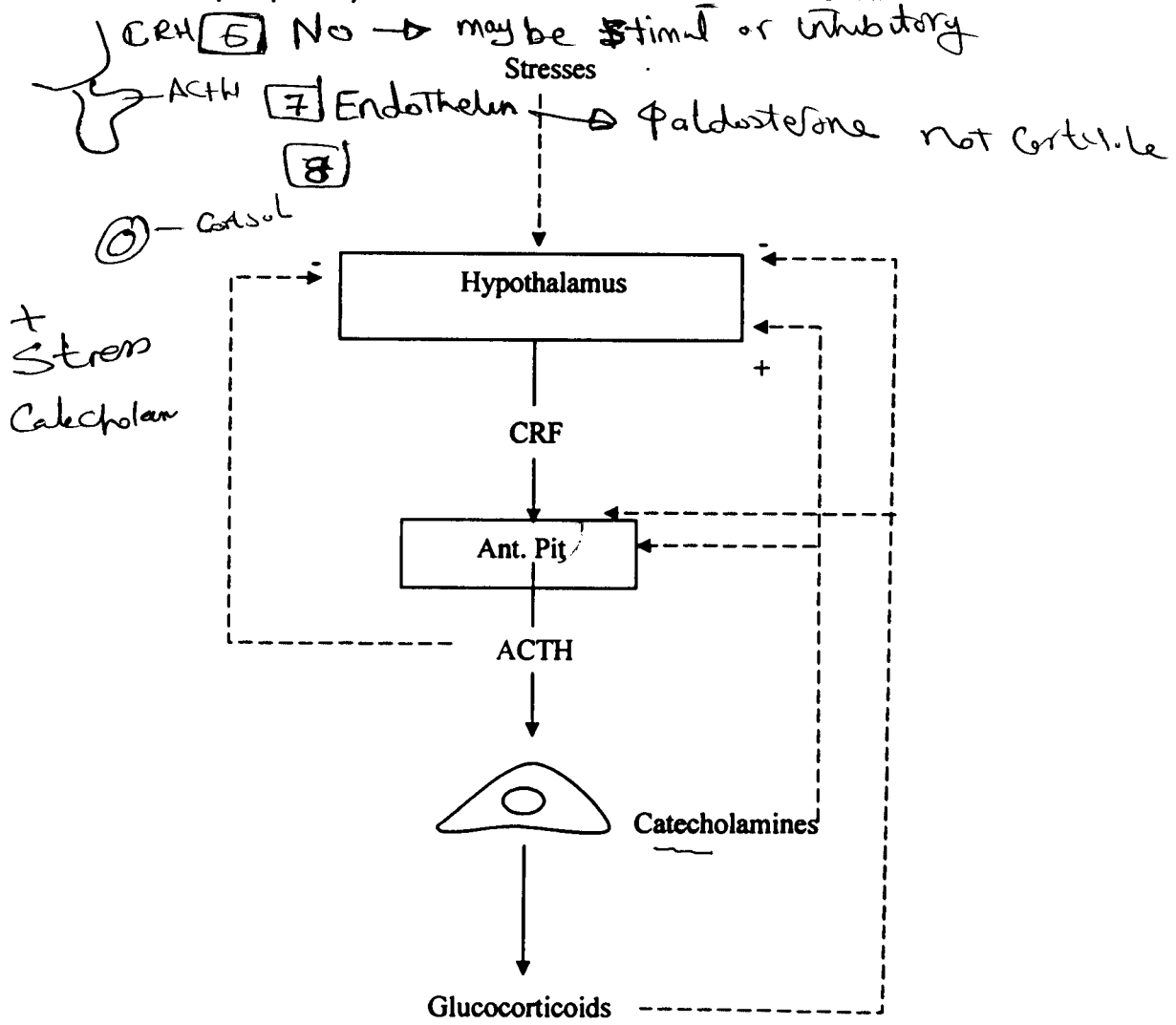
- CRH secretion has diurnal rhythm related to sleep i.e. circadian rhythm or biologic clock. The highest level occurs in the very early morning and the lowest level in near midnight.
- ACTH inhibits CRH release, through a short loop feed back.

3) Feed back control (negative feed back):-

- High level of glucorticoids inhibits both synthesis and release of ACTH.
- The level of this feed back is the hypothalamus mainly and pituitary gland also.

4) Role of stresses: During the time of stress (severe trauma, pyrogens, acute hypoglycemia, acute anxiety) very large quantities of CRH and ACTH are released.

5) Role of catecholamines: Adrenomedullary hormones (Epinephrine and norepinephrine) stimulate the release of CRH and ACTH.



Disturbance of function of adrenal cortex:

1- Hypofunction:- (Addison's disease).

2- Hyperfunciton:- 3 syndromes related to the three hormones.

a. Mineralocorticoids (aldosterone): Aldosteronism.

b. Glucocorticoids:- Cushing's disease.

c. Sex hormone:- Adrenogenital syndrome.

[redacted]

- Means hypofuntion of adrenal cortex.
- **Causes:-**
  1- Atrophy of adrenal cortex by autoimmune disease.
  2- Destruction of adrenal cortex by cancer or tuberculosis.
- **Manifestations:-**

1) Manifestation related to ↓ aldosterone:-

a. ↓ Plasma Na^+ (hyponatremia) and ↓ ECF volume (dehydration):- This is due to ↑ Na^+ and H_2O loss in urine (natriuresis and diuresis).

b. ↑ Plasma K^+ (hyperkalemia):- Due to ↓ K^+ secretion and excretion by the kidney.

c. ↑ Plasma H^+ (acidosis):- due to ↓ H^+ secretion and excretion by the kidney.

2) Manifestations related to ↓ glucocorticoids:-

a. Hypoglycemia.

b. Anemia.

c. Muscle weakness due to:-

1. ↓ energy sources (↓ plasma glucose amino acids and FFA).
2. Hyperkalemia.

d. Skin pigmentation:-

- It is more prominent in light exposed areas and pressure sites.
- It is due to ↑ plasma ACTH due to loss of feed back inhibition by glucocorticoids. ACTH has MSH like action.

3) Manifestation related to ↓ androgens: - Loss of body hair.

Note:- Addisonian crisis:- Means acute and severe attack in addisonian patients on exposure to stress. It is a life threatening condition and treated by:- 1. Large I.V. doses of glucocorticoids.
2. I.V. glucose.
3. I.V. saline for fluid replacement.

Aldosteronism: (Hypersecretion of aldosterone)

There are two types of aldosteronism primary and secondary.

1) Primary aldosteronism (Conn's disease):

- **Causes:** Adenoma or hyperplasia of zona glomerulosa leading to excessive aldosterone production.

- **Manifestations:-**
  1. **Hypokalaemia** due to excessive renal loss of K^+. It leads to:-
     a. Muscle weakness due to increased resting membrane potential.
     b. Hypokalaemic nephropathy (kidney damage) and polyuria.
     c. Impaired glucose tolerance.
  2. **Hypernatremia:** due to moderate Na^+ retension →↑ ECF volume and hypertension, however edema formation is limited due to release of atrial natriuretic peptide → natriuresis and diuresis (aldosterone escape phenomenon).
  3. **Alkalosis:-** Due to ↑ H^+ secretion by renal tubules. Alkalosis →↓ solubility product →↓ plasma Ca^{2+} and tetany.

2) Secondary aldosteronism:

- ↑ plasma level of aldosterone, that occur in various types of edema (heart failure, nephrotic syndrome, hepatic cirrhosis, toxemia of pregnancy).
- **Cause:-**
  1- Edema → renal ischemia and renin secretion →↑ aldosterone secretion.
  2- Liver disease →↓ inactivation of aldosterone →↑ aldosterone level in plasma.
- In this condition the aldosterone is not the primary cause of edema, however it potentiates the edema.

Cushing's syndrome (hypersecretion of glucocorticoids):-

- **Causes:-**
  1. Primary:- Due to adenoma of zona fasiculata.
  2. Secondary;- Due to ↑ ACTH secretion from anterior pituitary →↑ glucocorticoids and androgens.
- **Manifestations:-**

  1. **Metabolic effects:-**
     a. **Fat metabolism:-** Redistribution of body fat.
        - Mobilization of fat from its normal stores (lipolysis) as limbs → thin limbs and gluteal region.
        - Deposition of fat in abnormal sites (mainly the trunk → trunkal obesity) as.
          1. Face → moon face.
          2. Neck and supraclavicular region → buffalo neck.
          3. Upper back → buffalo hump.
     b. **Carbohydrate metabolism:-** Hyperglycemia (adrenal diabetes). If maintained → frank diabetes mellitus.
     c. **Protein metabolism:** - Catabolism →↓ protein content in:-

1. Skin → thin skin, poor wound healing and purplish striae (due to rupture of subcutaneous tissue → exposure of subcutaneous capillaries).
2. Muscles → muscles weakness.
3. Bones → osteoporosis → hypercalcemia and renal stones.

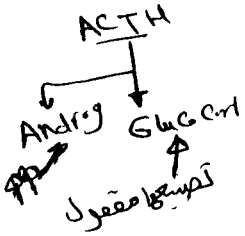
2. **Blood:-**
   a. ↑ RBCs count. Polycythemia
   b. ↓ lymphocytes →↓ immunity. Immune Suppression
3. **Mild mineralocorticoid like activity** → hypernatremia and hypokalemia.
4. **↑ androgen** → hirsutism.

Adrenogenital syndrome/:- It is due to ↑ adrenal androgens → development of musculine secondary sex characters. The manifestations depends on sex and age.

I- Adrenogenital syndrome in females/- Depends on age.

a. Before birth → pseudohermaphroditism:

Definition: A pseudohermaphrodite is an individual with the genetic constitution and gonads of one sex and the external genitalia of the other sex.



Cause: Congenital deficiency of the enzymes needed for glucocorticoid synthesis. In this condition , glucocorticoid secretion is deficient and ACTH secretion is consequently increased leading to formation of more androgens.

Mainfestations:

1. Labia majora are enlarged (like an open scrotum).
2. Labia minora are small and atrophic.
3. Clitoris is enlarged and bent (like penis).
4. vagina may not descend.
5. Uterus and ovaries are atrophic.
6. There may be some prostatic tissues.

Treatment:

1. Cortisol to suppress ACTH secretion.
2. Plastic surgery.

b. After birth: → Virilism virile = musculine = characteristic of man.

Causes: Adenoma or hyperplasia of zona reticularis leading to excessive secretion of androgen.

Manifestations:- :

(1) ↑ male characters

a. Hirsutism: increased face and body hair. Baldness occurs if there is genetic predisposition.
b. Enlargement of larynx and deeping of voice.
c. Increased muscle bulk.
d. Fat distribution like male (sharp angles).

(2) ↓ Female characters:-

a. Atrophy of genitalia and breasts.
b. Amenorrhea.
c. Enlarged clitoris.
d. Homosexuality.

(3) ↑17 ketosteroids in urine.

II- **Adrenogenital syndrome in male:** depend on age.

a. Children → precocious puberty.

- **Cause :** - Adenoma or hyperplasia of zona reticularis.
- **Manifestations:-**
  1- Increased muscularity and rapid somatic growth.
  2- Precocious development of male secondary sex characters as public and axillary hairs, deep voice, increased body hair etc.

b. Adults:- No obvious manifestations because it is obscured by virilizing effect of testosterone from testis.

Adrenal Medulla

- Adrenal medulla is a specialized sympathetic ganglion which is innervated by long preganglionic cholinergic fibres.
- There are two types of cells; epinephrine and norepinephrine secreting cells. The gland secretes 80 % epinephrine and 20% nor-epinephrine. However, the relative amounts depend on the type of stimuli for example,
  a. hypotension leads to increased secretion of norepinephrine.
  b. Hypoglycemia leads to increased secretion of epinephrine.

Synthesis of adrenomedullary hormones:

$$Phynylalanine \xrightarrow[Hydroxylase]{[phenylalanine]} Typo\sin e \xrightarrow[Hydroxylase]{Tyro\sin e.} DOPA(dihydroxyphenylalanin) \xrightarrow[Decarboxylase]{DOPA}$$

$$Dopa\min e \xrightarrow[Oxidase]{Dopa\min e} Noreadrenaline \xrightarrow[N.methyltransferase]{Methylation.by} Adrenaline$$

If the gland is denervated, the rate of resynthesis of epinephrine is decreased.

Metabolism of catecholamines:

1- Methylation (rapid): By catechol 0-methyl transferase (present in liver and kidney) to metanephrine and normetanephrine. These compounds are next conjugated to glucoronic acid and excreted in stool.

2- Oxidation (slow): By monoamine oxidase enzyme (MAO), (present in mitochondria) to 3,4 dihydroxy mandelic acid. This metabolic product is excreted in urine.

Secretion of catecholamines:

They are secreted mainly during stress as a part of generalized sympathetic stimulation (alarm response). They are secreted by:

1. Neuronal discharge: Pain, cold, drop of blood pressure (arterial baroreceptors), decrease blood volume (volume receptors) and emotional stress (rage and extreme anxiety).
2. changes in the chemical composition of the blood: hypoxia, insulin induced hypoglycemia.
3. Drugs: Parasympathomimetics as anticholine esterases and ganglionic stimulant (nicotine small doses).

Mechanism of secretion of catecholamines:

1. Acetylcholine released from preganglionic neurons depolarizes the adrenal cells; being a modified ganglion.
2. Calcium enter the cells of adrenal medulla.
3. Binding of secretory granules to cell membrane.
4. Release of catecholamines by exocytosis.

- Secretion is mediated through cAMP & requires ATP (energy).

Physiological effects of catecholamines:

I- On body systems:-

1) **Central nervous system:** Excitatory effects and sometimes euphoria. The stimulation of reticular activating system increases cortical alertness and awareness.

2) **Cardio vascular system:-**

a. on blood vessels:

1. Epinephrine constricts cutaneous & renal vessels. Epinephrine dilates skeletal and coronary vessels.
2. Norepinephrine produces generalized and more potent vasoconstriction.

b. On heart:

- Positive chronotropic effects: (increased heart rate).
- Positive inotropic effects: (increased force of contraction).

These two effects increase the cardiac output.

3) **Respiration:** A period of brief apnea (Adrenaline apnea) followed by stimulation of rate and depth of respiration.
4) **Smooth muscles:**
   - Relaxation of non sphincteric muscles of gastrointestinal tract, bronchioles and urinary tract.
   - Contraction of splenic capsule, sphincters of gastrointestinal tract, pilo erector muscles and dilator pupilae muscles.
   - Variable effect on uterus e.g., contraction of non pregnant uterus.

II- Metabolic Effects:

1. On skeletal muscles:
   a. Delayed onset of fatigue.
   b. Stimulate glycogenolysis → increased lactic acid dilatation of blood vessels.
2. On liver: Hepatic glycogenolysis → hyperglycemia and glucosuria.
3. On adipose tissue: Lipolysis → release of free fatty acids.
4. Calorigenic action: Increased oxygen consumption due to:
   - Metabolism of lactate mainly in liver.
   - Increased muscle tone.

Notes:

- Catecholamines act through cyclic AMP.
- Noradrenaline stimulates mainly alpha receptors→↑ ABP mainly.
- Adrenaline stimulates both alpha and beta receptors, but the beta activity predominates→ metabolic effects mainly.

Pheochromocytoma

- **Definition:-** Is a tumor of adrenal medulla that secretes large amount of adrenaline either continuously or in paroxysms.
- **Manifestations:-** Tachycardia and palpitation, hypertension, hyperglycaemia and increased BMR.
- **Diagnosis:-** depends on determination of urinary excretion of catecholamines over 300 microgram/ day. (normal value 20 – 100 ug/ day).