Lecture no.8

- **SYNTHESIS OF ADRENAL STEROIDS**
- Adrenal cortical hormones are steroids having the base structure of cyclopentano perhydrophenanthrine ring.
- All steroid hormones are synthesized from cholesterol. The cholesterol for steroid synthesis is mainly derived from circulating blood and is stored within steroid synthesizing cells in large quantities as lipid droplets or ester form. .
- Adrenal steroids are mostly C21 and C19 steroids.
- C19 steroids have androgenic activity andC21 are either mineralo or glucocorticoids.
- The difference between the mineralocorticoids (aldosterone) and glucocorticoids (cortisol) is that only the glucocorticoids have a hydroxyl group on C-17, the hydroxylation is done by **17 α -hydroxylase**, the enzyme present only in the cells of zona fasciculata but absent in zona glomerulosa.
- In zona glomerulosa, 11 hydroxylase and 17 hydroxylase are absent.
- 75% of glucocorticoid is carried in plasma in association with specific binding globulins, corticosteroid binding globulin (CBG) called *transcortin*, 20% in *albumin* and 5% in *free form*. 50% aldosterone is carried in *albumin*, 10% with *CBG* and the rest in *free-state*.
- Plasma half life of cortisol is about 60 to 90 min and aldosterone is 20 min.

GLUCOCORTICOIDS

Cortisol, corticosterone and cortisone are the naturally occurring adrenal cortical steroids.

cortisol

Glucocorticoids have primary effect on carbohydrate metabolism.

- **Hypoglycemia is a potent stimulus for cortisol release to maintain normal plasma glucose level during fasting**.
- **Cortisol is very potent and 95% of all glucocorticoid activity is provided by cortisol**.
- Corticosterone provides 4% of all glucocorticoid activity.
- Prednesolone, a synthetic corticosteroid is 4 times more powerful anti-inflammatory than cortisol. Dexamethasone, another synthetic corticoid is 30 times more powerful anti-inflammatory than cortisol.

Cortisol

1. Cortisol is a ***catabolic*** **and** ***diabetogenic*** **hormone**
2. Glucocorticoids have direct effect *on adipose tissue* where it increases therate of *lipolysis*, thus plasma free fatty acids.
3. It also potentiates the lipolytic actions of GH and epinephrine during fasting.
4. The corticoids redistribute body fat i.e. fat is lost from limbs and accumulated in head and trunk giving a pot belly appearance. In humans it gives a *moon face* appearance.
5. Protein catabolism is enhanced with an accompanying release of amino acids to support hepatic gluconeogenesis.
6. Increased urinary excretion of nitrogen and causes negative nitrogen balance that is accompanied by muscle wasting and reduced protein stores in the muscle .
13. Liver proteins and plasma proteins are increased contrary to protein depletion in other cells.

14. Cortisol decreases the synthesis of 1, 25 DHCC and blocks calcium absorption from GI tract, thus increases bone resorption and *decrease bone formation*.
15. Hyperactivity of cortisol depresses the development of cartilage and the formation of bone interrupting the growth.
16. Cortisol inhibits secretion of GH from the adenohypophysis.
17. Cortisol inhibits the synthesis of collagen and causes thinning of the skin and walls of capillaries.
18. The diurnal increase in cortisol level in early morning (6.00 to 8.00 A.M.) is essential for *normal arousal* and initiation of day time activities. An excess of cortisol interferes with sleep.
19. Glucocorticoids stimulates glomerular filtration rate and inhibit vasopressin activity at the level of distal tubule, thus play a role in *water diuresis* i.e., enhancement of water excretion.

Clinical effects of glucocorticoids

- *inhibition of inflammatory response(antiinflamatory effect)*.
- Cortisol causes *reduction in circulating lymphocytes*, eosinophils and basophils by causing lysis of these cells and also phagocytosis by WBCs but produces *neutrophilia*.
- Glucocorticoids *suppress immune response* by T lymphocytes and also *reduce the antibody production*.
- Glucocorticoids *inhibit the synthesis of inflammatory mediating compounds* such as prostaglandins, thromboxanes and leukotrienes that arise as a result of arachidonic acid metabolism of injured cells by stabilizing the lysosomal membrane.
- Cortisol inhibits the release of proteolytic enzymes and hyaluronidase from lysosome.

- Glucocorticoids are used to *inhibit allergic reaction* through its inhibitory action on the release of histamine from the granules of mast cells. Hence cortisol is useful in preventing death during allergy or anaphylaxis.
- Prolonged administration of cortisol inhibits proliferation of fibroblasts and synthesis and deposition of collagen fibrils and *prevents normal wound healing* after injury.
- Cortisol facilitates *in-utero* maturation of the GI tract, lung, CNS, retina and skin.
- It stimulates increased synthesis of surfactant and permits satisfactory breathing immediately after birth.
- In both males and females excess of glucocorticoids inhibit LH release, enhances the ability of the sex steroids to suppress gonadotropin secretions through negative feedback mechanism, thus delays the onset of puberty.
- Cortisol from the fetal adrenal cortex acts upon the placenta to reduce progesterone and increase estrogen secretion both of which promotes the synthesis and release of PGF2α and uterine contractions are stimulated to induce labor.

Regulationof Glucocorticoids

- Cortisol level rises in the early morning and declines in the afternoon and evening exhibiting a diurnal rhythm.
- A negative feedback system exists whereby glucocorticoids inhibit the release of CRH from the hypothalamus to decrease ACTH secretion by the pituitary. Cortisol has more potent negative feedback effect than corticosterone.
- Another factor that can modify the negative feed back control of glucocorticoids is stress, which stimulates the secretion of glucocorticoids to several folds.

- The adrenal cortical hormones are involved in the animal's adaptation to adverse stress known as ***general adaptation syndrome***.
- Failure of adrenal cortex to produce cortical hormones lead to a condition called ***Addison's disease*** in human beings, dogs, cats and horses.
- Clinical signs are anorexia,vomiting, dehydration, lethargy etc.

Hypersecretion of cortisol

Cushing's syndrome where fat is mobilized from lower part of the body and deposited in thoracic, abdominal regions and face (***moon face***).

- Other clinical signs include
- polyurea,
- polyphagia,
- skin pigmentation,
- poor wound healing and thin skin
- Bilateral alopecia.

MINERALOCORTICOIDS (C21)

- Aldosterone (*electrocortin*), and 11-deoxycorticosterone are naturally occurring mineralocorticoid of adrenal gland.
- Aldosterone is very potent and contributes 95% of all mineralocorticoid activity.
- 11-Deoxy corticosterone is $1/5^{th}$as active as aldosterone and secreted in very less amounts.
- Cortisol and cortisone have slight mineralocorticoid activity.

Physiological effects of mineralocorticoids.

- **Electrolyte balance**

- **blood pressure homeostasis**. It promotes *sodium retention* and *potassium and hydrogen ions secretions* at the level of the distal tubules of kidney.
- Aldosterone increases the sodium retention in the extra renal tissues like sweat glands, salivary glands and intestine.

Regulation of the Mineralocorticoids

- Aldosterone secretion is primarily regulated by (1) angiotensin-II and (2) K^+ concentration in the extracellular fluid
- Fall in systemic arterial blood pressure
- Decrease of Na ion concentration
- an increase in K^+
- Hypovolumia

  increases secretion of the *renin* from the juxtaglomerular cells of the kidney
- In the blood renin acts on angiotensinogen, (an alpha-2- globulin produced by the liver) and converts it to angiotensin-I.
- It is hydrolyzed by the enzyme angiotensin-converting enzyme (*ACE)* present in lungs and endothelial cells to ***angiotensin-II*** **which directly acts on adrenal cortex to release aldosterone**.
- Aldosterone promotes Na retention and K and H secretions in the distal tubules of kidney.

ADRENAL SEX HORMONES

- Zona reticularis produce mostly androgens (androstenedione, dehydroepiandrosterone) and minor amounts of glucocorticoids, progesterone and estrogen.
- About 10% of the circulating androgens in males and 50% in females come from adrenals.
- The sex steroids formation is controlled by ACTH.

ADRENAL MEDULLA

Chromaffin cells, neural ganglion cells

- The cells of the adrenal medulla that secrete the catecholamine hormones, are called chromaffin cells

Structure and regulation of hormone release

- The central, medullary region of the adrenal gland acts as an endocrine extension of the sympathetic nervous system.
- It contains cells (chromaffin cells) which lack axons but possess many of the other properties of postganglionic sympathetic neurones.
- Activation of sympathetic nerves leads to an increase in the circulating levels of the catecholamines, i.e. noradrenaline (norepinephrine) and adrenaline (epinephrine).

BIOSYNTHESIS OF CATECHOLAMINES

- **Synthesis of catecholamines begins with either of the amino acids *phenylalanine* or *tyrosine*.**
- **Biosynthetic pathway begins with the conversion of tyrosine to dihydroxy-phenylalanine (DOPA) by tyrosine hydroxylase (TH) which is the *rate-limiting enzyme*.**
- **The products of tyrosine metabolism including DOPA, dopamine, norepinephrine and epinephrine inhibit the activity of TH.**
- **DOPA is then converted to dopamine in the cytosol by the enzyme DOPA decarboxylase.**
- **Adrenaline and noradrenaline differ only in the terminal CH_3 group.**
- The conversion of dopamine to norepinephrine occurs within the chromaffin granules by a key enzyme dopamine- beta hydroxylase.

- Norepinephrine moves back into the cytosol where it is converted into epinephrine through the activity of phenylethanolamine-N-methyl- transferase (*PNMT*).
- Adrenal medulla is the primary source of epinephrine (also present in brain) and nor-epinephrine is secreted both by medulla and post ganglionic sympathetic neurons.
- Epinephrine secreting cells also secrete opioid peptides like met-enkephalins.
- About 50% of catecholamines are transported bound with albumin and 50% in free form.
- The catecholamines are degraded in many tissues but mainly in liver and kidney by the enzymes catechol-O-methyl transferase (*COMT*) and mono-amino oxidase (*MAO*).
- The plasma half life of catecholamines is about 2 min.

MECHANISM OF ACTION OF CATECHOLAMINES

- These hormones act in the same way as catecholamine neurotransmitters, i.e. they bind to α- and β-adrenoceptors on the target cell membrane.
- Noradrenaline (norepinephrine) is more effective than adrenaline (epinephrine) at α-receptors, while adrenaline (epinephrine) is the more potent agonist at β- receptors. Activation of these receptors modulates the intracellular concentrations of a variety of second messengers, e.g. levels of cAMP may rise or fall.
- The pattern of second messenger response actually observed varies from cell to cell and depends on the receptor subtype involved. These intracellular signals alter cell function, often through second messenger-dependent

kinases which phosphorylate important functional proteins and so alter their biochemical activities.

METABOLIC EFFECTS OF CATECHOLAMINES

- It is mediated mainly by β_2 -receptors.
- Epinephrine is ten times more potent than norepinephrine in the control of intermediary metabolism.
- The effects of epinephrine on glucose metabolism are similar to those of glucagon and opposite to insulin.
- Epinephrine *increases blood glucose* level (hyperglycemia) by promoting hepatic glycogenolysis by activating phosphorylase enzyme.
- Stimulation of α_1 -receptor favours gluconeogenesis.
- Glucocorticoids potentiate the effect of epinephrine on lipolysis.
- Both catecholamines produce *arterial vasoconstriction* through their a -receptor action.
- Epinephrine has high affinity for β_2 receptors and causes vasodilatation in heart and skeletal muscles and reduces peripheral resistance.
- Both epinephrine and norepinephrine interact with β_1 -receptors to increase both the *force of contraction* and *heart rate*.
- The action of epinephrine to *increase cardiac output* is a beneficial effect in situations as in *flight or fight*.
- Epinephrine increases systolic and decreases diastolic pressure, whereas norepinephrine increases both systolic and diastolic blood pressures.
- Epinephrine causes splenic contraction and increases RBC numbers in circulation.

- Epinephrine produces bronchodilatation by its action on b_2 receptor (norepinephrine has little effect) and increases both the *rate and depth of respiration*.
- Epinephrine, through its β-receptor activity, *relaxes the intestinal smooth muscles* and uterine muscles.
- It promotes erection of penis and ejaculation.
- Norepinephrine causes *contraction of uterine smooth muscles*.
- During cold catecholamines enhances the metabolic rate, non-shivering thermogenesis.
- Epinephrine constricts renal, splanchnic and cutaneous arterioles, but dilates the arterioles of the muscles to shunt the blood flow particularly to coronary and cerebral blood vessel.
- \By vasoconstriction conserve heat during exposure to cold.
- It also improves alveolar gaseous exchange by bronchial dilatation. Epinephrine favours Na^+ reabsorption by stimulating renin-angiotensin-aldosterone mechanism.