The acidophil cells secrete GH and PRL whereas the basophil cells secrete ACTH, TSH, FSH and LH/ICSH. Presently the pituitary cells are also named as follows :

1. Somatotrophs (secrete GH),
2. Mammotrophs (Secrete PRL),
3. Corticotrophs (secrete ACTH, β-LPH etc).
4. Thyrotrophs (secrete TSH),
5. Gonadotrophs (secrete FSH and LH/ICSH).

Posterior Pituitary

The posterior pituitary is an outgrowth of the hypothalamus. It contains the dilated ends of the axons of the hypothalamo-hypophyseal tract and is also called neurohypophysis (Fig. 9.6). The posterior pituitary releases two hormones : antidiuretic hormone (vasopressin) and oxytocin.

Intermediate lobe of Pituitary

This part of the pituitary is very much rudimentary in man (Fig. 9.6). It secretes different melanocyte stimulating hormones (MSH) : α-MSH, β-MSH and γ-MSH. It also secretes γ-lipotrophin and corticotrophin like intermediate lobe peptide (CLIP). The melanocyte stimulating hormones stimulate the melanocytes to synthesise melanin.

GROWTH HORMONE (GH)

Source

Growth hormone is secreted from the somatotrophs (acidophil cells) of the anterior pituitary gland.

Chemistry

It is a protein with 191 amino acids. It has structural and functional similarities with the placental somatotrophin.

Plasma level

Growth hormone concentration in plasma is about 3 ng/ml when estimated by RIA (radioimmunoassay). It should be below 5 ng/ml after intake of 100 gm of glucose.

Tibia test : It is an old method of estimation of GH by bioassay. Normally GH causes proliferation of epiphyseal cartilage. Using this fact, GH is estimated by injecting serum of the patient in hypophysectomised rat and then noting the width of the tibial epiphyseal cartilage in comparison to a control animal.

Functions

This hormone, in general, is responsible for growth of the body in hight as well as in weight, that is why it is called growth hormone. Its effect on different systems are as follows :

(1) **On skeletal system** : It helps in increasing length and girth of the bones by : (i) enlargement of cartilages, (ii) appearance of osteoblasts, (iii) increased deposition of Ca^{2+}, (iv) increasing thickness of epiphyseal plates through proliferation and maturation of the chondrocytes.

(2) **On protein metabolism** : It is anabolic in action; helps in amino acid uptake and increases protein synthesis and thus increases the lean body mass. This effect is like insulin but in many metabolic functions GH has anti-insulin effects.

(3) **On carbohydrate metabolism** : GH is hyperglycaemic and increases blood sugar level in fasting state, thus helps to fight substrate lack. Chronic action (due to persistent high level) of growth hormone is also hyperglycaemia. But in fed state (*i.e.*, after a meal, when there is plenty of substrate in the body) it helps in glucose uptake by the liver and muscle cells.

(4) **On lipid metabolism** : In fasting state of the body it causes lipolysis and increases FFA (free fatty acid) level of blood. But in fed state it prevents lipolysis.

(5) **On electrolyte metabolism** : It helps to increase all the electrolytes in the body, so that the same can be used for growth. GH helps in the absorption of Ca^{2+} from gut and reabsorption of different electrolytes in kidney.

(6) **On viscera** : It helps to increase in size as well as maintain normal structure of all the viscera including the heart, liver, kidney, etc. (probably brain is an exception).

(7) **On other endocrine glands** : GH is probably trophic to all endocrine glands. It acts on adrenal cortex with ACTH. It helps the androgens in increasing the sizes of the accessory sex organs.

(8) **On skeletal muscle** : Being anabolic it increases muscle mass of the body.

(9) **On milk production** : GH is trophic to the mammary glands and increases milk production.

(10) **On erythropoiesis** : It increases erythropoiesis.

Mechanism of Action

It binds to its receptor on the target cell membrane leading to activation of a tyrosine kinase and other events. All these lead to activation of various intracellular mechanisms leading to its function. Growth hormone acts by itself and also through production of somatomedins. GH on its own can increase blood sugar level, can cause lipolysis, protein synthesis, sodium retention, etc., and through production of somatomedins GH leads to cell division, glucose uptake, protein synthesis, general growth, etc.

SOMATOMEDINS

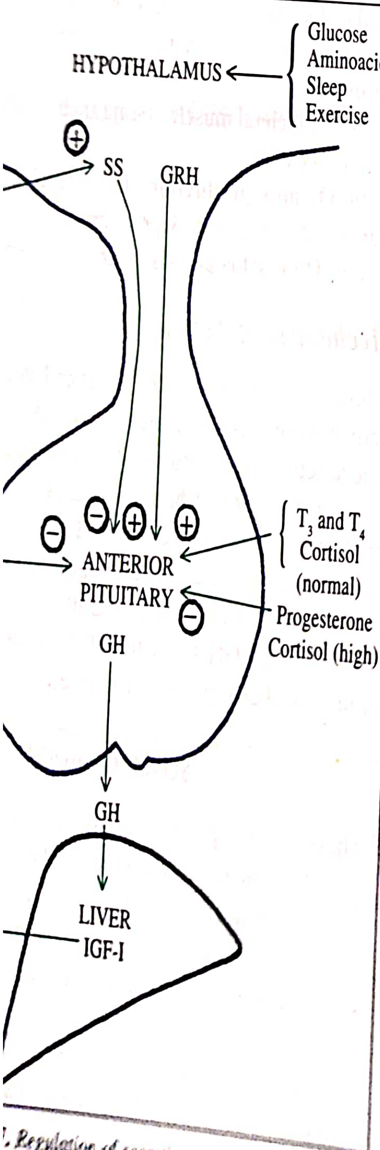
These are polypeptides produced due to the effects of growth hormone in various tissues. These are of two types : IGF-I and IGF-II (IGF = insulin like growth factor). IGF-I is produced in liver and in some other target tissues. IGF-I probably also circulates in blood to act in some other tissues (*e.g.*, pituitary).

IGF-II is probably responsible for growth and development in foetus. The interaction between GH and IFG-I may be as follows : GH acts on its target cell to bring some differentiation. These differentiated cells secrete IGF-I which then act locally as autocrine or paracrine agent to bring about proliferation and growth of the cells. Formation of somatomedins is decreased by cortisol, insulin lack, high levels of oestrogen, protein deficiency, etc.

...name of the somatomedins was sulphation ...they increase sulphate (chondroitin sulphate) ...in cartilages; other names like somatomedin A, ...in C were also used.
...somatomedins, many such growth factors are found ...e.g., NGF (nerve growth factor), EGF (epidermal ...or), etc.

...of Secretion

...one secretion is **increased** by :
...a polypeptide with 40 amino acids, is secreted ...alamus. It acts on the somatotrophs. GRH ...nder the feedback control of IGF-I (Fig. 9.7).
...acting on hypothalamus : (i) hypoglycaemia, ...some amino acids, and (iii) during sleep (stages
...acting on pituitary : (i) thyroid hormones, and ...vel of cortisol.
...also stimulates secretion of GH.



...Regulation of secretion of GH.

...secretion is **decreased** by :
...(SS), a polypeptide with 14 amino acids, ...ypothalamus. Secretion of SS is increased ...inhibits the somatotrophs. Somatostatin ...ine regulator in many places of the body, *e.g.*, islets of Langerhans, gastric mucosa, etc. SS is also found as neurotransmitter in brain.

(b) Agents acting on hypothalamus :
(i) hyperglycaemia, and
(ii) increased FFA level.

(c) Agents acting on pituitary :
(i) progesterone, and
(ii) high level of cortisol.

Applied Physiology

Abnormal secretion of GH leads to various abnormalities like :

(1) Dwarfism : Pituitary dwarfs are produced due to lack of growth hormone since infancy.

(2) Gigantism : Giants are produced due to increased secretion of GH before the union of epiphysis of long bones.

(3) Acromegaly : It is produced when GH secretion increases in adult life (after union of the epiphyses of long bones).

Dwarfism

Dwarfism means short stature (including height) (Fig. 9.8). If it results due to lack of growth hormone activity, then the condition is called **pituitary dwarfism.**

This may result from isolated growth hormone deficiency and also due to hypofunction of the pituitary as a whole (panhypopituitarism). These cases respond well to treatment by growth hormone.

Dwarfism may also occur in presence of the normal level of GH due to defect of GH receptors and then it is called Laron syndrome. These cases will not respond to treatment with growth hormone.

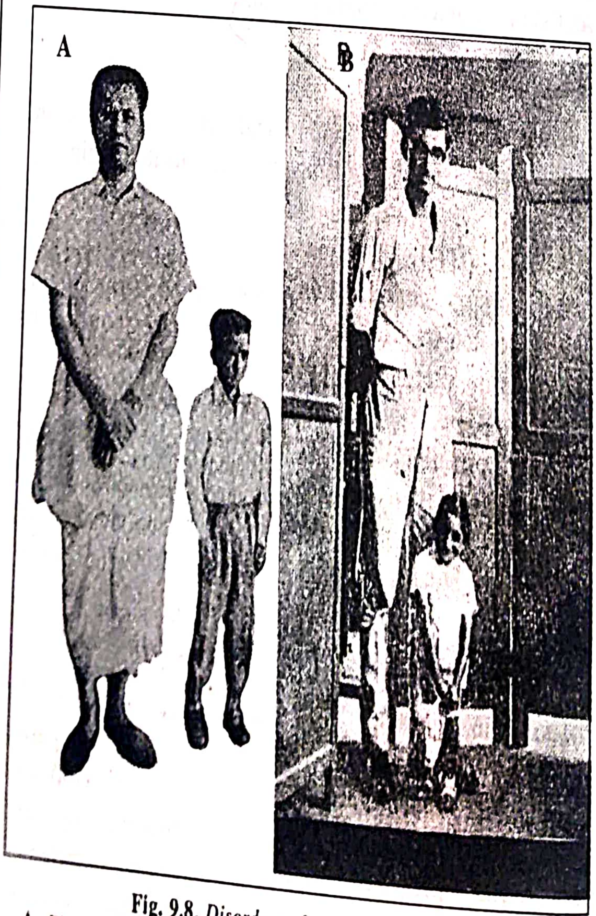


Fig. 9.8. *Disorders of anterior pituitary.*
A. *Pituitary dwarf, compared with a normal individual of same age.* (*Courtesy : Dr. S. N. Sahana, Dept. of Anatomy, National Med. College, Cal.*)
B. *Dwarf (12 years) compared with a normal boy of ...* (*Courtesy : Dr. S. M...*

African pigmies are short probably due to failure to increase IGF-I during puberty due to some postreceptor defect.

Dwarfism may also be produced due to other reasons :

(i) In hypothyroidism (cretin),

(ii) Precocious puberty (infantile Hercules)

(iii) Gonadal dysgenesis (Turner's Syndrome)

(iv) **Achondroplasia** : This condition results due to failure of the epiphyseal plates to grow due to genetic defect. The subject is short in height due to decreased length of the extremities but is otherwise normal including reproductive ability and intelligence. These dwarfs are frequently seen to act as clowns in circus.

(v) Constitutional dwarfs are of short height due to constitutional reasons but otherwise normal.

(vi) Renal dwarf results due to defect in the kidneys and drainage of nutrients.

Notes : 1. In pituitary dwarfism there is no thyroid deficiency but reproduction in them is not possible due to lack of sexual growth. This condition develops since childhood.

2. In Simmond's disease (pituitary deficiency), there may be associated hypothyroidism and the patient is adult.

3. In Seehan's syndrome (acute panhypopituitarism) : Diabetes insipidus is the hall mark. It results due to ischaemic necrosis of pituitary due to acute blood loss. *e.g.*, during childbirth (postpartum haemorrhage).

Gigantism

The person affected grows big like a giant (Fig. 9.9) and hence the name of this condition is gigantism. It results due to increased secretion of growth hormone before the union of the epiphyses of the long bones. The individual grows to a height of 7 to 8 ft. All the viscera are proportionally enlarged. The muscle mass also increases but later on the muscles become weak, hence the person is also called a weak giant.

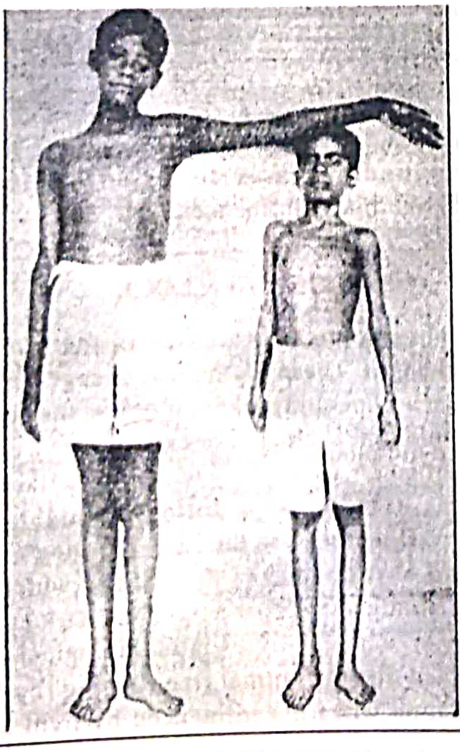


Fig. 9.9. *Gigantism (left) compared with a normal boy of same age (right). (Courtesy : Dr. Asoke Bagchi, Dept. of Neurosurgery, NRS Med. College, Cal.) after Human Physiology by Ghosh, Chakraborty and Sahana.*

They have a high level of FFA and also hyperglycaemia. Persistent hyperglycaemia leads to exhaustion of the β cells of the islets of Langerhans and results in diabetes mellitus (insulin receptors are also decreased by GH). This condition of increased GH secretion is associated with increased size of the pituitary, which leads to various pressure symptoms like headache, bitemporal hemianopia, etc.

> **HOUSSAY ANIMAL**
>
> In an animal, partial pancreatectomy leads to hyperglycaemia. This hyperglycaemia is corrected by hypophysectomy (*i.e.*, removal of pituitary). This type of animal with both pancreatectomy and hypophysectomy, which shows a comparatively low blood sugar level is called Houssay animal.

Acromegaly

This condition is produced due to increased GH secretion in adults when the epiphyses of the long bones have already fused. But as the epiphyses of the short bones are not yet united, the short bones grow excessively making the hands and feet large (like a gorrila), giving the name acromegaly (*i.e.*, growth of the acral or peripheral parts) (Fig. 9.10). Lower jaw becomes enlarged giving rise to the characteristic acromegalic facies (appearance of the face).

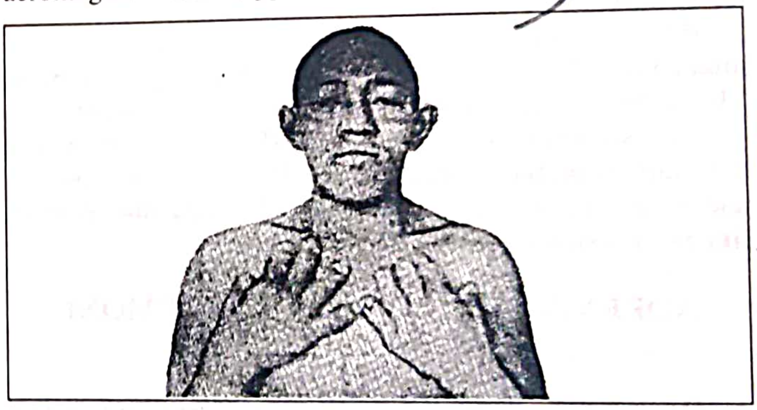


Fig. 9.10. *Acromegaly.*
(Courtesy : Dr. Asoke Bagchi, Dept. of Neurosurgery, NRS Med. College. Cal.) after 'Human Physiology' by Ghosh, Chakraborty and Sahana.

Other features of gigantism like diabetes mellitus, visual defects, etc., are also present but there is no increase in height.

PROLACTIN (PRL)

It is secreted from the mammotrophs of anterior pituitary and is a protein with 198 amino acids. It has similarity with human chorionic somatotrophin. Its secretion is pulsatile, *i.e.*, shows no fixed plasma level (2 to 15 ng/ml, females have higher values than males).

It helps in the development of the mammary glands. After childbirth, when oestrogen and progesterone levels become low, PRL helps in initiation and maintenance of lactation with the help of other hormones like insulin, thyroxine, cortisol, etc. It also helps in the synthesis of the milk proteins.

PRL inhibits synthesis and secretion of GnRH and leads to ammenorrhoea (no menstruation). As PRL secretion is high from the retina through the retinohypothalamic fibres via the suprachiasmatic nucleus. Melatonin (p. 323) secretion increases during the night and decreases in day time. It is suspected to be related to the cyclical changes inside the body.

Functions of ACTH

(1) It causes stimulation of the adrenal cortex and is also trophic to it (Trophic = which maintains health).

(2) It acts against stress.

(3) ACTH stimulates secretion of glucocorticoids mainly and also of adrenal androgens and mineralocorticoids.

(4) ACTH also stimulates the melanocytes in the skin, this is the cause of pigmentation in Addison's disease, where ACTH level is high.

(5) ACTH probably stimulates lipolysis.

STRESS

It is defined as the *sum of all nonspecific biological phenomena elicited by adverse external influence including damage and defence.* In stress, ultimately the existence of the organism is threatened. Stress may be due to substrate lack as in fasting. There may be emotional stress. Hypovolaemia, pain and trauma lead to stress reactions via reticular formation and hypothalamus. In stressful conditions the following changes are seen in the body :

4 CHAPTER

The Suprarenal glands

Suprarenal glands are two in number, situated on either side of the vertebral column on the top of each kidney. These are also called adrenal glands. Each gland has two parts forming two distinct endocrine glands : the central portion is called medulla and the outer portion is called cortex.

THE SUPRARENAL CORTEX

The cells in suprarenal cortex are arranged in three layers (Fig. 9.21A). From outside inwards these are :

(1) Zona glomerulosa,

(2) Zona fasciculata, and

(3) Zona reticularis.

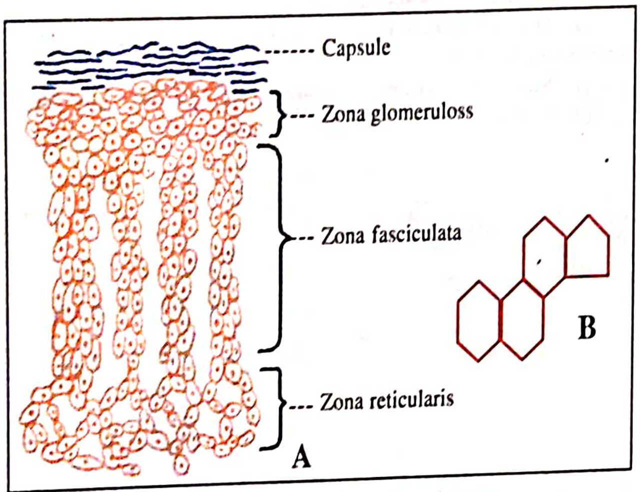


Fig. 9.21A. *Structure of suprarenal cortex.* **B.** *CPP ring.*

The hormones secreted by the suprarenal cortex are called corticoids or corticosteroids and are divided into three groups.

(1) **Glucocorticoids** (cortisol, corticosterone) are secreted mainly by the zona fasciculata and also from zona reticularis.

(2) **Mineralocorticoids** (aldosterone, 11-deoxycorticosterone) are secreted by the zona glomerulosa.

(3) **Sex steroids** (androstenedione, dehydroepiandrosterone) are secreted mainly by the zona reticularis.

Synthesis of Corticosteroids

The corticosteroids are steroid hormones. Other steroid hormones are oestrogens, progesterone, androgens, etc. All are lipid soluble and hydrophobic in nature. They have in common a CPP (cyclopentanoperhydrophenanthrene) ring (Fig. 9.21B). All these corticosteroids are synthesised from cholesterol. Different layers produce different groups of hormones due to their difference in enzyme content. For example, the zona glomerulosa has the enzyme 18-oxidase, which is necessary for synthesis of mineralocorticoids, but this enzyme is not present in other layers; on the other hand, the enzyme 17α-hydroxylase is not present here and this layer can not synthesise glucocorticoids.

For the synthesis of different corticosteroids the starting material is cholesterol which may be synthesised within the cells of suprarenal cortex from acetate or may be obtained from blood.

GLUCOCORTICOIDS

These are C_{21} steroids secreted mainly from the zona fasciculata and are synthesised from cholesterol.

Steps of Synthesis

Cortisol and corticosterone are the main glucocorticoids though many compounds (intermediates) are synthesised in this pathway in small amounts.

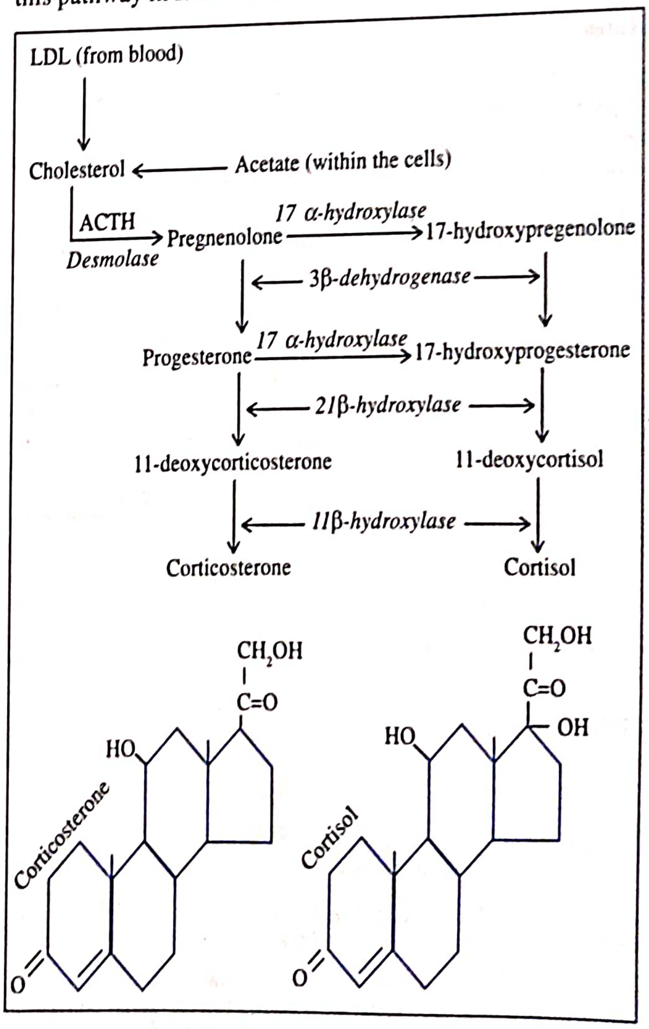
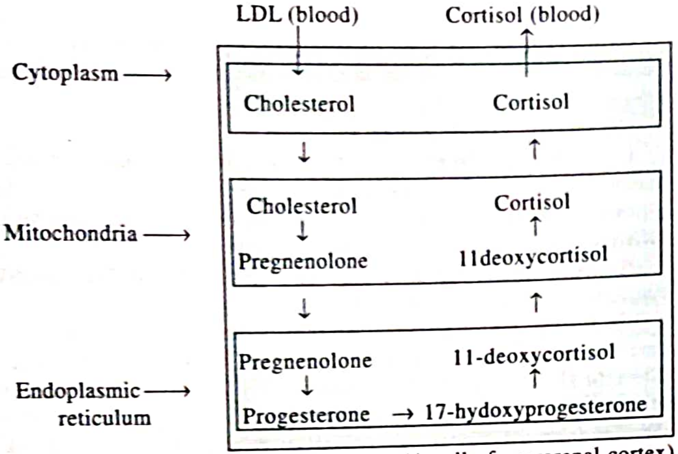


Fig. 9.22. *Synthesis of glucocorticoids.*

Synthesis of cortisol, which is the most important glucocorticoid, involves different parts of the cell as follows :



(A cell of suprarenal cortex)

Plasma level and Transport

Most of the hormones (90%) are combined with plasma proteins like CBG (corticosteroid binding globulin). The free form is responsible for the functions. If due to any reason (*e.g.*, oestrogen and thyroxine excess) CBG increases the total plasma hormone increases, but as the free form remains normal no abnormality in function can be detected. This type of situation normally occurs during pregnancy due to increased oestrogen.

Normal plasmal level (average values) :

Cortisol	—	13.5 μg/100ml
Corticosterone	—	0.6 μg/100 ml
ACTH	—	10 pg/ml.
Daily output of cortisol	—	10 to 25 mg.

Daily output of cortisol is more important than its plasma level which fluctuates throughout the day and night. There is highest plasma level in the early morning and a minimum level in the evening.

Degradation

Glucocorticoids are mostly metabolised in liver. The hormone meabolites are conjugated either with sulphate or with glucuronic acid and then excreted through urine. Some free hormones are also excreted through urine. The processes involved are :

(1) Cortisol ⟶ dihydrocortisol ⟶ Tetrahydrocortisol ⟶ Tetrahydrocortisol glucuronide.

(2) Cortisol ⟶ Cortisone ⟶ Cortisone sulphate ⟶ Tetrahydrocortisone glucuronide

(3) Cortisol and cortisone ⟶ 17 Ketosteroid ⟶ 17 Ketosteroid sulphate.

(4) Free hormone is also excreted through urine.

Mechanism of action of Glucocorticoids

Glucocorticoids, like all other steroid hormones, enter inside the target cells easily as these are lipid soluble. The hormones then bind to their cytoplasmic receptors. The hormone-receptor complex immediately goes to the nucleus and leads to gene expression. There is transcription and mRNAs are formed which ultimately lead to protein synthesis. These proteins then bring about the actions of the glucocorticoids.

Functions of Glucocorticoids

These were named as glucocorticoids, as in the past it was believed that they have major effects on glucose metabolism only. Glucocorticoids have actually widespread effects in different parts of the body affecting different physiological processes. As cortisol is the main hormone, in the following discussion glucocorticoids will actually mean cortisol.

(1) **Effects on Carbohydrate metabolism** : Glucocorticoids increase glycogen content of liver and skeletal muscle and increase neoglucogenesis by stimulating the production of the required enzymes. They increase absorption of glucose from the gut and also decrease peripheral utilisation of glucose. The net effect of the glucocorticoids on carbohydrate metabolism is hyperglycaemia (increased blood sugar level), hence, glucocorticoids are not given to the patients with diabetes mellitus.

(2) **Effects on Protein metabolism** : Glucocorticoids lead to protein breakdown and a negative nitrogen balance. But it should be remembered that the glucocorticoids act through protein synthesis.

(3) **Effects on Lipid metabolism** : They cause redistribution of fat (*i.e.*, lipolysis as well as deposition of lipids) in the body. Lipolysis is effected by inducing the hormone sensitive lipase. This effect is probably due to its permissive action on epinephrine and norepinephrine which are responsible for lipolysis.

(4) **Effects on Mineral metabolism** : Glucocorticoids increase body Na^+ store and deplete K^+ (*i.e.*, like the mineralocorticoids and this is called **overlapping action**). Glucocorticoids also lead to drainage of Ca^{2+} from the bones and depression of renal reabsorption of Ca^{2+} (**calciuric action**). Cortisol prevents absorption of Ca^{2+} in the gut.

(5) **Effects on Water excretion** : When there is deficiency of glucocorticoids, water retention occurs in the body. This extra water is eliminated after glucocorticoid administration. This effect is probably due to effects on renal circulation and thereby increasing GFR. This proves the role of these hormones in water balance.

(6) **Effects on Nervous system** : Personality change, irritability, apprehension, weakness, EEG changes, etc., which occur in glucocorticoid deficiency, are corrected by glucocorticoid therapy. Excess of these hormones lead to **euphoria** (a sense of well being).

(7) **Effects on CVS** : Glucocorticoids are positive inotropic *in vitro*. These hormones also increase the effects of catecholamines on heart (permissive action). Through the same permissive action, glucocorticoids help to increase smooth muscle tone and thus to maintain BP. This is further helped by their Na^+ retaining property and thereby increase of blood volume. Glucocorticoids also help to maintain normal permeability of the capillaries and are useful in treating cerebral oedema, angioneurotic oedema, etc.

(8) **Effects on Musculoskeletal system** : Normal level of glucocorticoids helps in bone formation, but an excess leads to bone destruction leading to osteoporosis. Their protein catabolic effect probably adds to the process by destruction of the protein part of the bone matrix. Glucocorticoids are responsible for muscle weakness and for steroid myopathy due to protein catabolic effects. But it is proved by different experiments that glucocorticoids definitely improve the performance of skeletal muscles, the mechanism of which is not properly established.

(9) **Effect on Blood** : Glucocorticoids decrease eosinophil and lymphocyte count but increase platelet, neutrophil and RBC count.

(10) **Effects on Immune system** : Glucocorticoids have profound effects on the immune system of the body. They decrease lymphocyte count and decrease the lymphatic tissues in the body. This is probably due to inhibition of interleukin formation and thus decreased proliferation of the lymphocytes. Glucocorticoids depress immunity as a whole and is used as immunosuppressive agent when needed (*e.g.*, in organ transplantation).

(11) **Anti-stress action** : Glucocorticoids are the main agents to fight stress. Secretion of glucocorticoids increases during stress through activation of hypothalamo-pituitary-adrenal axis (see p. 333).

(12) **Anti-inflammatory action** : Glucocorticoids are very much effective in prevention of inflammation (p. 43). This is probably due to inhibition of formation of the mediators of inflammation like thromboxanes, leukotriens, prostaglandins, etc. Along with this, these hormones also prevent breakdown of lysozyme. But as the glucocorticoids prevent inflammation, silent spread of infection occurs rapidly, so this action may prove costly. At the same time, a judicious use is of tremendous help in some cases of inflammation.

(13) **Wound healing** : Glucocorticoids prevent growth of fibroblasts and delay in wound healing.

(14) **Anti-allergic effect** : Glucocorticoids prevent liberation of histamine from the mast cells by antigen-antibody complexes and thereby prevent allergic manifestations. This property is utilised in the treatment of allergic diseases like eczema and also used in some cases of bronchial asthma.

(15) **Permissive action** : When simple presence of one hormone helps in the actions of another hormone, the first hormone is said to be permissive to the second. Glucocorticoids are permissive to epinephrine, which means that the presence of glucocorticoids helps in the action of epinephrine, which do not occur properly in the absence of glucocorticoids.

The actions of catecholamines to which the glucocorticoids are permissive are lipolysis, glycogenolysis, vascular response (vasoconstriction), bronchodilation, etc. These are also permissive to the hormone sensitive lipase, which leads to lipolysis.

Applied Physiology

Abnormalities in the functions of the suprarenal cortex lead to various diseases as follows :

(A) Those due to **increased glucocorticoid secretion**

(i) **Cushing s disease** is produced due to increased secretion of ACTH from the pituitary with consequent increase of glucocorticoid secretion from the cortex.

(ii) **Cushing s syndrome** is due to increased secretion from the adrenal cortex due to local cause, *e.g.*, hypertrophy of the gland.

Both the above conditions are also described as Cushing's syndrome (see below).

(iii) **Iatrogenic,** *i.e.*, due to administration of excess amount of glucocorticoids for long time for therapeutic purpose as in case of bronchial asthma.

(B) Those due to **decreased secretion**

(i). **Addison s Disease** : The original disease described by Thomas Addison was due to tuberculosis of the cortex with destruction of the cortex leading to deficiency of corticosteroids. At present, adrenocortical deficiency due to any reason is called Addison's disease.

(ii) Decreased secretion can also occur due to less ACTH from the pituitary as in **Seehan s syndrome** (p. 331).

(iii) **Iatrogenic** : If glucocorticoids are given to a patient for a long time and in high amount, then the adrenal cortices cease to function. When the glucocorticoid administration is stopped suddenly the patient develops an acute shortage of these hormones. This is because the steroid supplied from outside inhibits ACTH secretion by negative feedback and there is a minimum secretion from the cortex, *i.e.*, the cortex is depressed. When the supply from outside is stopped, secretion from the depressed suprarenal cortex becomes insufficient to meet the needs of the body and results in glucocorticoid deficiency. Hence, steroid therapy is always withdrawn gradually (tailing off).

Cushing's syndrome

It is due to glucocorticoid excess due to any reason and the causes are :

(i) Excess administration.

(ii) Excess secretion from adrenal cortex.

(iii) Excess ACTH leading to excess secretion.

(iv) Excess CRH secretion also increases glucocorticoid secretion.

Features

(i) Moon facies (the face become swollen and round). Sometimes there is prominent acne and facial hair growth in women (hirsutism).

(ii) Protein depletion leads to a very thin skin and subcutaneous tissue.

(iii) Increased blood sugar and FFA level.

(iv) There is truncal deposition of fat resulting in 'buffalo hump' due to excess deposition of fat in the back of the neck. The overall effect is truncal obesity.

(v) Retention of Na^+ and depletion of K^+.

(vi) Osteoporosis and myopathy.

(vii) Increased blood volume and blood pressure.

(viii) Lymphopenia and eosinopenia.

(ix) Prone to infections due to suppression of immunity.

(x) Delayed and defective wound healing.

(xi) Defects in the reproductive function.

(xii) There are mental changes like euphoria or even psychosis.

Addison's disease

It is due to corticosteroid deficiency and the causes are :

(i) **Acute** : Sudden withdrawal of glucocorticoid therapy. Acute stress in an undetected chronic case. Sudden damage of the gland.

(ii) **Chronic** : Addison's disease due to gradual damage of the cortex due to tuberculosis or other reasons. In this case as there is no feedback inhibition, ACTH level is usually high.

Features

These are due to corticosteroid deficiency as well as due to excess ACTH. These features are usually seen in the chronic disease. The acute cases, along with other features present with circulatory shock.

(i) Low blood sugar level, low muscle and liver glycogen, weakness (asthenia). There is increased sensitivity to insulin.

(ii) There is increased capillary permeability which leads to oedema. There is low BP and low GFR. There is also retention of waste products.

(iii) There is low BP due to loss fluid to the tissue spaces, decreased cardiac output, less responsiveness of the VSM to epinephrine and due to less blood volume caused by hyponatraemia owing to mineralocorticoid deficiency.

(iv) Muscle weakness is an important feature of glucocorticoid deficiency. It also occurs due to associated decrease in [Na^+] and increase in [K^+] owing to mineralocorticoid deficieney.

(v) Restlessness and lack of mental concentration.

(vi) There is anorexia (decreased appetite), constipation and intolerance to stress.

(vii) Increased ACTH leads to pigmentation of the skin and mucous membrane due to its melanocyte stimulating activity.

(viii) Features of mineralcorticoid and adrenal androgen deficiency are also seen (see below).

Addisonian crisis : It is the situation when there is increased requirement of glucocorticoids but the cortices cannot supply it. It typically occurs in the persons suffering from chronic deficiency of glucocorticods are subjected to any kind of stress. There is severe hypotension, shock and collapse. These cases are required to be supplied with large amount of glucocerticoids from outside to survive the crisis.

Adrenocortical function tests

(1) **Estimation of plasma cortisol** : It shows diurnal variation with a high level in the morning and less in the evening.

(2) **Metyrapone test** : Metyrapone, a compound, when given orally to a patient, causes inhibition of the enzyme 11β-hydroxylase and stoppage of cortisol synthesis. So cortisol level becomes low and ACTH level rises, but there should be a rise in the 11-deoxycortisol. Therefore, in this test if there is increased ACTH, decreased cortisol and increased 11-deoxycortisol, then it can be taken that both pituitary and suprarenal cortex are normal.

(3) **ACTH stimulation test** : ACTH is injected and normally there should be a rise in cortisol level.

Regulation of Glucocorticoid secretion

Though glucocorticoid secretion is primarily maintained through feedback regulation, there are various other factors affecting their secretion as follows :

(1) Hypothalamo → Pituitary → Adrenal cortex axis : (CRH → ACTH → Glucocorticoids).

This path is used mainly by the factors influencing the secretion of CRH, *e.g.*, circadian rhythm, stress, etc.

(2) Circadian rhythm : CRH pulses are highest in the early morning and lowest in the evening, there is a corresponding change in ACTH secretion. (Fig. 9.12) The glucocorticoid secretion is thus highest in the morning and lowest in the evening.

(3) Glucocorticoid feedback : It is a negative feedback. Plasma glucocorticoids act both at the level of hypothalamus and pituitary. This leads to inhibition of secretion of both CRH and ACTH when the plasma glucocorticoids are high. When glucocorticoid level is low, this inhibition is absent and glucocorticoid secretion automatically increases. This feedback is effected by the free glucocorticoids in plasma and not by the bound form or by the total amount.

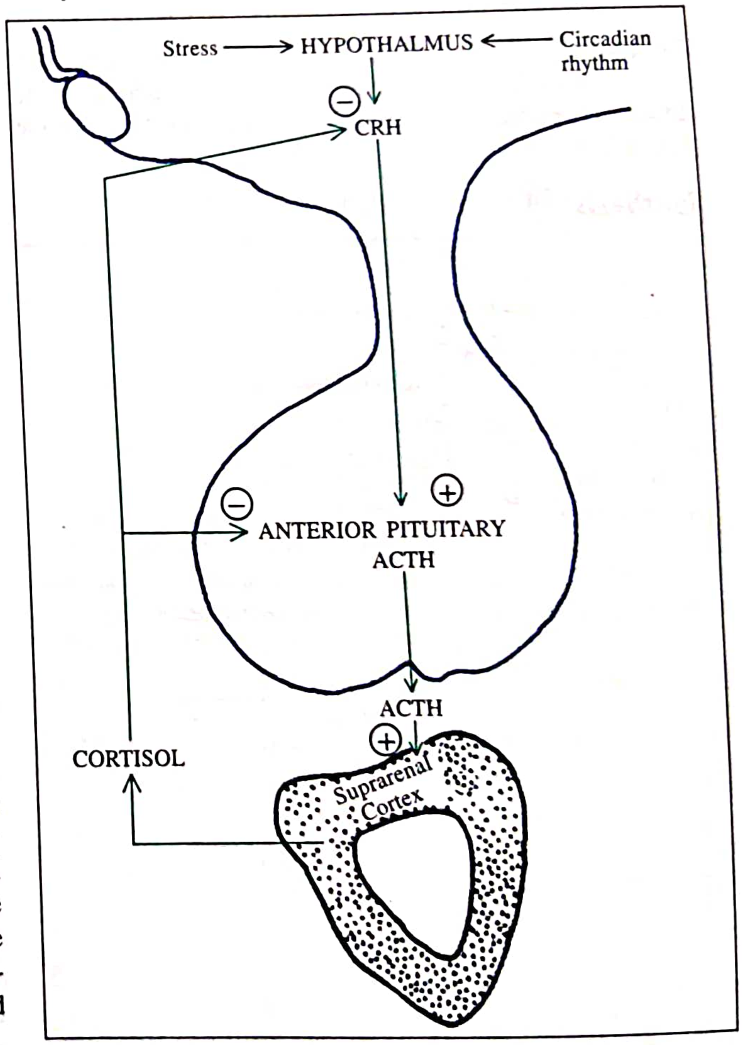


Fig. 9.23. *Regulation of secretion of cortisol.*

(4) Stress : It is a very important stimulus for glucocorticoid secretion (p. 333). This is mediated through hypothalamus and then via, CRH → ACTH → glucocorticoids. Secreted glucocorticoids help to fight stress by mobilising substrates (*e.g.*, by glycogenolysis), maintaining adequate circulation, etc. Stress induced stimulation overrides the feedback regulation and the circardian rhythm, so there is always a rise of secretion of glucocorticoids during stress.