REGULATION OF HORMONE SECRETION

Hormones secretion is strictly under control of several mechanisms.

a. **Neuroendocrinal Control Mechanism**

Nerve impulses control some endocrine secretion. Cholinergic sympathetic fibers stimulate cathecholamine secretion from adrenal medulla. Centres in the midbrain, brainstem, hippocampus, etc can send nerve impulses which react with the hypothalamus through cholinergic and bioaminergic neurons. At the terminations of these neurons they release acetylcholine and biogenic amines to regulate the secretions of hypophysiotropic peptide hormones from hypothalamic peptidergic neurons. Some of the endocrine releases are controlled by either stimulatory or inhibitory hormones from a controlling gland, e.g corticosteroids are controlled by coticotropins and thyroid hormonrs are controlled by thyroptropin from anterior pituitary. The tropins are further regulation by hypothalamic releasing hormones.

b. **Feedback Control Mechanism**

It is due mainly to negative feedback that such control is brought about. When there is a high blood level of a target gland hormone. It may inhibit the secretion of the tropic hormone stimulating that gland. Adrenal cortex secretes a hormone called cortisol which brings about the inhibition of secretion of corticotrophin from anterior pituitary and corticotropin releasing hormones from the hypothalamus by a long-loop feedback. This leads to reduction in cortisol secretion.

c. **Endocrine Rhythms**

There are certain cyclic rhythmic associated with the secretion of hormone over a period of time. When there is a cyclic periodicity of 24 hrs, it is called as circadian rhythm. However, if it is more than 24hrs, it is named as infradian rhythm and when it is less than 24 hrs it is called as ultradian rhythm. Due to rhythm the highest and lowest concentration of corticotrophin is normally found in the morning and around midnight. Growth hormone and prolactin rise in the early hours of deep sleep. Cortisol peak is found between 4am and 8am. Endocrine rhythms results from cyclic activities of a biological clock in the limbic system supplemented by the diurnal light-dark and sleep activity cycles and mediated by the hypothalamus.

Pituitary Hormones

Control of secretion

Secretion of hormones from anterior pituitary are controlled by

- Nervous mechanism: by release of regulatory factors from hypothalamus
- Hormonal mechanism by feedback inhibition

Hypothaciamic Releasing Factors

Control of hormone secretion from pituitary is in part modulated by regulating factors or hormone from the hypothalamus. The median eminence of hypothalamus is connected directly to the pituitary stalk. Within this stalk is a portal system of blood vessels required to maintain normal secretary activity of the pituitary gland. The activities of the cells of the anterior lobe are controlled by the nerve cells of the hypothalamus which send axons to the capillary beds. The nerve endings liberate chemical substances, hypothalamic releasing factors or hormones. At present 10 discrete regulatory factors have been described that may affect the synthesis as well as secretion of specific pituitary hormone. They are:

Hypothalamic Hormone or factor		**Abbreviation**
*	Corticotropin (ACTH) releasing hormone	CRH or CRF
*	Thyrotropin (TSH) releasing hormone	TRH or TRE
*	Follicle stimulating hormone (FSH)	FSH-RH or FSH-RF
*	Luteinizing hormone (LH) releasing hormone	LH-RH or LH-RF
*	Growth Hormone (GH)	GH-RH or GH-RF
	releasing hormone	GH-RF
*	Growth hormone release inhibiting	GH-RH or GIF
*	Prolaction (PL) release	PL-RIH or PL-RIF
*	Melanocyte stimulating hormones	mSH-RIH or
*	(MSH) release inhibiting hormone	MSH-RIF
*	Melanocyte stimulating hormone	MSH-RH or
*	(MSH) releasing hormone	MSH- RF

Hormones of the Anterior Pituitary

The hormones secreted by the anterior lobe of the pituitary gland are:

- Growth hormone and
- Pituitary tropic hormones such as protactin, gonadotropins (FSH and LH), thyrotropic hormones (TSH) and adrenocorticotropic hormones (ACTH)

Growth Hormone.(GH)

Growth Hormone (GH) or somatotropin (STH) was first isolated in sufficient quantity from cattle, now it has been prepared in crystalline form several species including man.

Chemistry

Growth hormone from all mammalian species consists of a single polypeptide with a molecular weight of about 21500. It consists of 191 amino acids. There are two disulfide bridges between the adjacent cysteine residue (52 and 165 and 183 189). Although there is a high degree of similarity in the amino acid sequences of human, bovine and porcine GH, only human GH or that of other primates is active in man. GH can bring about some of the actions of prolactin and human placental lactogen (HPL) due to amino acid homology.

Metabolic Role

Growth hormone has a variety of effects on different tissues. The hormones act slowly requiring from 1-2 hours to several days before it biological effects are detectable. This slow action and its stimulatory effects on RNA synthesis suggest that it is involved in protein synthesis. The hormone acts by binding to specific membrane receptors on its target cells. But its exact mechanism of action and second messenger are not yet known.

1. **Protein Synthesis**

Growth hormone brings about positive nitrogen balance by retaining nitrogen. It stimulates overall protein synthesis with an associated retention of phosphorus probably by increasing tubular reabsorption. Blood amino acid and urea level are decreased. It facilitates the entry of amino acids into the cell. In addition, growth hormone facilitates protein synthesis in muscle tissue by a mechanism independent of its ability to provide amino acids. This protein synthesis carries on even if the amino acid transport is blocked.

- Growth hormones increases DNA and RNA synthesis
- It increases the synthesis of collagen

2. **Lipid Metabolism**

Growth hormone brings about lipolysis in a mild way by mobilizing fatty acids from adipose tissue by activating the hormone sensitive triacylglycerol lipase. Thus it increases circulating fatty acids.

3. **Carbohydrate Metabolism**

Growth hormone is a diabetogenic hormone, antagonizes the effect of insulin. Hypersecretion of GH can result in hyperglycemia, poor sugar tolerance and glycosuria. Growth hormone produces.

- Hyperglycaemia by increasing gluconeogenesis
- It reduces insulin sensitivity and thereby decreases the hypoglycaemic effect of insulin
- It brings about glycostatic effect, i.e increases liver glycogen it can also increase muscle and cardiac glycogen level probably by reducing glycolysis.

4. **Effect on Growth of Bones and Cartilages**

Growth hormone when secreted in abnormally high concentration prolongs the growth of epiphyseal cartilages to cause over growth of long bones. Acromegaly is found in adults. Hyposecretion causes stunted stature due to premature cessation of growth of the epiphyseal cartilages and consequently of long bones.

- The effect of growth hormone partly depends upon its calcium anabolic action. It promotes the retention of calcium and phosphate which helps in ossification and osteogenesis.
- It enhances the incorporation and hydroxylation of proline in the matrix collagen, incorporation of amines into glycosaminoglycans of cartilage, incorporation of sulphate into matric proteoglycans like chondroitin sulphates, the synthesis of DNA and RNA in chondrocytes.
- The growth effects are mediated by a peptide called insulin-like growth factor I (IGF-I) or somatomedin – C)

5. **Prolactin Action**

Growth hormone has a sequence homology with prolactin. Growth hormone binds to membrane receptors for prolactin and stimulates the growth and enlargement of mammary gland.

6. **Ion or Minerial metabolism**

It is observed that the intestinal absorption of calcium is increased by GH, since the bone growth and development is stimulated by growth hormone. Growth hormone retains Na, Ca, K, Mg, and PO_4^{3-}

PITUITARY TROPIC HORMONES

In addition to GH, anterior pituitary gland secretes some tropic hormones usually called as pituitary tropins.

A tropin or tropic hormones is the one which influences the activities of other endocrine gland, principally those involved in stress and reproduction. These are carried by the blood to other target gland. The pituitary tropins are under the positive and negative control of peptide factors from hypothalamus. Further the tropic hormones are usually subject to feedback inhibition at the pituitary or hypothalamic level by hormone product of the final target gland. Prolactin (mammotropin), TSH (thyrotropin), FSH and LH (Gonadotropins), ACTH (Corticotropin) are the tropic hormones secreted by the pituitary gland.

A. Prolaction: PRL or Leuteotropic Hormone (LTH)

This is a monomeric simple protein (Mw23, 000). It contains 199 amino acids with three –s-s-linkages. It is secreted by lactotroph α-cells of anterior pituitary and has sequence homology with growth hormone.

Metabolic Role

- The main function of PRL is to stimulate mammary growth and the secretion of milk. By acting through specific glycoprotein receptors on plasma membrane of mammary gland cells, it stimulates mRNA synthesis. This ultimately leads to enlargement of breast (udder) during pregnancy. This is called mammotropic action.
- The synthesis of milk proteins such as lactalbumin, and casein takes place after parturition such an effect is called lactogenic action.
- Estrogen, thyroid hormones and glucocorticoids increases the number of prolactin receptors on the mammary cell membrane.
- Progesterone has the opposite effect.

B. **Thyrotrophic Hormone or Thyroid Stimulating Hormone (TSH)**

This is produced by basophil cells of anterior pituitary and is glycoprotein in nature. Its molecular weight is approximately 30,000. This consists of α and β submits.

- The α - subunit of TSH, LH and HCG and FSH are nearly identical
- The biological specificity of thyrotropin must therefore be in β -subunit. The α-subunit consist of 92 amino acids while β-subunit has 112 amino acids. Both α and β have several disulfide bridges. It carbohydrate content is 21% and it αand β chains bears two and one oligosaccharide chains linked by N-glycosidic linkages to specific asparagine residues. The chains are synthesized separately by separate structural genes and later undergo post-translation modification and glycosylation separately.

Metabolic Role

There are glycoprotein receptors on the thyroid cells membrane which binds to the receptor binding site on β-subunit of TSH. The complex then activates adenylate cyclase which catalyzes the formation of c-AMP which acts as the second messenger for most TSH actions an follows:

- TSH stimulates the synthesis of thyroid hormones at all stages such as Iodine uptake, organification and coupling.
- It enhances the release of stored thyroid hormones.
- It increases DNA content, RNA and translation of proteins, cell size.
- It stimulates glycolysis, TCA Cycle, HMP and phospholipids synthesis. Stimulation of last two does not involve c-AMP.
- It activates adipose tissue lipase to enhance the release of fatty acids (lipolysis)

C. ADRENOCORTICOTROPIC HORMONE (ACTH) OR CORTICOTROPIN: It is a single polypeptide containing 39 amino acids in its structure with a molecular weight of 4500 two forms have been isolated, α-corticotropin and β-corticotropin. Biological activity of ACTH resides in the first 23 amino acids from N-terminal end. The sequence of these 23 amino acids in the peptide chain is the same in all species tested. The remaining biologically inactive 16 amino acid residue varies accordingly to sources. ACTH is synthesized as a part of precursor peptide of mol.wt of 31500 with 260 amino acids. ACTH contains sequence of amino acids common for LPH, MSH and the endorphins. The precursor molecule is synthesized as a glycoprotein called pro-opiomelanocortin peptide (POMC). Various proteolytic enzymes hydrolyze POMC to give different peptides. Thus POMC is broken down into

- ACTH
- β-lipotropin (LPH). β-LPH is further cleaved into γ-LPH and endophins.

METABOLIC ROLE

The principal actions of corticotrophin are exerted on the adrenal cortex and extra adrenal tissue. ACTH increases the synthesis of corticosteroids by the adrenal cortex and also stimulates their release form the gland. Profound changes in the adrenal structure, chemical composition and enzymatic activity are observed as a response to ACTH. Total protein synthesis is found to be increased. Thus, ACTH produces both a tropic effect on steroid production and tropic effect an adrenal tissue. It is observed that ACTH has specific receptors on cells of fasciculata which increases c-AMP levels in the cell. This activation is calcium dependent. This result in DNA content aid RNA is transcribed. This leads to proliferation of fasciculata cells and growth of adrenal cortex.

- ACTH also stimulates the synthesis and secretion of glucocorticoids.
- ACTH is found to increase the transfer of cholesterol from plasma lipoproteins into the fasciculata cells.
- The ACTH induces rise in c-AMP, bring about phosphorylation and activation of cholesterol esterase. The enzyme action ultimately makes a large pool of free cholesterol.
- It activates the rate limiting enzyme for conversion of cholesterol to pregnenolone.
- It activates dehydrogenases of HMP to increase the concentration of NADPH required for hydroxylation.
- By activating adenylate cyclase of adipose tissue, it increases intracellular c-AMP which in turn activates hormone sensitive lipase. This enzyme is involved in lipolysis which increases the level of free fatty acids.
- It leads to increase ketogenesis.
- Direct effects on carbohydrate metabolism include :
- Lowering of blood glucose
- Increase in glucose tolerance
- Deposition of glycogen in adipose tissue is increased, regarded as due to stimulation of insulin secretion.
- It has MSH activity due to homology in amino acid sequence.

D. PITUITARY GONADOTROPINS

These tropic hormones influence the function and maturation of the testes and ovary, and are of two types.

- Follicle stimulating hormone (FSH)
- Luteinizing hormone (LH)

Both of them are glycoproteins with sialic acid, hexose and hexosamine as the carbohydrate moiety. Molecular weight of FSH is 25000 and that of LH is 40000. FSH, LH are dimers of α and β-chains linked non covalently. The α-chain is identical for TSH, FSH and LH of the same species. The β-chain of human FSH and LH has respectively 118 and 112 amino acid residues. Each chain has several disulfide bridges. A large precursor protein molecule for α and β chains is synthesized separately in gonadotroph β-cells.

METABOLIC ROLE OF FSH

It brings about it action by specific receptor binding and c-AMP

In females:

- It promotes follicular growth
- Prepares the Graafian follicle for the action of LH
- Enhances the release of estrogen induced by LH

In males:

- It stimulates seminal tubule and testicular growth
- Plays an important role in maturation of spermatozoa.

Role of FSH in Spermatogenosis

The conversion of primary spermatocytes into secondary spermatocytes in the seminiferous tubules is stimulated by FSH. In absence of FSH spermatogenesis cannot proceed. However, FSH by itself cannot cause complete formation of spermatozoa. For its completion testosterone is also required. Thus, FSH seems to initiate the proliferation process of spermatogenesis, and testosterone is apparently necessary for final maturation of spermatozoa. Since the testosterone is secreted under the influence of LH, both FSH and LH must be secreted for normal spermatogenesis.

Metabolic Role of LH

This hormone is also known as interstitial cells stimulating hormone (ICSH)

In females

- It causes the final maturation of Graafian follicle and stimulates ovulation
- Stimulates secretion of oestrogen by theca and granulosa cells.
- It helps in the formation and development of corpus luteum for luteinization of cells.
- In conjunction with luteotropic hormone (LTH) it is concerned with the production of estrogen and progesterone by the corpus luteum.

- In the ovary it can stimulate the non-germinal elements, which contain the interstitial cells to produce the androgens, androstenedione, dihydroepiandronstenedione (DHEA) and testosterone.

ACTION OF LH IN OVULATION (Ovulatory surge for LH): It is necessary for final follicular growth and ovulation. Without this hormone, even though large quantities of FSH are available the follicle will not progress to the stage of ovulation. LH acts synergistically with FSH to course rapid swelling of follicles shortly before ovulation. It is worth noting that especially large amount of LH called ovulatory surge is secreted by the pituitary during the day immediately preceding ovulation.

REGULATION OF TESTOSTERONE SECRETION BY LH: Testosterone is produced by the interstitial cells of leydig only when the testes are stimulated by LH from the pituitary gland, and the quantity of testosterone secreted varies approximately in proportion to the amount of LH available. Thus in males LH stimulate the development and functional activity of leydig cells (interstitial) and consequently testicular androgen.

ENDORPHINS AND ENCEPHALINS

Endorphins are a group of polypeptides which influence the transmission of nerve impulse. They are also known an opioides, because they bind to those receptors which bind opiates like morphine and play a role in pain perception. The opiodes first discovered were two penta-peptides in the brain and were named encephalin. They are of two types:

* Methionine - encephalin

* Leucine - encephalin

FORMATION OF ENDORPHINS

β – lipoprotein (β-LPH) is the precursor for endorphin, all the three type α, β and γ and also for β-MSH.

β- lipotprotein (β-LPH) is derived from the precursor molecule “Pro-opiomelanocortin peptide (POMC). It is a single chain polypeptide containing 93 amino acids.

γ-LPH containing 60 amino acids is a part of β-LPH

POMC ⟶ β-LPH

(93 a.a.) (β -lipoprotein)

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Endorphins β -MSH

(α, β, Y)

TYPES OF ENDORPHINS

There are three types of endorphinsα, β.y

- The sequence of 31 amino acids at the C-terminal of β-LPH, (Obtained from POMC) i.e amino acid 104 to 134 gives β endorphin
- α- endorphin (104 to 117 amino acid) containing 17 amino acids less than the β from the C terminal end.
- γ-endorphin (104 to 118) containing 16 amino acid less than the β from the C-terminal end.

FUNCTION

Endorphins bind to the same CNS receptors like the morphine opiates and they play a role in the endogenous control of pain perception. They have highs analgesic potency than morphine.