**COURSE TOPIC: MECHANISM OF HORMONE ACTIONS**

**COURSE: BCH 204**

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**HORMONES**

Hormones are chemical messengers secreted directly into circulation by endocrine (ductless) gland cells to act on another type of cells usually at a distance. OR

A hormone is a chemical messenger, secreted in trace amounts by one type of tissue and carried by the blood to a target tissue elsewhere in the body to stimulate a specific biochemical or physiological activity.

Hormones initiate biochemical reactions and control diverse metabolic processes resembling enzymes but they act in small amounts and are used up in the process. Enzymes are not used up in a reaction. Instead, they catalyze, so they can be used to speed up the same reaction over and over again.

They differ from enzymes because they are produced by an organ other than that which they ultimately perform their action.

They are secreted into the blood stream prior to use. Enzymes are not secreted into the blood stream.

Structurally, they are not always protein. The known hormones include proteins of MW ≤ 30,000 small polypeptides; single amino acids and steroids e. g insulin.

**FACTORS AFFECTING THE REGULATION OF HORMONE AT A TARGET ORGAN**

* Rate of synthesis and secretion of the stored hormone from the endocrine gland of origin.
* Specific transport system in the plasma in some cases.
* Conversion to a more active form.
* Hormone specific receptors in the target cell, cytosol or membranes which differ from tissue to tissue.
* Ultimate degradation of the hormone usually in the liver or kidney.

**MECHANISM OF ACTION OF HORMONES ON TARGET CELLS**

Based on mechanism of action, the hormones may be classified into two

* Hormones with cell surface receptors
* Hormones with intracellular receptors

**Hormones acting through cell surface receptors**

The hormones acting through cell surface receptors are further categorized as thus:

* Hormones acting through cyclic-AMP (cAMP)
* Hormones acting through calcium
* Hormones acting through PIP2 cascade
* Hormones acting through the Diacylglycerol (DAG) pathway

**Action of hormones acting through c-AMP**

Here, Adenylate cyclase converts ATP to c-AMP (31, 51 – cyclic AMP) and phosphodiesterase hydrolyses c-AMP to 51 AMP.

 Adenylate cyclase phosphodiesterase

ATP 31, 51-c-AMP 51- AMP

* Hormone (H) combines with the specific receptor (R) on the plasma membrane to form H-R complex.
* H-R complex then activates the regulatory component of the protein designated as G protein.
* G proteins are so named because they are bound to GTP.
* The G protein is a membrane protein consisting of alpha, beta and gamma subunits
* G protein then carries the excitation signal to adenylate cyclase. It should be noted that the hormone is not passed through the membrane; but only the signal is passed; hence this mechanism is called **signal transduction.**
* At first, the G protein is in an inactive form in the absence of the hormone. Once it senses the hormone, it then leads to the activation of G-protein. This is only possible when the alpha subunit of G protein dissociates from the beta and gamma subunit and then binds to the GTP directly as α- GTP.
* α-GTP then interacts with other intracellular signaling enzymes such as adenylate cyclase or phospholipase-C which generates second messenger (c-AMP).

**Action of hormones acting through calcium**

The intracellular concentration of calcium is much lower than the extracellular concentration. Hormones can increase the cytosolic calcium level by the following mechanisms:

* By altering the permeability of the membrane.
* The action of Ca-H+- ATPase pump which extrudes calcium in exchange for H+
* By releasing the intracellular calcium stores.
* When calcium binds to Calmodulin, it leads to a conformational change which has a role in regulating various kinases.

**Action of hormones acting through PIP2 Cascade**

* Intracellular messengers generated from phosphatidyl inositol di-phosphate (PIP2) which is a membrane phospholipid are inositol-triphosphate (IP3) and diacyl glycerol (DAG)
* Binding of hormones like serotonin to cell surface receptor triggers the activation of the enzyme, **phospholipase- C** which hydrolyses the phosphatidyl inositol di-phosphate (PIP2) to diacylglycerol (DAG) and inositol triphosphate (IP3).

**Action of hormones acting through Diacylglycerol (DAG)**

DAG, the messenger formed by the hydrolysis of PIP2 activates protein kinase C which in turn would phosphorylate other target proteins.

**HYPOTHALAMIC AND PITUITARY HORMONES**

The hypothalamus produces two types of endocrine factors:

* The hypothalamic neuropeptides
* The hypothalamic releasing factors

**The Hypothalamic Neuropeptides**

The hypothalamic neuropeptides are produced by supraoptic and paraventricular nuclei of the hypothalamus. These neurohormones are **Anti-diuretic hormone** and **Oxytocin.** They are synthesized in hypothalamus and transported to the posterior pituitary. They are thus called **posterior pituitary hormones**.

**ANTI-DIURETIC HORMONE (ADH)**

* It is also called vasopressin. If arginine is replaced by lysine, it is called lysine vasopressin.

Cys Tyr Phe Cys Tyr Ile

 S S

 S S

Cys Asn Gln Cys Asn Gln

Pro **Arg** Gly NH2 Pro Arg Gly NH2

 Structure of ADH. Structure of Oxytocin

Key: Cys-Cystein Tyr- Tyrosine Phe- Phenylalanine Asn- Asparagine Asn- Asparagine Gln-Glutamine Pro- Proline Arg- Arginine Gly- Glycine S- disulfide bonds.

* Its main action is to prevent dieresis. So, it reduces urine output.
* ADH acts on the distal convoluted tubules of the kidney, producing resorption or absorption of water
* The regulation of ADH secretion is through the osmolality of blood. Lowering of the osmolality (haemodilution) suppresses ADH secretion. Conversely, an increase in the osmolality (haemoconcentration or dehydration) leads to stimulation of ADH secretion.
* Deficiency of ADH results in diabetes inspidus. It is characterized by excretion of large volumes of dilute urine.
* Excess secretion of ADH often results from ectopic production of ADH by malignant tumours.

**OXYTOCIN**

* Oxytocin means to stimulate birth.
* Oxytocin acts on the oestrogen primed uterus.
* The synthetic derivative of oxytocin known as Pitocin, is used to induce labour.
* Oxytocin has an effect on the mammary glands where suckling generates a neurogenic reflex which stimulates the production of oxytocin expelling milk into milk ducts from the acini.

**Hypothalamic releasing factors are thyroxine releasing hormone (TRH), gonadotropin releasing hormone (GnRH), Growth hormone releasing hormone (GHRH), somatostatin and corticotropin releasing factors (CRF).**

**HORMONES OF ANTERIOR PITUITARY**

Anterior pituitary hormones are tropic in nature, stimulating the secretion of hormones from target organs. Secretions of all these hormones are under the control of hypothalamic releasing or inhibitory factors.

**GROWTH HORMONE (GH)**

* It is also called somatotropin.
* Plasma concentration of GH is less than 2ng/ml during day time with secretory peak appearing 3 hr after meals. Maximum level of GH is seen during sleep.
* Hypoglycaemia stimulates GH secretion and hyperglycaemia suppresses it.
* GH increases the uptake of amino acids by cells, enhances protein synthesis and produces positive nitrogen balance.
* The overall effect of GH is to stimulate growth of soft tissues, cartilage and bone. It is anabolic.
* Excess secretion by GH secreting tumour leads to **Gigantism in children** and **Acromegaly in** **adults**
* Deficiency of GH secretion in early childhood results in pituitary dwarfism. It is treated by giving GH produced by recombinant technology.

**ADRENOCORTICOTROPIC HORMONE (ACTH)**

* It is secreted as a large precursor molecule, known as pro-opio-melanocortin (POMC) with a molecular weight of 32 kD
* The secretion of POMC is under the control of CRF.
* ACTH is released from the pituitary in a pulsatile manner with a definite diurnal rhythm
* ADH secreting tumours of pituitary will cause Cushings disease.

**THYROID STIMULATING HORMONE (TSH)**

* TSH increases the secretion of thyroid hormones by stimulating all the steps of production of synthesis of thyroxine.
* It acts through c-AMP by binding with a receptor on thyroid cell surface.
* High levels of TSH may occur due to primary hypothyroidism and lack of feedback control.

**LEUTEINISING HORMONE (LH) and FOLLICLE STIMULATING HORMONE (FSH)**

* They are both regarded as gonadotropins from pituitary.
* The placenta also produces human chorionic gonadotropin (hCG)
* FSH stimulates growth of ovarian follicles in females and spermatogenesis in males.
* Testosterone in males (secreted by Leydig interstitial cells) and progesterone in females (secreted by corpus luteum) are increased under the influence of LH.
* Puberty does not set in until the pulsatile secretion of LHRH is started by hypothalamus.

**THYROID HORMONES**

* Daily requirement of iodine is 150-200 micro grams/day. Its sources are drinking water, fish, cereals, vegetables and iodinated salt.
* 80% of the total iodine in the body is stored in the thyroid gland.
* In most parts of the world, iodine is a scarce component of the soil. Upper regions of mountains generally contain less iodine. Such areas are called goitrogen belts e.g Himalayan region.
* The programme of iodination of common salt has resulted in increased availability of iodine.
* Ingredients in foodstuffs, which prevent utilization of iodine, are called goitrogens.
* Goitrogens are found in cassava, maize, millet, sweet potatoes and beans.
* Cabbage and tapioca contain thiocyanate which inhibits iodine uptake by thyroid.
* The only biological role of iodine is in the formation of thyroid hormones, thyroxin (T4) and tri iodothyronine (T3).

**METABOLIC EFFECTS OF THYROID HORMONE**

* Calorigenic effect or thermogenesis is the major effect of thyroid hormone.
* Basal metabolic rate (BMR) is increased and thyroxin increases cellular metabolism
* Effect of T4 is stimulation of RNA synthesis and consequent increase in protein synthesis.
* Higher concentration of T3 causes protein catabolism and negative nitrogen balance
* Loss of body weight is a prominent feature of hyperthyroidism.
* Fatty acid metabolism is increased
* Cholesterol degradation is increased and hence cholesterol level in blood is decreased, which is another hallmark of hyperthyroidism.

**ASSESSMENT OF THYROID FUNCTION**

* Measurement of T4 and T3 levels in blood by Radioimmunoassay (RIA) or by ELISA form the basis of laboratory diagnosis of thyroid diseases.
* In hyperthyroidism, thyroid hormone levels are increased while in hypothyroidism, T3 and T4 levels are reduced.
* In hypothyroidism, cholesterol level in blood is increased. It is not diagnostic because hyper-cholesterolaemia is seen not only in hypothyroidism but also in diabetes mellitus, hypertension, obstructive jaundice and nephrotic syndrome. However, cholesterol level is a useful index in monitoring the effectiveness of the therapy in thyroid conditions.
* Hyperthyroidism is also referred to as thyrotoxicosis. Here, patients have an increased rate of metabolism, weight loss, tachycardia, fine tremors, sweating, diarrhea, emotional disturbances, anxiety and sensitivity to heat.

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