

HORMONE OF MIDDLE LOBE OF PITUITARY

MELANOCYTE STIMULATING HORMONES

The hormones secreted by intermediate lobe or middle lobe of pituitary gland are called melanocyte stimulating hormones or MSH. POMC is the precursor molecule which is cleaved by proteases to give ACTH and β -lipotropin. The ACTH is further cleaved to β -MSH which has 13 amino acids. There is also α -MSH which is present in larger quantities. Amino acids 11-17 of β -MSH are common to both α -MSH and ACTH. MSH darkens the skin and is involved in skin pigmentation by deposition of melanin by melanocytes.

HORMONE OF POSTERIOR PITUITARY LOBE

The hormones have been isolated and characterized from extracts of posterior pituitary gland. They are

- Vasopressin (pitressin) or Arginine Vasopressin (ADH)
- Oxytocin

Both are small peptides containing nine amino acids. Oxytocin differs from vasopressin with respect to 3rd and 8th amino acid residues. Their biological activities depend on C-terminal glycnamide, the side chain amide group of glutamine and asparagine, the hydroxyphenyl group of tyrosine and the intra-chain –s-s-linkage between cysteine of 1st and 6th amino acid. Posterior pituitary hormones are synthesized in neuro-secretory neuron. They are stored in the pituitary in association with two proteins neurophysin I and II with molecular weight, of 19000 and 21000 respectively. The release of these two hormones is independent of each other.

METABOLIC ROLES OF VASOPRESSIN

1. Antidiuretic action: Antidiuretic effect is its main function. It reabsorbs water from the kidneys by distal tubules and collecting ducts. It is found to be mediated through formation of c-AMP. It is released due to rise in plasma osmolarity. This leads to formation of hypertonic urine having low volume, high specific gravity and high concentration of Na^+ , Cl^- , PO_4^{3-} and urea. Halothane, colchicine and vinblastine inhibit antidiuretic effect of vasopressin.

CLINICAL IMPORTANCE

- Condition of *Diabetes insipidus* is described due to failure in secretion or action of vasopressin. It is characterised by very high volumes of urine output up to 20-30 litre per day with a low specific gravity and excessive thirst.
- In primary, central or neurohypophyseal diabetes insipidus, vasopressin secretion is poor.
- In nephrogenic diabetes insipidus, kidney cannot respond to vasopressin due to renal damage. The damage is common in psychiatric patients on lithium therapy.
- Inappropriate vasopressin secretion is characterized by persistently hypertonic urine, progressive renal loss of Na^+ with low plasma levels of Na^+ , symptoms of water intoxication like drowsiness, irritability, nausea, vomiting, convulsions, stupor and coma. It could be due to pulmonary infection and ectopic ADH secretion from lung tumor.
- Urea-retention effect: permeability of medullary collecting ducts to urea is increased by vasopressin. This leads to retention of urea and subsequently contributes to hypertonicity of the medullary interstitium. Urea retention effect can be reversed by phloretin.
- Pressor Effect: It stimulates the contraction of smooth muscles and this causes vasoconstriction by increasing cytosolic Ca^{2+} concentration.
- Glycogenolytic effect: By increasing intracellular calcium concentration.

METABOLIC ROLES OF OXYTOCIN

- Contraction of smooth muscle is the primary function of oxytocin. There are basically two effects, one on mammary glands called galactobolic effect and the other on uterus called as uterine effect.
- 1. **Galactobolic Effect:** This is released due to neuroendocrinal reflex such as sucking of nipples. By doing so it causes that contraction of myo-epithelial cells around mammary alveoli and ducts and the smooth muscle surrounding the mammary milk sinuses. Estrogen increases the number of oxytocin receptors during pregnancy while progesterone decreases the same and also inhibits the secretion of oxytocin.
- 2. **Uterine effects:** It is found to be elevated at full term pregnancy. It causes contraction of uterine muscle for childbirth. Estrogen enhances while progesterone decreases oxytocin receptors as well as its secretion. Oxytocin is also secreted during coitus by the female uterus which promotes the aspiration of semen into the uterus. This is also augmented by rise in estrogen in the follicular phases of menstrual cycle.

THYROID GLAND AND ITS HORMONES

Hormones produced by Thyroid gland

- Follicular cells: produces T4, T3 and reverse T3
- Parafollicular C-cells: produces calcitonin (hence also called thyrocalcitonin)

- **THYROID HORMONES**

- The principal hormones secreted by the follicular cells of thyroid are
- Thyroxine (T4)
- Tri-iodothyronine (T3)
- Reverse T3

CHEMISTRY OF THYROID HORMONE

- The hormones T4, T3 and reverse T3 are iodinated amino acid tyrosine. The iodine in thyroxine accounts for 80% of the organically bound iodine in thyroid venous blood. Small amounts of “reverse” tri-iodothyronine, monoiodotyrosine (MIT) and other compound are also liberated.

BIOSYNTHESIS OF THYROID HORMONE

- Two raw materials (substrates) required by thyroid gland to synthesize the thyroid hormone are:
- Thyroglobulin
- Iodine
- Thyroglobulin: Thyroid hormone are synthesized by the iodination of tyrosine residue of a large protein called thyroglobulin

CHEMISTRY OF THYROGLOBULIN

- Thyroglobulin is a dimeric of glycoprotein, 19s in type (a macroglobulin) with a molecular weight of 660,000
- The receptor tyrosine molecules are present in this macroglobulin protein, each molecule containing 115 tyrosine residues.
- Carbohydrates accounts for 8 to 10% of the weight of thyroglobulin and iodide for about 0.2 to 1.0% depending on the iodine content of the diet. The carbohydrates are N-acetyl glucosamine, mannose, glucose, galactose, fucose and sialic acid.
- About 70% of the iodide in thyroglobulin exists as inactive precursors monoiodotyrosine (MIT) and di-iodotyrosine (DIT) while 30% is in the iodothyronyl residues T4 and T3.

- When iodine supplies is sufficient, T4; T3 ratio is about 7:1. In iodine deficiency, the ratio decreases, including MIT/DIT ratio. T3 and T4 after being synthesized remains in the bound form until it is secreted. When they are secreted the peptide bonds are hydrolyzed and free T3 and T4 enter the thyroid cells, cross them and are discharged into the capillaries

THYROID ACINAR CELLS HAVE THREE FUNCTIONS

- They synthesize thyroglobulin and store as colloid in follicles
- They collect and transport iodine for synthesis of the hormones in the colloid
- They remove T3 and T4 from thyroglobulin secreting the hormones into the circulation.

TRANSPORT

Within the plasma, T4 and T3 are mostly transported almost entirely in association with two proteins, the so called thyroxine binding proteins” which act as specific carrier agents for the hormones.

Two main carrier proteins are:

- Thyroxine-binding globuline (TBG)
- Thyroxine binding prealbumin (TBPA)
- When large amount of T4 and T3 are present and the binding capacities of the above two specific carrier proteins are saturated, the hormones can be bound to serum albumin. Approximately about 0.05% of the circulating thyroxine is in the free unbound form. Free T3 and T4 are the metabolically active hormones in the plasma

MECHANISM OF ACTION OF THYROID HORMONE

- Thyroid hormones are transported into their target cells by a “carrier mediated” active transport system of the cell membrane. Target organs include; liver, kidneys, adipose tissue, cardiac, neurons, lymphocytes, etc.
 1. Nuclear Action: T4 and T3 pass into the nucleus and bind directly to specific high affinity “nuclear receptors” which are histone chromatin proteins of specific genes. This receptor hormone binding increases the action of nuclear DNA dependent RNA polymerase increasing gene transcription, which in turn enhances m-RNA synthesis and induces synthesis of specific protein and enzyme.

1. Na^+ - K^+ - ATPase pump:

Thyroid hormone exerts most of metabolic effects by increasing O_2 -consumption. It has been suggested that much of the energy utilized by a cell is for driving the Na^+ - K^+ -ATPase pump. Thyroid hormones enhance the function of this pump by increasing the number of pump units, almost in all cells.

- **TRANSLATION OF PROTEINS**

Thyroid hormones may stimulate translation of proteins by directly increasing the binding of amino acid t-RNA complex to ribosome or by increasing the activity of peptidyl transferase or translocase enzymes.

METABOLIC ROLE OF THYROID HORMONES

1. *Effect on protein metabolism*

- * In hypothyroid children and in physiological doses, thyroid hormones when given in small doses, favour protein anabolism, leading to N-retention (positive N-balance) because they stimulate growth.
- * Large, unphysiological doses of thyroxine, cause protein catabolism, leading to negative N-balance.

CLINICAL SIGNIFICANCE

- The catabolic response in skeletal muscle in cases of hyperthyroidism is sometimes so severe that muscle weakness is a prominent symptoms and creatinuria is marked, called thyrotoxic myopathy. The K^+ liberated during protein catabolism appears in urine and there is an increase in urinary hexosamine and uric acid excretion.
- Effect on bone proteins: Mobilization of bone proteins leads to hypercalcaemia and hypercalciuria with some degree of osteoporosis.
- Effect on skin: The skin normally contains a variety of proteins combined with polysaccharides hyaluronic acid and chondroitin sulphuric acid.
- Clinical significance; in hypothyroidism, these complexes accumulate, promoting water retention, which produces characteristic puffiness of the skin, when thyroxine is administered, the proteins are mobilized and diuresis continues until the puffiness (myxoedema) is cleared.

- **2. Effects on Carbohydrate metabolism**

- Net effect on carbohydrate metabolism:

- Increase in blood sugar (hyperglycaemia), and glycosuria

- Increase glucose utilization, and decreased glucose tolerance. Thyroid hormones are therefore, antagonistic to insulin

Thyroid hormone increase the rate of absorption of glucose from intestine

Decreased glucose tolerance may be contributed to also by acceleration of degradation of insulin.

Note: Diabetes mellitus is aggravated by coexisting thyrotoxicosis or by administration of thyroid hormone.

- Increased hepatic glycogenolysis, because they enhance the activity of Glucose-6-phosphatase

- In addition there is increased sensitivity to catecholamine; they potentiate the glycogenolytic effect of epinephrine by increasing the β -adrenergic receptors on hepatic cell membrane.

- Stimulate glycolysis as well as oxidative metabolism of glucose via TCA cycle and also increasing HMP shunt. Thyroxine increases the activity of G6PD enzyme in liver.

- Thyroid hormone causes a decrease of glycogen store in the liver and to a lesser extent, in the myocardium and skeletal muscle.

- At the same time, thyroid hormones increase hepatic gluconeogenesis by increasing the activities of pyruvate carboxylase and PEP carboxykinase.

3. Effect on Lipid Metabolism

- Increase lipolysis in adipose tissue thus increasing plasma FFA. This effect is rather indirect in the sense it increase sensitive, to catecholamine, by increasing the β -adrenergic receptor on adipose cell membrane.

- They may stimulate, at the same time lipogenesis by increasing the activities of malic enzymes, ATP citrate lyase and G6 PD.

- Cholesterol despite the fact that hepatic synthesis of cholesterol and phospholipids is depressed following thyroidectomy and is increased in thyrotoxicosis, the concentration of cholesterol and to lesser extent phospholipids in plasma is increased in hypothyroidism and decreased in hyperthyroidism.

Decreased value in hyperthyroidism is explained as follows:

Although thyroid hormones increase the rate of biosynthesis of cholesterol, they increase

- The rate of degradation
- Increase the formation of bile acids (cholic acid/ deoxycholic) acid and
- Increase biliary excretion, to a greater extent accounting for the lowered blood concentration.

Lipoproteins

The concentration of plasma lipoproteins of Sf 10-20 class (LDL) is frequently increased in hypothyroidism and decreased in thyrotoxicosis or following administration of thyroid hormones to normal subjects

2. Calorigenic Action

Thyroid hormones increase considerably O₂-consumption and oxygen coefficient of almost all metabolically active tissues.

Exceptions are Brain, testes, uterus lymphnodes, spleen and anterior pituitary. There is increase in heat production and BMR. These effects is due to:

- Induction of glycerol-3-P-dehydrogenase and other enzymes involved in mitochondrial oxidation.
- More important is increased activity and increased units of Na⁺-K⁺ ATPase pump. It hydrolyzes ATP for transmembrane expression of Na⁺, leading to enhanced heat production, O₂-consumption and oxidative phosphorylation.

5. Vitamins

- Administration of large amounts of thyroid hormones increases the requirement of certain members of vitamin B-complex (thiamine, pyridoxine, pantothenic acid) and for vitamin C. There are presumably related to the stimulation of oxidative and catabolic processes.
- Thyroxine is necessary for hepatic conversion of carotene to vitamin A and the accumulation of carotene in the blood stream in hypothyroidism is responsible for yellowish tint of the skin.

PARATHYROID GLANDS AND THEIR HORMONES

The parathyroid glands are intimately concerned with regulation of the concentration of

Ca and PO₄ ions in the blood plasma. This is accomplished by secretion of a hormone parathormone (PTH) by the chief cells, the net effect of which is:

- To increase the concentration of Ca and
- decrease the PO₄.

In addition to its effects on plasma ionized Ca via its action on bone, parathormone controls renal excretion of Ca and P₀₄.

PARATHORMONE (PTH)

Chemistry: Parathormone is a linear polypeptide consisting of 84 amino acids. N-terminal amino acid is alanine and C-terminal is glutamine. Bovine PTH has Mwt of 9500. PTH from different species differs only slightly in structure.

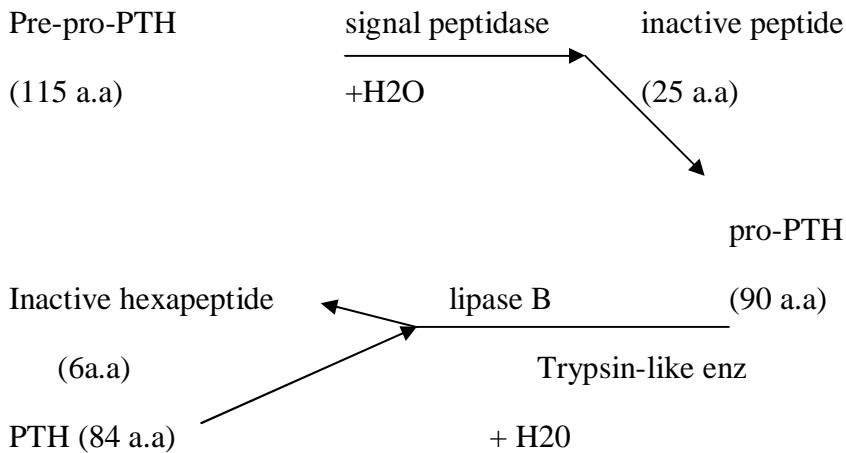
CORE OF ACTIVITY

Studies on the synthetic PTH indicate that the amino acid sequence 1 to 29 or possibly 1 to 34 from N-terminal end is essential for the physiologic actions of this hormone on both skeletal and renal tissues.

Methionine is important amino acid and necessary for calcium mobilization effect. The N-terminal end up to 34 amino acids possesses the receptor binding ability.

Biosynthesis

PTH is initially synthesized in chief cells as a pro-hormone.



- Pre-pro PTH: consisting of 115 amino acids is first formed in polysomes adhering on the rough ER membrane
- Pro-PTH: before the formation of Pre-pro PTH is completed its N-terminal end protrudes into the lumen of rough ER and a signal peptidase of rER membrane hydrolyzes the molecules to split off 25 a.a and thus pre-pro PTH is changed to pro-PTH having 90 amino acids.
- PTH: pro-PTH is transferred to rER lumen end moves to Golgi cisternae. A trypsin like enzymes called lipase B hydrolyses its N terminal amino acids and remove 6 amino acids rich in basic amino acids and thus converting pro-PTH to PTH. PTH thus formed is packaged and stored in secretory vesicles. Increased c-AMP concentration and a low Ca^{2+} level stimulates it release from secretory vesicles. On the other hand, a high concentration at Ca^{2+} stimulates the degradation of the stored PTH in secretory vesicles instead of it release.

MECHANISM OF ACTION

PTH increases serum Ca^{2+} level by acting on bones kidney and intestines.

- Increasing cAMP level: PTH bind to specific receptor on the plasma membrane of bone cells, renal tubules cells, it activates the adenyl cyclase to form c-AMP in the cells. C-AMP acts as the “second messenger” which activate specific C-AMP dependent protein kinase which phosphorylate and thereby modulate the activities of specific proteins in the bone cell and kidney cells.
- Role of Ca^{2+} : c-AMP also increases the Ca^{2+} concentration in these cells, which in turn may act as a messenger to modulate the activities of some intracellular proteins.
- PH change in tissue: the hormone increase the amounts of both lactic and citric acid in the tissues and both of these acids may act to aid bone resorption.

METABOLIC ROLE OF PTH

The actions of PTH are reflected in the consequences of:

- its administration and
- removal of the parathyroid glands

A. The most conspicuous metabolic consequences of administration of PTH are:

- increase in serum Ca^{2+} concentration
- Decrease in serum inorganic PO_4 concentration.
- Increased urinary PO_4
- Removes Ca from bones particularly if dietary intake of Ca is inadequate.
- Increase in citrate content of blood plasma, kidney and bones
- Activates Vit. D in renal tissue by increasing the rate of conversion of 25-OH-Cholecalciferol to 1, 25-di-OH-cholecalciferol, by stimulating α -1-hydroxylase enzymes
- Effect on Mg metabolism
PTH has been reported to exert an influence on Mg metabolism. Primary hyperparathyroidism has been found to be associated with excessive urinary excretion of Mg and negative magnesium balance.

B. Actions on different Organs:

a. Action on kidneys: PTH acts through by increasing c-AMP. PTH binds to specific receptors on plasma membrane of renal cortical cells of both proximal and distal tubules and stimulates adenylyl cyclase to produce c-AMP. c-AMP then is transported to apical/luminal part of the cell where it activated c-AMP dependent protein kinase, which phosphorylates specific proteins of the apical membrane to affect the several mineral transport across the membrane.

- PTH decreases the Trans-membrane transport and reabsorption of filtered Pi in both proximal and distal tubular cells and increases the urinary excretion of inorganic phosphate (Phosphaturia effect).
- Fall in serum PO_4 level leads to mobilization of PO_4 from bones, which also mobilizes Ca^{2+} along with it, resulting to hypercalcaemia.
- PTH stimulate α -1-hydroxylase enzyme located in mitochondria of proximal convoluted tubule cells, which converts 25-OH cholecalciferol to 1, 25-di-OH cholecalciferol which in turn increases the intestinal and renal absorption of Ca^{2+} resulting to hypercalcaemia..
- PTH inhibits the transmembrane transport of K^+ and HCO_3^- to decrease their reabsorption by renal tubules.

- PTH increases the transmembrane transport and reabsorption of filtered Ca^{2+} in the distal tubules resulting initially to decrease urinary excretion of Ca^{2+} . But later on, PTH induced hypercalcaemia enhances the amount of filtered Ca^{2+} which increases the renal excretion.

b. Action on Bones

PTH binds to specific receptors present on membrane of osteoclasts, osteoblast and osteocytes and increases c-AMP level in these cells which act through c-AMP dependent protein kinases.

Following actions are seen.

- Osteoclastic activity: it stimulates the different action and maturation of precursors cells of osteoclasts to mature osteoclasts.
- Osteoclastic osteolysis: PTH stimulates the osteoclasts through “second messenger” c-AMP to increase the resorption of bones which enhances mobilization of Ca and P from bones.
- Osteocytic osteolysis: PTH also stimulates osteocytes which increase bone resorption thus mobilizing Ca^{2+} and Pi; there occurs enlargement of bones lacunae.

- Action on alkaline phosphatase:

Alkaline phosphatase activity varies as per PTH concentration. At low concentrations, PTH stimulates the sulfation of cartilages and increases the number of osteoblast and alkaline phosphates activities of bone osteoblasts. At higher levels of physiological concentrations, PTH inhibits alkaline phosphatase activity and collagen synthesis in osteoblast and decreases the Ca^{2+} retaining capacity of bones. PTH induced rise in intracellular c-AMP in osteoclast and osteocytes leads to secretion of lysosomal hydrolases and collagenases which increase breakdown of collagen and MPS in bones matrices.

C. Action on intestinal mucosa

PTH does not act directly on intestinal mucosal cells as the cells do not possess the specific receptors for PTH. But it increases the absorption of Ca^{2+} and PO_4 through production 1, 25-dioH cholecalciferol (Calcitriol).

CALCITONIN

Calcitonin is a calcium regulating hormone. It is proved that calcitonin originates from special cells, called c-cells, parafollicular cells. C-cells constitute an endocrine system which are derived from neural crest and are found in thyroid, parathyroids and in thymus.

CHEMISTRY

Calcitonin is a single chain lipophilic polypeptide having a most 3600. As many as four separate active fractions have been isolated and they have been designated as α , β , γ and δ -calcitonin. Amino acids sequences of calcitonin have now been established. It contains 32 amino acids; N-terminal amino acid is cysteine, and C- terminal prolinamide. An inter chain disulphide bridge joins two cysteine residue between position I and 7. Low number of ionizable groups are present, 5 of 6 possible – COOH groups been amidated. Isoleucine and lysine are absent conspicuously from the molecule. There is high content of Aspartic acid and threonine.