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Review Article

AN OVERVIEW ON THYROID HORMONE ACTIONS ON LIPIDS AND ITS METABOLISM

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ABSTRACT

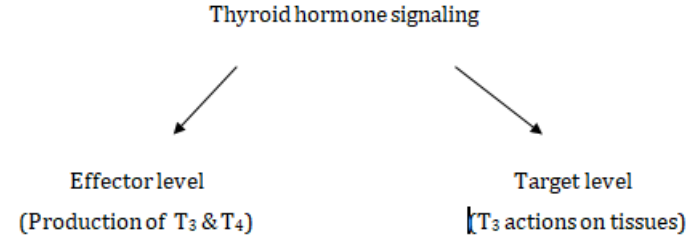
Thyroid hormone acts on all major metabolic pathways. Thyroid hormone well-known action is an increase in basal energy expenditure obtained acting on carbohydrate and lipid metabolism. Thyroid hormones affect synthesis, mobilization, and degradation of lipids. The main effects of thyroid hormone on lipid metabolism include: (a) induction of HMG-CoA reductase, (b) enhance lipolysis by acting on catecholamines, (c)regulation of LXR-α, (d) activation of corepressor, (e) stimulation of LDL receptor, (f) induction of 7-α hydroxylase. By the above mechanisms, thyroid hormone may increase or decrease cholesterol synthesis and degradation. In hyperthyroidism, cholesterol synthesis gets decreased and cholesterol elimination get increased. In hypothyroidism, cholesterol synthesis gets increased and cholesterol elimination gets decreased.

KEYWORDS: *Thyroid Hormone, Lipid Metabolism, Hyperthyroidism, Hypothyroidism, Cholesterol.*

INTRODUCTION

Thyroid gland: Thyroid gland is a butterfly-shaped bi-lobular endocrine located anterior and inferior to the larynx. The two lobes are connected by Isthmus. It is covered by a thin fibrous capsule. The fibrous capsule has an inner and an outer layer. The arterial supply is through Superior and inferior thyroid arteries. The venous drainage is through Inferior, middle and Superior thyroid veins. The gland is covered by a thin connective tissue capsule that enters the gland and forms lobular units. Lobule contains a cluster of follicles which are 100-200micrometers in diameter A basement membrane surrounds each follicle. The follicular cells are low columnar, cuboidal or squamous cells. When they are inactive they are squamous. Follicular cells produce thyroglobulin which is stored as a colloid in the lumen and these cells also contain thyrotropin receptors in the basolateral membrane.

Thyroid hormone production: Hypothalamus contains neuron nucleus that releases Thyrotropin Releasing Hormone. It travels to anterior pituitary through the hypophyseal portal. Anterior pituitary contains thyrotrope cells. These cells produce TSH (Thyroid Stimulating Hormone) which is a glycoprotein. This glycoprotein enters into the blood and stimulates the thyroid gland to release T_3 & T_4.



Synthesis, storage, and release:

Iodide trapping: Iodide is absorbed in the stomach and duodenum, cleared by thyroid and kidneys, eliminated through urine. The follicular cells of thyroid gland trap iodide ions from the blood into the cytosol by active transport by Iodide pump located on the basal membrane [1]. It transports 2sodium ions and one Iodide ion into the cell. TSH stimulates Iodide pump. The trapped iodine is carried into the apical membrane of thyroid glands by A transporter called pendrin. TSH binds with TSH receptors which are coupled to both Gs and Gq proteins that activate both cAMP pathway and phosphoinositol/Calcium (IP/Ca2+) second messenger signaling pathway. Gs pathway promotes iodide uptake and thyroid hormone secretion whereas Gq is rate-limiting for the synthesis of the hormone by stimulating iodide organification [3]. When iodide doses get increased, the iodine organification increases and then decreased. This effect is said to be Wolff-chaikoff effect [6]. Iodide concentrating mechanism is not only found in the thyroid but also in the skin, salivary glands, gastric mucosa, intestine, mammary glands, and placenta but these are not stimulated by TSH [2].

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Synthesis of thyroglobulin: Thyroglobulin which is a 660kDa dimeric protein that is synthesized in Rough endoplasmic reticulum of thyroid follicular cells. It is modified in Golgi apparatus and packed in secretory vesicles. These vesicles undergo exocytosis and release Thyroglobulin into the lumen of the gland.

Oxidation of iodide: oxidation of iodide is carried out by Thyroid peroxidase enzyme in the presence of H2O2 which yields iodinum ions, hypoiodous acids(HOI), enzyme-linked hypoiodous(E-OI) [2].

Iodination of tyrosine: The amino acids of thyroglobulin such as tyrosine get iodinated. Binding of iodine with thyroglobulin is termed as organification of thyroglobulin [1]. Binding of one iodine atom gives T_1 (monoiodotyrosine) and two iodine atoms give T2 (diiodotyrosine). A sticky material that gathers and stored in the lumen of follicle called as Colloid.

Coupling of T_1 & T_2: Two T_2 molecules join to yield T4 (thyroxine). One T_1 and one T_2 yield T3 (triiodothyronine). These steps are catalyzed by thyroid peroxidase enzyme [2].

Pinocytosis and digestion of colloid: The thyroid cells form a pseudopod extension that closes colloid to form pinocytic vesicles. The lysosomes fuse with these vesicles to form digestive vesicles which contain digestive enzymes. The proteases digest the thyroglobulin molecule and release T3, T4 [1]. The residues of T1 and T2 are deiodinated and released iodide is reutilized [2].

Secretion of thyroid hormone: The hormones are lipid soluble such that they can easily diffuse through the plasma membrane into interstitial fluid and then into the blood.

Transport in the blood: T_3 & T_4 are bound to different thyroid hormone carrying proteins like Thyroxine-binding globulin, transthyretin, human serum albumin.

At target tissue [5], THs enter into the cell through membrane transporters like monocarboxylate transporters MCT8 & MCT10. Others include heterodimeric L-type amino acid transporters (LATs) – LAT1, LAT2 & other anion transporting polypeptide (OATP) family. T_4 is normally secreted in greater quantity than T_3. But T_3 is more potent. In the cell, T_4 is converted into T_3 by the action of deiodinases.

Regulation: It is by a negative feedback mechanism.

Action: The thyroid hormone receptors are nuclear receptors which contain

- An amino acid terminal domain(A-B domain)
- A central DNA binding domain(DBD)
- A carboxyl-terminal ligand binding domain

T_3, T_4 are lipophilic such that they can pass through cell membrane easily. T_4 is converted to T_3 by deiodinase.

There are three types of deiodinase-

Type 1- they are present at thyroid, liver, and kidney

Type 2- Pituitary gland, brain, brown fat, thyroid gland

Type 3- Inactivates T_4. Present in placenta but not active in healthy individuals.

T_3 binds 10-15 times greater affinity than T_4 [9].

T_3, T_4 enters into the cytoplasm. T_3 enters into the nucleus through Nuclear pore complex which guards the entry and exit of nuclear proteins. Importins & Exportins recognize and mediate their transport.

The thyroid hormone receptor binds to Thyroid response element (TRE) as monomer, homodimer or heterodimer with Retinoid X Receptor, the major functional form of the receptor [5, 8].

TH+TR+RXR Bind with the location of DNA (TRE). This leads to transcription and mRNA is formed. It undergoes translation and yields proteins.

In the absence of ligand to TR, corepressors such as Nuclear Receptor Corepressor (N-COR1) & (N-COR2) and histone deacetylase are bound, that leads to repression of target gene expression.

In the presence of ligand, TR undergoes a conformational change. Coactivators such as SRC-1 (Steroid receptor coactivator1) and histone acetyltransferase gets bound and lead to a change in chromatin structure and transcription of the target gene.

In simple,

T_4, T_3 enters into the nucleus.

T_3 binding causes dissociation of corepressors from thyroid receptor.

Coactivators are recruited to the T_3 bound receptor.

Gene expression is altered [9].

Types of receptors:

TR α- There are $TR\alpha_1$, $TR\alpha_2$ and $TR\alpha_3$

Location: $TR\alpha_1$- Bone, GI tract, cardiac and skeletal muscle, CNS.

$TR\alpha_2$-Brain, bone, heart, and kidney

$TR\alpha_3$- Brain, kidney, testis, skeletal muscle& adipose tissue

$TR\alpha_2$ & $TR\alpha_3$ lack the ability to bind with T_3 because differ in length and amino acid composition in the C-terminal region when compared with $TR\alpha_1$.

TR β – There are $TR\beta_1$, $TR\beta_2$, $TR\beta_3$, $TR\beta_4$.

Location: $TR\beta_1$- Liver, kidney, inner ear

$TR\beta_2$- Hypothalamus, pituitary, cochlea, and retina

$TR\beta_3$- It is found only in rats.

$TR\beta_4$- Brain and kidney.

$TR\alpha_1$ and $TR\beta_1$ - Interact with importins and exportins respectively

$TR\alpha_1$ control the lipogenesis in white adipose tissue

TRβ regulates the activity of lipogenic and lipolytic enzymes in the liver [4, 5, 7, 9].

Functions of Thyroid Hormone:

- Increases BMR
- Calorigenic effect
- Stimulate protein synthesis
- Increases lipolysis
- Enhance cholesterol excretion
- Enhance utilization of lipid substrate
- Increases triglycerides transport and synthesis
- Increases lipoprotein lipase activity

- Maintains heart rate
- Increased cholesterol secretion is due to increased LDL receptors on the liver cells.

Lipids:

Lipids are the substances which may be called as organic substances relatively insoluble in water, soluble in organic substances and they are related to fatty acids and utilized by the living cells.

Classification of lipids:

They are broadly classified into simple, complex, derived and miscellaneous lipids, which are further subdivided into different groups.

A) Simple lipids:

1) Esters of fatty acids with alcohols: a) fats and oils, b)waxes

B) Complex or compound lipids:

1) Phospholipids:
   a) glycerophospholipids,
   b) sphingophospholipids.
2) Glycolipids.
3) Lipoproteins: a) HDL (High density lipoprotein),
   b) LDL (low density lipoprotein),
   c) VLDL (very low density lipoprotein),
   d) IDL (intermediate density lipoprotein),
   e) Chylomicrons.

C) Derived lipids: glycerol and other alcohols.

D) Miscellaneous lipids: carotenoids, squalene [11].

Out of all these, we mainly focus on lipoproteins, as our assumption is mainly based on lipoproteins.

Lipoproteins: These are molecular complexes of lipids with proteins. For the circulation of lipids, lipoproteins are used as vehicles.

a) ***HDL:*** Collect fat molecules from the tissues or cells of the body, and take it back to the liver.
b) ***LDL:*** Carry fat molecules around the body. Sometimes it is referred to as bad lipoprotein.
c) ***IDL:*** They are intermediate particles between LDL and VLDL.
d) ***VLDL:*** They carry newly synthesized triglycerides from the liver to adipose tissue.
e) ***Chylomicrons:*** They carry triglycerides from intestine to liver, to skeletal muscle, and to adipose tissue.

Apolipoproteins: these are proteins that bind with lipids to form lipoproteins and to transport lipids in blood and lymph.

Classification of Apoliporoteins:

a) Apolipoprotein A: Apo-A1, Apo-A2, Apo-A4
b) ApolipoproteinB: Apo-B48, ApoB100
c) Apolipoprotein C: Apo-CI, Apo-CII, Apo- CIII, Apo- CIV
d) Apolipoprotein D
e) Apolipoprotein E
f) Apolipoprotein H
g) Apolipoprotein L
h) Apolipoprotein(a)

Transport of Lipids:

Lipids which are insoluble can be solubilized in association with proteins to form lipoproteins in which form lipids are transported in the circulation.

Lipid metabolism:

Lipid delivery pathway (Apo-B): Apo-B containing lipoproteins originate from two sources which include intestine: ApoB48 and liver: ApoB100. The newly assembled Apo-B lipoproteins secreted from the intestine or liver into the lymph or plasma respectively. Apo-E, Apo-CII, Apo-CIII are secreted along with Apo B. These may acquire from HDL. With the attachment of proteoglycans on capillary endothelium, the remodeling process begins. Here, Apo-CII activates lipoprotein lipase (LPL) which hydrolyzes the lipoprotein core triglycerides into free fatty acids which diffuse through the capillary to muscle or adipose cells. As the fatty acids exit, the lipoprotein becomes smaller granules. In the remodeling of ApoB100 lineage, hepatic lipase (HL) transforms IDL to LDL. During the pathway remnants of ApoB48 and ApoB100 pathway shed Apo-E, Apo-CII, Apo-CIII which then reassociate with HDL. Eventually, most Apo-B remnants are recycled into the liver through the LDL receptor protein (LRP) or LDL receptors. Chylomicron remnants and LDL may become targets for arterial wall macrophage. Excess Apo-B particles can invade the arterial wall become oxidized and taken up by macrophage receptors creating cell buildup that leads to atheroma.

ApoA1 (HDL) metabolism: Excess cholesterol in macrophage triggers upregulation of **ABCA1** transporter and hydrolyzes which converts cholesterol ester in lipid pool to free cholesterol. The ABCA1 transporter operates to harvests this free cholesterol and delivers to the cell membrane and will disacquired by poorly lipidated ApoA1 to create nascent HDL. The transporter shuttles back and forth transferring cholesterol from the macrophage to HDL. The free cholesterol on HDL surface is esterified by Lecithin-cholesterol acetyltransferase (LCAT). The cholesterol ester then moves to the core of the lipoprotein forming the more spherical mature HDL3. Further removing of cholesterol by HDL3 occurs through **SRB1** receptors in membrane cholesterol pools. As HDL3 collects more cholesterol and is acted on by LCAT it expands to HDL2.

ABCA1 and SRB1 are key devices for cholesterol efflux. However, HDL also collects the cholesterol both from lipid rafts and caveolae within the cell membrane. By this mechanism, cholesterol gets efflux from the macrophage [12]. [Fig. 1]

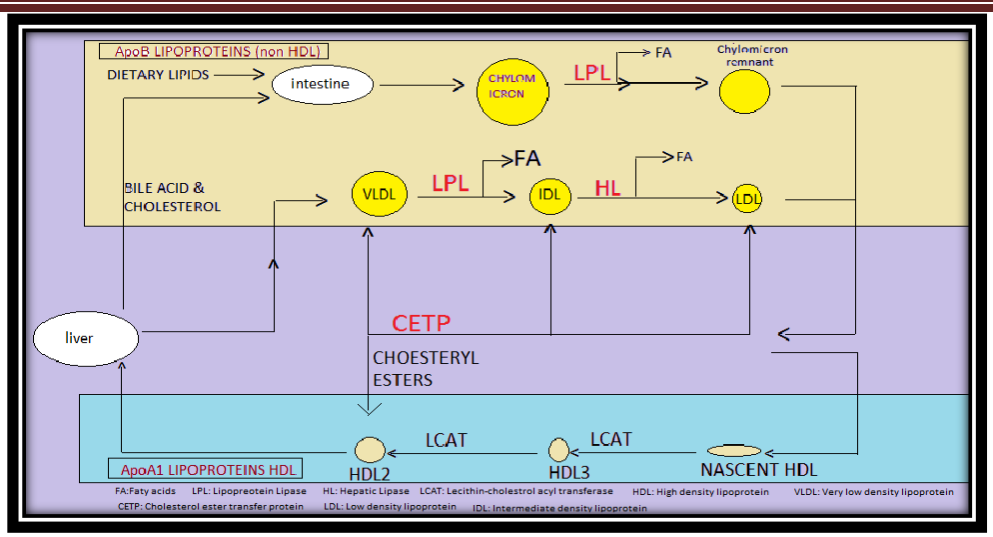

Fig. 1: ApoA1 (HDL) metabolism

Thyroid Hormone Effect on Lipid Metabolism:

Regulation of lipid metabolism on the liver by the thyroid is primarily dependent on specific actions of T_3, TR-β, and nuclear hormone receptor crosstalk [14].

Thyroid hormone influences lipid metabolism majorly through the following mechanisms. It includes: a) inhibiting HMG-CoA reductase, b) enhancing elimination of cholesterol in bile) competition at DR4 site of ABCA1 gene d) activation of corepressor e) action at LDL receptor f) by the action of catecholamines [Fig. 2].

a) HMG-CoA Reductase: Thyroid hormone stimulates hepatic de novo pathway by inducing HMG-CoA reductase that helps in converting HMG-CoA to mevalonate in the biosynthesis of cholesterol synthesis. In hyperthyroidism, there is an increased intracellular cholesterol synthesis and viceversa [18].

***b) Catecholamines action on Lipolysis by Thyroid Hormone*:** In hyperthyroidism patients, increased levels of T3 lead to increase in mRNA levels of lipolytic β2 AR which down-regulates the phosphodiesterase activity which is responsible for the conversion of CAMP to 5'AMP.This condition led to the accumulation of CAMP in the fat cell which enhances lipolysis [13].

c) Competition at DR-4 site of abca1 gene: Thyroid receptor and liver x receptor compete at DR-4 site of ABCA1(ATP binding cassette transporter A1 gene) promoter. Liver x receptor α auto-regulates LXR- α promoter. LXREs are present in the upstream region of LXR-α promoter, therefore auto-regulation is exerted through LXREs of LXR. TR-β1 and LXR-α bind to RXR and forms a dimer and compete at DR4 site of ABCA1 gene. Therefore from the above points, we conclude that TR-β also regulates the human LXR-α promoter [10, 15].

d) Activation of co-repressor: If thyroid hormone binds to thyroid receptors, then the thyroid hormone induces conformational changes in the receptor that modifies interactions with accessory transcription factors. In the absence of thyroid hormone binding, the apo receptor binds to co-repressor proteins which inhibit gene transcription. Co-repressor protein histone deacetylase helps in regulating cholesterol synthesis. Inhibition of this co-repressor protein results in decreased cholesterol levels [9, 16].

e) LDL Receptor: Thyroid hormone stimulates LDL-R gene transcription results in increased cholesterol uptake and increased cholesterol synthesis. SREBP-2 is another regulator of the LDL-R gene. Thyroid hormone induces SREBP-2 gene expression which in turn modulates LDL-R gene expression. Due to the tandem arrangement of TRE and SREBP response element (SRE), nuclear coregulation takes place. SREBP-2 mRNA is suppressed, if T3 levels are low [19].

f) CYP7A1: Conversion of cholesterol to bile acid is required to maintain homeostasis of cholesterol. LXR-α mRNA expression is induced by thyroid hormone, which results in the induction of 7-α-hydroxylase (CYP7A1), an enzyme which is responsible for the elimination of cholesterol through bile acids [17].

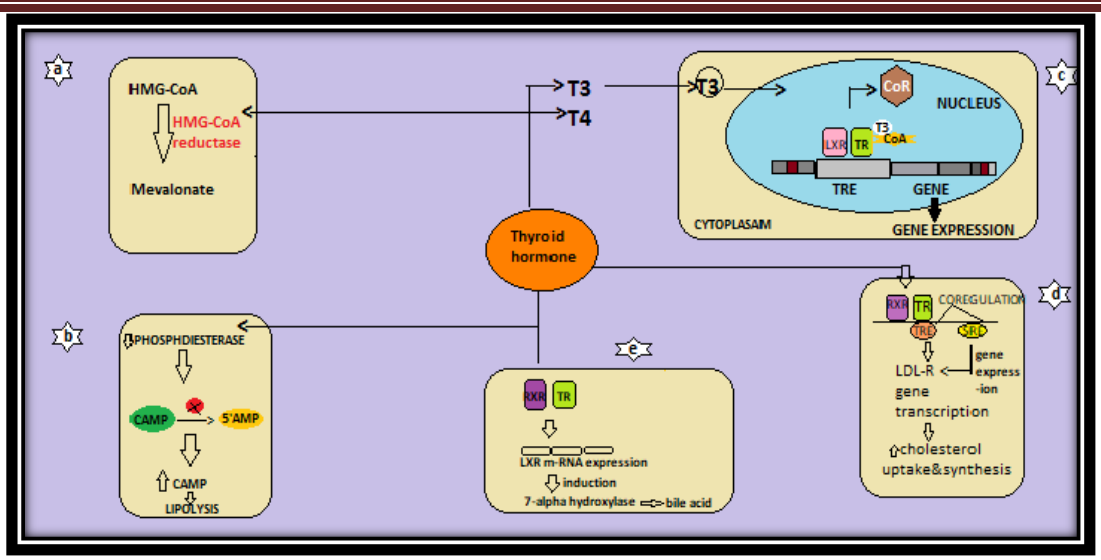

Fig. 2: Thyroid Hormone Effect on Lipid Metabolism

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