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LIPID METABOLISM AND THYROID HORMONE : A REVIEW

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ABSTRACT

Thyroid hormone , secreted by thyroid gland have a profound effects on the lipid metabolism. It exerts its action mainly by its genomic action. It diffuses from the extracellular fluid across the plasma membrane and go directly into the nucleus. The cognate receptor binds to the thyroid hormone response element [TRE].It regulates the gene expression of key enzymes involved in lipid metabolism by modulating their transcription.Thyroid hormone induces acetyl CoA carboxylase,fatty acid synthase,malic enzyme and thereby favours fatty acid synthesis.Paradoxically it also favours oxidation of fatty acids by enhancing the expression of carnitine palmitoyl transferase.Thyroid hormone is closely associated with lipoprotein metabolism,known to decrease triglycerides by enhanced activity of lipoprotein lipase and hepatic lipase activities.It is universally accepted that this hormone lowers cholesterol content of low density lipoprotein by affecting the expression of LDL receptors and clearance of LDL.It also has important role in stabilizing the mRNA coding for the rate limiting enzyme of cholesterol biosynthesis, HMG CoA reductase. Cholesterol clearance is affected as this hormone influences the enzymes of bile acid synthesis.This review discusses the effect of thyroid hormone in lipid metabolism in detail and lipid variations that occur in hypo and hyperthyroid conditions. The effects of thyroid hormone on the lipid metabolism makes it a potential molecule to develop a class of drugs which can modify the lipid levels.Clinical trials are going on to test the use of thyroid hormone analogues in the treatment of hyperlipidemias.

KEYWORDS:fatty acid synthesis,oxidation of fatty acids, lipoproteins, hyperthyroidism, hypothyroidism

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INTRODUCTION

Humans synthesize fatty acids using acetyl CoA derived primarily from carbohydrates. This pathway is known as complete or *de novo* synthesis of fatty acids and it occurs in the cytoplasm. Primary sites are liver, adipocytes, brain, kidney and mammary gland.The process occurs when the cells have abundance of energy (high energy charge in the cell i.e. high carbohydrate intake) and therefore have a high ATP content.Requirements are enzymes like Acetyl CoA carboxylase,FattyAcid synthase complex and Cofactors like NADPH, ATP, Mn^{++}, biotin and bicarbonate. The synthesis of long chain fatty acids is an essential metabolic pathway for the storage of energy and the provision of subcellular structural components. The pathway is under both hormonal and dietary control to adjust the supply of fatty acids to the requirements and the necessity of storing dietary energy.Lipogenesis converts surplus glucose and other intermediates like pyruvate,lactate assisting the anabolic phase of the feeding cycle.In the liver, the activity of FAS is regulated through nutrients and hormones (1). Starvation causes a decrease in the activity of the enzyme, and refeeding restores it (2,3). The rate of lipogenesis is high in the well fed state and lipolysis occurs by restricted calorie intake ,high fat diet and in conditions like diabetes mellitus. These conditions are associated with high concentrations of plasma free fatty acids and an inverse relationship exists between hepatic lipogenesis and concentrations of plasma free fatty acids.

De novo synthesis of fatty acids and thyroid hormone

Lipogenesis is affected by bothshort term (allosteric modification of preexisting enzymes,substrate flux) and long term (new enzyme synthesis)mechanisms (4, 5).Thyroid hormone is a stimulator offatty acid synthesis in the liver (6-8). Although some studies have shown modest effects,a few reports showed an 18-fold difference in lipogenicrates per gram liver between hypo- and hyperthyroid rats(9). Increased synthesis of fatty acids in white adipose tissue was reported by Diamant etal. (7) and Gnoni et al. (10). Hyperthyroidism is associated with elevated fatty acid synthesis (FAS) and low hormone status with the lowered synthesis.The effects of altered thyroid status on FAS take place at the level of enzymes.The enzymes of hepatic lipogenesis that are elevated in hyperthyroidism are, acetyl CoA carboxylase ,fatty acid synthase multi enzyme complex,NADPH generating glucose 6 phosphate dehydrogenase,6 phosphogluconate dehydrogenase,ATP Citrate lyase,malate dehydrogenase (7,11-18) .Hypothyroidism shows a decline in these enzyme levels(13,19,20).Messenger RNA encoding fatty acid synthase is found to be elevated on treatment with thyroxine (14,21,22). The most responsive tissue for thyroid hormone is liver, in which lipogenesis increased 16-fold between hypo- and hyperthyroid animals. Thus, liver is a relatively minor site for fatty acid synthesis in hypothyroid rats and the major site in hyperthyroidism. It is also observed that thyroid hormone dramatically affects the extent to which the liver contributes to total lipogenesis in the rat. This contribution ranges from 5% in the hypothyroid animal to 34% in the hyperthyroid animal (9). In liver, thyroid hormone stimulates fatty acid synthesis by increasing enzyme mass, and this, in turn, is a pretranslational effect (8, 23-25). Although lipogenesis is stimulated by thyroid hormone in other tissues, no other site experiences such extreme changes.Animal experiments prove that in brown adipose tissue, fatty acid synthesis isuniquely stimulated in the hypothyroid state (26,27). The other tissue that is least responsive for thyroid hormone is lung(10).The effects of thyroid hormone in white adipose tissue are not clear. Previous studies have recorded stimulations and inhibitions of fatty acid synthesis or its

constituent enzymes by thyroid hormone treatment (7, 8,10,28). In addition, while some observed a stimulation of lipogenesis by hypothyroidism (4), others reported an inhibition under the same circumstances (10, 29).The basis for these discrepant results could not be explained by rat strain, sex, treatment, or adipose site etc. Although adipose tissue lipogenesis decreases with age (30), both stimulations and inhibitions of lipogenic parameters are reported in young (29,31) and relatively mature (7,8) animals. Some studies have found that the effects of thyroid hormone in epididymal fat appeared to parallel those in liver, although large variations were seen (9). Little is known about T3 regulation of fatty acid synthesis in white adipose depots other than epididymal fat. Lesser stimulations by thyroid hormone were seen in heart and kidney. Lung and brain were among the nonresponsive tissues(24). Muscle is not considered to be a lipogenic tissue, although it contains significant amounts of a unique isoform of Acetyl CoA Carboxylase (32-36). When we analyze these studies, we clearly arrive at the conclusion that the effects of thyroidhormone on the fatty acid synthetic pathway are tissue specific.The mechanisms underlying the tissue-specific regulation of fatty acid synthesis by thyroid hormone are not clear. Available evidence suggests that thyroid hormone,acting via its nuclear receptor, activates the genes involved in lipogenesis (25,37). Nikodem and co-workers(24, 38) investigated the tissue-specific regulation of the rat malic enzyme gene. Their results are very much inaccordance with those reported here.Liver was the most responsive tissue, this was attributed to a stabilization of the malic enzyme precursor RNA within the nucleus (38). Hepatic lipogenesis is increased in hyperthyroid states or in response to T3 injection (7,28,39-46). T3 influences lipid metabolism through the hepatic regulation of some key Thyroid Response Element (TRE) - bearing genes, including the lipogenic fatty acid synthase and malic enzyme (47,48), the mitochondrial fatty acid oxidation rate-controlling enzyme carnitine palmitoyltransferase-I (CPT-I) (49,50). T3 is known to regulate gene transcription via the binding of hormone/receptor complexes to T3 response elements (TREs) located on the promoter of a variety of genes (51). TREs bind the T3 receptors (TRs) belonging to the nuclear receptor superfamily (52). The latter can form homodimers or interact with other nuclear receptors, such, as RXR (retinoid X receptor), to form heterodimers (53, 54). The heterodimers bind preferentially to Direct Repeats separated by four nucleotides (DR4) (55). A similar effect of refeeding is also observed on the mRNA expression level and stability, as well as on the transcription (56-60). It was also shown that T3 (61) increase the FAS mRNA expression level.

Oxidation of fatty acids and thyroid hormone

There are conflictingreports regarding thyroid hormone regulation of white adipose tissue lipogenesis most likely to be resolved by its lipolytic effects (62,63). It has been shown that lipolysis is enhanced in hyperthyroid animals because the adipose tissue has an increased sensitivity to catecholamines, although conflicts exist (64,65). Enhanced lipolysismay be accompanied by decreased lipogenesis, because of inhibitory effects of both long chain fatty acyl coenzyme-A and cAMP on the activities of acetyl coenzyme-A carboxylase and fatty acid synthase (66). Thus,in hyperthyroid white adipose tissue, a potential stimulation of fatty acid synthesis may be masked by a concurrentin direct inhibition of the same pathway. The extent of this inhibitory influence would depend not only on the thyroid state of the animal, but also on the level of circulating catecholamines, which is very difficult to control. This was tested by preparing isolated adipocytes from rats in different thyroid states. By incubating them in uitro, influence of circulating catecholamines was removed. Under these circumstances, cells from hyperthyroid animals were three times more lipogenically active than those taken from eu- or hypothyroid rats (9). Oxidation of fatty acids(ß oxidation) is a major pathway for

energy production,in which there will be removal of two carbon units at a time.The major steps involved are; i.activation of fatty acid to fatty acyl CoA with the utilization of two high energy phosphate bonds ii.transport of acyl group across the mitochondrial membrane with the help of carnitine shuttle and iii. series of oxidation requiring $FADH_2$ and NADH followed by hydration reactions. The simultaneous acceleration of fatty acid synthesis and fatty acid oxidation (i.e lipogenesis and lipolysis) (67-76) in hyperthyroid state is paradoxical .Both the processes inhibit each other;

- Increased hepatic malonyl CoA concentration (stimulator of fatty acid synthesis) diminishes fatty acid oxidation by inhibiting CPT-I (carnitine palmitoyl transferase –I)(76-85).
- Increased plasma free fatty acid concentration (stimulator of fatty acid oxidation) opposes fatty acid synthesis.

Simultaneous stimulation of fatty acid synthesis and oxidation results in wastage of energy ,the cycle becomes futile,energy lost escapes as heat i.e . thermogenesis,the characteristic feature of thyrotoxicosis. Hyperthyroidism is characterized by increased basal metabolic rate and hence the energy demand .Key enzymes of glycolysis are independent of thyroid hormone (86-88) because of which this pathway cannot meet the energy requirement. Enhanced lipolysis that occurs in this state meets the energy requirement(89-91).This is supported by elevated free fatty acids detected in hyperthyroidism,both in humans and in experimental animals(90,92-95). The metabolic disposition of long chain fatty acids by the liver appears to be reciprocally related to esterification and oxidative pathways.The magnitude of either of these pathways determines the net turnover rate of free fatty acids.In hyperthyroidism elevated turnover of free fatty acids was accompanied by high oxygen consumption (68,72,96).Increased rate of fatty acid oxidation can be attributed to elevated activity of total CPT(carnitine palmitoyl transferase enzymes-both I and II)(97),required for the transport of fatty acyl CoA from cytosol to mitochondria. Sufficient evidence is available to support that hyperthyroidism is associated with increased ß –oxidation of fatty acids(92,98,99). Muscle acetyl CoA carboxylase is thought to play a role in regulating rates of muscle fatty acid oxidation by controlling levels of malonyl-CoA, an inhibitor of CPT- I (100-102). Muscle contraction activates AMP Kinase which in turn phosphorylates acetyl CoA carboxylase and inactivates it (103-107). The consequent decline in malonyl-CoA relieves inhibition of CPT- I, allowing fatty acid oxidation to proceed. Thyroid hormone activates AMPKinase secondary to heightened metabolic rateand exerts similar effect. As a result fatty acid oxidation increases to support the elevated rate of energy consumption. On the contrary ,in hypothyroidism,energy derivation from lipolysis was reduced in post-absorptive phase (108-110). Sufficient evidences suggest a decrease in circulating free fatty acids in hypothyroids. Fasting also fails to rise fatty acids in humans as well as in experimental animals (98,111,112).Decreased or unchanged ß –oxidation of fatty acids were reported in these patients.The same effect was also proved in propyl thiouracil induced hypothyroid state (92,98,99).This effect can be attributed to low CPT activity in hypothyroidism. Oxidation of short and medium change fatty acids which are independent of CPT for transport across the mitochondrial membrane is unaffected by the thyroid hormone status. Increased fatty acid oxidation leads to ketone body production by the liver,known as ketosis.This doesnot occur in vivo unless there is an increase in the levels of circulating free fatty acids that arise from lipolysis of triacylglycerols in adipose tissue. Free fatty acids are the precursors of ketone bodies in liver.In fed as well as fasting conditions, liver extracts 30% of free fatty acids passing through it.In the liver they can have three fates;

- Can be oxidized
- May undergo ketogenesis
- Esterified in to triacyl glycerol or phosphor lipids

- ✓ ß oxidation is regulated in the fed state,at the level of CPT-I which is inhibited by malonyl CoA , an intermediate of denovo synthesis of fatty acids.
- ✓ With the onset of starvation,acetyl CoA carboxylase is inhibited by acyl CoA,reduces malonyl CoA levels which relieves the inhibition on CPT-I.This allows more acyl CoA to be oxidized.
- ✓ With an increase in free fatty acids, ß oxidation is enhanced resulting in the production of excess acetyl CoA,which can either enter TCA cycle or undergo ketogenesis.With heightened ketogenesis less acetyl CoA enters TCA cycle.

In hyperthyroidism increased free fatty acid turnover was accompanied by increased ketogenesis .The similar results were reported in post-absorptive period(96,113,114).On treating hyperthyroidism,both ketone body formation as well as free fatty acid levels decrease(72,96).On supplementing thyroid hormone to hypothyroid patients,ketogenesis is elevated(96).

Triacylglycerol metabolism and thyroid hormone

After undergoing oxidation and ketogenesis,rest of the free fatty acids can get esterified to acylglycerol and transported out of liver as VLDL.Thyroid hormones influence verylow density lipoprotein triglyceride metabolism andclinical studies have demonstrated an inverse correlationbetween thyroid status and plasma triglyceride levels. Plasma triglycerol is the net process of several metabolisms – absorption of dietary fat , chylomicron (CM),endogenous synthesis of very low density lipoproteins(VLDL) by liver and its secretion to plasma and clearance of these particles from the plasma are the major determinants. Hepatic synthesis of TG is reciprocally related to the rate of fatty acid oxidation.As hyperthyroidism is associated with a high rate of oxidation of fatty acids as well as increased rate of fatty acid synthesis,less fatty acid incorporated for TG synthesis. Instead of this fatty acids are utilized for phospholipids. TG synthesis and VLDL secretion is directly proportional to the substrates available. Free fatty acids are not the limiting factors in hyperthyroidism. Enzymes of TG synthesis,diglyceride acyl transferase and phosphotidate phospho hydrolase are never the limiting entities in hyperthyroidism. It is glycerol 3 phosphate that becomes the limiting factor.

TG levels are variable in hyperthyroidism;found to be elevated (109),lowered (93,115,116) or unchanged (117,118). Hyperthyroid patients exhibit elevated rates of clearance of VLDL and normal or decreased circulating TG levels (119), whereas treatment with thyroid hormones (TH) is associated with elevation in both lipoprotein lipase and hepatic lipase activities (120-122) and concomitantly with a tendency to loweringof triglyceride (119,120,122). A few studies have attributed to the low TG levels to diminished esterification of fatty acids in these patients (113,115).It was also hypothesized that elevated clearance gives rise to low TG levels in these patients(123).

Elevation of plasma TG is associated with hypothyroidism(124-127). Indeed, hypertriglyceridemia is clearly associated withhypothyroidism in obese patients, who are characterized byattenuated rates of clearance of very low density lipoprotein(VLDL), relative to those in obese euthyroid subjects (119).Such elevation in TG levels has been attributed to low lipoproteinlipase (9) or low hepatic lipase activities(119,121,122). A majority of the invesigators found elevated TG levels in hypothyroidism(128-130). A few of the researchers suggested a halved fractional clearance rate of TG in them(123).

Lipoprotein Metabolism

VLDL is secreted by hepatic parenchymal cells. Newly secreted "nascent" VLDL receives apolipoproteins C and E, from HDL in the circulation . Apo B100 is the major apoprotein in VLDL formation. After metabolism to IDL, VLDL may be taken up by the liver directly via the LDL (apo B-100, E) receptor, or it may be converted to LDL. Only

one molecule of apo B-100 is present in each of these lipoprotein particles, and this is conserved during the transformations. Thus, each LDL particle is derived from a single precursor VLDL particle. In humans, a relatively large proportion of IDL forms LDL, accounting for the increased concentrations of LDL in humans compared with many other mammals.

The liver and many extrahepatic tissues express the LDL (apo B-100, E) receptor. Approximately 30% of LDL is degraded in extrahepatic tissues and 70% in the liver .The primary function of LDL particles is to provide cholesterol to the peripheral tissues (or return it to the liver). They do so by binding to cell surface membrane.LDL uptake is by clathrin coated cell membrane pits which is a receptor mediated endocytosis.

High density lipoprotein (HDL) takes part in both triglyceride and cholesterol metabolism. HDL is synthesized and secreted from both liver and intestine .Apo C and apo E are synthesized in the liver and transferred from liver HDL to intestinal HDL when the latter enters the plasma. Nascent HDL consists of discoid phospholipid bilayers containing apo A and free cholesterol.Lecithin:cholesterol acyltransferase (LCAT) and apo A-I—bind to the discoidal particles, and the surface phospholipid and free cholesterol are converted into cholesteryl esters and lysolecithin. The nonpolar cholesteryl esters move into the hydrophobic interior of the bilayer, whereas lysolecithin is transferred to plasma albumin. Thus, a nonpolar core is generated, forming a spherical, pseudomicellar HDL covered by a surface film of polar lipids and apolipoproteins. The class B scavenger receptor B1 (SR-B1) has been identified as an HDL receptor with a dual role in HDL metabolism. In the liver and in steroidogenic tissues, it binds HDL via apo A-I, and cholesteryl ester is selectively delivered to the cells. In the tissues, on the other hand, SR-B1 mediates the acceptance of cholesterol from the cells by HDL, which then transports it to the liver for excretion via the bile (either as cholesterol or after conversion to bile acids) in the process known as reverse cholesterol transport . HDL_3, generated from discoidal HDL by the action of LCAT, accepts cholesterol from the tissues via the SR-B1 and the cholesterol is then esterified by LCAT, increasing the size of the particles to form the less dense HDL_2. HDL_3 is then reformed, either after selective delivery of cholesteryl ester to the liver via the SR-B1 or by hydrolysis of HDL_2 phospholipid and triacylglycerol by hepatic lipase. This interchange of HDL_2 and HDL_3 is called the HDL cycle. A second important mechanism for reverse cholesterol transport involves the ATP-binding cassette transporter A1 (ABCA1). ABCA1 is a member of a family of transporter proteins that couple the hydrolysis of ATP to the binding of a substrate, enabling it to be transported across the membrane. ABCA1 preferentially transfer cholesterol from cells to HDL.

Lipoprotein metabolism and thyroid hormone

Products of catabolism of VLDL are IDL and LDL metabolism of which will be directly affected by T4(131,132).Uptake of LDL is promoted by T3(133).Hormone replacement therapy in hypothyroid patients enhances receptor mediated clearance of LDL in vivo (89).Since LDL is cholesterol rich particle, clearance of LDL lowers cholesterol levels.Majority of reported data concludes that thyroid hormone lowers serum cholesterol,primarily that within LDL fraction. T3 influences lipid metabolism through the hepatic regulation of rate-limiting enzyme in bile acid synthesis (134), and the sterol regulatory element-binding protein, which in turn activates the low density lipoprotein receptor (LDLr) and other genes directly involved in cholesterol homeostasis (135). Universally it is accepted that in hyperthyroidism there is decline in total LDL (136,137), LDL –cholesterol (138-148) and apolipoprotein B(137-139,149).These effects are reversed by antithyroid drugs(136,137,143). It is also associated with low intermediate density lipoprotein,decreased LDL:HDL ratio. Studies in hypothyroid rats demonstrated that hepatic apoB synthesis undergoes a T3-dependent switch in apoB isoform production after the administration of supraphysiological doses of TH (150). This suggests that thyroid hormone reduces the synthesis of apo B100.

More specifically, these studies revealed the virtual elimination of apoB100 production (150). The molecular mechanism underlying this switch in hepatic apoB isoform synthesis was later shown to reside in a T3-dependent induction of apoB mRNA editing, the posttranscriptional process by which a C to U change is introduced into the nuclear transcript encoding apoB and thereby directly alters the proportions of hepatic apoB isoforms synthesized (151). T3 deficiency leads to elevated cholesterol levels in blood plasma that can be normalized, however, by T3 substitution(152). The liver is central in cholesterol metabolism, balancing hepatic cholesterol synthesis and hepatic uptake of plasma lipoproteins from the circulation against the excretion of hepatic cholesterol andbile acids in the bile (153). T3 can influence the metabolism of cholesterol at several critical steps in theliver (154): the low-density lipoprotein (LDL) receptor (LDL-R), which mediates cholesterol uptake from the circulation, 3-hydroxy-3-methylglutaryl coenzyme A reductase, controlling cholesterol biosynthesis, and cholesterol 7 hydroxylase, the rate-limiting enzyme in the synthesis of bile acids where cholesterol is used as substrate.Studies have demonstrated that a 30 fold increase in hepatic HMG CoA reductase mRNA was due to 5 fold increase in rate of transcription coupled with a marked stabilization of reductase mRNA(155).

Thyroid function disorders lead to changes in lipoprotein metabolism. Both plasma low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) increase in hypothyroidism and decrease in hyperthyroidism. Changes in LDL-C relate to altered clearance of LDL particles caused by changes in expression of LDL receptors on liver cell surfaces. Changes in cholesterol ester transfer activity partly explain changes in HDL-C. It has been suggested that the magnitude of these changes is related to polymorphisms of involved genes. It is well known that thyroid dysfunction leads to changes in lipoprotein metabolism. Plasma low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) levels increase in hypothyroidism and decrease in hyperthyroidism (156). Furthermore, clearance of chylomicron remnants is decreased in hypothyroidism(157). Changes in LDL-C are mainly attributable to altered clearance of LDL-C from plasma by changes in the number of LDL receptors on liver cell surfaces (158). Because the promoter of the LDL receptor gene contains a thyroid hormone responsive element (TRE), T3 could modulate gene expression of the LDL receptor (159). HDL-C metabolism is complex, and changes in plasma levels are due, in part, toremodeling of HDL-C particles by hepatic lipase and cholesterol ester transfer protein (CETP) (160). Activity of both enzymes decreases in hypothyroidism and increases in hyperthyroidism,correlating with plasma HDL-C (161). The magnitude of changes in plasma LDL-C and HDL-Clevels, after restoration of the euthyroid state, varies from patient to patient . The extent of these changes depends both on the severity and duration of the thyroid dysfunction and on the degree of pretreatment hypercholesterolemia (162).

CONCLUSION

The effects of thyroid hormone on the lipid metabolism makes it a potential molecule to develop a class of drugs which can modify the lipid levels.Clinical trials are going on to test the use of thyroid hormone analogues in the treatment of hyperlipidemias. P Reed Larsen suggests that chemical analogs of thyroid hormone can be engineered to create a desired effect, such as suppression of LDL cholesterol levels, without producing systemic thyrotoxicosis (163).Eprotirome ,a thyroid hormone analogue therapy was tried in a 12 week study,which was found to reduce LDL-cholesterol,apo B,Lp(a) and TG.Minimal changes in TSH was seen.No cardiovascular side effects were reported.(164).Several new types of therapy are in clinical trials.It may take several years before any of these drugs get in to market. Issues of long term safety and benefit on cardiovascular outcomes remain to be resolved.

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