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Thyroid Hormone Signaling and the Liver (Manuscript # HEP-20-0303)

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List of abbreviations:

TH, thyroid hormone;
DNL, de novo lipogenesis;
FAO, fatty acid oxidation, beta-oxidation;
TAG, triacylglycerol, triglyceride;
NAFLD, non-alcoholic fatty liver disease;
T3, triiodothyronine;
T4, tetraiodothyronine;
TR, thyroid hormone receptor;
TRE, thyroid hormone response element;
NCoR1, nuclear receptor corepressor 1;
NCoR2/SMRT, nuclear receptor corepressor 2/silencing mediator of retinoid and thyroid hormone receptors;
HDAC3, histone deacetylase 3
RCT, reverse cholesterol transport;

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Abstract

Thyroid hormone (TH) plays a critical role in maintaining metabolic homeostasis throughout life. It is well-known that the liver and the thyroid are intimately linked with TH playing important roles in de novo lipogenesis (DNL), beta-oxidation (FAO), cholesterol metabolism, and carbohydrate metabolism. Indeed, patients with hypothyroidism have abnormal lipid panels with higher levels of low-density lipoprotein (LDL) levels, triglycerides (TAG), and apolipoprotein B levels. Even in euthyroid patients, lower serum free thyroxine levels are associated with higher total cholesterol levels, LDL, and TAG levels. In addition to abnormal serum lipids, the risk of non-alcoholic fatty liver disease (NAFLD) increases with lower free thyroxine levels. As free thyroxine rises, the risk of NAFLD is reduced. This has led to numerous animal studies and clinical trials investigating TH analogs, and TR agonists as potential therapies for NAFLD and hyperlipidemia. Thus, TH plays an important role in maintaining hepatic homeostasis and this continues to be an important area of study. A review of TH action and TH actions on the liver will be presented here.

Thyroid Hormone Signaling and Action

The two main forms of TH are triiodothyronine (T3), the active form of TH, and tetraiodothyronine (T4), a prohormone activated by deiodinases at the cellular and circulatory level. Secretion of TH (primarily T4) from the thyroid gland is regulated by the thyrotrophs of the anterior pituitary, which secrete thyroid-stimulating hormone. The anterior pituitary is controlled by neurons in the hypothalamus which secrete thyrotropin-releasing hormone. After TH is secreted from the thyroid, it is taken up by transporters on cell membranes and deiodinases within the cell specifically regulate the amount of T3 available to act intracellularly.[1, 2]

The actions of T3 are mediated by the thyroid hormone receptor (TR), which is primarily a nuclear receptor that acts as a T3-inducible transcription factor. There are two major isoforms of the TR, TRα and TRß, and expression of TR isoforms is tissue-dependent. TRα is the predominant receptor in bone and heart whereas TRß is the predominant receptor in liver and kidney. The TR forms a heterodimer with another nuclear receptor, the retinoid X receptor (RXR), and binds to thyroid hormone response elements (TREs) in regulatory regions of target genes. Expression of target genes is regulated by TR's recruitment of co-regulator proteins. Classically, in the absence of T3, the nuclear receptor corepressor 1 (NCoR1) and the silencing mediator of retinoid and thyroid hormone receptors (SMRT; NCoR2) are recruited by the TR/retinoid X receptor heterodimer to inhibit gene transcription via histone deacetylation by histone deacetylase 3 (HDAC3). In the presence of T3, co-activators are recruited, while co-repressors are dismissed, and TH responsive gene expression occurs.[1] Figure 1.

There is evidence that response element independent TH signaling and action, termed noncanonical TH signaling, which is mediated by cytoplasmic TRs, or other proteins that bind TH or TRs, exists.[3] Noncanonical TH signaling was explored because of the rapid onset of some actions of TH are inconsistent with genomic actions.[4] Recent work suggests that canonical signaling is the primary mediator regulating the hypothalamic-pituitary-thyroid axis (via TRß) but that serum and liver TAG levels are influenced by noncanonical TH action.[5]

The Role of Co-Activators and Co-Repressors in TH Signaling

Subunits of the corepressor complex include NCoR1, SMRT/NCoR2, and HDAC3.[6] In the presence of TH, TRs release the corepressor complex and recruit coactivator complexes. Coactivator complexes consist of the steroid receptor coactivator (SRC) family, CBP/p300 and other transcriptional activators. As a result of coactivator recruitment, histone acetylation and transcriptional activation occurs. These coregulators bind to multiple nuclear receptors including the TR, peroxisome proliferator-activated receptor, retinoic acid receptor. and liver X receptor integrating lipid homeostasis.[7] Importantly, the ratio between corepressors and coactivators recruited can be altered by their levels of expression. Thus, sensitivity to a set amount of T3 can be enhanced in the absence of corepressors. [8]

Embryonic knock-out (KO) of NCoR1, SMRT, HDAC3 and SRC-3 is lethal so hepatocyte-specific, loss-of-function models have been used and have led to critical insights into these proteins.[9-13] For example, the deletion of NCoR1 in hepatocytes leads to hepatosteatosis due to increased lipogenesis.[14, 15] And, while NCoR1 and SMRT are highly homologous modular proteins, they have distinct roles. For example, SMRT specifically targets RAR action.[15, 16] Additionally, in contrast to NCoR1, if SMRT is deleted globally in a post-natal fashion mice develop profound obesity.[17]

The role of coregulators in TH action has been examined. Mice have been developed that express a hypomorphic NCoR1 allele (NCoRΔID), which cannot interact with the TR.[8, 18] These mice develop normally but demonstrate enhanced TR target gene expression as compared to WT mice, consistent increased sensitivity to TH.[18] Genome wide human studies support the role of NCoR1 in mediating tissue sensitivity to TH with a recent large analysis showing that increased NCoR1 levels are associated with higher free T4 levels.[19] SRC-1-deficient mice have an altered set point of some TH responsive genes, consistent with the idea that the NCoR1/SRC-1 ratio controls sensitivity to TH.[20] Thus, the set-point of the HPT axis is determined by the balance of coactivators and corepressors.

Cholesterol metabolism

Since the 1930s it has been known that TH is one of the most significant regulators of serum cholesterol levels.[21] TH plays several roles in regulating hepatic cholesterol metabolism including synthesis, endocytosis via the LDL-receptor (LDL-R), and peripheral uptake and hepatic excretion via reverse cholesterol transport (RCT). Conflicting data exist with regards to TH status on TAG and HDL levels.

A. Biosynthesis

3-hydroxy-3-methylglutaryl coenzyme A (*HMG-CoA*) reductase catalyzes the rate-limiting step in cholesterol biosynthesis, HMG-CoA to mevalonate.[22, 23] This enzyme is highly expressed in the liver and is the primary site of feedback regulation by cholesterol.[23-25] In addition to TH, estrogen, glucagon, insulin, and glucocorticoids have been shown to alter HMG-CoA reductase expression but it is thought TH has the largest impact on HMG-CoA reductase.[23]

In rats, HMG-CoA reductase activity and cholesterogenesis increase beginning 30 hours after T3 administration and peak within 48-72 hours.[26] HMG-CoA reductase protein and mRNA levels increase and mRNA is stabilized in the presence of T3.[22, 27] Despite the T3-mediated increase in HMG-CoA reductase activity, cholesterol levels drop.[28] No TRE sequences have been found upstream of the HMGR gene but several genes that promote HMG-CoA reductase expression are activated by T3, including upstream stimulatory factor-2 (*Usf-2*), sterol regulatory element binding protein 2 (*Srebp2*), and nuclear factor-y (*NF-Y*).[29]

B. LDL-R Mediated Endocytosis

The hepatic LDL-R mediates endocytosis of LDL, removing LDL from circulation, lowering serum LDL levels. Transcription of LDL-R mRNA is under the control of SREBPs and SREBP2 is particularly important.[30-33] In animal studies, TH induces LDL-R gene expression. [28, 34, 35] This is thought to be from two mechanisms- direct regulation through TR recruitment to the LDL-R

promoter, where TREs are located and indirect by activation of *Srebp2*, which then activates the LDL-R.[36, 37]

TH administration rapidly lowers cholesterol levels and treating hypothyroidism lowers cholesterol levels in humans.[38] This is attributed to an increase in receptor-mediated LDL catabolism, consistent with aforementioned animal studies.[39] TH also lowers LDL levels through reducing proprotein convertase subtilisin/kexin type 9 (*PCSK9*) levels, which is seen with administration of the TH analog eprotirome, including in patients already on maximal statin therapy.[40, 41] Also, subclinical hypothyroidism is associated with higher levels of *PCSK9*.[42]

C. Reverse Cholesterol Transport (RCT)

RCT is a critical process by which the body maintains cholesterol homeostasis. It is the transport of excess cholesterol in peripheral tissue by HDL to the liver for excretion as bile acids.[43] RCT is important because many cells and tissues cannot break down cholesterol and excess cholesterol is toxic to cells.[43] TH acts on both the peripheral tissue and the liver in many steps of this pathway.[44]

Peripherally, cholesterol efflux is in part mediated by adenosine triphosphate (ATP) binding cassette transporter ABCA1 to ApoA1, a lipid-poor apolipoprotein.[43] TH increases ApoA1 levels in HDL by stimulating hepatic lipase, facilitating cholesterol efflux.[35, 45, 46] Cholesteryl ester transfer protein (CEPT) is a transport protein that transfers neutral lipids between lipoproteins, playing a role in RCT and HDL metabolism. CEPT levels correlate with free T4 levels.[47]

Within the liver, TH induces cholesterol 7 alpha-hydroxylase (*Cyp7A1*), the rate-limiting enzyme converting cholesterol into bile acids. Rodent studies showed that T3 and TRß agonists induce Cyp7a1 and increase fecal excretion of bile acids.[35, 48] Although human data at first was mixed, later in vitro studies confirmed that in human hepatocytes, *CYP7A1* is a direct TR target and T3 induces *CYP7A1* in human liver cells.[49] Clinical trial data from patients treated with KB2115, a synthetic TRß agonist, showed a reduction in serum LDL and a dose-dependent increase in serum C4, a plasma

marker of cholesterol to bile acid conversion.[50] Reductions in *CYP7A1* activity are associated with higher levels of TC and LDL, translating to an increase risk of coronary artery disease in humans, supporting this enzymes clinical relevance.[51, 52]

The last step of RCT is excretion of bile acids, or cholesterol, into the bile.[43] This process is mediated by ATP-binding cassette transporters, subfamily G, member 5- ABCG5, and member 8- ABCG8.[53, 54] T3 treatment increases levels of *Abcg5* and *Abcg8* gene expression and increases biliary cholesterol excretion in mice. Mice lacking *Abcg5* show no change in biliary cholesterol excretion with T3, highlighting the role of T3 and *Abcg5* in RCT.[55]

Fatty acid β-oxidation Figure 2.

Fatty acid beta-oxidation (FAO) is the process by which long-chain fatty acids are oxidized for energy during times of energy depletion.[56, 57] Cytosolic lipases mediate the release of free fatty acids (FFA) from TAGs for FAO.[58] Hepatic lipase activity is reduced in hypothyroidism, which is reversed with TH treatment in animal and human studies.[59-61] TH stimulates hepatic lipophagy, increases the amount of lipid laden autophagosomes, where TAGs are broken down to FFAs, and is necessary for FFA delivery to mitochondria.[62, 63]

Mitochondria are known TH targets and play a key role in FAO via the electron transport chain and tricarboxylic acid (TCA) cycle.[63-65] Carnitine palmitoyltransferase-1α (*Cpt1α*) is the rate-limiting enzyme of FAO and TH stimulates *Cpt1* transcription.[66] Indirectly, TH acts through *Sirt1* and *PPARα* to increase levels of Cpt1.[67-69] TH also induces mitochondrial enzymes required for FAO and oxidative phosphorylation including *Mcad, Pdk4, Ucp2, Acot2 and Acox1*.[70-73] Additionally, TH increases mitochondrial biogenesis and mitophagy via induction of the nuclear receptors PGC-1α and ERRα to increase mitochondrial turnover and ensures mitochondrial quality control.[74] Induction of these nuclear receptors may be the primary mechanism driving mitochondrial activity.[74]

De novo lipogenesis

The process by which glucose is synthesized into fatty acids is called de novo lipogenesis. Fatty acids are then esterified to form TAGs and either packaged into very low-density lipoprotein (VLDL), stored as fat droplets, or used for synthesizing and repairing cellular parts. DNL is a tightly controlled metabolic process, active in the fed state and suppressed during fasting.[75] TH is an activator, both directly and indirectly, of DNL.

A. Direct mechanisms

The first, committed step in hepatic fatty acid synthesis is the carboxylation of acetyl CoA to malonyl CoA, catalyzed by acetyl CoA carboxylase alpha (*ACC*).[64] T3 stimulates transcription of *ACC* and a TRE is present in one of the two *ACC* promoters.[76] T3 stimulation of *ACC* is enhanced by binding sterol regulatory element-binding protein-1c (*SREBP1c*), a key enzyme in lipogenesis.[77]

Fatty acid synthetase (*Fasn*) is a multifunctional enzyme that primarily catalyzes the formation of palmitate, a long-chain saturated fatty acid, from acetyl-CoA and malonyl-CoA.[78-80] Similar to *ACC*, *Fasn* expression is stimulated by T3 and a TRE has been localized to the *Fasn* promotor.[81-83]

TH-responsive Spot14 (*Thrsp*; also known as *Spot14*) is induced by TH and required for hepatic DNL.[84-87] There is a TRE in the *Thrsp* promoter in both rodent and human genes and *Thrsp* overexpression promotes TAG accumulation in liver further supporting direct effects of T3 on DNL.[88, 89]

B. Indirect mechanisms

NADPH, which is generated by malic enzyme (*ME*), provides energy for DNL. In chick embryo hepatocytes, T3 increases ME transcription.[90] TREs have been located in the *ME* promoter and T3 activation of *ME* is distinct from *ACC*.[91, 92] In this way, TH helps provide the energy needed for DNL.

There are many transcription factors that work together to activate DNL. Carbohydrate responsive element binding protein (*ChREBP*) is one such factor that has a role in activating several lipogenic genes including *FASN*, *ACC*, and ATP citrate lyase (*ACLY*).[93] Both mouse and human *ChREBP* promoter activity is increased in the presence of T3 consistent with an increase in *ChREBP* gene expression and protein levels is seen with T3 administration.[94, 95] Recent work from our laboratory and others suggest that the TH-signaling system also regulates *ChREBP* levels. *ChREBP* is a potent lipogenic regulator and thus it remains very plausible that TH is able to augment lipogenesis indirectly via *ChREBP*.

SREBP-1c is one of the most important genes in DNL and it's targets include lipogenic genes *FASN*, *ACC*, *ACLY*, and stearoyl-CoA desaturase-1 *(SCD1)*.[96, 97] The data regarding how TH changes levels of *SREBP1c* remains mixed. In mice, *Srebp-1c* has been shown to be negatively regulated by T3.[98] In chick embryo hepatocytes, T3 treatment increases the amount of mature *Srebp-1*.[99] Hep G2 cells, which are human hepatocytes derived from hepatocellular carcinoma, increase *SREBP-1* levels with T3 treatment.[100] Further studies are needed to clarify the exactly how TH might alter SREBP-1 expression.

TH and NAFLD

As free T4 levels drop, the risk of NAFLD increases across the spectrum of euthyroidism and hypothyroidism.[101] Conversely, NAFLD is associated with hypothyroidism.[102] TH, TH metabolites, TRß agonists and liver specific analogs have been studied as potential therapeutics for treating both serum dyslipidemias and as a potential therapy for NAFLD. T4, T3 and TH metabolites, including 3,5-diiodo-L-thyronine (T2) and 3-iodothyronamine (T1AM), have been evaluated.[103-105] Many of the drugs have unwanted side-effects, however, resmetirom may be promising. Sinha et al. (2018) recently extensively reviewed this topic.[106] This remains an active area of study given the need to find effective treatment for NAFLD. The tables below serve as a brief overview of the most studied compounds. Table 1. Table 2.

TH and Carbohydrate Metabolism

Similar to lipid metabolism, the role TH plays in glucose homeostasis and insulin sensitivity is complex and mixed. Hyperthyroidism is associated with elevated levels of basal hepatic glucose production, increased levels of gluconeogenesis and glucose utilization. This is countered by TH actions on skeletal muscle, which increase glucose uptake peripherally.[107] Hypothyroidism is associated with suppressed levels of gluconeogenesis.[68] There is a positive correlation between plasma TH levels and hepatic glucose production in hyperthyroid patients, which resolves with treatment of hyperthyroidism.[108] This is in part due to induction of phosphoenolpyruvate carboxykinase (PEPCK), a key mediator of gluconeogenesis.[109] This data was reviewed by Mullur (2014) and Sinha and Singh et al. (2014).[68, 110]

Summary

TH acts through multiple pathways in the liver to maintain hepatic homeostasis, often in contrasting ways. Despite activation of DNL and an increase in FA uptake, hepatic TAG levels remain stable after TH administration. This is due to the strong induction of FAO, mitophagy, and lipolysis. In terms of cholesterol metabolism, TH induces HMG-CoA reductase, facilitates LDL-R mediated endocytosis, and promotes cholesterol excretion as bile acids. TH analogs and TR agonists remain a promising area of research for the treatment of NAFLD, though unwanted side-effects have hampered development. TH also plays a role in hepatic gluconeogenesis and insulin sensitivity. Given this intimate link, it is clear that further focus on the physiology of TH action in the liver is required.

Figure 1: Gene Regulation by the TR and its co-regulators. In the absence of T3, gene expression is inhibited by the CoR complex. In the presence of T3, CoA's are recruited, allowing gene expression to occur.

Figure 2: DNL (dashed) and FAO (bold) and important enzymes responsive to TH. Substrate for DNL is FFA or glucose, which is metabolized to acetyl-CoA via the TCA cycle. *Fasn, ACC,* and *Thrsp* key enzymes controlling DNL. *Cpt1α, Mcad, Ucp2, and Pdk4* are all involved in FAO and directly or indirectly acted on by TH.

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Table 1: **TR agonists that have been studied for use in the treatment of serum lipid disorders and NAFLD.** Specifically targeting TRß by selecting drugs with higher TRß affinity has been a common strategy to target TH signaling in the liver.

MGL-3196 (Resmetirom) - TR-selective agonist (Binding affinity: TRβ>TRα.)			
	Study Findings	Adverse Events	Source
human	Adults with biopsy proven NASH (fibrosis stages 1 – 3) randomly assigned resmetirom had relative and absolute hepatic fat reduction and reduction/resolution in NAS and NASH features on liver biopsy. Improvement in markers of liver injury and fibrosis (AST, ALT, GGT, PRO-C3) Reduction in serum LDL, TAG, apoB levels.	Diarrhea and nausea.	(111)
	Multiple dose, two-week study of healthy adults showed reduction in LDL, HDL beginning at 50 mg dose and TAG and apoB beginning at 80 mg dose.	No change to blood pressure or heart rate. No increases in liver enzymes.	(112)
KB2115 (eprotirome) – Hepatic specific, TR-selective agonist (Binding affinity: TRβ>TRα).			

	Study Findings	Adverse Events	Source
human	Reduction in serum TC, LDL, apoB in patients with hyperlipidemia. Serum TAG reduction on 200 mg dose but not 100 mg dose.	Transient increase in ALT. No change in heart rate or markers of bone turnover.	(113)
	Reduction in serum TC, LDL, TAG in patients with familial hypercholesteremia.	Dose-dependent increase in ALT and AST. Increase in GGT, ALP, conjugated bilirubin.	(114)
	Reduction in serum TC, LDL, HDL, TAG in statin-treated patients.	Transient, reversible increase in ALT which did not meet statistical significance.	(41)
	Short term safety study. Reduction in serum TC, LDL in overweight patients with total cholesterol >5.0 mmol/liter.	Mild, non-significant increase in serum hepatic enzymes.	(50)
GC-1 (sobetirome) – TR-selective agonist (Binding affinity: TRβ>TRα). Has not been studied in humans.			
	Study Findings	Adverse Events	Source

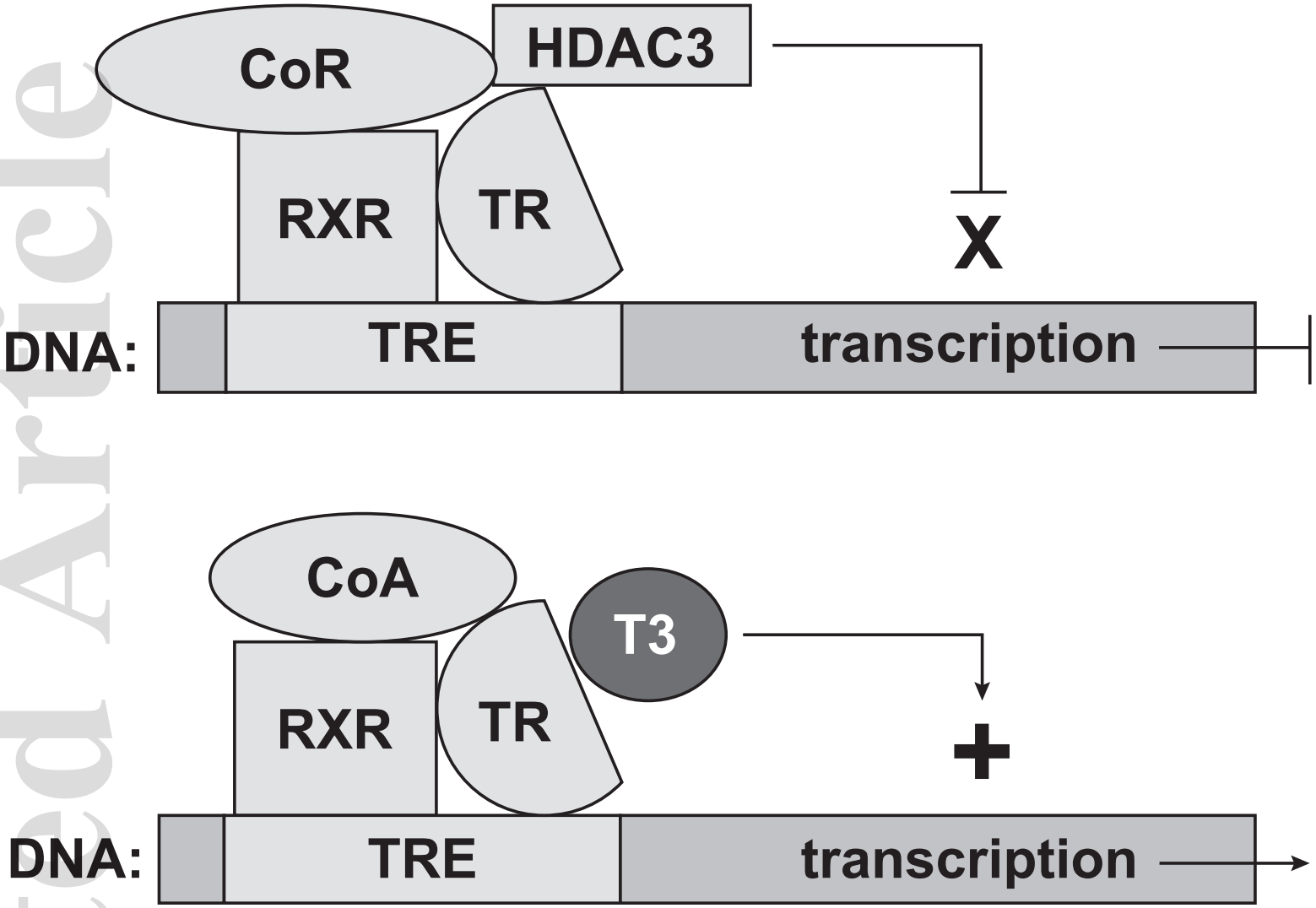
mouse	Reduction in serum LDL, increase in serum HDL, and no change to serum or hepatic TAG in cholesterol-fed mice.	None reported.	(48)
rat	Fisher rats treated with diet-induced fatty liver and steatohepatitis saw reduction in liver TAGs.	Increase in ALT and AST levels. No side effects on heart rate.	(103)
MB07811 (VK2809) - Prodrug that undergoes first pass intrahepatic activation. Selective TRβ agonist.			
	Study Findings	Adverse Events	Source
	Phase 2 randomized, double-blind trial of patients with NAFLD and elevated LDL levels showed reduction of hepatic fat content by at least 30% and reduction in LDL.	No serious adverse events reported.	(115)
	Phase 1 double-blind, randomized control trial assessing safety and tolerability in patients with mildly elevated cholesterol levels. Dose dependent reduction of LDL, TAG, Lp(a), apoB levels.	No serious adverse events reported. Trial lasted 14 days.	(116)

Table 2: **TH and TH metabolites have been studied in the treatment of hyperlipidemia and NAFLD.**

Levothyroxine (LT4) - The inactive form of thyroid hormone, and preferred treatment of hypothyroidism.			
	Study Findings	Adverse Events	Source
human	Euthyroid, diabetic men with steatosis as measured by magnetic resonance spectroscopy were treated with low dose LT4 to achieve TSH 0.34-1.70 mIU/L. After 16 weeks, intrahepatic lipid content was reduced without change to TC, LDL, HDL.	3 men experienced chest discomfort, classified as grade 1 (mild).	(117)
	Hypothyroid patients with TSH > 10 mIU/L were treated with LT4 showed a reduction in the prevalence of NAFLD as measured by ultrasound. Also had reduction in TC, LDL, TAG.	None reported.	(118)

Triiodothyroacetic acid (Triac) – Naturally occurring TH metabolite and analogue with high TR affinity.			
	Study Findings	Adverse Events	Source
human	Euthyroid women with a goiter had a drop in HDL and no change to LDL and TAG serum levels.	Non-significant trend towards reduced bone density at the hip.	(119)
	Reduction in serum TC, LDL, and apoB levels in patients who were surgically hypothyroid s/p total thyroidectomy for thyroid cancer.	Increase ALP and increase excretion of pyridinoline and deoxypyridinoline thought to reflect increase skeletal turnover.	(120)
Diiodothyronine (T2) – Naturally occurring TH metabolite.			
	Study Findings	Adverse Events	Source
rat	Rats on HFD treated with T2 showed reduction in hepatic fat accumulation, serum and liver TAG accumulation, and less body weight gain compared to controls on HFD without T2 treatment.	None reported.	(121)

	Rats on HFD treated with T2 had a reduction in hepatic TAG and ceramide accumulation with induction in autophagy/lipophagy.	None reported.	(104)
3-iodothyronamine (T1AM) – Naturally occurring TH metabolite.			
	Study Findings	Adverse Events	Source
mouse	Spontaneously overweight female mice treated with low and high dose T1AM showed reduction in body weight and TC but an increase in serum TAG on high dose T1AM compared to controls.	None reported.	(105)



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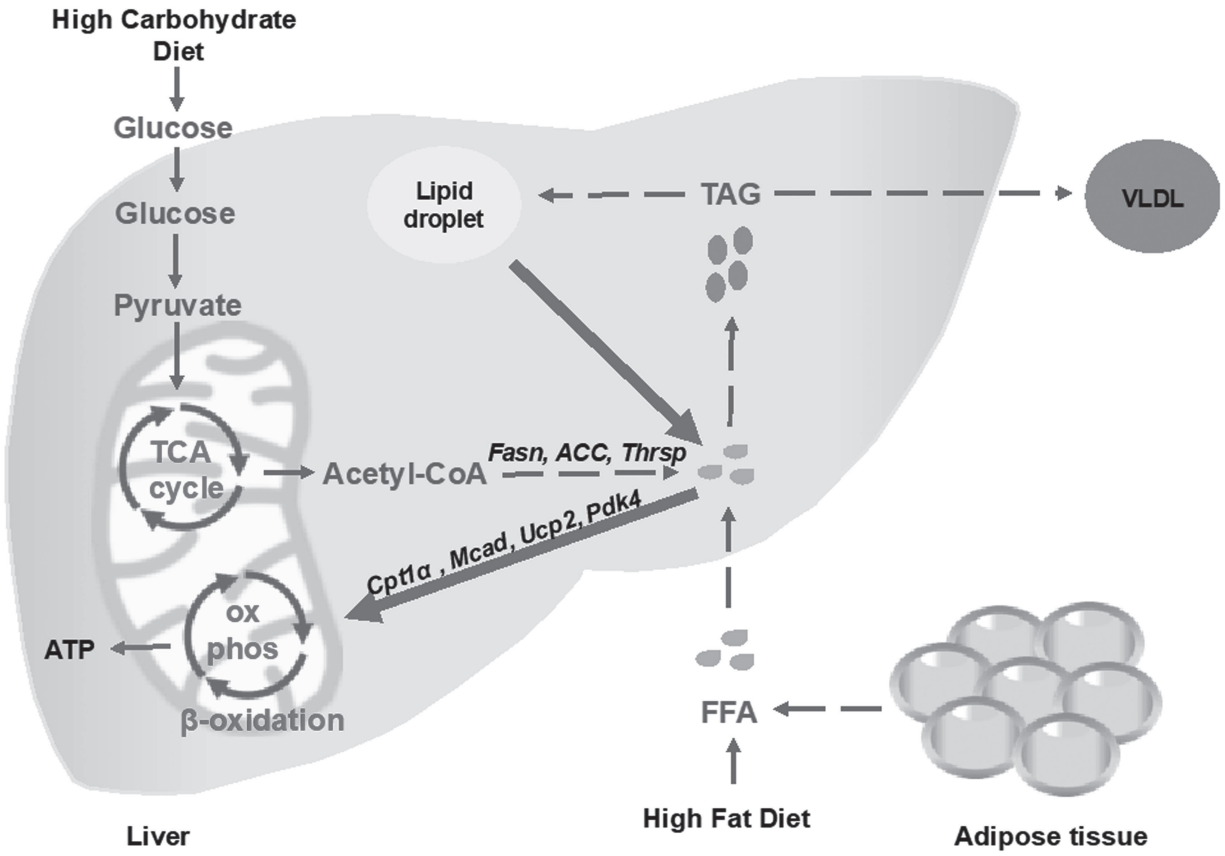

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