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# Direct effects of thyroid hormones on hepatic lipid metabolism

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## Abstract

It has been known for a long time that thyroid hormones have prominent effects on hepatic fatty acid and cholesterol synthesis and metabolism. Indeed, hypothyroidism has been associated with increased serum levels of triglycerides and cholesterol as well as non-alcoholic fatty liver disease (NAFLD). Advances in areas such as cell imaging, autophagy and metabolomics have generated a more detailed and comprehensive picture of thyroid-hormone-mediated regulation of hepatic lipid metabolism at the molecular level. In this Review, we describe and summarize the key features of direct thyroid hormone regulation of lipogenesis, fatty acid β-oxidation, cholesterol synthesis and the reverse cholesterol transport pathway in normal and altered thyroid hormone states. Thyroid hormone mediates these effects at the transcriptional and post-translational levels and via autophagy. Given these potentially beneficial effects on lipid metabolism, it is possible that thyroid hormone analogues and/or mimetics might be useful for the treatment of metabolic diseases involving the liver, such as hypercholesterolaemia and NAFLD.

In mammals, thyroid hormones are critical regulators of metabolism, development and growth. Many of the metabolic activities regulated by thyroid hormones are related to the anabolism and/or catabolism of macromolecules that affect energy homeostasis during different nutritional conditions, such as proteins, lipids and carbohydrates. Indeed, it has long been appreciated that the thyroid hormones $T_3$ and $T_4$ have direct effects on both cholesterol and fatty acid synthesis and metabolism. Increased levels of LDL cholesterol and HDL cholesterol in the serum can be associated with hypothyroidism, whereas their levels are decreased by thyroid hormone administration and in hyperthyroidism1. Similarly, serum levels of triglycerides can be increased in hypothyroidism, and the reverse is observed in hyperthyroidism1. High-dose $T_3$ has previously been used to promote weight loss and treat hypercholesterolaemia in patients with obesity2. Although beneficial effects were reported,

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serious cardiac problems and loss of lean body mass limited any further development of $T_3$ as a therapy2.

Most of the effects of thyroid hormones on hepatic lipid homeostasis are controlled by transcriptional regulation of target genes that are involved in these homeostasis pathways. However, many of the enzymes, transporters, carrier proteins and cell-signalling proteins involved in hepatic lipid homeostasis can also be regulated by metabolite concentration, cellular energy status and post-translational modifications that occur downstream of the transcriptional effects of thyroid hormone3,4. Although much is known about lipid synthesis and metabolism at the biochemical and physiological levels, examination of cell-signalling and metabolomic changes in conjunction with transcriptional effects by thyroid hormones has provided a more detailed understanding of the actions of thyroid hormones on lipids in the liver.

In this Review, we examine the direct thyroid-hormone-mediated effects on hepatic lipogenesis and lipid metabolism, regulation of cholesterol biosynthesis and clearance and thyroid hormone receptor (THR)-independent effects of thyroid hormones on hepatic lipid metabolism as well as the potential application of thyroid hormones and/or thyroid hormone analogues for the treatment of hypercholesterolaemia and non-alcoholic fatty liver disease (NAFLD). Although we primarily focus on the direct effects of thyroid hormone on hepatic lipid metabolism, there is evidence for indirect regulation of hepatic lipid metabolism by thyroid hormone via the central nervous system that might have a notable physiological role5,6.

## Hepatic lipid metabolism

### Thyroid hormone receptors in hepatic lipid metabolism

The THRs are members of the nuclear hormone receptor family and function as ligand-dependent transcription factors7. There are two THR genes (*THRA* and *THRB*) that encode two isoforms, α (THRα) and β (THRβ), respectively. Both isoforms are expressed in most tissues; however, THRβ is the major form expressed in the liver8,9, whereas THRα is highly expressed in heart and bone. THRs are predominantly nuclear owing to nucleo–cytoplasmic shuttling, although a small residual pool of THRs exists in the cytoplasm10. THRs can bind to the thyroid hormone response elements (TREs) of their target genes in the absence of ligand and recruit a co-repressor complex with histone deacetylase activity to repress the transcription of positively regulated genes. Upon ligand binding, co-repressors are released owing to conformational changes in the THR, and a co-activator complex with histone acetyltransferase activity is recruited to the target gene promoter to activate transcription. Additionally, thyroid hormones can regulate transcription by altering the function of other transcription factors11–13 (such as activation of forkhead box protein O1 (FOXO1) by thyroid hormones3,4), modulating cell-signalling cascades through protein–protein interactions (such as the regulation of phosphoinositide 3-kinase (PI3K) by THRβ14) or binding to proteins other than THRs (such as binding to αvβ3 integrin)15.

The role of THRβ in hepatic lipid metabolism was first established in studies of mice with a dominant negative mutation in *Thrb* (*Thrb*$^{PV/PV}$). These mice develop enlarged livers with

hepatic steatosis by 4–5 months of age16. The *Thrb*$^{PV/PV}$ mouse phenotype is attributed to increased peroxisome proliferator-activated receptor-γ (PPARγ) signalling and decreased THR-mediated fatty acid β-oxidation, which leads to lipid accumulation in the liver16. Consistent with these findings, thyroid hormone and THRβ-specific ligands also reduce hepatic triglyceride content17,18. By contrast, mice expressing the dominant negative mutation in the THRα gene locus, *Thra*$^{PV/PV}$, and THRα-null mice, all had reduced liver weights and decreased lipid accumulation16,19 owing to decreased lipogenesis, suggesting that THRα is involved in that process. Surprisingly, unlike the *Thra*$^{PV/PV}$-mutant mice, male mice with a dominant negative Pro398His mutation introduced into the *Thra* gene locus exhibit hepatic steatosis20. This increase in steatosis is due to interference in PPARα binding to its promoter response element by the Pro398His mutant receptor, leading to decreased PPARα-mediated transcription of genes encoding proteins involved in fatty acid oxidation20.

The precise mechanism (or mechanisms) that underlies the differences in hepatic lipid metabolism between *Thra*$^{PV/PV}$ and *Thrb*$^{PV/PV}$ and the various THRα mutant and knockout mice is not known; however, differential recruitment of co-repressors could have a contributing role. Notably, mice with double and single knockouts of the nuclear co-repressors silencing mediator of retinoid acid and THR (SMRT; also known as NCOR2) and nuclear receptor co-repressor (NCOR1) show notable changes in hepatic lipid synthesis and storage, especially when NCOR1 is knocked out21. In addition to THR, other important regulators of intracellular thyroid hormone levels (such as deiodinases22) and thyroid hormone transporters23 can also regulate hepatic lipid metabolism.

## Thyroid hormones and hepatic fatty acid uptake

Thyroid hormones stimulate lipolysis from fat stores in white adipose tissue and from dietary fat sources to generate circulating free fatty acids (FFAs), which are the major source of lipids for the liver (Fig. 1). FFAs enter hepatocytes via protein transporters such as fatty acid transporter proteins (FATPs), liver fatty acid binding proteins (L-FABPs) and fatty acid translocase (FAT; also known as CD36)24. A study from 2009 suggests that fatty acid transporters are regulated by THRs25. Radiolabelled fatty acid infusion studies have shown that fatty acid uptake from triglyceride-rich lipoproteins is increased in the presence of thyroid hormones in a tissue-specific manner as hyperthyroidism increased triglyceride-derived fatty acid uptake in oxidative tissues such as liver and muscle, whereas hypothyroidism increased triglyceride-derived fatty acid uptake in white adipose tissue and decreased its uptake in liver25. In addition, hepatic FAT and FABP expression levels are suppressed in animal models of postnatal hypothyroidism26,27. Although these studies indicate that thyroid hormones might be important in regulating FFA uptake in the liver, the precise mechanisms by which thyroid hormones alter FFA uptake are currently unclear.

## Hepatic lipogenesis and triacylglycerol assembly

Triglyceride production can come from exogenous FFAs in the circulation or intracellular FFAs generated by glycolysis and lipogenesis from glucose supplied by excess dietary intake. The process of converting glucose to fatty acids, termed ‘de novo lipogenesis’, is tightly regulated by hormones and nutritional status. De novo lipogenesis and subsequent

triacylglycerol synthesis involve a number of key enzymatic processes, including elongation and desaturation of fatty acid precursors, production of fatty acids, triacylglycerol synthesis and VLDL assembly28. Thyroid hormones are a well-known inducer of hepatic de novo lipogenesis, as they stimulate the transcription of several key genes involved in lipogenesis in rodents such as fatty acid synthase (*Fasn*), acetyl-CoA carboxylase alpha (*Acc1*; also known as *Acaca*), malic enzyme (*Me*) and thyroid hormone-responsive Spot14 homologue (*Thrsp*; also known as *Spot14*) (Fig. 1). After their synthesis, FFAs are typically esterified to triacylglycerol, after which they can be packaged into VLDL, stored as fat droplets or used to make and/or repair cellular constituents.

Thyroid hormones regulate the expression of many of the genes involved in lipogenesis by binding to their specific THR29–32. However, in addition to regulating lipogenic gene expression directly, thyroid hormones also indirectly control the transcriptional regulation of hepatic lipogenesis as a result of their effects on the expression and activities of other transcription factors, such as sterol regulatory element-binding protein 1C (SREBP1C), liver X receptors (LXRs) and carbohydrate-responsive element-binding protein (ChREBP), which all have crucial roles in hepatic lipogenesis33. Thyroid hormones directly induce the gene expression of the LXRs34 and ChREBP35 in hepatic cells via the recruitment of THRs to the promoters of these genes.

The mechanism for the regulation of SREBP1C by thyroid hormone in humans is not known. In mice, one study reported that *Srebp1c* transcription was negatively regulated by thyroid hormone via a putative negative thyroid hormone response element (nTRE)36, but another group has shown that *Srebp1c* transcription is also upregulated by non-genomic thyroid hormone signalling37. Although thyroid hormone increases the expression of genes involved in de novo lipogenesis, it does not cause a net increase in mouse hepatic levels of triacylglycerol38. The major reason for this lack of increase is due to upregulated metabolism of FFAs by thyroid hormones; however, downregulation of the key desaturase enzyme stearoyl-CoA desaturase 1 (SCD1) by thyroid hormones as observed in humans might also contribute39. The mechanism by which thyroid hormones downregulate SCD1 in humans is not yet understood, but it seems to occur in a TRE-independent manner39. Similarly, thyroid hormones decrease the activity of glycerol-3-phosphate acyltransferase 3 (GPAT3)40, which is needed for triacylglycerol synthesis in rat hepatocytes.

Thyroid hormones also reduce apolipoprotein B100 (Apo B100) levels in the livers of rats, which decreases the production of VLDL and LDL41. Indeed, in humans, serum levels of triglycerides are normal or slightly decreased in hyperthyroidism, whereas they are normal or increased in hypothyroidism1,42. Thyroid hormones also modulate the relative amounts of circulating lipoproteins as highlighted by the fact that levels of HDL are increased in hypothyroidism owing to the decreased activity of cholesteryl ester transfer protein (CETP) and hepatic lipase1.

In addition to their effects on the neutral lipids and triacylglycerol, thyroid hormones seem to decrease the biosynthesis of hepatic sphingolipid and phospholipid species. In 2005, a report showed that thyroid hormones increase de novo sphingolipid synthesis in the livers of rats43. However, using metabolomics analyses, we found that the administration of thyroid

hormones prevents the production of hepatic sphingolipids in rats that are fed a high-fat diet44. Furthermore, thyroid hormones can alter the intracellular concentration of several phospholipid species, such as phosphatidylcholine, phosphatidylserine and cardiolipin45.

## Lipolysis and hepatic fat oxidation

Although thyroid hormones stimulate lipogenesis, there is a net reduction in total hepatic triglycerides during hyperthyroidism46 due to fatty acid metabolism occurring at a higher rate than fatty acid synthesis. Mobilization, degradation and β-oxidation of fatty acids by thyroid hormones all contribute to the increased overall rate of fatty acid metabolism (Fig. 1). In particular, thyroid hormones increase the activity of hepatic lipases, lipophagy and mitochondrial oxidation of fatty acids, which are the primary processes used by the liver to reduce steatosis.

The catabolic actions of thyroid hormone on hepatic lipids are primarily mediated by the mobilization of FFAs from stored triacylglycerol and their subsequent β-oxidation. The release of FFAs from triacylglycerol stores in hepatocytes is mediated by the enzymatic activities of cytosolic lipases47. The two major cytosolic lipases in the liver are hepatic lipase and adipose triglyceride lipase (ATGL; also known as PNPLA2). The expression and activity of hepatic lipase are sensitive to thyroid hormone status48. In both animals and humans, hypothyroidism is associated with a decline in hepatic lipase activity, which can be recovered with thyroid hormone replacement therapy49 (Fig. 1). The regulation of ATGL expression and activity by thyroid hormones in hepatic cells is less clear. However, a 2015 study did suggest that thyroid hormones increase the recruitment of ATGL to lipid droplets to facilitate lipolysis50. Zinc-α2-glycoprotein, which is encoded by *AZGP1*, stimulates lipolysis in humans and induces a reduction in body fat in mice51. Interestingly, thyroid hormones increase the expression of zinc-α2-glycoprotein in hepatic cells, which might also contribute to the lipolytic action of thyroid hormones52.

## Regulation of lipophagy by thyroid hormones

Lysosomal acid lipase/cholesteryl ester hydrolase (LAL) is another critical regulator of hepatic triacylglycerol lipolysis in addition to the cytosolic lipases53. The delivery of triacylglycerols to lysosomes is mediated by an autophagic process known as lipophagy54,55. This specific type of autophagy involves the engulfment of triacylglycerol stored in the fat droplets by autophagosomes, followed by autophagosomal–lysosomal fusion that delivers the triacylglycerols to lysosomes for degradation and hydrolysis into FFAs54,55. Thyroid hormones increase the number of lipid-laden autophagosomes and lysosomes in both human hepatic cells and mouse liver in a THR-dependent manner56 (Fig. 1). Moreover, inhibition of autophagy and/or lipophagy in vivo markedly reduces thyroid-hormone-induced acylcarnitine flux and ketogenesis, which is the final step in β-oxidation56. Although the precise mechanism for induction of lipophagy by thyroid hormones is not clear, the induction of β-trophin (C19orf80; also known as ANGPTL8) by thyroid hormones might be a necessary priming step for the recruitment of autophagic machinery to triacylglycerols stored in fat droplets57.

Observations from our group suggest that thyroid hormones also activate lysosomal biogenesis by inhibiting mammalian target of rapamycin complex 1 (MTORC1) activity and activating the transcriptional activity of transcription factor EB (TFEB; R.A.S., B.K.S. and P.M.Y., unpublished observations), which controls the expression of many genes that encode proteins involved in autophagy and lysosomal genes and is known to regulate lipophagy58. Additionally, thyroid hormones activate NAD-dependent protein deacetylase sirtuin 1 (SIRT1) to decrease FOXO1 acetylation and phosphorylation4. These post-translational modifications increase the transcriptional activity and nuclear localization of FOXO1, which, in turn, induces the expression of several genes associated with autophagy59.

## Effects of thyroid hormones on peroxisomal fat oxidation

A primary function of peroxisomal β-oxidation is to shorten very long-chain fatty acids (>16 carbon atoms) so that they can be further metabolized within mitochondria. Researchers have known for decades that thyroid hormones regulate both the number and expression levels of the peroxisomal enzymes60–66. However, the mechanisms by which thyroid hormones regulate peroxisome synthesis and function are currently unknown.

## Regulation of mitochondrial fatty acid oxidation by thyroid hormones

Mitochondria are the major sites for fatty acid metabolism and are classic targets for thyroid hormone action in the liver67. Thyroid hormones regulate mitochondrial biogenesis and function in hepatocytes via coordinated signals emanating from both the nuclear and mitochondrial genome68. The nuclear regulation of mitochondrial content by thyroid hormones is primarily due to regulation of the PPARγ co-activator 1α (PGC1α)–nuclear respiratory factor 1 (NRF1)–transcription factor A, mitochondrial (mtTFA) axis68. Thyroid hormones are known to increase protein levels of PGC1α, which acts as a co-transcriptional regulation factor that induces mitochondrial biogenesis by activating NRF1 to promote the expression of mtTFA68. In addition to the PGC1α–NRF1–mtTFA axis, THRs have been reported to be localized within mitochondria and to regulate transcription from the mitochondrial genome69. The rate-limiting enzyme for mitochondrial β-oxidation is carnitine *O*-palmitoyltransferase 1, liver isoform (CPT1-Lα), which is transcriptionally stimulated by thyroid hormones in hepatocytes70 (Fig. 1) and inhibited by malonyl-CoA that is generated by acetyl-CoA carboxylase during fatty acid synthesis. In 2013, thyroid-hormone-mediated activation of SIRT1 activity was shown to induce PGC1α activity and regulate *CPT1A* mRNA expression71. Thyroid hormones also regulate *CPT1A* gene expression by increasing PPARα signalling in the liver12. Notably, PPARα is required for thyroid-hormone-mediated induction of fibroblast growth factor 21 (FGF21), a protein that regulates hepatic fat catabolism72. Thyroid hormones increase the expression of other mitochondrial enzymes needed for fatty acid β-oxidation, including medium-chain acyl-CoA dehydrogenase (MCAD)73, pyruvate dehydrogenase kinase isoform 4 (PDK4)74 and mitochondrial uncoupling protein 2 (UCP2)75. Moreover, data from our group suggest that oestrogen-related receptor-α (ERRα; also known as ESRRA) also regulates thyroid-hormone-induced expression of CPT1-L and mitochondrial β-oxidation via PGC1α (R.A.S., B.K.S. and P.M.Y., unpublished observations).

In addition to stimulating mitochondrial activity and fatty acid β-oxidation, thyroid hormones couple lipophagy with the removal of mitochondria that have been damaged by reactive oxygen species (ROS) generated from an increase in oxidative phosphorylation. In 2015, we showed that thyroid hormones maintain the quality of hepatic mitochondria by autophagic removal of mitochondria, known as mitophagy76. ROS generated by thyroid-hormone-mediated oxidative phosphorylation initiate a $Ca^{2+}$–calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2)–5′-AMP-activated protein kinase (AMPK) signalling cascade. The activation of this signalling cascade results in the activation of serine/threonine-protein kinase ULK1 (a key mitophagic protein), which translocates into the mitochondria. ULK1 recruits autophagy-related proteins (that is, ATG proteins), which are required for nascent autophagosome formation, and initiates mitochondrial clearance76. Additionally, hepatic mitophagy seems to be coupled with mitochondrial biogenesis as both processes are induced by thyroid hormones76,77. This tight association between mitochondrial activity and mitochondrial turnover ensures the maintenance of a healthy mitochondrial pool that can sustain increased lipid handling induced by thyroid hormones.

## Cholesterol biosynthesis and clearance

Thyroid hormones help maintain the basal serum levels of cholesterol that are needed to meet the body's normal requirements for cellular synthesis and turnover (Fig. 2). Thyroid hormones regulate serum levels of cholesterol by stimulating cholesterol biosynthesis, export (primarily as VLDL and LDL), reverse transport from peripheral tissues, hepatic reuptake via LDL receptors (LDLRs) and conversion into bile acids in the liver78. In rats, thyroid hormones induce the expression of hydroxymethylglutaryl-CoA reductase (*Hmgcr*) and farnesyl pyrophosphate synthetase (*Fdps*) to promote cholesterol synthesis in the liver79. Thyroid hormones also strongly induce the gene and protein expression of Apo A1 and scavenger receptor class B member 1 (SRB1), which increases cholesterol efflux from peripheral tissues to HDL in the reverse cholesterol transport pathway80,81. Furthermore, thyroid hormones can increase HDL metabolism by stimulating CETP activity82.

In rats, the major mechanism by which thyroid hormones decrease serum levels of cholesterol is through the induction of hepatic LDLRs to increase cholesterol clearance81. LDLR is also regulated by SREBP2, which itself is transcriptionally regulated by thyroid hormones83 in rodents and humans. Furthermore, thyroid hormones can increase the transcription of both mouse and human LDLR-related protein 1 (*LRP1*), a lipoprotein involved in the removal of chylomicron remnants and VLDL84. Within the liver, thyroid hormones also increase the expression of rat cholesterol 7α-hydroxylase (CYP7A1), the rate-limiting enzyme that converts cholesterol into bile acids in the reverse cholesterol transport pathway, and decrease expression of Apo B protein, the major apolipoprotein in LDL, to reduce serum levels of LDL cholesterol even further85,86. In addition, thyroid hormones can promote the excretion of bile acids in the liver and intestines, which are the last steps of the reverse cholesterol transport pathway, by stimulating mouse ATP-binding cassette subfamily G member (*Abcg5*/*Abcg8*) complex gene transcription, directly and independently from its effects on LXRs87.

Finally, in addition to the transcriptional regulation of genes involved in cholesterol synthesis, reverse cholesterol transport and bile secretion88, thyroid hormones might use microRNAs (miRNAs) to regulate serum levels of cholesterol. Thus, thyroid hormones induce expression of human miR181d, which decreases the expression of caudal-type homeobox protein 2 (CDX2), a transcription factor that activates sterol *O*-acyltransferase 2 (SOAT2). SOAT2 is critical for the conversion of cholesterol to cholesterol esters89, the preferred form of cholesterol within LDL. This example of thyroid hormones using miRNAs demonstrates that thyroid hormones might use a non-TRE-mediated mechanism to lower serum levels of cholesterol.

## Non-transcriptional effects

Previously, research suggested that the only mode of action of thyroid hormones was the transcriptional regulation of target genes via THRs binding to TREs and the recruitment of co-activators to increase RNA polymerase binding to the basal transcriptional protein complex. Surprisingly, $T_3$ and $T_4$ exert biological actions that do not require THRs binding to DNA or the absence of THRs90,91. Thus, $T_3$ activates PI3K–RACα serine/threonine-protein kinase (AKT) signalling via a non-genomic mechanism92. This signalling mechanism has been implicated in the regulation of *FASN* expression by $T_3$. The inhibition of $T_3$-mediated induction of *FASN* expression by PI3K and extracellular-signal-regulated kinase 1 (ERK1) inhibitors further suggests that there are other non-transcriptional mechanisms that control hepatic lipogenesis by thyroid hormones32. Thyroid hormones can also regulate hepatic lipid metabolism by activating the cAMP–protein kinase A (PKA) and $Ca^{2+}$–AMPK pathways93–95.

In addition to $T_3$ and $T_4$, the thyroid hormone derivative 3,5-diiodothyronine has been extensively studied for its ability to regulate hepatic lipid metabolism via non-THR-mediated signalling96. In vitro and in vivo studies show that 3,5-diiodothyronine increases fatty acid oxidation in hepatocytes and supresses the lipogenic pathways97–103. Notably, 3,5-diiodothyronine directly activates SIRT1, which leads to the deacetylation of PGC1α and activation of its transcriptional activity in order to induce expression of the genes required for fatty acid oxidation104. 3,5-Diiodothyronine also modulates the activities and localization of hepatic lipases to increase lipid mobilization from fat droplets50. In addition, in a mouse model of familial hypercholesterolaemia, 3,5-diiodothyronine exerts beneficial effects on lipid metabolism by reducing serum levels of LDL cholesterol by an LDLR-independent mechanism86. Thus far, there is no evidence to suggest that reverse $T_3$ regulates transcription by nuclear THRs or has any non-transcriptional effects on metabolism and/or cell signalling.

## TSH and hepatic lipid metabolism

Although hypothyroidism-associated increased hepatosteatosis is thought to result from a decrease in serum levels of thyroid hormone, studies have suggested that when the levels of TSH in the serum are high, TSH binds to TSH receptors in the liver to modulate lipid metabolism. In vivo rodent studies show that TSH receptors are expressed in hepatocytes and can be stimulated by TSH to induce hepatosteatosis via SREBP1C105. TSH also

supresses the synthesis of hepatic bile acid via an SREBP2–hepatocyte nuclear factor 4α (HNF4α)–CYP7A1 signalling pathway106. Moreover, TSH inhibits cholesterol synthesis by increasing AMPK-mediated phosphorylation of HMGCR to inhibit HMGCR activity107. Collectively, these findings support the notion that TSH itself can regulate both hepatic lipid and cholesterol homeostasis; however, in vivo studies confirming the direct action of TSH, independent from thyroid hormone, are very difficult to interpret because of the concomitant reduction in the serum levels of thyroid hormone.

## Metabolic diseases of the liver

### Thyroid hormone effects on hypercholesterolaemia

Since the early 1950s, we have known that thyroid hormone status in humans is inversely related to levels of LDL cholesterol108. Moreover, thyroid hormone supplementation leads to improvements in lipid and lipoprotein profiles in patients with hypothyroidism109. Early studies of levothyroxine and the thyroxine enantiomer dextrothyroxine showed promising effects in reducing serum levels of LDL cholesterol but were discontinued owing to serious adverse effects from cardiac, bone and muscle toxicity110–112. Nonetheless, promising results from these studies led to the development of liver-selective and THR isoform-specific thyroid hormone mimetics as potential lipid-lowering agents113,114. The first liver-selective thyromimetic, 3,3-dibromo-3′-pyridazinone-1-thyronine (L-94901), was described in 1986 (REF. 115) (Table 1). This compound has cholesterol-lowering effects in hypothyroid rats without any deleterious effects on the heart115. Similarly, three other compounds (CGH-509A, CGS-23425 and T-0681) have shown efficacy in lowering serum levels of LDL cholesterol116,117; however, the development of these compounds for clinical use has not been actively pursued.

2,5-Diiodothyropropionic acid (DITPA) is the first THR-selective thyromimetic to display slightly higher affinity for THRβ than THRα. In a clinical trial that lasted for 6 months, DITPA therapy moderately decreased serum levels of total cholesterol and LDL cholesterol in patients with congestive heart failure118. GC-1 (also known as sobetirome) belongs to the first generation of more specific THRβ agonists and reduces serum levels of cholesterol and triglyceride in animal models of obesity119. In a phase I study, a 2-week treatment regimen of GC-1 reduced serum levels of LDL cholesterol by up to 41% in healthy participants120. Furthermore, GC-1 reduces the cholesterol content in plaques along the aortic arterial walls of apolipoprotein E (APOE)-deficient mice121. Another THRβ-specific thyromimetic, KB-141, decreases plasma levels of cholesterol in both rodents and primates, primarily through stimulation of the reverse cholesterol pathway122. The THRβ-specific analogue KB2115 (also known as eprotirome) has similar effects on plasma levels of cholesterol and is the first thyroid hormone mimetic designed for the treatment of dyslipidaemia that has reached phase III trials. When administered with statin therapy, eprotirome further decreases levels of LDL cholesterol, triglycerides and lipoproteins in patients with hypercholesterolaemia123. Another THRβ-specific thyromimetic, MGL-3196, has been developed for the treatment of hypercholesterolaemia and is currently in a phase I trial124.

Another class of thyromimetics are liver-selective prodrugs and/or their metabolites that bind to THR with a high affinity. Hepatic CYP450 enzymes activate some of these compounds, a

process that generates the active metabolites, which have a short half-life. Therefore, most of the thyromimetic actions of this class of thyromimetics are confined to the liver, and thus, adverse effects in non-hepatic tissues are minimized. One such drug, MB07811, is effective in reducing serum levels of LDL cholesterol and total cholesterol in rabbits, dogs and monkeys125. This drug is safe on the basis of a phase Ib clinical study126 and was carried forward for a phase II trial127.

Although the majority of patients with mild hypothyroidism have little or no derangements in serum levels of triglyceride and VLDL1, some patients with severe hypothyroidism exhibit hypertriglyceridaemia1. Similar to levothyroxine replacement in hypothyroidism, thyroid hormone mimetics can also decrease hypertriglyceridaemia, a known risk factor for atherosclerosis that is independent of levels of LDL cholesterol. Thus, GC-1 reduces serum levels of triglyceride by >50–60% in hypothyroid and normal mice128. Similarly, both KB-141 and MB07811 markedly reduce serum levels of triglycerides in normal and obese mice17,129.

## Effects of thyroid hormones in NAFLD

NAFLD is a global epidemic with an incidence of 30% or more among adults in both developed and developing countries130. NAFLD is considered to be a hepatic manifestation of the metabolic syndrome and is closely associated with the development of other metabolic risk factors such as type 2 diabetes mellitus, hyperlipidaemia and coronary artery disease131. NAFLD represents a spectrum of liver diseases that includes excessive accumulation of lipids in the hepatocytes that is initially benign (hepatosteatosis) but progresses to a more advanced stage with inflammation (non-alcoholic steatohepatitis (NASH)) and culminates in fibrosis accompanied by increased inflammation, apoptosis and scarring of liver tissue (cirrhosis)132. Patients with NAFLD also have an increased risk of hepatocellular carcinoma133. The long-term complications of NAFLD have made it the most common cause for liver transplantation in the United States133.

Several epidemiological studies conducted in countries from around the world show an inverse relationship between serum levels of thyroid hormone and the incidence of NAFLD134,135. Similarly, Asian patients with NAFLD had significantly lower levels of serum-free $T_4$ than control patients in a cross-sectional study of 878 elderly Chinese euthyroid participants (11.12 ± 1.43 pmol/l versus 11.58 ± 1.47 pmol/l; $P < 0.001$)136. In another report, subclinical hypothyroidism, even within the range of upper-normal TSH levels, was significantly associated with NAFLD in a concentration-dependent manner137. Overt hypothyroidism is even more closely associated with NAFLD and is a risk factor that is independent from other known metabolic risk factors, thus confirming the strong clinical relationship between these two conditions137,138.

In paediatric populations, children with obesity who have increased TSH levels have more severe hepatosteatosis than children with obesity but normal TSH139. Of note, two studies from 2014 and 2016 demonstrate that serum levels of free $T_3$, free $T_4$ and the free $T_3$:free $T_4$ ratio are inversely associated and that TSH levels are associated with NAFLD in the general population, even among those within the reference range for euthyroid participants140,141. In addition to the deleterious effects of decreased serum levels of thyroid hormone on

hepatic lipid homeostasis, it is possible that increased TSH per se might promote the development of NAFLD by stimulating lipogenesis in the liver105. In addition, the intrahepatic thyroid hormone concentration and/or thyroid hormone signalling could be decreased in the livers of patients with NAFLD142–144. Although the cause (or causes) of such resistance to thyroid hormone action in the liver is not clear, studies from the past three decades suggest that intracellular fatty acids impair THR activity145. Additionally, the mRNA and protein expression levels of type 1 iodothyronine deiodinase (DIO1), the enzyme that converts $T_4$ to $T_3$ in the liver, are very sensitive to serum levels of thyroid hormone. Therefore, decreased expression and activity of DIO1 could lead to intrahepatic hypothyroidism by reducing the conversion of $T_4$ to $T_3$. Of note, decreased serum $T_3$ and increased reverse $T_3$ have been reported in patients with advanced NASH146.

Data from our groups suggest that reduced intrahepatic concentrations of thyroid hormone transporters, THR and nuclear co-activators of THR are other mechanisms that could potentially regulate thyroid hormone signalling in NAFLD (R.A.S., B.K.S. and P.M.Y., unpublished observations). Notably, exogenous thyroid hormones, thyroid hormone analogues and a novel glucagon–thyroid hormone hybrid molecule can all reduce hepatosteatosis in NAFLD147,148. Many factors exist that contribute to the progression of NAFLD, such as diet, endocrine status and gene polymorphisms; thus, decreased intrahepatic concentrations of thyroid hormones might be found in only a subset of patients with NAFLD. Further studies of serum markers for thyroid hormone action on hepatic function, such as sex hormone-binding globulin, ferritin, cholesterol or acylcarnitines, could provide potential tools to evaluate intrahepatic thyroid hormone status149,150.

Several preclinical studies of thyroid hormone analogues have demonstrated their efficacy in reducing lipid accumulation in animal models of NAFLD96 (Table 1). GC-1 is a synthetic thyroid hormone analogue that preferentially binds THRβ1 in an isoform-specific manner and has the same affinity for THRβ1 as $T_3$. Similar to $T_3$, GC-1 prevents and reverses hepatosteatosis in rats fed a diet that induces NASH148. Furthermore, GC-1 lowers liver weight, the liver weight:body weight ratio and serum levels of triglycerides in these same animals. In addition to decreasing hepatic lipid accumulation, GC-1 also decreases lipoperoxidation and reduces liver injury, as the increases in serum levels of aspartate transaminase (AST) and alanine transaminase (ALT) fall after GC-1 treatment148. These findings suggest that GC-1 is an excellent thyromimetic for the treatment of NAFLD provided it has the requisite safety profile.

MB07811 is an oral THRβ-specific agonist that targets the liver to reduce hepatic steatosis in rats and mice17. MB07811 reduces hepatic triglycerides by increasing hepatic β-oxidation, mitochondrial respiration rates and expression of genes involved in β-oxidation. The aforementioned thyromimetic KB2115 can also improve NAFLD in rats151. In addition, 12 weeks of therapy with KB2115 lowered serum levels of cholesterol in patients who were taking statins, suggesting that KB2115 is a safe chronic therapy, as the authors of the study did not report cardiac or bone toxicity123. Unfortunately, despite these beneficial effects, the clinical trials of KB2115 were terminated as a parallel 12-month dosing study in dogs showed adverse effects on cartilage152. These findings suggest that thyroid hormone analogues have other adverse effects in addition to those known to occur in bone and heart.

Researchers will need to perform careful preclinical testing for adverse effects before clinical studies for other compounds are undertaken.

In 2016, one group reported the generation of a hybrid molecule, which contains both thyroid hormone and glucagon147, that reduces hepatosteatosis in NAFLD without bone or heart adverse effects. This compound has opened an exciting new area for synthetic bi-hormonal therapy of metabolic diseases, as one hormone targets a specific tissue whereas the other has intracellular activity. The thyroid hormone metabolite 3,5-diiodothyronine is also able to reduce hepatic insulin resistance and decrease hepatosteatosis, suggesting that it is an attractive candidate for the treatment of NAFLD, particularly as it does not seem to have the systemic adverse effects of $T_3$ and $T_4$ (REF. 44).

A noteworthy point is that 15% of patients with NASH have hypothyroidism compared with 7.2% of patients with normal liver function153. A 2012 study found that patients with NASH had a higher risk of hypothyroidism than patients with NAFLD without NASH and that hypothyroidism increased the risk of NASH154. A further study showed that NASH and advanced fibrosis occurred more frequently in both patients who were hypothyroid and patients who were subclinically hypothyroid155. These studies suggest that hypothyroidism and subclinical hypothyroidism also increase the risk of NASH in addition to hepatosteatosis142. Although these observations suggest a potential beneficial effect of thyroid hormones on NASH, thus far, there have not been any animal or human interventional studies demonstrating that thyroid hormones or thyroid hormone analogues can prevent or block the progression to NASH.

Decreased levels of thyroid hormone have been associated with an increased incidence of hepatocellular cancer in humans156. In addition, thyroid hormones have been shown to be anti-neoplastic in liver cancers157. Hepatocellular cancer occurs in patients with NASH, and many THR mutations have been reported in patients with hepatocellular cancer158. The presiding hypothesis is that THRs serve as tumour suppressors, primarily by inhibiting WNT signalling, the expression of cyclin-dependent kinase 2 (CDK2) and cyclin E and by stimulating TGFβ signalling. The suppression and stimulation of these signalling pathways are thought to lead to cell cycle arrest at the G1 phase159. Therefore, the suppressive activity of thyroid hormones is hypothesized to be blocked in the presence of mutant THRs. However, there have been no studies that definitively demonstrate that thyroid hormones can prevent hepatocellular cancer in animals or patients with NASH and/or fibrosis.

## Conclusions and future perspectives

Advances in our understanding of the cellular and molecular mechanisms of fatty acid and cholesterol synthesis and metabolism have led to a better appreciation for the role of thyroid hormones and THRs in maintaining normal hepatic lipid homeostasis. We now understand the lipid derangements that can occur in hypothyroidism and hyperthyroidism at a deeper, more mechanistic, level. It is possible that some of the control points in the signalling pathways that regulate triglyceride and cholesterol levels within the liver and serum are modulated by thyroid hormones and thus could be potential drug targets for thyromimetics or other drugs. Additionally, serum levels of free $T_3$, free $T_4$ and levels of TSH characterize

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the sufficiency of the hypothalamic–pituitary–thyroid axis; however, they might not accurately reflect intrahepatic levels of thyroid hormones, which can be reduced in the livers of patients with NAFLD.

Studies from the past several years suggest that thyroid hormone analogues that are specific for THRβ or THRβ in the liver, or analogues that are bi-hormonal, are potential therapies for metabolic conditions such as hypercholesterolaemia and NAFLD. Although the actions of thyroid hormones on hepatic fatty acid and cholesterol metabolism have been topics of interest to basic scientists and clinicians for many years, the new advances in our knowledge in these areas that are presented in this Review provide stronger rationales and tools for using thyroid hormone or thyromimetic drugs to treat hepatic metabolic disorders.

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**Key points**

- Thyroid hormones regulate hepatic lipid metabolism in a cell autonomous manner
- Thyroid hormone receptors (THRα and THRβ) differentially regulate hepatic lipid metabolism
- Thyroid hormone induces the expression of genes that encode proteins involved in hepatic lipogenesis
- Thyroid hormone couples autophagy to mitochondrial fat oxidation to induce ketogenesis
- Thyroid hormone induces reverse cholesterol transport
- Thyroid hormone analogues and/or mimetics offer therapeutic alternatives for treatment of lipid-associated hepatic pathologies

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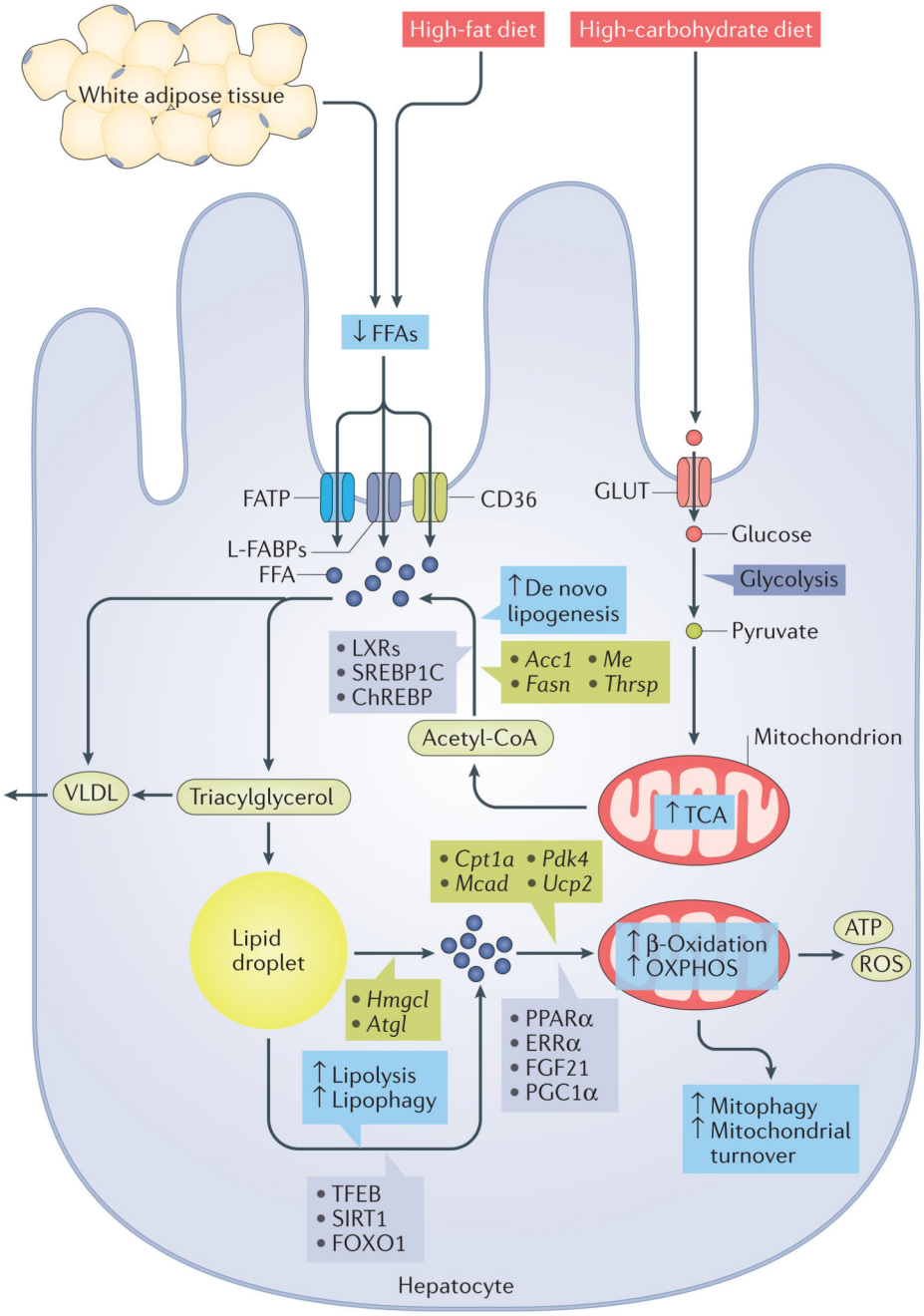


**Figure 1. Thyroid hormone effects on hepatic lipid metabolism.**

Thyroid hormone stimulates lipolysis from fat stores in white adipose tissue and from dietary fat sources (high-fat diets) to generate free fatty acids (FFAs) that enter the hepatic cells via protein transporters such as fatty acid transporter protein (FATP), liver fatty acid binding protein (L-FABP) and CD36. Thyroid hormone induces de novo lipogenesis (DNL) via the transcription of several key lipogenic genes such as *Acc1*, *Fasn, Me* and *Thrsp*. In addition, thyroid hormone indirectly controls the transcriptional regulation of hepatic DNL by regulating the expression and activities of other transcription factors such as sterol

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regulatory element-binding protein 1C (SREBP1C), liver X receptors (LXRs) and carbohydrate-responsive element-binding protein (ChREBP). DNL is also driven by the influx of high levels of carbohydrate or glucose derived from high-carbohydrate diets via glucose transporters (GLUTs), which are shuttled to FFA generation. FFAs are typically esterified to triacylglycerol and subsequently packaged into VLDL for export or stored as intracellular lipid droplets. Triacylglycerol stored as lipid droplets can also be hydrolysed back to FFAs via classic lipases and lipophagy (by regulating transcription factor EB (TFEB), NAD-dependent protein deacetylase sirtuin 1 (SIRT1) and forkhead box protein O1 (FOXO1)), undergo mitochondrial β-oxidation by the activity of various co-activators or nuclear receptors (such as peroxisome proliferator-activated receptor-α (PPARα), oestrogen-related receptor-α (ERRα), fibroblast growth factor 21 (FGF21) and PPARγ co-activator 1α (PGC1α)) and target the transcription of genes such as *Cpt1a*, *Mcad* (also known as *Acadm*), *Pdk4* and *Ucp2*. ↑/↓ depicts the positive or negative effect that thyroid hormone action has on the cellular process shown, respectively. OXPHOS, oxidative phosphorylation; ROS, reactive oxygen species; TCA, tricarboxylic acid.

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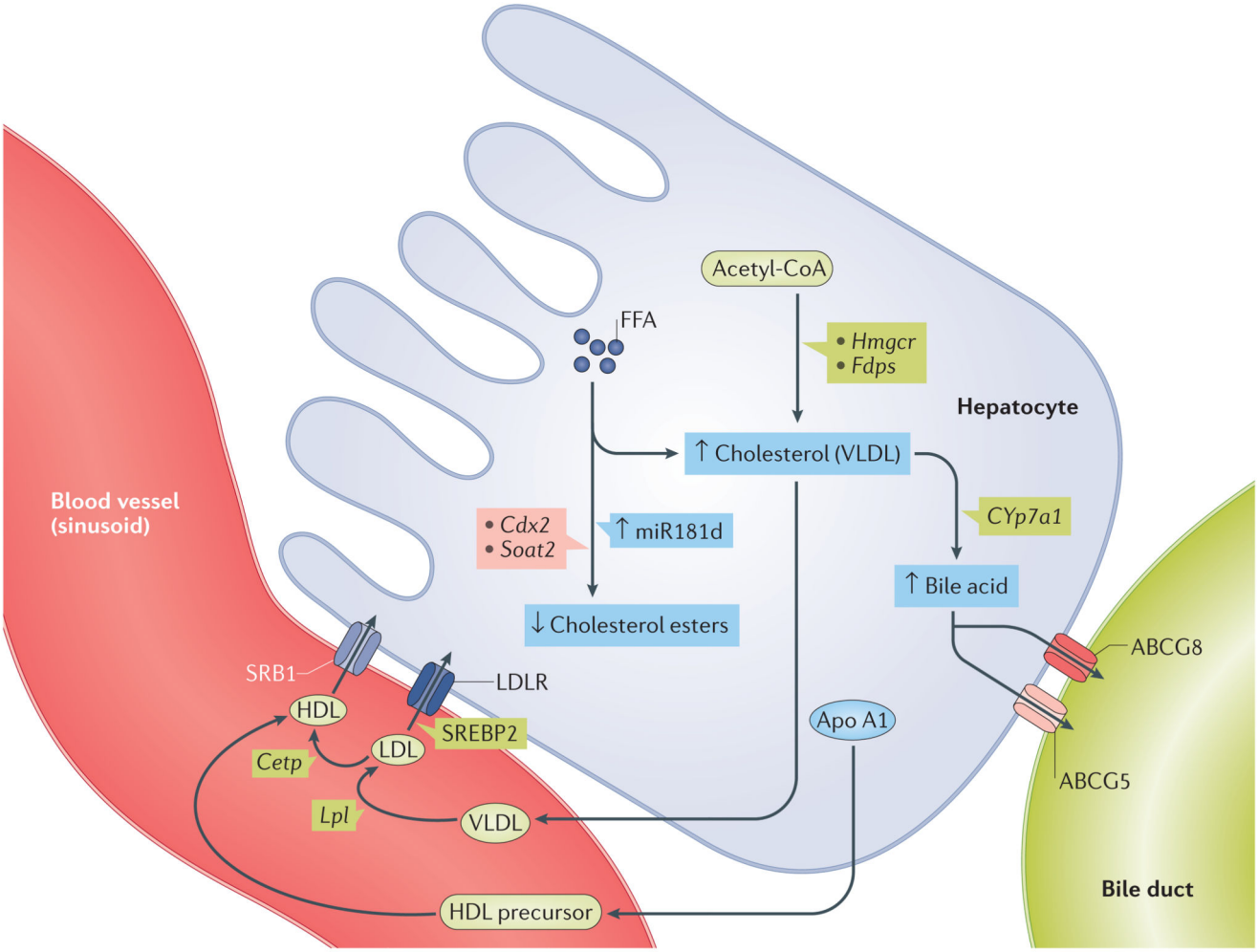


**Figure 2. Thyroid hormone regulation of cholesterol biosynthesis and clearance.**

Thyroid hormone stimulates cholesterol formation (mostly as VLDL) from its precursors and acetyl-CoA. Thyroid hormone increases the expression of *Hmgcr* and *Fdps* to promote hepatic cholesterol synthesis. Thyroid hormone also strongly induces the gene and protein expression of apolipoprotein A1 (Apo A1), scavenger receptor class B member 1 (SRB1) and sterol regulatory element-binding protein 2 (SREBP2), which then increase LDL receptor (LDLR) levels to increase cholesterol efflux from peripheral tissues to HDL through the reverse cholesterol transport pathway. Thyroid hormone increases HDL metabolism by stimulating cholesteryl ester transfer protein (CETP) activity. Thyroid hormone also increases expression of cholesterol 7α-hydroxylase (CYP7A1), which converts cholesterol into bile acids in the reverse cholesterol transport pathway. Thyroid hormone promotes the excretion of bile acids by directly increasing ATP-binding cassette subfamily G member 5/8 (*Abcg5*/*Abcg8*) transporter gene transcription. Additionally, thyroid hormone induces miR181d expression, which then decreases the expression of caudal-type homeobox protein 2 (CDX2) transcription factor and the *Soat2* gene to inhibit

cholesterol ester formation. ↑/↓ shows increase or decrease in thyroid hormone action, respectively. FFA, free fatty acid.



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## Table 1

### Thyroid hormone analogues and/or mimetics and their biological effects

| Thyroid hormone analogues and/or mimetics | Biological effects | Species | Refs |
|---|---|---|---|
| L-94901 | Lowers cholesterol | Mouse | 115 |
| CGH-509A | Lowers cholesterol | Rat | 117 |
| CGS-23425 | Lowers cholesterol | Rat | 117 |
| T-0681 | Lowers cholesterol | Mouse | 116 |
| DITPA | Lowers cholesterol | Human | 118 |
| GC-1 (sobetirome) | Lowers cholesterol, triglyceride, blood glucose, adipose tissue and atherosclerosis | Mouse | 119–121 |
| KB-141 | Lowers cholesterol, triglyceride, adipose tissue and blood glucose | Monkey, rat and mouse | 122 |
| KB2115 (eprotirome) | Lowers cholesterol and triglyceride | Human | 123 |
| MGL-3196 | Lowers cholesterol and triglyceride | Human | 124 |
| MB07811 | Lowers cholesterol, triglyceride and blood glucose | Human | 126 |
| 3,5-Diiodothyronine | Lowers blood glucose and triglyceride and improves hepatic insulin resistance | Rat | 44,103 |