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REVIEW

Cross-talk between the thyroid and liver: A new target for nonalcoholic fatty liver disease treatment

Yue-Ye Huang, Aaron M Gusdon, Shen Qu

Yue-Ye Huang, Shen Qu, Department of Endocrinology and Metabolism, Shanghai 10th People's Hospital, School of Medicine, Tongji University, Shanghai 200072, China
Shen Qu, Department of Endocrinology and Metabolism, Nanjing Medical University, Nanjing 210029, Jiangsu Province, China
Aaron M Gusdon, Department of Neurology and Neuroscience, Weill Cornell Medical College, New York, NY 10065, United States
Author contributions: Qu S wrote the manuscript; Huang YY provided all the reference and edited the manuscript; Gusdon AM was also involved in editing the manuscript.
Correspondence to: Shen Qu, Professor, Department of Endocrinology and Metabolism, Shanghai 10th People's Hospital, School of Medicine, Tongji University, No301 Middle Yanchang Road, Shanghai 200072, China. qushencn@hotmail.com
Telephone: +86-021-66302531 Fax: +86-021-66302531
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Abstract

Nonalcoholic fatty liver disease (NAFLD) has been recognized as the most common liver metabolic disease, and it is also a burgeoning health problem that affects one-third of adults and is associated with obesity and insulin resistance now. Thyroid hormone (TH) and its receptors play a fundamental role in lipid metabolism and lipid accumulation in the liver. It is found that thyroid receptor and its isoforms exhibit tissue-specific expression with a variety of functions. TRβ1 is predominantly expressed in the brain and adipose tissue and TRβ2 is the major isoform in the liver, kidney and fat. They have different functions and play important roles in lipid metabolism. Recently, there are many studies on the treatment of NAFLD with TH and its analogues. We review here that thyroid hormone and TR are a potential target for pharmacologic treatments. Lipid metabolism and lipid accumulation can be regulated and reversed by TH and its analogues.

Key words: Thyroid hormone; Thyroid hormone receptor; Nonalcoholic fatty liver disease; Obesity

Core tip: The clinical findings that nonalcoholic fatty liver disease (NAFLD) patients have more prevalence of subclinical hypothyroidism and patients with hypothyroidism may develop fatty liver give the evidence that dyslipidemia and fatty liver have some relationship with thyroid dysfunction, and thyroid hormone and its receptor may be a therapeutic target for NAFLD. We review here that thyroid hormone and TR are a potential target for pharmacologic treatments that can benefit NAFLD patients a lot.

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INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a burgeoning health problem that affects one-third of adults and is associated with obesity and insulin resistance. Its pathogenesis remains poorly understood, and therapeutic options are limited. Here, we discuss recent treatment insights into NAFLD that focus primarily on its relationship with thyroid function.

THYROID HORMONE AND ITS RECEPTORS

Thyroid hormone (TH) regulates cellular and tissue me-

tabolism throughout the body. The active form of TH, 3,3',5-triiodo-L-thyronine (T3), controls gene expression in target tissues by binding to its cognate nuclear receptors (TRs), which are ligand-inducible transcription factors. In the presence of T3, TRs activate transcription by binding to T3-response elements (TREs) of the target genes and forming coactivator complexes containing histone acetyltransferase activity[1]. In the absence of T3, TRs recruit corepressors, such as nuclear receptor corepressor (NCoR) and silencing mediator of retinoid and thyroid receptors, which form a complex with transducin β-like protein 1 and histone deacetylase 3 that has histone deacetylase activity on the promoters of target genes that repress basal transcription[2].

Two TR isoforms, TRα and TRβ, have been identified. They share high sequence homology in the functional DNA and T3-binding domains, but differ greatly in the lengths and sequences of the amino-terminal A/B domains. Studies of mice deficient in either of these two TR genes or both TR genes indicate that TR isoforms have both redundant roles and specific functions[3]. TRα1, TRβ1, and TRβ2 isoforms bind T3; however, TRα2 does not. TRα2 functions, at least *in vitro*, as a TRα1 and TRβ1 antagonist[4]. Activation of TRs affects a multitude of physiological processes ranging from embryonic development to maintenance of energy homeostasis in adults. Excess TH can result in some therapeutically desirable effects, such as increased metabolic rate, increased lipolysis, lowered cholesterol levels, improved heart contractility, and suppressed thyroid-stimulating hormone (TSH) levels. At the same time, systemic thyrotoxicosis can lead to undesirable effects, including tachycardia, arrhythmia, muscle wasting, nervousness, fatigue, and loss of bone mass[5]. A series of studies in mice with inactivation or mutation of different TR isoforms[6-12], as well as studies in patients with resistance to TH, suggest that TR isoforms selectively mediate tissue-specific TH responses[13].

There is a tissue-specific expression pattern for TRs. TRβ2 is the major isoform in the liver, kidney, and thyroid, and TRβ1 is predominantly expressed in the brain and adipose tissue[14-17]. There is also a general consensus that TRα mediates the effects of TH on the heart, whereas TRβ mediates its effects on plasma cholesterol and TSH secretion. Therefore, the development of T3 analogues with preferential binding to TRβ may induce the beneficial effects of T3 while avoiding undesirable side effects.

EFFECTS OF TH ON HEPATIC LIPID METABOLISM

TH maintains lipid homeostasis *via* its effects on gene expression in target organs, including the liver and adipose tissues. T3 has profound and diverse effects on lipid metabolism and lipid accumulation in the liver. In the liver, TRβ is responsible for mediating the majority of the actions of T3, whereas in other tissues, such as the heart and brown adipose tissue (BAT), TRα is the main mediator of TH effects[18,19].

T3 exerts strong effects on hepatic carbohydrate and lipid metabolism in both anabolic and catabolic states. Elevated levels of T3 in hyperthyroidism are associated with increased lipolysis and lower body weight. In contrast, lower levels of T3 in hypothyroidism are associated with cold intolerance, weight gain, reduced lipolysis, and cholesterol clearance. Mice devoid of all TR isoforms exhibit decreased body temperature and basal metabolic rate, growth retardation, and an increased amount of fat tissue[20,21]. T3 increases the expression of several genes involved in hepatic lipogenesis by increasing the expression of lipogenic genes such as fatty acid synthase (FAS), Thrsp (Spot14), acetyl-CoA carboxylase (ACC1)[22], acyl-CoA synthetase 5, fatty acid transporter protein, malic enzyme, and glucose-6-P dehydrogenase. It also induces the expression of genes involved in fatty acid oxidation, such as fatty acid transporter (Fat), fatty acid-binding protein, lipoprotein lipase (LPL)[23], and carnitine palmitoyltransferase-1 alpha (Cpt-1α)[24]. Cpt-1α is a key rate-limiting enzyme in mitochondrial fatty acid oxidation. Many of these metabolic genes (*e.g.*, malic enzyme, Fas, and Cpt-1α) in the liver are directly regulated by the interaction between T3 and TR, as TREs have been identified in promoters of these genes[25]. However, the regulation of lipid homeostasis by T3 is complex and tissue dependent, as it involves the coordinated regulation of several target tissues, mainly adipose tissue and the liver. The tissue-dependent manner of lipid regulation *via* TH was uncovered using knockin mice harboring identical mutations in the TRα (TRα1PV mouse) and TRβ (TRβPV mouse) genes. TRα gene mutations dramatically decrease the mass of both the liver and white adipose tissue (WAT). In contrast, TRβ gene mutations markedly increase liver mass with an excess deposition of lipids, but no significant abnormality is observed in WAT. Molecular studies showed that the expression of lipogenic genes was decreased in WAT of TRα1PV mice, but not in TRβPV mice. Markedly increased lipogenic enzyme expression and decreased fatty acid β-oxidation activity contribute to adipogenic steatosis and lipid accumulation in the liver of TRβPV mice. In contrast, reduced expression of genes critical for lipogenesis mediates decreased liver mass with lipid scarcity in TRα1PV mice.

TH action is mediated by a complex interaction between TRs and other nuclear receptors, including the PPARs and the liver X receptor (LXR), which respond to circulating metabolite levels[26,27]. Cross-talk between TH signaling and these nutrient-responsive factors occurs through a variety of mechanisms, including but not limited to competition for retinoid X receptor (RXR), transcriptional co-factors, DNA-binding sites, or transcriptional cofactors.

Studies in several animal models, including the PPARα KO mouse, have demonstrated that hepatic steatosis occurs when nuclear receptors involved in metabolic control are inactivated. In both humans and animal

models, obesity is associated with lipid deposition in the liver, which can lead to fibrosis and even cirrhosis[28,29]. In both human and murine microarray studies, the greatest change in liver gene expression as a consequence of hepatic lipid accumulation is the downregulation of a set of T3-responsive genes, including genes involved in energy metabolism[19,30].

Autophagy of lipid droplets, termed "lipophagy," is a major pathway of lipid mobilization in hepatocytes[31-33], and its inhibition has been linked to the development of fatty liver and insulin resistance[34-36]. TH is a well-known metabolic regulator of energy expenditure that activates fatty acid β-oxidation in mammals[37]. However, the precise mechanism of this effect has not yet been revealed. During periods of starvation, autophagy degrades cytoplasmic materials, producing amino acids and fatty acids that can be used to synthesize new proteins or generate ATP for cell survival[38]. Derangement of the autophagic response has been implicated in several pathological hepatic conditions, such as ischemia, reperfusion, viral infections, acute injury, α1-antitrypsin deficiency, hepatocellular carcinoma, alcoholic liver disease, and NAFLD[36,39,40].

"Lipophagy"[31] leads to the degradation of intracellular lipid droplets, and this process is believed to provide fatty acid substrates for β-oxidation[41]. Such lipophagy is coupled to the effects of T3 stimulation in altering the levels of a broad array of hepatic lipid-related metabolites, which is consistent with a key role for T3 as an important regulator of fatty acid delivery to mitochondria and mitochondrial metabolism. Autophagy is a stress-induced catabolic process, conserved in all eukaryotes, involving fusion of autophagosomes with lysosomes and resulting in degradation of cytoplasmic cargo. T3 induces lipophagy in cultured liver cell lines, and it induces hepatic autophagy *in vivo* coupled with ketogenesis, resulting in a lipolytic-metabolomic profile. Moreover, TH stimulation of autophagy and lipid metabolism is TR dependent and modulated by NCoR corepressor activity. These findings suggest that T3 plays an important role in the regulation of hepatic autophagy, which is a critical step for the amelioration of NAFLD.

THYROID MALFUNCTION IN DYSLIPIDEMIA AND NAFLD PATIENTS

The most frequent metabolic syndrome disorders are dyslipidemia and NAFLD. The pathogenesis of NAFLD is a complex, multifactorial process characterized by insulin resistance and other endocrine disorders. TH can stimulate the expression of uncoupling proteins in the mitochondria of adipocytes and skeletal muscle and modulate adrenergic receptor numbers by enhancing responsiveness to catecholamines[42], thus controlling metabolic and energy homeostasis. TH influences body weight, thermogenesis, lipolysis, and metabolism of cholesterol and bile acids. Thyroid dysfunction is associated with hepatic lipid peroxidation and oxidative stress in experimental models[43,44], raising the question of the role of hypothyroidism in NAFLD patients. The prevalence of hypothyroidism in patients with NASH is twice as high as in controls[45]. NASH is twice as common in postmenopausal compared with premenopausal women, and hormonal replacement therapy decreases the risk of steatosis. This association seems plausible, taking into consideration that thyroid dysfunction can lead to hyperlipidemia, obesity, and insulin resistance[46], all of which are major components of metabolic syndrome[47,48] and are implicated in the pathogenesis of NAFLD.

The mechanism of hypothyroidism-induced hyperlipidemia has been shown to be due to a decrease in cholesterol excretion and a marked increase in apoB lipoproteins due to decreased catabolism and turnover secondary to a reduced number of low-density lipoprotein (LDL) receptors on the liver cell surface[49]. Thus, common findings in patients with hypothyroid are increased levels of total and LDL cholesterol. In hypothyroidism, a reduced removal rate of triglycerides from plasma and an accumulation of intermediate LDL (IDL) have also been reported. Thus, NAFLD can develop in hypothyroid patients due to increased LDL and deposition of triglycerides in the liver.

In addition to hyperlipidemia and obesity, hypothyroidism has been associated with insulin resistance[50]. There is a strong link between insulin resistance and excessive deposition of triglycerides in hepatocytes. A recent study investigated the frequency of metabolic syndrome in hypothyroid patients. These authors studied 100 patients with overt hypothyroidism, 100 patients with subclinical hypothyroid, and 200 healthy controls. The authors found that the HOMA index was higher in the hypothyroid group than in the control ($P = 0.008$) and subclinical hypothyroid groups ($P = 0.014$). Metabolic syndrome prevalence was 44% in the hypothyroid group and 33% in the control group ($P = 0.016$)[51].

Thyroid dysfunction commonly occurs in the elderly population, and overt thyroid dysfunction is associated with some liver abnormalities. Xu *et al*[52] performed a cross-sectional study among 878 euthyroid elderly Chinese, in which 227 (25.85%) subjects fulfilled the diagnostic criteria for NAFLD. Patients with NAFLD had significantly lower levels of serum-free thyroxine (FT4) than control patients (11.12 ± 1.43 pmol/L *vs* 11.58 ± 1.47 pmol/L; $P < 0.001$). The prevalence of NAFLD decreased in proportion to progressively higher serum FT4 levels ($P < 0.001$). Age-, gender-, and smoking status-adjusted correlation analysis showed that serum FT4 levels were negatively correlated with body mass index, waist circumference, and triglyceride and serum uric acid levels (all with $P < 0.05$). Stepwise logistic regression analysis showed that serum FT4 level was significantly associated with the risk for NAFLD. These results suggest that thyroid function, even within the reference range, is associated with NAFLD in elderly people.

TH may interfere with the regulation of lipid and carbohydrate metabolism, and correlate with the severity

of NAFLD; however, these results are still under debate. Mazo *et al*[53] performed a retrospective evaluation of clinical and metabolic correlations between hypothyroidism and NAFLD. Clinical, biochemical, and histological investigations of 103 NAFLD patients exhibiting drug-treated hypothyroidism were conducted. Steatosis was present in 32.0% of the population and nonalcoholic steatohepatitis was present in 68.0%. Females were the majority in both groups. A link was identified between hypothyroidism and markers of glucose and lipid homeostasis, but not with severity of NAFLD.

Hepatic steatosis can progress to hepatocyte injury, inflammation, and fibrosis in the presence of potential synergistic factors such as oxidative stress from β-oxidation, increased expression of inflammatory cytokines by NF-κB-dependent pathways, and adipocytokines[54-56]. This is called the "multi-hit hypothesis" and has been used to describe the pathogenesis of NAFLD[57]. Lipid peroxidation and oxidative stress are both believed to play important roles in the progression of disease from steatosis to NASH[56,58]. Previous experimental data regarding thyroid dysfunction and hepatic lipid peroxidation have shown that, in a state of hyperthyroidism, TH elevation stimulates the metabolic rate, possibly leading to reactive oxygen species generation, lipid peroxidation, and liver cell damage[43,44]. On the other hand, reduced levels of oxidative stress accompanying hypothyroidism might be responsible for the experimental results indicating that hypothyroidism protects from hepatic fibrosis[59]. This concept correlates with the absence of an association between hypothyroidism and steatosis or NASH. In some studies, mainly with obese NAFLD patients, hypothyroidism appears to contribute to the major components of metabolic syndrome, leading primarily to the accumulation of fat. However during progression to NASH, additional results are needed, with emphases on the role of oxidative stress and lipid peroxidation.

POTENTIAL PHARMACOLOGIC TREATMENT WITH TH IN BASIC RESEARCH AND CLINICAL PRACTICE

The current pharmacologic treatment for NAFLD is limited, relying mostly on weight loss[60-62]. Insulin-sensitizing agents, such as thiazolidinediones, have been shown to decrease hepatic steatosis by promoting fat redistribution to the liver.

TH

T3 treatment in rats stimulates thermogenesis from fatty acid β-oxidation as a result of lipolysis and increased caloric intake[63]. Lipogenesis is also stimulated by T3. However, this effect occurs to a much lesser extent and is mainly seen in the context of restoration of depleted fat stores after a period of energy deficit[64]. Previous studies have shown that treatment with T3 itself, or with selective agonists of TRβ, may improve the metabolic status of diet-induced obese rodents[13,65,66].

Recently, mice treated with T3 showed a dose-dependent increase in hepatic *FGF21* expression with significant induction at doses as low as 100 μg/kg. *FGF21* expression is downstream of the nuclear receptor peroxisome proliferator-activated receptor α (*PPAR*α). PPARα knockout mice treated with T3 did not have an increase in FGF21 expression, indicating that hepatic regulation of *FGF21* by T3 in the liver is *via* a *PPAR*α-dependent mechanism. In contrast, in WAT, *FGF21* expression was suppressed by T3 treatment, with other T3 targets being unaffected. In cell culture studies with an *FGF21* reporter construct, three transcription factors were required for the induction of *FGF21* expression: *TR*β, *RXR*, and *PPAR*α. These findings indicate a novel regulatory pathway whereby T3 positively regulates hepatic *FGF21* expression, presenting a novel therapeutic target for diseases such as NAFLD.

In addition, prolonged T3 treatment promotes the catabolism of fatty acids by increasing the expression and activity of Cpt-1α, a rate-limiting enzyme for transport and β-oxidation of fatty acids in the mitochondria[25]. Thus, the catabolism of fatty acids is a cardinal metabolic feature of prolonged hyperthyroidism[63]. T3 stimulates the shuttling of free fatty acids (FFAs) for delivery into mitochondria[67]. While this process is well described, the T3-regulated cellular pathways that lead to the generation of FFAs from stored lipid droplets in the liver are not very well understood. In that way, T3 treatment is beneficial to patients with high TSH and high FFA levels.

TRα inhibition

TRα or TRβ gene knockout mouse models display a range of defects in lipogenesis, lipolysis, cholesterol metabolism, and fatty acid oxidation. Francois[68] reported that TRα gene knockout mice are protected from diet-induced hepatic insulin resistance. With the goal of examining whether TRα would be a potential therapeutic target to prevent diet-induced NAFLD and insulin resistance, they assessed insulin action in high-fat diet fed TRα gene knockout (Thra-0/0) and wild-type mice using hyperinsulinemic-euglycemic clamps combined with $^{3}H/^{14}C$-labeled glucose to assess basal and insulin-stimulated rates of glucose and fat metabolism. Body composition was assessed by ^{1}H magnetic resonance spectroscopy, and energy expenditure was measured using indirect calorimetry. Thra-0/0 mice were lighter, leaner, and manifested greater whole-body insulin sensitivity than wild-type mice during the clamp, and these results could be attributed to increased insulin sensitivity both in the liver and peripheral tissues. Increased hepatic insulin sensitivity could be attributed to decreased hepatic diacylglycerol content, resulting in decreased activation of protein kinase C and increased insulin signaling. Therefore, TRα inhibition represents a novel pharmacologic target for the treatment of NAFLD, obesity, and type 2 diabetes.

TRβ agonists

The use of TR agonists for the treatment of NAFLD has not been considered viable because TH increases FFA flux from the periphery to the liver, induces hepatic lipogenesis, and therefore could potentially contribute to steatosis. However, specifically targeting TRβ could provide therapeutic benefit while avoiding the potential of nonselective TR agonists to increase hepatic FFA accumulation. MB07811 is an orally active liver-targeted TRβ agonist. Cable[29] reported a reduction of hepatic steatosis in rats and mice after treatment with MB07811.The purpose of these studies was to assess the effects of MB07811 on whole body and liver lipid metabolism of normal rodents and rodent models of hepatic steatosis. Animal studies showed that MB07811 markedly reduced hepatic steatosis as well as plasma FFA and triglyceride levels. In contrast to MB07811, treatment with T3 induced adipocyte lipolysis *in vitro* and *in vivo*, but had a diminished ability to decrease hepatic steatosis. This finding suggests the influx of FFA from the periphery to the liver may partially counteract the antisteatotic activity of T3. Clearance of liver lipids by MB07811 results from accelerated hepatic fatty acid oxidation, a known consequence of hepatic TR activation, as reflected by increased hepatic mitochondrial respiration rates, changes in hepatic gene expression, and increased plasma acyl-carnitine levels. Transaminase levels remained unchanged or reduced, and no evidence of liver fibrosis or other histological liver damage was observed after treatment with MB07811 for up to 10 wk. Additionally, MB07811, unlike T3, did not increase heart rate or decrease pituitary TSHβ expression. Therefore, MB07811 represents a novel class of liver-targeted TR agonists with beneficial LDL cholesterol-lowering properties that may provide additional therapeutic benefit to hyperlipidemic patients with concomitant NAFLD.

LXR activator

TH action is mediated by interactions between TRs and nuclear receptors such as LXR, and Thrsp is known to be regulated by a variety of transcription factors, including TR, PXR, and CAR. Thrsp has been reported to be a lipogenic gene in cultured hepatocytes, suggesting an important role for Thrsp in the pathogenesis of NAFLD. Hepatic overexpression of Thrsp increases triglyceride accumulation with enhanced lipogenesis in the liver of C57Bl/6 mice, whereas hepatic Thrsp gene silencing attenuates the fatty liver phenotype in db/db mice. It has been reported that the LXR activator TO901317 induces Thrsp expression in the liver of wild-type and LXRβ gene-deficient mice, but not in LXRα or LXRα/β double knockout mice. Emerging *in vitro* evidence also points to a critical role for LXR in regulating Thrsp transcription in hepatocytes. New evidence[69] also shows that Thrsp is upregulated in the liver of db/db mice and high-fat diet-fed mice, two models of murine NAFLD. The expression of Thrsp depends on LXRα *via* an SREBP1c-dependent mechanism. TO901317 treatment significantly enhances hepatic SREBP1c expression and activity in wild-type mice but fails to induce Thrsp expression in SREBP-1c gene-deficient mice. TO901317 treatment and LXRα overexpression fail to induce, whereas overexpression of SREBP1c significantly increases, Thrsp promoter activity. Moreover, deletion of the SRE site completely abolishes SREBP1c-induced Thrsp transcription. These findings demonstrate that Thrsp is a lipogenic liver gene that is induced by the LXR agonist through an LXRα-mediated, SREBP1c-dependent mechanism. Thrsp may therefore represent a potential therapeutic target for the treatment of NAFLD.

TRβ-specific agonist GC-1

GC-1 is a synthetic TH analogue that is relatively selective for both the binding and activation functions[13] of TRβ1 over TRα1. GC-1 has several structural differences with respect to the natural hormone T3, including replacement of the three iodine residues with methyl and isopropyl groups, replacement of the biaryl ether linkage with a methylene linkage, and replacement of the amino acid side chain with an oxyacetic acid side chain[70]. GC-1 binds TRβ1 with the same affinity as T3 does, but GC-1 binds TRα1 with an affinity approximately 10 times lower than that of T3, both *in vitro* and *in vivo*[71]. The differential effects of GC-1, compared with those of T3, on the thermogenesis by BAT[72], tadpole metamorphosis[73], and the development of bone and central nervous system[74-76] may be the result of GC-1 selectivity for TRβ[77]. On the other hand, the selective effects of GC-1 may also be related to the body distribution of the TR isoforms. In agreement with studies in which the TRβ gene was disrupted[78], GC-1 has almost no effect on the heart, which expresses mainly TRα1, but does lower serum levels of cholesterol and triglycerides, in agreement with the predominant expression of TRβ1 in the liver. Other studies also suggest that the selective actions of GC-1 might be explained by differential tissue uptake, since GC-1 presents a clear tissue-specific accumulation[79]. It has been shown, for example, that GC-1 accumulates selectively in the liver as compared in the heart. The tissue/plasma ratio was similar for GC-1 and T3 in the liver but was 30-times lower in the heart[71]. It is well known that thyrotoxicosis affects body composition, reducing both fat and lean mass[80,81]. In primates, treatment with GC-1 increases oxygen consumption and reduces body weight, but its effects on body composition have not yet been determined. Treatment with GC-1 increases the metabolic rate, has no effect on food intake, and decreases fat mass while sparing lean mass in rats. These data illustrate the potential of GC-1 for the selective activation of TRβ in rats to induce UCP1 gene expression, while only minimally mediating synergism between TH and the sympathetic nervous system. The use of GC-1 or other TRβ-selective agonists in rodents and primates has recently been shown to increase energy expenditure and decrease fat mass and plasma levels of cholesterol[82], while sparing the heart[71] and skeletal system[83]. The TRβ-specific agonist GC-1 increases energy expenditure and prevents fat

mass accumulation in rats.

The effect of GC-1 on biological processes has not yet been demonstrated. The effects of 6-wk treatment with T3 (daily injections of 3 or 6 μg/100 g body weight) or GC-1 (equimolar doses) on different metabolic parameters in adult female rats were investigated by Villicev[13]. Whereas all animals gained weight (17-25 g) equally with T3 or GC-1 treatment, only T3 treatment increased food intake (50%-70%). Oxygen consumption was significantly and equally increased (50%-70%) by T3 and GC-1. Analysis of body composition by dual-energy X-ray absorptiometry (DEXA) revealed that whereas control animals gained about 80% of fat mass, T3- or GC-1-treated animals lost 70%-90% and 20%, respectively. Analysis of the carcasses showed that T3 treatment resulted in a 14%-74% decrease in fat content, whereas GC-1 treatment resulted in only a 15%-23% reduction. The gain in lean mass by DEXA and carcass protein content were unaffected by either T3 or GC-1 treatment. However, the masses of individual skeletal muscles were negatively affected by T3, but only marginally by GC-1. These findings highlight the potential use of GC-1 for the treatment of obesity and metabolic syndrome.

GC-24

BAT is a tissue specialized in adaptive thermogenesis with the expression of mitochondrial uncoupling protein 1 (UCP1) in response to cold induction. In contrast to WAT, the main function of BAT is to dissipate energy, not to store it. Therefore, the conversion of WAT to BAT is sought as a possible strategy to treat obesity. In rats fed a high-calorie diet, GC-24 confers resistance to diet-induced obesity through the promotion of energy expenditure[84]. In addition, a recent case report[85] indicates that in a diabetic patient with extreme insulin resistance due to a mutation in the insulin receptor gene, TH induces BAT and ameliorates diabetes.

Overall, TH or TR dysfunction can serve as another mechanism that is related to fatty liver and obesity. Evidence based on animal models and clinical phonemes can lead us to further explore the pathway between thyroid and fatty tissues or the liver. With an understanding of a functional thyroid, we believe that TH analogues and receptor agonists will be potential pharmacologic targets in patients with NAFLD in the near future.

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