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

Huang *et al.* A new target for nonalcoholic fatty liver disease treatment

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**Abstract**: **N**onalcoholic fatty liver disease (NAFLD) has been recognized as the most common liver metabolic disease, 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 an fundamental role in lipid metabolism and lipid accumulation of liver. It is found 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 function and play important roles in lipid metabolism. Recently, there are a lot of research in the treatment of NAFLD with TH and its analogues. We review here that thyroid hormone and TR are potential pharmacologic treatments target. Lipid metabolism and lipid accumulation can be regulated and reversed by TH and its analogues.

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**Key words**: Thyroid hormone; Thyroid hormone receptor; Non-alcoholic fatty liver disease; Obesity

**Core tip:** The clinical finding has given the evidence that Nonalcoholic fatty liver disease (NAFLD) patients had more prevalence of subclinical hypothyroidism and the patients with hypothyroidism may develop fatty liver. This give the evidence that dyslipidemia and fatty liver had some relationship with thyroid dysfunction and thyroid hormone and its receptor maybe a target to treat NAFLD. In this review, we summarized the recently research achievement which focus on thyroid hormone in seeking for a new pharmacologic treatment.

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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 metabolism 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 co-repressor (NCoR) and silencing mediator of retinoid and thyroid receptors (SMRT), which form a complex with transducin β-like protein 1 (TBL1) and histone deacetylase 3 (HDAC3) 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 affect 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, suggests 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 during 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 via increased 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 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 livers 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](http://www.google.com.hk/search?newwindow=1&safe=strict&hl=zh-CN&biw=1648&bih=505&site=webhp&q=pathological+hepatic&spell=1&sa=X&ei=3r47UuPHNseViQfhtYGgDQ&ved=0CCcQvwUoAA) 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 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 that result 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](http://www.ncbi.nlm.nih.gov/pubmed?term=Xu%20C%5BAuthor%5D&cauthor=true&cauthor_uid=21521285) *et al*[52] performed a cross-sectional study among 878 euthyroid elderly Chinese, in which 227 (25·85%) subjects fulfilled the diagnostic criteria of NAFLD. Patients with NAFLD had significantly lower levels of serum-free thyroxine (FT4) than control patients (11.12 ± 1.43 *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, as well as 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 when present with 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 has 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 (PPARα). 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 PPARα-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: TRβ, RXR, and PPARα. 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 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 3H/14C-labeled glucose to assess basal and insulin-stimulated rates of glucose and fat metabolism. Body composition was assessed by 1H 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 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 non-selective TR agonists to increase hepatic FFA accumulation. MB07811 is an orally active liver-targeted TRβ agonist. [Cable](http://www.ncbi.nlm.nih.gov/pubmed?term=Cable%20EE%5BAuthor%5D&cauthor=true&cauthor_uid=19072834)[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 weeks. 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 livers 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 livers 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 livers 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 reduce 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 a 6-week 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 conducted 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 treatments with TH analogues and receptor agonists will be potential pharmacologic targets in patients with NAFLD in the near future.

**REFERENCES**

1 **Yen PM**. Physiological and molecular basis of thyroid hormone action. *Physiol Rev* 2001; **81**: 1097-1142 [PMID: 11427693]

2 **Ishizuka T**, Lazar MA. The nuclear receptor corepressor deacetylase activating domain is essential for repression by thyroid hormone receptor. *Mol Endocrinol* 2005; **19**: 1443-1451 [PMID: 15695367 DOI: 10.1210/me.2005-0009]

3 **Forrest D**, Vennström B. Functions of thyroid hormone receptors in mice. *Thyroid* 2000; **10**: 41-52 [PMID: 10691312]

4 **Katz D**, Lazar MA. Dominant negative activity of an endogenous thyroid hormone receptor variant (alpha 2) is due to competition for binding sites on target genes. *J Biol Chem* 1993; **268**: 20904-20910 [PMID: 8407924]

5 **Motomura K**, Brent GA. Mechanisms of thyroid hormone action. Implications for the clinical manifestation of thyrotoxicosis. *Endocrinol Metab Clin North Am* 1998; **27**: 1-23 [PMID: 9534024 DOI: 10.1016/S0889-8529(05)70294-2]

6 **Fowler PB**, McIvor J, Sykes L, Macrae KD. The effect of long-term thyroxine on bone mineral density and serum cholesterol. *J R Coll Physicians Lond* 1996; **30**: 527-532 [PMID: 8961207]

7 **Fraichard A**, Chassande O, Plateroti M, Roux JP, Trouillas J, Dehay C, Legrand C, Gauthier K, Kedinger M, Malaval L, Rousset B, Samarut J. The T3R alpha gene encoding a thyroid hormone receptor is essential for post-natal development and thyroid hormone production. *EMBO J* 1997; **16**: 4412-4420 [PMID: 9250685 DOI: 10.1093/emboj/16.14.4412]

8 **Johansson C**, Vennström B, Thorén P. Evidence that decreased heart rate in thyroid hormone receptor-alpha1-deficient mice is an intrinsic defect. *Am J Physiol* 1998; **275**: R640-R646 [PMID: 9688704]

9 **Wikström L**, Johansson C, Saltó C, Barlow C, Campos Barros A, Baas F, Forrest D, Thorén P, Vennström B. Abnormal heart rate and body temperature in mice lacking thyroid hormone receptor alpha 1. *EMBO J* 1998; **17**: 455-461 [PMID: 9430637 DOI: 10.1093/emboj/17.2.455]

10 **Göthe S**, Wang Z, Ng L, Kindblom JM, Barros AC, Ohlsson C, Vennström B, Forrest D. Mice devoid of all known thyroid hormone receptors are viable but exhibit disorders of the pituitary-thyroid axis, growth, and bone maturation. *Genes Dev* 1999; **13**: 1329-1341 [PMID: 10346821]

11 **Gauthier K**, Plateroti M, Harvey CB, Williams GR, Weiss RE, Refetoff S, Willott JF, Sundin V, Roux JP, Malaval L, Hara M, Samarut J, Chassande O. Genetic analysis reveals different functions for the products of the thyroid hormone receptor alpha locus. *Mol Cell Biol* 2001; **21**: 4748-4760 [PMID: 11416150 DOI: 10.1128/MCB.21.14.4748-4760.2001]

12 **Flamant F**, Poguet AL, Plateroti M, Chassande O, Gauthier K, Streichenberger N, Mansouri A, Samarut J. Congenital hypothyroid Pax8(-/-) mutant mice can be rescued by inactivating the TRalpha gene. *Mol Endocrinol* 2002; **16**: 24-32 [PMID: 11773436 DOI: 10.1210/me.16.1.24]

13 **Villicev CM**, Freitas FR, Aoki MS, Taffarel C, Scanlan TS, Moriscot AS, Ribeiro MO, Bianco AC, Gouveia CH. Thyroid hormone receptor beta-specific agonist GC-1 increases energy expenditure and prevents fat-mass accumulation in rats. *J Endocrinol* 2007; **193**: 21-29 [PMID: 17400799 DOI: 10.1677/joe.1.07066]

14 **Bradley DJ**, Towle HC, Young WS. Spatial and temporal expression of alpha- and beta-thyroid hormone receptor mRNAs, including the beta 2-subtype, in the developing mammalian nervous system. *J Neurosci* 1992; **12**: 2288-2302 [PMID: 1607941]

15 **Bradley DJ**, Towle HC, Young WS. Alpha and beta thyroid hormone receptor (TR) gene expression during auditory neurogenesis: evidence for TR isoform-specific transcriptional regulation in vivo. *Proc Natl Acad Sci U S A* 1994; **91**: 439-443 [PMID: 8290545 DOI: 10.1073/pnas.91.2.439]

16 **Cook CB**, Kakucska I, Lechan RM, Koenig RJ. Expression of thyroid hormone receptor beta 2 in rat hypothalamus. *Endocrinology* 1992; **130**: 1077-1079 [PMID: 1733708 DOI: 10.1210/en.130.2.1077]

17 **Yen PM**, Sunday ME, Darling DS, Chin WW. Isoform-specific thyroid hormone receptor antibodies detect multiple thyroid hormone receptors in rat and human pituitaries. *Endocrinology* 1992; **130**: 1539-1546 [PMID: 1537303 DOI: 10.1210/en.130.3.1539]

18 **Erion MD**, Cable EE, Ito BR, Jiang H, Fujitaki JM, Finn PD, Zhang BH, Hou J, Boyer SH, van Poelje PD, Linemeyer DL. Targeting thyroid hormone receptor-beta agonists to the liver reduces cholesterol and triglycerides and improves the therapeutic index. *Proc Natl Acad Sci U S A* 2007; **104**: 15490-15495 [PMID: 17878314 DOI: 10.1073/pnas.0702759104]

19 **Perra A**, Simbula G, Simbula M, Pibiri M, Kowalik MA, Sulas P, Cocco MT, Ledda-Columbano GM, Columbano A. Thyroid hormone (T3) and TRbeta agonist GC-1 inhibit/reverse nonalcoholic fatty liver in rats. *FASEB J* 2008; **22**: 2981-2989 [PMID: 18434432 DOI: 10.1096/fj.08-108464]

20 **Golozoubova V**, Gullberg H, Matthias A, Cannon B, Vennström B, Nedergaard J. Depressed thermogenesis but competent brown adipose tissue recruitment in mice devoid of all hormone-binding thyroid hormone receptors. *Mol Endocrinol* 2004; **18**: 384-401 [PMID: 14630998 DOI: 10.1210/me.2003-0267]

21 **Kindblom JM**, Gevers EF, Skrtic SM, Lindberg MK, Göthe S, Törnell J, Vennström B, Ohlsson C. Increased adipogenesis in bone marrow but decreased bone mineral density in mice devoid of thyroid hormone receptors. *Bone* 2005; **36**: 607-616 [PMID: 15780976 DOI: 10.1016/j.bone.2005.01.017]

22 **Feng X**, Jiang Y, Meltzer P, Yen PM. Thyroid hormone regulation of hepatic genes in vivo detected by complementary DNA microarray. *Mol Endocrinol* 2000; **14**: 947-955 [PMID: 10894146 DOI: 10.1210/me.14.7.947]

23 **Flores-Morales A**, Gullberg H, Fernandez L, Ståhlberg N, Lee NH, Vennström B, Norstedt G. Patterns of liver gene expression governed by TRbeta. *Mol Endocrinol* 2002; **16**: 1257-1268 [PMID: 12040013 DOI: 10.1210/me.16.6.1257]

24 **Mynatt RL**, Park EA, Thorngate FE, Das HK, Cook GA. Changes in carnitine palmitoyltransferase-I mRNA abundance produced by hyperthyroidism and hypothyroidism parallel changes in activity. *Biochem Biophys Res Commun* 1994; **201**: 932-937 [PMID: 8003033]

25 **Jackson-Hayes L**, Song S, Lavrentyev EN, Jansen MS, Hillgartner FB, Tian L, Wood PA, Cook GA, Park EA. A thyroid hormone response unit formed between the promoter and first intron of the carnitine palmitoyltransferase-Ialpha gene mediates the liver-specific induction by thyroid hormone. *J Biol Chem* 2003; **278**: 7964-7972 [PMID: 12493735 DOI: 10.1074/jbc.M211062200]

26 **Buroker NE**, Young ME, Wei C, Serikawa K, Ge M, Ning XH, Portman MA. The dominant negative thyroid hormone receptor beta-mutant {Delta}337T alters PPAR{alpha} signaling in heart. *Am J Physiol Endocrinol Metab* 2007; **292**: E453-E460 [PMID: 16985257 DOI: 10.1152/ajpendo.00267.2006]

27 **Araki O**, Ying H, Furuya F, Zhu X, Cheng SY. Thyroid hormone receptor beta mutants: Dominant negative regulators of peroxisome proliferator-activated receptor gamma action. *Proc Natl Acad Sci U S A* 2005; **102**: 16251-16256 [PMID: 16260719 DOI: 10.1073/pnas.0508556102]

28 **Silveira MG**, Mendes FD, Diehl NN, Enders FT, Lindor KD. Thyroid dysfunction in primary biliary cirrhosis, primary sclerosing cholangitis and non-alcoholic fatty liver disease. *Liver Int* 2009; **29**: 1094-1100 [PMID: 19291181 DOI: 10.1111/j.1478-3231.2009.02003.x]

29 **Cable EE**, Finn PD, Stebbins JW, Hou J, Ito BR, van Poelje PD, Linemeyer DL, Erion MD. Reduction of hepatic steatosis in rats and mice after treatment with a liver-targeted thyroid hormone receptor agonist. *Hepatology* 2009; **49**: 407-417 [PMID: 19072834 DOI: 10.1002/hep.22572]

30 **Pihlajamäki J**, Boes T, Kim EY, Dearie F, Kim BW, Schroeder J, Mun E, Nasser I, Park PJ, Bianco AC, Goldfine AB, Patti ME. Thyroid hormone-related regulation of gene expression in human fatty liver. *J Clin Endocrinol Metab* 2009; **94**: 3521-3529 [PMID: 19549744 DOI: 10.1210/jc.2009-0212]

31 **Singh R**, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, Tanaka K, Cuervo AM, Czaja MJ. Autophagy regulates lipid metabolism. *Nature* 2009; **458**: 1131-1135 [PMID: 19339967 DOI: 10.1038/nature07976]

32 **Cahová M**, Daňková H, Páleníčková E, Papáčková Z, Kazdová L. The autophagy-lysosomal pathway is involved in TAG degradation in the liver: the effect of high-sucrose and high-fat diet. *Folia Biol (Praha)* 2010; **56**: 173-182 [PMID: 20974050]

33 **Ding WX**, Li M, Yin XM. Selective taste of ethanol-induced autophagy for mitochondria and lipid droplets. *Autophagy* 2011; **7**: 248-249 [PMID: 21150309 DOI: 10.4161/auto.7.2.14347]

34 **Yang L**, Li P, Fu S, Calay ES, Hotamisligil GS. Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. *Cell Metab* 2010; **11**: 467-478 [PMID: 20519119]

35 **Amir M**, Czaja MJ. Autophagy in nonalcoholic steatohepatitis. *Expert Rev Gastroenterol Hepatol* 2011; **5**: 159-166 [PMID: 21476911 DOI: 10.1586/egh.11.4.]

36 **Kaushik S**, Singh R, Cuervo AM. Autophagic pathways and metabolic stress. *Diabetes Obes Metab* 2010; **12** Suppl 2: 4-14 [PMID: 21029294 DOI: 10.1111/j.1463-1326.2010.01263.x]

37 **Cioffi F,** Lanni A, Goglia F. Thyroid hormones, mitochondrial bioenergetics and lipid handling. *Curr Opin Endocrinol Diabetes Obes* 2010; **17:** 402-407 [PMID: 20625286 DOI: 10.1097/MED.0b013e32833cf354]

38 **Kuma A**, Hatano M, Matsui M, Yamamoto A, Nakaya H, Yoshimori T, Ohsumi Y, Tokuhisa T, Mizushima N. The role of autophagy during the early neonatal starvation period. *Nature* 2004; **432**: 1032-1036 [PMID: 15525940 DOI: 10.1038/nature03029]

39 **Rautou PE**, Mansouri A, Lebrec D, Durand F, Valla D, Moreau R. Autophagy in liver diseases. *J Hepatol* 2010; **53**: 1123-1134 [PMID: 20810185 DOI: 10.1016/j.jhep.2010.07.006]

40 **Tacke F**, Trautwein C. Controlling autophagy: a new concept for clearing liver disease. *Hepatology* 2011; **53**: 356-358 [PMID: 21254183 DOI: 10.1002/hep.24090]

41 **Liu K**, Czaja MJ. Regulation of lipid stores and metabolism by lipophagy. *Cell Death Differ* 2013; **20**: 3-11 [PMID: 22595754 DOI: 10.1038/cdd.2012.63]

42 **Lin SY**, Wang YY, Liu PH, Lai WA, Sheu WH. Lower serum free thyroxine levels are associated with metabolic syndrome in a Chinese population. *Metabolism* 2005; **54**: 1524-1528 [PMID: 16253643 DOI: 10.1016/j.metabol.2005.05.020]

43 **Das K**, Chainy GB. Modulation of rat liver mitochondrial antioxidant defence system by thyroid hormone. *Biochim Biophys Acta* 2001; **1537**: 1-13 [PMID: 11476958]

44 **Messarah M**, Boumendjel A, Chouabia A, Klibet F, Abdennour C, Boulakoud MS, Feki AE. Influence of thyroid dysfunction on liver lipid peroxidation and antioxidant status in experimental rats. *Exp Toxicol Pathol* 2010; **62**: 301-310 [PMID: 19540741 DOI: 10.1016/j.etp.2009.04.009]

45 **Liangpunsakul S**, Chalasani N. Is hypothyroidism a risk factor for non-alcoholic steatohepatitis? *J Clin Gastroenterol* 2003; **37**: 340-343 [PMID: 14506393]

46 **Maratou E**, Hadjidakis DJ, Kollias A, Tsegka K, Peppa M, Alevizaki M, Mitrou P, Lambadiari V, Boutati E, Nikzas D, Tountas N, Economopoulos T, Raptis SA, Dimitriadis G. Studies of insulin resistance in patients with clinical and subclinical hypothyroidism. *Eur J Endocrinol* 2009; **160**: 785-790 [PMID: 19141606 DOI: 10.1530/EJE-08-0797]

47 **Khan U**, Sowers JR. Cardiometabolic syndrome and thyroid dysfunction. *J Cardiometab Syndr* 2007; **2**: 81-83 [PMID: 17684467]

48 **Shantha GP**, Kumar AA, Jeyachandran V, Rajamanickam D, Rajkumar K, Salim S, Subramanian KK, Natesan S. Association between primary hypothyroidism and metabolic syndrome and the role of C reactive protein: a cross-sectional study from South India. *Thyroid Res* 2009; **2**: 2 [PMID: 19272156 DOI: 10.1186/1756-6614-2-2]

49 **Duntas LH**. Thyroid disease and lipids. *Thyroid* 2002; **12**: 287-293 [PMID: 12034052 DOI: 10.1089/10507250252949405]

50 **Adams AC**, Astapova I, Fisher FM, Badman MK, Kurgansky KE, Flier JS, Hollenberg AN, Maratos-Flier E. Thyroid hormone regulates hepatic expression of fibroblast growth factor 21 in a PPARalpha-dependent manner. *J Biol Chem* 2010; **285**: 14078-14082 [PMID: 20236931 DOI: 10.1074/jbc.C110.107375]

51 **Erdogan M**, Canataroglu A, Ganidagli S, Kulaksızoglu M. Metabolic syndrome prevalence in subclinic and overt hypothyroid patients and the relation among metabolic syndrome parameters. *J Endocrinol Invest* 2011; **34**: 488-492 [PMID: 20651468 DOI: 10.3275/7202]

52 **Xu C**, Xu L, Yu C, Miao M, Li Y. Association between thyroid function and nonalcoholic fatty liver disease in euthyroid elderly Chinese. *Clin Endocrinol (Oxf)* 2011; **75**: 240-246 [PMID: 21521285 DOI: 10.1111/j.1365-2265.2011.04016.x]

53 **Mazo DF**, Lima VM, Stefano JT, Rabelo F, Faintuch J, Oliveira CP. Gluco-lipidic indices in treated hypothyroidism associated with nonalcoholic fatty liver disease. *Arq Gastroenterol* 2011; **48**: 186-189 [PMID: 21952703]

54 **Byrne CD**, Olufadi R, Bruce KD, Cagampang FR, Ahmed MH. Metabolic disturbances in non-alcoholic fatty liver disease. *Clin Sci (Lond)* 2009; **116**: 539-564 [PMID: 19243311 DOI: 10.1042/CS20080253]

55 **Farrell GC**, Larter CZ. Nonalcoholic fatty liver disease: from steatosis to cirrhosis. *Hepatology* 2006; **43**: S99-S112 [PMID: 16447287 DOI: 10.1002/hep.20973]

56 **Lewis JR**, Mohanty SR. Nonalcoholic fatty liver disease: a review and update. *Dig Dis Sci* 2010; **55**: 560-578 [PMID: 20101463 DOI: 10.1007/s10620-009-1081-0]

57 **Jou J**, Choi SS, Diehl AM. Mechanisms of disease progression in nonalcoholic fatty liver disease. *Semin Liver Dis* 2008; **28**: 370-379 [PMID: 18956293 DOI: 10.1055/s-0028-1091981]

58 **Tiniakos DG**, Vos MB, Brunt EM. Nonalcoholic fatty liver disease: pathology and pathogenesis. *Annu Rev Pathol* 2010; **5**: 145-171 [PMID: 20078219 DOI: 10.1146/annurev-pathol-121808-102132]

59 **Loria P**, Carulli L, Bertolotti M, Lonardo A. Endocrine and liver interaction: the role of endocrine pathways in NASH. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 236-247 [PMID: 19347015 DOI: 10.1038/nrgastro.2009.33]

60 **Petersen KF**, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI. Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. *Diabetes* 2005; **54**: 603-608 [PMID: 15734833 DOI: 10.2337/diabetes.54.3.603]

61 **Klein S**, Mittendorfer B, Eagon JC, Patterson B, Grant L, Feirt N, Seki E, Brenner D, Korenblat K, McCrea J. Gastric bypass surgery improves metabolic and hepatic abnormalities associated with nonalcoholic fatty liver disease. *Gastroenterology* 2006; **130**: 1564-1572 [PMID: 16697719 DOI: 10.1053/j.gastro.2006.01.042]

62 **Lim EL**, Hollingsworth KG, Aribisala BS, Chen MJ, Mathers JC, Taylor R. Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol. *Diabetologia* 2011; **54**: 2506-2514 [PMID: 21656330 DOI: 10.1007/s00125-011-2204-7]

63 **Oppenheimer JH**, Schwartz HL, Lane JT, Thompson MP. Functional relationship of thyroid hormone-induced lipogenesis, lipolysis, and thermogenesis in the rat. *J Clin Invest* 1991; **87**: 125-132 [PMID: 1985090 DOI: 10.1172/JCI114961]

64 **Holness MJ**, French TJ, Schofield PS, Sugden MC. The relationship between fat synthesis and oxidation in the liver after re-feeding and its regulation by thyroid hormone. *Biochem J* 1987; **247**: 621-626 [PMID: 3426552]

65 **Bryzgalova G**, Effendic S, Khan A, Rehnmark S, Barbounis P, Boulet J, Dong G, Singh R, Shapses S, Malm J, Webb P, Baxter JD, Grover GJ. Anti-obesity, anti-diabetic, and lipid lowering effects of the thyroid receptor beta subtype selective agonist KB-141. *J Steroid Biochem Mol Biol* 2008; **111**: 262-267 [PMID: 18621127 DOI: 10.1016/j.jsbmb.2008.06.010]

66 **Grover GJ**, Mellström K, Malm J. Therapeutic potential for thyroid hormone receptor-beta selective agonists for treating obesity, hyperlipidemia and diabetes. *Curr Vasc Pharmacol* 2007; **5**: 141-154 [PMID: 17430219 DOI: 10.2174/157016107780368271]

67 **Liu YY**, Brent GA. Thyroid hormone crosstalk with nuclear receptor signaling in metabolic regulation. *Trends Endocrinol Metab* 2010; **21**: 166-173 [PMID: 20015660 DOI: 10.1016/j.tem.2009.11.004]

68 **Jornayvaz FR**, Lee HY, Jurczak MJ, Alves TC, Guebre-Egziabher F, Guigni BA, Zhang D, Samuel VT, Silva JE, Shulman GI. Thyroid hormone receptor-α gene knockout mice are protected from diet-induced hepatic insulin resistance. *Endocrinology* 2012; **153**: 583-591 [PMID: 22147010 DOI: 10.1210/en.2011-1793]

69 **Wu J**, Wang C, Li S, Li S, Wang W, Li J, Chi Y, Yang H, Kong X, Zhou Y, Dong C, Wang F, Xu G, Yang J, Gustafsson JÅ, Guan Y. Thyroid hormone-responsive SPOT 14 homolog promotes hepatic lipogenesis, and its expression is regulated by Liver X receptor α through a sterol regulatory element-binding protein 1c-dependent mechanism in mice. *Hepatology* 2013; **58**: 617-628 [PMID: 23348573 DOI: 10.1002/hep.26272]

70 **Chiellini G**, Apriletti JW, Yoshihara HA, Baxter JD, Ribeiro RC, Scanlan TS. A high-affinity subtype-selective agonist ligand for the thyroid hormone receptor. *Chem Biol* 1998; **5**: 299-306 [PMID: 9653548]

71 **Trost SU**, Swanson E, Gloss B, Wang-Iverson DB, Zhang H, Volodarsky T, Grover GJ, Baxter JD, Chiellini G, Scanlan TS, Dillmann WH. The thyroid hormone receptor-beta-selective agonist GC-1 differentially affects plasma lipids and cardiac activity. *Endocrinology* 2000; **141**: 3057-3064 [PMID: 10965874 DOI: 10.1210/en.141.9.3057]

72 **Ribeiro MO**, Carvalho SD, Schultz JJ, Chiellini G, Scanlan TS, Bianco AC, Brent GA. Thyroid hormone--sympathetic interaction and adaptive thermogenesis are thyroid hormone receptor isoform--specific. *J Clin Invest* 2001; **108**: 97-105 [PMID: 11435461 DOI: 10.1172/JCI12584]

73 **Furlow JD**, Yang HY, Hsu M, Lim W, Ermio DJ, Chiellini G, Scanlan TS. Induction of larval tissue resorption in Xenopus laevis tadpoles by the thyroid hormone receptor agonist GC-1. *J Biol Chem* 2004; **279**: 26555-26562 [PMID: 15056670 DOI: 10.1074/jbc.M402847200]

74 **Morte B**, Manzano J, Scanlan T, Vennström B, Bernal J. Deletion of the thyroid hormone receptor alpha 1 prevents the structural alterations of the cerebellum induced by hypothyroidism. *Proc Natl Acad Sci U S A* 2002; **99**: 3985-3989 [PMID: 11891331 DOI: 10.1073/pnas.062413299]

75 **Manzano J**, Morte B, Scanlan TS, Bernal J. Differential effects of triiodothyronine and the thyroid hormone receptor beta-specific agonist GC-1 on thyroid hormone target genes in the b ain. *Endocrinology* 2003; **144**: 5480-5487 [PMID: 12959999 DOI: 10.1210/en.2003-0633]

76 **Freitas FR**, Capelo LP, O'Shea PJ, Jorgetti V, Moriscot AS, Scanlan TS, Williams GR, Zorn TM, Gouveia CH. The thyroid hormone receptor beta-specific agonist GC-1 selectively affects the bone development of hypothyroid rats. *J Bone Miner Res* 2005; **20**: 294-304 [PMID: 15647824 DOI: 10.1359/JBMR.041116]

77 **Bleicher L**, Aparicio R, Nunes FM, Martinez L, Gomes Dias SM, Figueira AC, Santos MA, Venturelli WH, da Silva R, Donate PM, Neves FA, Simeoni LA, Baxter JD, Webb P, Skaf MS, Polikarpov I. Structural basis of GC-1 selectivity for thyroid hormone receptor isoforms. *BMC Struct Biol* 2008; **8**: 8 [PMID: 18237438 DOI: 10.1186/1472-6807-8-8]

78 **Johansson C,** Gothe S, Forrest D, Vennström B, Thorén P. Cardiovascular phenotype and temperature control in mice lacking thyroid hormone receptor-beta or both alpha1 and beta. *Am J Physiol* 1999; **276:** H2006-2012 [PMID: 10362681]

79 **Baxter JD**, Webb P, Grover G, Scanlan TS. Selective activation of thyroid hormone signaling pathways by GC-1: a new approach to controlling cholesterol and body weight. *Trends Endocrinol Metab* 2004; **15**: 154-157 [PMID: 15109613 DOI: 10.1016/j.tem.2004.03.008]

80 **Lönn L**, Stenlöf K, Ottosson M, Lindroos AK, Nyström E, Sjöström L. Body weight and body composition changes after treatment of hyperthyroidism. *J Clin Endocrinol Metab* 1998; **83**: 4269-4273 [PMID: 9851762 DOI: 10.1210/jc.83.12.4269]

81 **Riis AL**, Jørgensen JO, Gjedde S, Nørrelund H, Jurik AG, Nair KS, Ivarsen P, Weeke J, Møller N. Whole body and forearm substrate metabolism in hyperthyroidism: evidence of increased basal muscle protein breakdown. *Am J Physiol Endocrinol Metab* 2005; **288**: E1067-E1073 [PMID: 15657093 DOI: 10.1152/ajpendo.00253.2004]

82 **Grover GJ**, Egan DM, Sleph PG, Beehler BC, Chiellini G, Nguyen NH, Baxter JD, Scanlan TS. Effects of the thyroid hormone receptor agonist GC-1 on metabolic rate and cholesterol in rats and primates: selective actions relative to 3,5,3'-triiodo-L-thyronine. *Endocrinology* 2004; **145**: 1656-1661 [PMID: 14701670 DOI: 10.1210/en.2003-0973]

83 **Freitas FR**, Moriscot AS, Jorgetti V, Soares AG, Passarelli M, Scanlan TS, Brent GA, Bianco AC, Gouveia CH. Spared bone mass in rats treated with thyroid hormone receptor TR beta-selective compound GC-1. *Am J Physiol Endocrinol Metab* 2003; **285**: E1135-E1141 [PMID: 12965872 DOI: 10.1152/ajpendo.00506.2002]

84 **Amorim BS**, Ueta CB, Freitas BC, Nassif RJ, Gouveia CH, Christoffolete MA, Moriscot AS, Lancelloti CL, Llimona F, Barbeiro HV, de Souza HP, Catanozi S, Passarelli M, Aoki MS, Bianco AC, Ribeiro MO. A TRbeta-selective agonist confers resistance to diet-induced obesity. *J Endocrinol* 2009; **203**: 291-299 [PMID: 19713219 DOI: 10.1677/JOE-08-0539]

85 **Skarulis MC**, Celi FS, Mueller E, Zemskova M, Malek R, Hugendubler L, Cochran C, Solomon J, Chen C, Gorden P. Thyroid hormone induced brown adipose tissue and amelioration of diabetes in a patient with extreme insulin resistance. *J Clin Endocrinol Metab* 2010; **95**: 256-262 [PMID: 19897683 DOI: 10.1210/jc.2009-0543]

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