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THYROID HORMONE ANALOGUES FOR THE TREATMENT OF METABOLIC DISORDERS: NEW POTENTIAL FOR UNMET CLINICAL NEEDS?

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Abstract

Objective—To provide a comprehensive review of the discovery and development of selective thyroid hormone receptor agonists and provide a discussion of their use in hyperlipidemia, obesity, and type 2 diabetes mellitus.

Methods—Preclinical and clinical English language literature from 1930 to present was reviewed and thematically summarized.

Results—Human trials have shown that thyroid hormone receptor β (TR β) agonists effectively lower low-density lipoprotein, triglycerides, apolipoprotein B, and lipoprotein(a) levels. In preclinical studies, TR β agonists enhance reverse cholesterol transport and decrease atherosclerosis in selected models. While animal data suggest these drugs may have additional utility to modulate weight and improve glucose homeostasis, human studies have not shown similar results.

Conclusion—TR β agonists are a novel therapeutic class for lipid management. Their mechanism of action for lipid lowering is distinct from statin drugs, suggesting a strong possibility for synergistic effects with combined therapy. The long-term effects of these drugs on cardiovascular outcomes, however, are unknown. Recently, the development of the most promising agent in this class, eprotirome, was halted over toxicology concerns following long-term canine studies. Consequently, the future of contemporary TR β agonists is unclear. The creation of a next generation of TR β agonists that provide additional tissue specific effects or bind TR β with even higher selectivity may lead to improved safety and efficacy and allow for their application to other metabolic disorders like obesity and type 2 diabetes mellitus.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

INTRODUCTION

Nearly one third of adults in the United States are obese, while 8.3% have diabetes and 1 in 6 has hyperlipidemia. The incidences of these three related disorders are projected to increase over the next two centuries (1-5). Collectively, they serve as important risk factors for coronary heart disease (CHD), and their prevalence is a key contributor to the prediction that teens in the United States will experience a shorter life span than their parents (6,7).

While public health measures will be needed to reverse these trends, clinical data suggest that patients may not derive the expected benefit from current therapies. Statins are the mainstay of treatment for hyperlipidemia and decrease low-density lipoprotein (LDL) levels by 20% to 60% (8). In 2000, the Lipid Treatment Assessment Project reviewed LDL levels of patients with hyperlipidemia on a stable dose of lipid lowering therapy for 3 months. Only 38% of patients achieved LDL targets set by the National Cholesterol Education Program, including 68% of low risk patients, 37% of high risk patients, and 18% of patients with CHD (9). In 2010, Lipid Treatment Assessment Project 2 showed some improvement; however, persons with diabetes still only met their LDL goals 67% of the time, and nondiabetics met their goal 75% of the time (10). These findings are likely related to several factors, including impaired adherence, lack of efficacy, and physician inertia (11).

The management of diabetes shows similar disappointing trends. To decrease the risk of microvascular complications, the American Diabetes Association recommends a hemoglobin A_{1c} (A1C) level of <7% for nonpregnant adults (12). Data collected from the 2004 National Health and Nutrition Examination Survey suggest that only 57% of diabetics attained an A1C level of <7%. A recent study showed that while 54% of diabetics met the A1C goal, a significantly lower percentage achieved both A1C and LDL goals concurrently (13). Certain high-risk populations fare even worse. In the Look Action for Health in Diabetes (AHEAD) study, 49% of white patients met their A1C goal, but only 39.4% of African Americans and 38.4% of Hispanic patients had adequate glucose control (14).

Obesity is a common comorbidity associated with diabetes and hyperlipidemia. Likewise, obesity is associated with significantly increased mortality from CHD (15). Pharmacological options, however, for weight-related disorders are limited (16). Lifestyle and dietary modification are marginally effective in motivated populations, but weight regain is common (17).

At present, there is a large unmet clinical need for effective treatments for hyperlipidemia, diabetes, and obesity. Thyroid hormone agonists or mimetics are an emerging therapeutic class with potential utility in a number of metabolic disorders. In this article, we review the history of thyroid hormone agonists and discuss the current clinical and preclinical data highlighting the efficacy of these compounds to improve lipids, facilitate weight loss, impact glucose tolerance, and potentially prevent atherosclerosis.

THYROID HORMONES ACT AT TARGET TISSUES

The thyroid gland secretes thyroxine (T₄) and lesser amounts of triiodothyronine (T₃); T₃ is the active form of hormone, and it is formed in peripheral tissues by T₄ deiodination. Thyroid hormone production is controlled by thyroid stimulating hormone (TSH), which is secreted by the anterior pituitary gland. T₃ and T₄ act directly on the pituitary and hypothalamus to regulate TSH production through a classical feedback loop. Thyroid hormones control a variety of physiologic functions including growth, development, and metabolism (18-20).

Thyroid hormones act at target tissues by binding to thyroid hormone receptors (TRs), which belong to the nuclear receptor superfamily. TRs function as hormone modulated transcription factors and bind target genes to activate or repress transcription. There are two isoforms of the thyroid hormone receptor (TR), α and β , which are encoded by genes located on chromosomes 17 and 3, respectively. Multiple splice variants of TR α and β have been described with the major isoforms being TR α 1 and TR β 1 (hereafter referred to as TR α and TR β). While TR α and β are both widely expressed and their messenger RNAs (mRNAs) can be found in most tissues, there are temporal and spatial differences in the amount of expression of distinct isoforms. These differences could account for some tissue specific actions, but this remains an area of active research. For the purposes of this discussion, it is useful to note that TR β is more highly expressed in the liver, while TR α is more highly expressed in the heart and bone (21-23).

THE RATIONALE FOR SELECTIVE THYROID HORMONE AGONISTS IN THE TREATMENT OF HYPERCHOLESTEROLEMIA

The idea of selective TR modulation providing health benefits has developed from clinical observations and basic science discoveries. The first informing theme comes from observations of patients with hypothyroidism and hyper-thyroidism. Hypothyroid individuals experience weight gain, fatigue, lethargy, constipation, and cold intolerance, and have increased serum and LDL cholesterol levels. There is evidence that even mild hypothyroidism can lead to reduced cardiac systolic function and the development of pleural and pericardial effusions. In contrast, patients with hyperthyroidism are hypermetabolic. They experience weight loss, muscle and fat wasting, anxiety, heat intolerance, palpitations, tachycardia, sweating, tremors, and diarrhea. Hyperthyroidism also leads to decreased serum cholesterol, increased bone reabsorption, and osteoporosis (19).

Despite a litany of negative effects, thyroid hormone excess has two undeniably positive benefits: reductions in cholesterol and body weight. In fact, epidemiological studies suggest that patients with hypothyroidism experience accelerated atherosclerosis. The Rotterdam study demonstrated a higher prevalence of myocardial infarction in women with subclinical hypothyroidism in comparison with euthyroid women (24). Clinicians first identified the relationship between thyroid hormone status and serum cholesterol as early as 1930 (25). In initial trials of supraphysiologic doses of thyroid hormone in euthyroid individuals, however, it was impossible to decrease cholesterol without increasing blood pressure and heart rate (HR) (26-29).

Statins are currently the most frequently prescribed cholesterol-lowering medications, and nearly 1 in 16 Americans is prescribed a statin (30). The cardiovascular benefits of statins are widely accepted and have been demonstrated in innumerable studies (31). Statins work by inhibiting the rate-limiting enzyme in cholesterol bio-synthesis, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, leading to decreased hepatic cholesterol synthesis and enhanced hepatic LDL receptor cycling. Statins also modestly raise high-density lipoprotein (HDL) levels (32).

The mechanism for LDL and cholesterol lowering by thyroid hormones and TR agonists is complex, but importantly, distinct from statins. Thyroid hormones and TR agonists increase expression of hepatic LDL receptors, leading to enhanced clearance of serum LDL (33). They act to decrease apolipoprotein (apo)B levels, which is the major protein component of LDL (34). In addition to these effects on serum LDL, thyroid hormone agonists decrease lipoprotein(a) [Lp(a)] levels. Lp(a) is a proinflammatory cholesterol particle, and serum levels are independently associated with cardiovascular events (35). In addition, they impact several aspects of reverse cholesterol transport, the pathway through which extrahepatic

cholesterol (from peripheral tissues and atheromas) is delivered back to the liver by HDL and targeted for excretion in feces (36). TR stimulation enhances synthesis of apoA-1, the predominant lipoprotein in HDL (37), and increases hepatic uptake of cholesterol from HDL through increased activity of scavenger receptor class B type I (SR-BI) (38).

TR stimulation also increases activity of liver cholesterol 7 α hydroxylase, which converts cholesterol into bile acids for fecal excretion and increases expression of adenosine triphosphate-binding cassette transporters G5 and G8 (ABCG5/8). This has been shown to play a role in biliary sterol secretion (33). Collectively, these changes result in an overall increase in the rate of fecal bile acid excretion (38). Through inhibition of sterol regulatory element binding protein-1 (SREBP-1) transcription, TR stimulation also decreases fatty acid synthesis and assembly of very-low-density lipoprotein (VLDL), leading to reduced triglycerides and maintenance of the HDL pool for reverse cholesterol transport (RCT) (33). Table 1 summarizes the mechanisms underlying the lipid-lowering effect of thyromimetics.

RATIONAL DRUG DESIGN GUIDED BY HUMAN AND MOUSE MUTATIONS

The second driving force behind the development of selective TR analogues has been an enhanced understanding of differential tissue specific TR α and TR β effects (apart from differences in expression levels). This understanding has been informed by the syndrome of resistance to thyroid hormone (RTH). RTH is an autosomal dominant disorder caused by a mutation in TR β , which results in reduced ligand binding. Patients retain normal function of TR α . At the level of the pituitary (where TR β predominates), T₃ affinity is reduced and unable to suppress TSH production. TSH levels are inappropriately normal or elevated, and T₄ and T₃ are elevated. Affected individuals have a goiter and some manifestations of hypothyroidism. Interestingly, however, they exhibit tachycardia, suggesting that HR is modulated through TR α (51). Studies in knockout mice provide further insight into the differential effects of TR isoforms. TR α knockout mice are bradycardic (52). In contrast, TR β knockout mice phenocopy individuals with RTH (53).

Bone is an additional key site of thyroid hormone action, and analysis of TR knockout mice has provided insight about thyroid hormone effects on the skeleton. Hypothyroidism in children results in growth retardation, short stature, and delayed bone maturation, while juvenile hyperthyroidism leads to accelerated growth, advanced bone age, and short stature (54-57). Adult thyrotoxicosis leads to an imbalance between osteoblastic and osteoclastic activity, and the net effect leads to increased bone loss (58). TR α expression is at least 12-fold higher than TR β in adult bone (23). TR α knockout mice have reduced bone remodeling and osteosclerosis (54). Because TR β mutant mice have elevated levels of T₄/T₃ and cannot suppress TSH, their bone phenotype is one of increased remodeling and osteoporosis. Collectively, the effect of thyroid hormone on the bone appears to be modulated primarily through TR α (55).

EARLY ATTEMPTS AT THERAPEUTIC THYROID HORMONE MODULATION

Taken together, insights from preclinical and clinical observations have proven that the therapeutic index for administration of thyroid hormone to stimulate weight loss and lower cholesterol is much too narrow. Therefore, agents that selectively stimulate TR β are required to provide desirable effects of thyroid hormone, while avoiding harmful effects on the heart and bone. The Coronary Drug Project was the earliest trial of a thyroid hormone analogue, and it tested dextrothyroxine, the D-enantiomer of T₄. The Coronary Drug Project was conducted from 1966 to 1975 and was designed to test five strategies for lowering cholesterol in men with previous myocardial infarction. The results were disappointing as overall mortality increased with dextrothyroxine despite reductions in serum cholesterol. Interestingly, mortality was lower in patients with a resting HR less than 70 and no angina at

the time of enrollment (59). Later mechanistic studies show that the D-enantiomer can bind TR with high affinity; however, the biological effects vary by tissue, with the liver being more susceptible and sensitive than the heart (60,61). The negative results of the Coronary Drug Project could possibly be explained by high rates of contamination of dextrothyroxine preparations with the L-enantiomer (62). Studies performed using purer preparations have validated the ability of this compound to lower LDL as well as Lp(a) levels without appreciable changes in weight or HR (63).

The decarboxylation and deamination of thyroid hormone leads to a number of metabolites, collectively referred to as acetic acid analogs. These compounds include triiodothyroacetic acid (triac) and tetraiodothyroacetic acid. Triac has a 3.5-fold higher affinity for TR β in comparison with T₃ and a 1.5-fold higher affinity for TR α , suggesting greater induction of TR β effects (64). In contrast, tetraiodothyroacetic acid has higher TR α selectivity (65). A study in athyrotic individuals showed that triac successfully reduced total and LDL cholesterol levels without increasing HR. Triac, however, caused an increase in bone turnover, and its widespread use has not been pursued (66).

One of the first chemically synthesized thyroid hormone analogues was 3,5-diiodothyropropionic acid (DITPA), which binds TR α and β with nearly identical affinities. In addition to regulating HR, TR stimulation improves systolic and diastolic function and decreases peripheral vascular resistance (67-69). DITPA appears to have inotropic selectivity, and has been pursued as a congestive heart failure (CHF) therapy (70). In a recent randomized clinical trial in patients with stable CHF, DITPA had no effect on CHF symptoms and was generally poorly tolerated. After 24 weeks of treatment, LDL levels decreased by 30%. Patients lost an average of 11 pounds, but gastrointestinal side effects were common (42). A follow-up analysis of more detailed metabolic parameters was performed. Although beneficial effects were noted on cholesterol and weight, DITPA resulted in increased serum markers of bone turnover, suggesting a negative effect at the level of the bone. No other active studies for DITPA have been identified on the clinicaltrials.gov website (71).

CONTEMPORARY THYROID HORMONE MIMETICS

In 1995, Wagner, while working in the late John Baxter's laboratory, reported the X-ray structure of the ligand-binding domain (LBD) of rat TR α (72). This was the first reported structure of a LBD for a nuclear receptor and indicated that the LBD had to fold around the ligand in order for TR to achieve its active conformation. Comparisons of TR α and TR β showed that most residues lining this pocket were conserved (72). This seminal work demonstrated that it might be difficult to develop compounds that offer selectivity between TR α and TR β .

Despite these limitations, a number of contemporary TR β agonists have been developed and studied in animals and humans. Sobetirome or GC-1 was developed by T.S. Scanlan and has since been acquired by QuatRx Pharmaceuticals (Ann Arbor, Michigan). Sobetirome binds TR β with an affinity similar to T₃ but binds TR α with a 10-fold lower affinity (73). Sobetirome is thought to preferentially accumulate in the liver (39). Recent studies in rats have shown that sobetirome is capable of activating expression of T₃-responsive genes in cardiomyocytes, yet preclinical and clinical data suggest that GC-1 is not associated with an increase in HR (39,74).

Karo Bio AB (Huddinge, Sweden), which was founded by John Baxter, has developed two compounds in this setting. KB141, a compound with an 8-fold higher binding affinity for TR β in comparison with TR α , has positive pre-clinical data but has not been pursued (44,45). KB2115, or eprotirome, is a compound that has been studied in Phase I and Phase II

studies as a monotherapy for hypercholesterolemia (34). Although described in the clinical literature as having “modest” TR β selectivity (34), a recent report suggested that KB2115 has a 22-fold higher affinity for TR β in comparison with TR α (75).

MB07811 is a liver specific pro-drug that undergoes first pass hepatic metabolism, generating the TR agonist MB07344, which has an approximately 15-fold higher affinity for TR β (33). The design of MB07811 is one of the first applications of a drug development approach referred to as “HepDirect” targeting. This approach involves masking phosphate or phosphonate groups to provide a neutral charge in order to increase absorption. During first pass metabolism, prodrugs are activated by the P450 enzyme cytochrome P450, family 3, subfamily A to release active compound (76). A liver-targeted TR β agonist is advantageous for two reasons. First, the liver is the site of cholesterol biosynthesis. Therefore, a liver-directed TR agonist may more potently decrease its synthesis. Secondly, this approach may provide additional protection against negative extrahepatic effects (33). In the remainder of our review, we will focus on these contemporary agents and describe the available data supporting their use in the treatment of metabolic disorders. Table 2 summarizes the relative TR β selectivity of compounds discussed in this review.

THYROMIMETICS FOR THE TREATMENT OF HYPERLIPIDEMIA AND ATHEROSCLEROSIS

A number of preclinical studies in rodents and primates have been performed to evaluate the lipid lowering effects of contemporary TR agonists [reviewed in (78)]. In general, these agonists reduce cholesterol levels in mice and primates fed a normal diet by approximately 25-35% (38,44,45). In mice fed a high-fat diet, TR agonists reduce total cholesterol by 61-67% (33). Importantly, human data have also been reported for these compounds. Sobetirome was studied in a Phase 1 trial, and results were published in an abstract at the 2008 Endocrine Society meeting (41). Sobetirome reduced LDL by 41% over 2 weeks and was well tolerated. However, despite these results and a wealth of positive preclinical results, there are currently no active trials for this compound (71). Sobetirome is no longer listed as a compound in the pipeline by QuatRx (79).

MB07811 has been tested in a Phase 1 trial. A press release suggested the drug was well tolerated in a 14-day trial and lowered “placebo-adjusted” LDL levels by 15-41% and “placebo-adjusted” triglyceride levels by 30% (80). Interestingly, MB07811 and MB07344 have been studied in combination with a statin in several preclinical models. As predicted, the combination was synergistic and lowered cholesterol by an additional 20% in comparison with the thyromimetics alone (81). These drugs have since been acquired by Ligand Pharmaceuticals (La Jolla, California), but they are no longer listed as compounds in the pipeline (82). A Phase II study of MB07811 was planned but terminated prior to enrollment (ClinicalTrial.gov accession number NCT00879112) (71).

The Karo Bio compound, eprotrirome has been studied in two human clinical trials. In a double-blind, placebo-controlled trial, 24 patients were randomized to receive increasing doses of eprotrirome for two weeks. Total cholesterol and LDL decreased by 40%, while no change was noted in HDL levels. No serious adverse events were noted, and HR was not affected at the maximal doses (43). Eprotrirome was evaluated in another double-blind, placebo-controlled trial in patients on a stable dose of statin who demonstrated persistent LDL levels above 116 mg/dL. Participants were treated with increasing doses of eprotrirome at 25 μ g, 50 μ g, or 100 μ g daily for 12 weeks. Eprotrirome 100 μ g/day decreased LDL by 32%, apoB by 30%, triglycerides by 33%, and Lp(a) by 43%. There were no significant changes in TSH, total T₃, or free T₃ levels. However, there was a dose-dependent reduction in total and free T₄. There were no observed changes in body weight, HR, or blood pressure,

and no evidence of increased bone turnover (34). While eprotirome showed great promise in early clinical studies, recent long-term toxicology studies in canines resulted in cartilage damage. Due to this unanticipated and potentially serious adverse effect, Karo Bio terminated the eprotirome program in February 2012 (83).

Notwithstanding recent toxicology developments with eprotirome, contemporary TR agonists remain potent lipid lowering agents. The true test of a lipid-lowering drug, however, rests in its ability to mitigate atherosclerosis and reduce cardiovascular events. TR agonists increase various components of RCT, suggesting they should be antiatherogenic. To date, the only human study to have addressed this outcome was the Coronary Drug Project. T-0681 (formerly KAT-681) is a liver-specific thyromimetic that was studied in New Zealand white rabbits fed a high cholesterol diet for 8 weeks. T-0681 reduced total cholesterol, triglyceride levels, and atherosclerotic surface area by 80% (47). A follow-up study in atherosclerosis-prone apoE knockout mice interestingly showed a slight increase in plaque formation following 4 weeks of T-0681 treatment, but a significant reduction after 8 weeks. T-0681 was also shown to enhance *in vivo* macrophage RCT (46).

THYROID HORMONE RECEPTOR MODULATION AND WEIGHT REDUCTION

Thyroid hormone exerts a number of effects on energy metabolism, including increases in both obligatory and facultative thermogenesis, adenosine triphosphate expenditure, oxygen consumption, stimulation of uncoupling proteins, fatty acid β oxidation, and lipolysis [reviewed in (84-86)]. Similarly, hyperthyroidism leads to weight loss due to a combination of increased basal metabolic rate and fat loss (87,88). Weight loss, however, is also secondary to bone and muscle wasting (19). Interestingly, a recent double blind, crossover intervention showed that substitution of thrice daily T_3 in place of a traditional T_4 replacement strategy in hypothyroid individuals led to significant weight loss and improvements in LDL cholesterol and apoB levels. These results suggest that T_3 and T_4 may have differential effects at the tissue level that could be exploited therapeutically (89). Studies of knockout mice suggest that both thyroid hormone receptors play some role in the modulation of energy metabolism, but the predominant receptor is unclear (90). Pharmacological studies suggest that the beneficial and harmful metabolic effects of hyperthyroidism may, however, be separated through selective receptor stimulation. Treatment of rats with 3 μ g T_3 /100 g body weight and equimolar amounts of GC-1 (3 μ g GC-1/100 g body weight) both resulted in a loss of fat mass. In contrast, T_3 caused widespread loss of muscle mass, while GC-1 had no effect (50). A similar study showed that high dose GC-1 had no effect on bone mass, while T_3 led to bone loss (91). GC-1 and KB141 reduced body weight by 3-4% and 7% in free-feeding primates after 1 week, respectively, and increased oxygen consumption without impacting HR (40,45).

Preclinical data suggest it is possible to uncouple increased metabolic rate and fat loss from deleterious effects on muscle, bone, and heart. Interestingly, however, no weight loss was observed in the clinical trials conducted with eprotirome (34,43). This could be due to the low doses of the drug and short study durations (78). Interestingly, DITPA use led to weight loss (42). However, this was observed in patients with CHF, where cachexia is common. Furthermore, DITPA resulted in significant gastrointestinal symptoms in treated subjects, which may explain the observed weight loss (92).

Newer compounds may help definitely address whether selective thyroid hormone modulation is a viable pharmacologic option for weight loss. Moving forward, compounds that are highly selective for $TR\beta$ and/or adipose tissue may be more efficacious in promoting weight modulation. To impact cholesterol metabolism, current agents have been purposefully or serendipitously targeted to the liver, an approach which may have little

impact on energy balance. GC-24 is a second-generation molecule with an affinity for TR β that is 40-fold higher than TR α . Unlike T₃, GC-24 did not prevent weight gain under conditions of diet-induced obesity, but percent body fat was significantly decreased in treated rats. Fat deposition in the liver was also prevented. In the same report, rats treated with GC-24 who were fed a normal diet had decreased body weight gain over time. More modest effects on serum cholesterol were observed in comparison with liver-specific agonists such as GC-1. A second report suggested that GC-24 had unique metabolic actions to specifically activate brown adipose tissue thermogenesis (93). In a follow-up study, GC-24 was shown to prevent diet-induced obesity in mice. The mechanism was not clear, as energy expenditure and caloric intake did not differ from high-fat diet treatment alone. The effects of GC-24 on brown adipose tissue were less robust in this report. Although further studies are needed to fully characterize the effects of selective TR β activation on energy metabolism, it is possible that newer compounds with even higher levels of β selectivity or tissue-specific effects will be useful. Moving forward, these compounds will prove helpful in determining which metabolic effects of thyroid hormone can be definitively ascribed to TR α or TR β .

TYPE 2 DIABETES MELLITUS (T2DM)

Historically, hyperthyroidism is associated with impaired glucose tolerance, which has been attributed to a number of different mechanisms, including impaired insulin action, impaired gluconeogenesis, excess lipolysis, increased serum free fatty acid levels, and decreased insulin secretion (94-96). These mechanisms suggest that glucose intolerance in the setting of hyperthyroidism is due to a combination of peripheral insulin resistance and impairments in β cell function. Older clinical studies support the idea that the exacerbation of the diabetic state in hyper-thyroidism involves increased gluconeogenesis, increased intestinal absorption of carbohydrates, and β cell exhaustion if hyperthyroidism is prolonged (97-102). In contrast, preclinical data suggest that selective TR β agonists may have beneficial effects on glucose homeostasis. In leptindeficient mice, 2 weeks of KB141 treatment improved glucose tolerance and insulin sensitivity in a dose-dependent manner with no effect on HR. These improvements, however, occurred in the context of significant reductions in body weight. A second study reported that KB141 and MB07811 reduced blood glucose levels in mice fed a high-fat diet for 2 weeks. Again, these improvements occurred in the context of weight reduction. In that same report, lean rats were treated with suprapharmacologic doses of T₃ or MB07811 for 5 days. Rats treated with T₃ had a significant increase in blood glucose with no changes in plasma insulin and a 13% reduction in body weight. In contrast, rats given suprapharmacological doses of MB07811 had no change in body weight, blood glucose, or insulin levels (33).

While TR β activation in these studies is not associated with worsening of glucose homeostasis (as is seen with hyperthyroidism), it is unclear whether TR β activation will have effects on glucose homeostasis that are independent of effects on weight. Furthermore, weight reduction is seen only in preclinical studies and at higher doses. Interestingly, GC-24, the highly selective TR β agonist, improved glucose tolerance in rats fed a high-fat diet, and this improvement occurred in the absence of changes in body weight (93). Future studies should be designed to test these metabolic outcomes in both preclinical and human studies.

A key question that emerges is whether TR β activation will directly modulate peripheral insulin action or pancreatic β cell function. With regard to the latter, T₃ treatment has been shown to increase pancreatic β cell proliferation and survival under certain experimental conditions (103). T₃ also activates PI3K/AKT (also known as protein kinase B) signaling pathways, through TR β suggesting that effects on the β cell may be nongenomic in origin

(104). *In vivo*, T₃ attenuates streptozotocin-induced β cell death (105). Our own data show that TR β expression is approximately 4-fold higher than TR α in a rat insulinoma cell line (Fig. 1). Additional studies are needed to fully determine the direct effect of thyromimetics on the human β cell.

CONCLUSION

Selective thyroid hormone receptor β agonists offer a new therapeutic class for lipid management. These agents are effective in lowering LDL, triglycerides, apoB, and Lp(a). The long-term effects on atherosclerosis are unknown, and further outcome studies in this area will be needed. Since thyromimetics affect pathways distinct from those regulated by statins, there is great potential for synergy between TR β agonists and statins. With the recent termination of the eprotirome program, however, the future of the current generation of thyroid hormone receptor agonists for the treatment of hyperlipidemia is unclear. Preclinical studies show that thyromimetics may be useful in the treatment of obesity and T2DM, but future mechanistic studies in humans will be necessary. A key consideration is that improvements in weight and glucose homeostasis are seen with higher doses than those required to see improvements in cholesterol. These observations may be due in part to the relative liver specificity of most contemporary agonists. The creation of a second generation of highly selective TR β agonists or compounds that have additional tissue-specific effects (e.g. at the level of adipose tissue) may be more efficacious in other metabolic disorders, such as obesity and T2DM.

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Abbreviations

ABCG5/8	adenosine triphosphate-binding cassette transporters G5 and G8
A1C	hemoglobin A _{1c}
apo	apolipoprotein
CHD	coronary heart disease
DITPA	3,5-diiodothyropropionic acid
HDL	high-density lipoprotein
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
HR	heart rate
LBD	ligand-binding domain
LDL	low-density lipoprotein
Lp(a)	lipoprotein(a)
RCT	reverse cholesterol transport
RTH	resistance to thyroid hormone
SREBP-1	sterol regulatory element binding protein-1

SR-BI	scavenger receptor class B type I
T2DM	type 2 diabetes mellitus
TR	thyroid hormone receptor
T₃	triiodothyronine
T₄	thyroxine
triac	triiodothyroacetic acid
TSH	thyroid-stimulating hormone

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Fig. 1.

Thyroid hormone receptor (TR) β expression in a rat pancreatic β cell line is 4-fold higher than TR α expression. Ribonucleic acid (RNA) was isolated from induced insulin secretion-1 (INS-1) 832/13 rat insulinoma cells. *A*, Quantitative real-time polymerase chain reaction (PCR) (qRT-PCR) threshold cycles demonstrating linearity of amplification for TR α , TR β , and β -actin primer sets using serial 2-fold dilutions of INS-1 reversed-transcribed RNA. The x-axis is displayed in logarithmic scale. *B*, Reverse-transcribed RNA was subjected to qRT-PCR of TR α and TR β transcripts using equally efficient primers from Panel A.

*Significantly different ($P < 0.05$) in comparison with TR α transcript levels. Results are displayed as the means $\pm$ standard error of the mean (SEM).

Table 1**Lipid Modifying Effects of Thyroid Hormone Agonists**

Biological Effects	Preclinical models (rodents, rabbits, monkeys)	Human studies
Decrease low-density lipoprotein cholesterol	GC-1 (38,39,40)	GC-1 (41)
	DITPA (42)	KB2115 (34,43)
	KB141 (33,44,45)	
	MB07811 (33)	
Decrease lipoprotein(a)	GC-1 (40)	KB2115 (34,43)
	KB141 (45)	
Decrease apolipoprotein B		KB2115 (34)
Modulate reverse cholesterol transport		
Increase SRB1	GC-1 (38)	
	T-0681 (46)	
Increase CYP7A1	GC-1 (33,38)	
	T-0681 (46)	
	KB141 (44)	
	MB07811 (33)	
Decrease SREBP1	GC-1 (33)	
Increase ABCG5 and ABGC8	T-0681 (46)	
Decrease atherosclerosis	T-0681 (46,47)	
Decrease triglycerides	GC-1 (38,38,40)	KB2115 (34,43)
	DITPA (48)	DITPA (49)
	KB141 (33,40,44,45)	
	MB07811 (33)	
Weight Reduction	GC-1 (44,45,50)	DITPA (42)
	KB141 (45)	
	GC-24 (46)	

Abbreviations: ABCG5/8 = adenosine triphosphate-binding cassette transporters G5 and G8; CYP7A1 = cholesterol 7 α -hydroxylase; DITPA = 3,5-diiodothyropropionic acid; GC-1 = sobetirome; SRB1 = scavenger receptor class B1; SREBP1 = sterol regulatory element-binding protein-1

Table 2

Thyroid Hormone Receptor Selectivity of Relevant Thyroid Hormone Receptor Agonists

Compound	Thyroid hormone receptor β selectivity (relative to thyroid hormone receptor α)
Triac	2-fold to 3-fold (64,77)
3,5-diiodothyropropionic acid (DITPA)	Binds with equal affinity to TR β and TR α . DITPA binds both receptors with approximately 100-fold lower affinity in comparison with triiodothyronine (70)
KB141	8-fold (45)
Sobetirome	10-fold (73)
KB2115 (eprotrirome)	22-fold (75)
MB07344 ^a	15-fold (76)
GC-24	40-fold (77)

^a MB07811 is a prodrug of MB07344.