Thyroxine mimetics

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Thyroid hormones influence heart rate, serum lipids, metabolic rate, body weight, and multiple aspects of lipid, carbohydrate, protein, and mineral metabolism. Although increased thyroid hormone levels can improve serum lipid profiles and reduce fat, these positive effects are counterbalanced by the harmful effects on the heart, muscle, and bone. Thus, attempts to use thyroid hormones for cholesterol-lowering and weight loss purposes have so far been limited. However, over the past decade, thyroid hormone analogs that are capable of uncoupling the beneficial effects from the deleterious effects have been developed. Such drugs could serve as powerful new tools to address two of the largest medical problems, namely atherosclerosis and obesity. Aggressive reduction in LDL-cholesterol by the use of statins is a cornerstone of preventive cardiovascular risk, but additional therapies to prevent atherosclerosis and its clinical sequelae are still needed. Thyromimetics selective for the liver or the thyroid hormone receptor isoform β1 constitute a novel approach to treat dyslipidemia. In preclinical studies, selective thyromimetics were clearly shown to reduce plasma cholesterol and protect from atherosclerosis through the upregulation of hepatic LDL receptor and promotion of the so-called reverse cholesterol transport. Notably, there is the first evidence from on-going clinical trials that selective thyromimetics may reduce plasma cholesterol in humans also. Most importantly, thyromimetics has a synergistic action when used in combination with 3-hydroxy-3-methylglutaryl CoA reductase inhibitors. Animal data have further suggested that thyromimetics might be useful in the treatment of obesity, hepatic steatosis, and atherosclerosis.

Keywords:
dyslipidemia, nuclear receptors, obesity, selective thyromimetics

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Introduction

Thyroid hormones (THs) are crucial for normal development. They exert their actions primarily by binding to the nuclear receptors that regulate gene transcription through interaction with thyroid hormone response elements in the promoter/regulatory region of the specific genes [1]. THRA located on chromosome 17 and THRB on chromosome 3 code for the TRα and β isoforms, respectively [2].

The expression of the TR isoforms is tissue-dependent and developmentally regulated [3].

TRβ1 is predominantly expressed in liver, kidney, brain, heart, and thyroid. TRβ2 is mainly expressed in brain, retina, and inner ear, whereas TRβ3 is predominantly expressed in kidney, liver, and lung [4]. TRα1 and TRα2 are expressed at the highest levels in brain but are also the major TR isoforms in bone and heart [5].

THs exert their effects by stimulation of TH receptors, which have different tissue distribution and metabolic targets. TRβ is predominant in liver and is mainly responsible for the effects on cholesterol and lipoprotein metabolism, whereas TRα is the most important in fat, muscle, and heart [6].

The past: the rise and fall of early thyroid hormone analogs as lipid-modifying agents

It has been known since 1930 that hyperthyroidism is associated with reduced plasma cholesterol levels [7], and since then many efforts were made to exploit the ability of THs to lower cholesterol levels [8]. In initial studies in the 1950s, a low dosage of dessicated thyroid led to a significant reduction in plasma cholesterol, 'escape' occurred after 20–30 weeks of treatment. Patients treated with high doses of dessicated thyroid were not refractory to the treatment, but a large number presented with tachycardia, angina pectoris, diarrhea, weight loss, and insomnia, in brief, with overt hyperthyroidism [9]. Thus, studies on thyroid preparations were stopped at that time, and the search for synthetic analogs began.

A large number of TH analogs were synthesized and tested in the experimental animal models for their lipid-lowering activity. Of all these analogs tested in animal studies first one was dextrothyroxine (D-T4).

In the late 1960s, a large clinical trial on D-T4 therapy was conducted as a part of The Coronary Drug Project by the National Institutes of Health, which aimed to answer the question as to whether cholesterol reduction may prevent coronary heart disease. The study was terminated after an average follow-up of

36 months because of a higher proportion of deaths in the D-T4-treated group, although this difference did not reach statistical significance. However, the design and performance of this study may not have been sufficient to elucidate the lipid-lowering effect of D-T4 in humans. First, subsequent investigations revealed the preparations used in the D-T4 study to be contaminated with as much as 0.5% levothyroxine, the enantiomer of D-T4, equivalent to a dosage of 30 μg/day, which may have been the only active metabolite in the study. Second, the deaths occurred in patients already carrying high cardiovascular morbidity at the initiation of the study, including angina pectoris, congestive heart failure, and tachycardia [9].

With the introduction of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) inhibitors, usually known as 'statins', into clinical practice to lower plasma cholesterol in the mid 1980s, efforts on the development of TH analogs slowed. It was during this time period, however, that the first novel 'selective' compounds mimicking the cholesterol-lowering actions of TH were developed (Fig. 1).

β-Selective thyromimetics

Selective thyromimetics are the synthetic structural analogs of THs that have tissue-specific TH actions [10]. TRβ selective compounds are of special interest as they mediate LDL-cholesterol lowering and fat loss by targeting the TRβ1 isoform in the liver, whereas they do not alter the heart rate mediated through the TRα1 isoform in the heart [11,12].

The first liver-selective, cardiac-sparing thyromimetics were produced by substitution of iodine moieties by arylmethyl groups at the 3′ position [13]. Tiratricol and other structural TH analogs such as 3,5-diiodothyropropionic acid followed soon thereafter [14]. The development of these TRβ selective compounds paved the way for the resurgence of thyromimetics as lipid-modifying drugs.

In the last few years, several cardiac-sparing TH analogs have entered human clinical trials, with an advantage of a more detailed pharmacological analysis. In the last few years, several TH analogs have entered human clinical trials [15].

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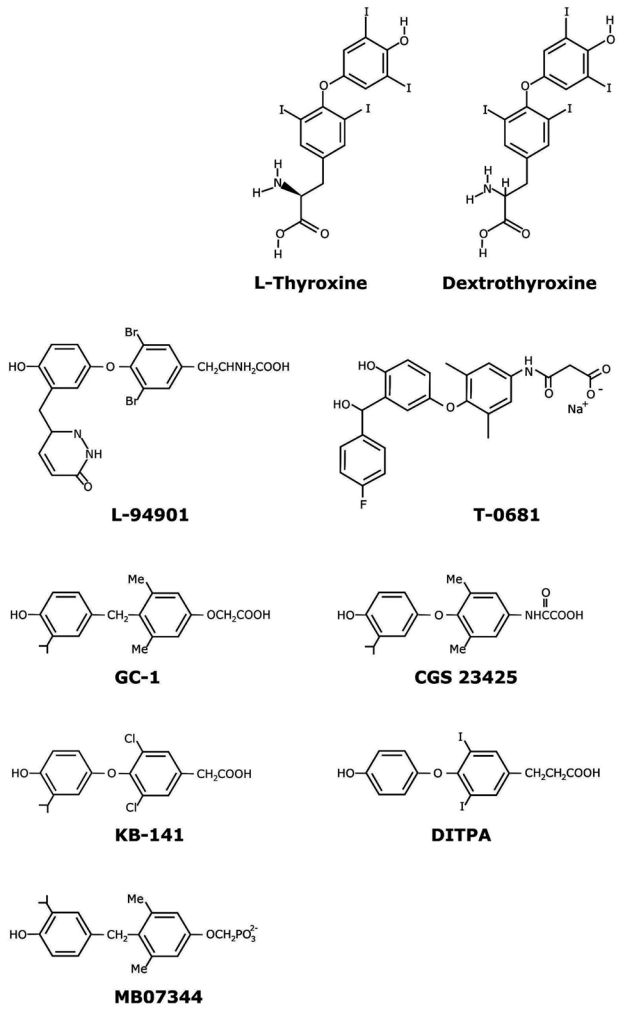
Figure 1



Chemical structure of thyroxine mimetics.

Diiodothyropropionic acid

One of the first TH analogs was diiodothyropropionic acid (DITPA), an acronym for 3,5-diiodothyropropionic acid. It differs chemically from T4 in the absence of iodides at the 3′, 5′ positions and in the substitution of a propionic acid side chain for the alanine side chain and has a modestly higher affinity for the TRβ compared with the TRα. In Sprague–Dawley rats and New Zealand white rabbits, DITPA increased the cardiac output by reducing the end-diastolic pressure [14].

These hemodynamic changes were not associated with an increased heart rate. Thus, experimental data suggested that DITPA might improve inotropic effects without positive chronotropic effects on the heart. However, DITPA-treated mice demonstrated high prevalence of fatal cardiac rhythm abnormalities during in-vivo ischemia and/or reperfusion [16].

A pilot study on the use of DITPA in 19 patients showed promising results with increased cardiac index and decreased vascular resistance index. However,

DITPA was poorly tolerated in the phase II clinical trial patients (n = 86) with congestive heart failure.

After 24 weeks, it reduced serum LDL-cholesterol by 30% and increased cardiac index by 18%, but there was no evidence for a symptomatic benefit in congestive heart failure [17]. DITPA was also associated with a significant reduction in body weight of 5.7 kg and a significant rise in serum osteocalcin, *N*-telopeptide, and deoxypyridinoline levels, indicating an increased bone turnover on DITPA [18,19].

Eprotirome

The chemical name of eprotirome (KB2115) is 3-[[3,5-dibromo-4-[4-hydroxy-3-(1-methylethyl)-phenoxy]-phenyl]-amino]-3-oxopropanoic acid. Eprotirome, first presented at American Thyroid Association meeting 2008, has seven-fold greater affinity for the β-isoform of the TH receptor than does T_3, and its precursor KB141 has a modestly higher affinity for the TRβ isoform in the liver when compared with the TRα isoform in the heart [20].

Most importantly, eprotirome is not only TRβ-selective, such as KB141, but also its tissue uptake is highly liver-selective and there is only minimal uptake in the nonhepatic tissues [21]. There is a considerable amount of human data from clinical trials on eprotirome, bringing this substance near to clinical application and registration approval [22]. In a study conducted on 98 hyperlipidemic patients randomized to 16 weeks of eprotirome at 100 or 200 mcg/day or placebo, eprotirome resulted in about 25% reduction in LDL and apolipoprotein B, along with 37% decrease in lipoprotein A at 100 mcg and 45% decrease at 200 mcg. Triglycerides decreased by 25% in patients with normal baseline levels and by 40% in hypertriglyceridemic individuals. No cardiac, bone, or muscle effects were noted with eprotirome. A mild transient elevation in the liver enzymes was noted [21].

A second phase II study involving 189 patients demonstrated that eprotirome, added to treatment with atorvastatin or simvastatin, achieved additional lipid reductions (LDL reduction 22–32%) comparable in magnitude with eprotirome monotherapy.

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Phase III programs to evaluate eprotirome's safety profile at longer treatment regimes as well as its efficacy profiles have been initiated in patients with heterozygous familial hypercholesterolemia [23] in February 2012 but stopped because of cartilage damage.

Sobetirome

GC-1 [3,5-dimethyl-4-(4´-hydroxy-3´ isopropylbenzyl)-phenoxy acetic acid] is one of the best characterized thyromimetics. It binds TRβ1 with the same affinity as T3 but binds TRα1 with approximately a 10-fold lower affinity [24]. Experimental data from animal models showed that sobetirome reduced LDL-cholesterol by 41%, fat mass, and hepatic steatosis without increasing the heart rate. Phase I clinical studies tested the therapeutic concept of cholesterol lowering and found sobetirome to be generally well tolerated at all doses studied. Twenty-four patients were enrolled in this phase I trial and received multiple doses of sobetirome over 2 weeks [24]. LDL-cholesterol was reduced up to 41% at daily doses of 100 μg in patients with nonenriched LDL levels.

Furthermore, phase II and III human clinical trials have not yet been started [25,26].

MB07811

Pharmacokinetic studies in rats demonstrated that the prodrug (2*R*,4*S*)-4-(3-chlorophenyl)-2-[(3,5-dimethyl-4-(4´hydroxy-3´-isopropylbenzyl) phenoxy)methyl]-2-oxido-[1,3,2] dioxaphosphonane (MB07811) undergoes first pass hepatic extraction and that cleavage of the prodrug generates the negatively charged TR agonist (3,5-dimethyl-4-(4´hydroxy-3´-isopropylbenzyl)phenoxy) methylphosphonic acid (MB07344), which distributed poorly in most tissues and was rapidly eliminated into the bile [27,28].

In rats and mice, MB07811 reduced not only cholesterol and triglyceride levels [28], but also hepatic steatosis [26]. Furthermore, MB07811 had additive effects on LDL-cholesterol lowering when used in combination with atorvastatin in rabbits, dogs, and monkeys [29].

The human phase Ib clinical trial also showed reduced LDL-cholesterol and triglyceride levels [10].

The planned phase II clinical trial (Clinical Trial.gov accession number: NCT00879112) was terminated before initiation and the developing company (Metabasis Therapeutics Inc.) was acquired by Ligand Pharmaceuticals Incorporated in January 2010. To our knowledge, clinical trials on MB07811 have not been resumed [29] (Table 1).

Table 1 Different thyromimetics used in clinical trials

Thyromimetics	Indication	Effect	Clinical trial
Diiodothyropropionic acid	Heart failure (NYHA II–IV)	No benefit	Phase II
Sobetirome	Dyslipidemia	↓LDL-C	Phase Ia
Eprotirome	Dyslipidemia	↓LDL-C, ↓lipoprotein A	Phase II
MB07811	Dyslipidemia	↓LDL-C, ↓triglycerides	Phase Ib

LDL-C, LDL-cholesterol.

Therapeutic use of thyromimetics in dyslipidemia

Several animal models [28–30] and recent human trials [18–20] have provided sound evidence that thyromimetics can serve as pharmacological tools to modify serum lipids without affecting the heart rate. Similar to T3, thyromimetics reduced total serum cholesterol in rodents [29].

(1) The mechanism for LDL-cholesterol lowering by thyromimetics is different from that of HMG-CoA reductase inhibitors, that is statins, which are currently the first-hand drugs for the treatment of hypercholesterolemia.
(2) Antiatherogenic effects of selective thyromimetics: one main mechanism of action is the upregulation of the LDL receptor (LDLr) in the liver, which leads to a strong reduction in plasma LDL particles, associated with a significant reduction in plasma total cholesterol and triglycerides.
(3) Another mechanism affecting plasma cholesterol and triglyceride levels is the inhibition of hepatic transcription factor, sterol regulatory element-binding protein 1 (SREBP1), resulting in reduced VLDL assembly.
(4) Promotion of the so-called reverse cholesterol transport, which describes the transport of cholesterol from extrahepatic tissues, for example plaque macrophages, back to the liver for fecal excretion.
(5) Selective thyromimetics increase hepatic expression of the HDL receptor, scavenger receptor B-I (SRBI), which increases the clearance of HDL-cholesterol without affecting the HDL particle number, thus promoting the delivery of HDL-cholesterol deriving from atherosclerotic macrophages.
(6) In addition, in humans, HDL-cholesterol can be transferred to LDL particles through the cholesteryl ester transfer protein (CETP) and be cleared through hepatic LDLr. Hepatic cholesterol, in turn, is excreted into the bile either directly by the transporters ABCG5 and ABCG8 (ABCG5/G8) or after conversion into bile acids by cholesterol 7α-hydroxylase (CYP7A1); both mechanisms are promoted by selective thyromimetics.
(7) Finally, thyromimetics reduce the intestinal absorption of dietary sterols, most likely because of competition with sterols of biliary origin.

Therapeutic use in obesity and hepatic steatosis

THs reduce body fat by increasing the basal metabolic rate. Most thyromimetics recapitulate this effect on fat reduction without muscle wasting and tachycardia [23–25] (Fig. 2).

Sobetirome reduces body fat up to 8% in lean Wistar rats compared with controls [25]. This may be due to an enhanced fatty acid β-oxidation and increases in O_2 consumption and body temperature. However, sobetirome is less effective than THs in promoting weight loss.

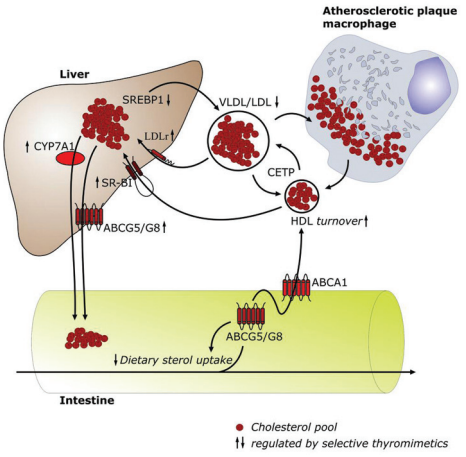
Sobetirome also prevented the development and progression of hepatic steatosis in Fischer rats by increased mitochondrial and peroxisomal fatty acid β-oxidation and reduced levels of inflammatory markers [31–33].

Similarly, MB07811 reduced hepatic steatosis through increased fatty acid oxidation in rats and mice [26]. As obesity is a major risk factor for type 2 diabetes mellitus, the reduction of hepatic and body fat may be beneficial for glucose homeostasis too [10].

There was also a loss of weight in the phase II clinical trial with DITPA [17] but not in the other human trials with thyromimetics [18,19]. This different effect on body weight is probably because of the different grade of selectivity of the thyromimetic used and the different characteristics of the study populations.

In the study by Goldman and colleagues, patients with congestive heart failure were recruited, whereas in the other studies patients with heart failure (NYHAN2) were excluded. Thus, reduction in body weight in the phase II clinical trial with DITPA may reflect the effects of DITPA on hemodynamic parameters and not the genuine effect of DITPA on body fat.

Figure 2



Lipid-lowering mechanism of thyromimetics (30).

However, long-term human studies are needed to clear these issues, whether thyromimetics will be of use in the treatment of obesity and hepatic steatosis.

Potential harmful effects

The selectivity of thyromimetics for TRβ and/or the liver is not absolute but is a relative one. Although not affecting the heart rate, muscle, and bone catabolism at therapeutic doses, excessively high doses of thyromimetics do have positive chronotropic effects [21,29].

Dosing regimens in further clinical trials and postmarketing surveillance should take into account that there is a defined therapeutic window for this pharmacological class.

Clinical experience with modestly selective DITPA has already shown that there was an increased bone turnover in patients receiving DITPA [18,19]. Patients with pre-existing congestive heart failure were recruited in the clinical trial testing the thyromimetic DITPA in a phase II study by Landenson *et al.*, but it was found that the patients poorly tolerated the modestly selective DITPA. These complications are reminiscent of the earlier experience with unselective TH compounds.

Upcoming phase III clinical trials will show whether the new-generation thyromimetics are safe, as positive chronotropic effects are untoward and deleterious in patients with congestive heart failure.

The regulation of the hypothalamic–pituitary–thyroid axis will be clearly affected by the application of a TRβ selective compound, as this receptor is also expressed in the pituitary gland and regulates the feedback loop over thyroid-stimulating hormone. Thus, thyromimetics might theoretically induce a complicated mixture of tissue-selective hyperthyroidism and hypothyroidism. In humans, eprotirome reduced serum T4. Although there were no significant effects on thyroid-stimulating hormone or T3 serum levels [18,19,21], patients receiving eprotirome must be monitored for potential hepatic toxicity, as mild and reversible increases in the levels of serum alanine aminotransferase were observed by Ladenson and colleagues [18,19].

Conclusion

At present, the major indication for the therapeutic use of thyromimetics seems to be the treatment of dyslipidemia. Most importantly, thyromimetics have a synergistic action when used in combination with HMG-CoA reductase inhibitors [18,19]. To our knowledge, there is no information available whether these lipid-lowering effects will translate into a better clinical outcome of hard primary cardiovascular endpoints. The plethora of genomic and nongenomic physiological targets of TH action makes it difficult to anticipate further clinical implications of this resurging novel class of drugs. The upcoming phase III human trials will tell whether selective thyromimetics will find their place in the treatment of dyslipidemia, obesity, and atherosclerosis. Animal data have further suggested that thyromimetics might be useful in the treatment of obesity, hepatic steatosis, and atherosclerosis. However, only long-term phase III clinical trials will tell whether the observed lipid-lowering effects of thyromimetics will improve the cardiovascular outcome in humans too. At the moment, the treatment of dyslipidemia seems to be the major indication for the therapeutic use of thyromimetics, which are now rapidly moving from bench to bedside.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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