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REVIEW ARTICLE

THYROMIMETICS FOR ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

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SUMMARY

Over the past decades, analogues mimicking the lipid-lowering properties of thyroid hormones without deleterious effects on the heart have been developed. These selective thyromimetics have been shown to lower low-density lipoprotein (LDL) cholesterol, to promote the reverse transport of cholesterol from atherogenic macrophages back to the liver, to induce bile acid production and to promote biliary secretion of sterols, ending up in elevated excretion of excess cholesterol. As a consequence, treated animals displayed a marked reduction in the atherosclerotic lesion area. Current clinical trials have shown that thyromimetics significantly reduce plasma LDL cholesterol in hyperlipidemic individuals. Moreover, selective thyromimetics have a synergistic effect on the reduction of LDL cholesterol when used in combination with statins. In conclusion, current data suggest that selective thyromimetic compounds could serve as powerful new tools to prevent the development of atherosclerosis in humans.

INTRODUCTION

Atherosclerosis still represents the leading cause of death in Western societies. While reduction of low-density lipoprotein (LDL) cholesterol is a primary target of cardiovascular prevention, increasing attention has focused on high-density lipoprotein (HDL) cholesterol as a secondary target. Concerning the latter, there has been a recent paradigm shift from HDL cholesterol concentration to the functional role of HDL in reverse cholesterol transport (RCT), a concept describing the dynamic process by which extrahepatic (peripheral) cholesterol is returned to the liver via HDL for excretion in the bile, and ultimately the feces (1-3). Most nonhepatic cells, for example macrophages, accumulate cholesterol by the uptake of lipoproteins and de novo synthesis, and are unable to catabolize cholesterol. Excess unesterified cholesterol is toxic to cells and initiates local inflammation; accordingly, hyperlipidemia leads to the migration of macrophages into the arterial wall, which represents a crucial step in the development of atherosclerosis.

Novel therapeutic strategies aim not only to lower LDL cholesterol, but also to promote RCT from atherogenic macrophages back to the liver, and/or to promote hepatobiliary flux of excess cholesterol to disrupt the vicious cycle that occurs in the vasculature in atherosclerosis. There have been important approaches to promote RCT, one of which consisted of the infusion of recombinant apolipoprotein A-I (apoA-I), the major protein of HDL. Treatment of humans with apoA-I liposomes led not only to the stimulation of fecal sterol excretion, but was also shown to significantly reduce coronary atherosclerosis, as measured by intravascular ultrasound (4, 5).

It has been a long trip from the concept of using thyroid hormone (TH) analogues as lipid-lowering agents to their first applications, the failure of early attempts and the current resurgence of this promising drug class. It had been known since 1930 that hyperthyroidism is associated with reduced plasma cholesterol levels (6), and since then, many efforts were made to exploit the ability of TH to lower cholesterol (7, 8). From the 1950s through the 1970s, a large number of TH analogues were synthesized and tested in experimental animal models for their lipid-lowering activity (summarized in 9), and some of them were also tested in humans. Noteworthy, one large clinical trial with a preparation of dextrothyroxine was conducted in the late 1960s as part of *The Coronary Drug Project* by the National Institutes of Health (NIH), which aimed to answer the question as to whether cholesterol reduction may prevent coronary heart disease (10). The study was terminated after an average follow-up of 36 months due to a higher proportion of deaths in the dextrothyroxine-treated group, most likely due to the lack of selectivity of the compound and a consequently higher rate of cardiovascular

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events (11, 12). Twenty years later, different TH receptor isoforms (TRα, TRβ) were cloned (13, 14) and their tissue-specific expression was characterized (reviewed in 15, 16). It was found that the β1 isoform of TR is the form predominantly expressed in the liver (80% of TH binding in this organ), and that the effect of TH on plasma cholesterol is mediated by TRβ1 (17-19). Evidence that TH-induced tachycardia is mediated by TRα1 came from studies in TRα knockout mice, which displayed a slow pulse rate that could not be increased by administration of even large doses of triiodothyronine (20, 21).

Thus, a lipid-lowering compound mimicking TH function without deleterious effects on the heart would be selective for either the liver, TRβ1 or both.

SELECTIVE THYROMIMETICS

The first selective thyromimetic compound was described in 1986, long before the discovery of TR isoforms. This compound, **SK&F-L-94901**, exhibited preferential binding to hepatic TR and minor selectivity for cardiac TR (22, 23). SK&F-L-94901 reduced plasma cholesterol levels in animal models at doses that did not induce cardiotoxic side effects. Other organ- and/or TRβ1-selective compounds with lipid-lowering properties in animals have been described: GC-1 (**sobetirome**; QuatRx Pharmaceuticals), **KB-141** and KB-2115 (**eprotirome**) (both from Karo Bio), **T-0681** (Kissei) and **MB-07811** (Metabasis). Further selective agonists are **CGS-23425** (Novartis) and **DITPA** (3,5-diiodothyropropionic acid), compounds no longer under active development (Fig. 1).

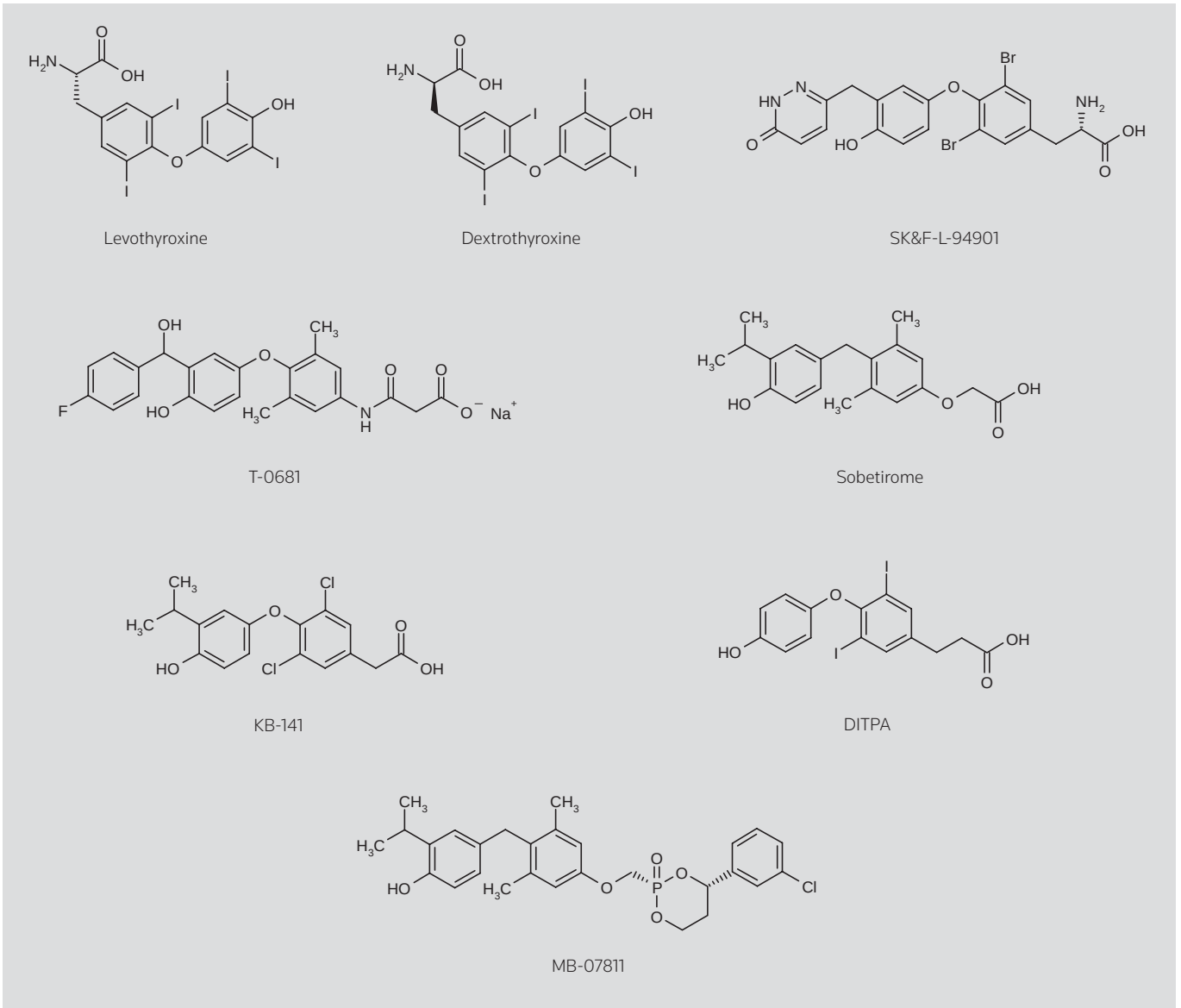

Figure 1. Chemical structures of levothyroxine and its enantiomer dextrothyroxine, used in an early clinical trial to treat dyslipidemia; organ-selective SK&F-L-94901 and T-0681; and TRβ1-selective eprotirome, sobetirome, CGS-23425, KB-141, DITPA and MB-07811.

The primary mechanism responsible for the TRβ1 selectivity of sobetirome relates to the presence of the oxoacetate at position 1; this oxoacetate moiety forms enhanced polar interactions with conserved arginine residues in a hydrophilic part of the TRβ pocket. A similar mechanism of selectivity was exploited in KB-141, although weaker contributions were also made by the thyronine ring substituents. TR isoform selectivity arises because the region that rearranges to accommodate the phenyl extension group appears to be more flexible in TRβ than in TRα. The organ selectivity of thyromimetics is thought to be related to high rates of first-pass liver uptake, as well as differences in cellular uptake and retention mechanisms (24). Of note, sobetirome and eprotirome combine both organ and TRβ1 selectivity, which may enhance hepatic targeting. A further interesting approach to enhance hepatic targeting was the development of the liver-selective prodrug MB-07811, which is activated within hepatocytes by enzymatic cleavage and exhibits poor distribution into other tissues (25). However, the development of this agent has been suspended.

THYROMIMETICS LOWER LDL CHOLESTEROL

In cynomolgus monkeys, an animal model resembling a human-like lipoprotein profile, KB-141 and sobetirome were shown to reduce plasma cholesterol in a dose-dependent manner by up to 30% (26-28). The consistently observed reduction in plasma cholesterol levels upon thyromimetic treatment was thought to be mainly the result of increased LDL cholesterol plasma clearance through increased LDL receptor expression in the liver, similar to that described for TH action (29-31).

Evidence for hepatic upregulation of the LDL receptor by thyromimetics came from studies in mice, where MB-07811 and KB-141 increased LDL receptor transcription (25). However, sobetirome failed to induce LDL receptor mRNA expression in hypercholesterolemic mice (32). Rabbits treated with the organ-selective thyromimetic T-0681 displayed markedly decreased plasma LDL cholesterol levels, which was associated with a strong increase in hepatic LDL receptor protein levels. The LDL receptor mediates the uptake of holo-LDL particles. Accordingly, plasma levels of apolipoprotein B (apoB), the major protein of LDL, were found to be decreased in animals treated with selective thyromimetics (33). Of note, mechanistic data from studies in mice demonstrated that LDL receptor expression is crucial for the effect of selective thyromimetics on lipid metabolism, as LDL receptor knockout mice did not respond to treatment with MB-07811 or T-0681 (25, 34).

In various animal models, including mice, rats and rabbits, thyromimetics also decreased plasma triglyceride (TG) levels, which are naturally associated with apoB-containing lipoproteins such as LDL and very-low-density lipoprotein (VLDL) (summarized in 24). Therefore, a reduction in plasma TG levels may reflect the increased uptake of LDL particles into liver cells. Conversely, as suggested by Baxter and Webb (24), the inhibition of hepatic transcription factor sterol regulatory element-binding protein 1 (SREBP-1) may reduce VLDL assembly. We conclude that the reduction in plasma LDL particles observed in several studies is likely to have resulted from enhanced hepatic clearance, reduced secretion into plasma, or a combination of both.

Eprotirome and sobetirome were also shown to lower serum lipoprotein(a) (Lp[a]) levels in cynomolgus monkeys (–50%), as well as in humans (–40%) (26, 38, 49). Lp(a) consists of an LDL-like particle containing apolipoprotein(a), which is linked to apoB-100 through a disulfide bond that gives it structural homology with plasminogen, conferring atherothrombotic properties (35, 36). Due to its prothrombotic properties, Lp(a) is a good predictor of coronary heart disease. To date, there have been no effective agents to lower Lp(a) levels and thyromimetics may constitute a powerfool tool to inhibit thrombosis at sites of plaque rupture.

THYROMIMETICS INDUCE BILIARY STEROL METABOLISM

In humans, cholesterol lost via the feces consists of approximately 50% acidic (= bile acids) and 50% neutral sterols, emphasizing the fact that conversion to bile acids represents a major pathway for cholesterol elimination (37).

Parini and colleagues demonstrated that sobetirome and KB-495, both liver-selective TRβ1 activators, induce hepatic expression of cytochrome P450 7A1 (CYP7A1), the rate-limiting enzyme for conversion of cholesterol to bile acids, which was associated with increased fecal bile acid and neutral sterol excretion (32, 38). Similarly, the selective thyromimetic VIA-3196 was recently shown to induce hepatic expression of CYP7A1. Moreover, VIA-3196 was found to induce hepatic expression of the bile salt export pump (BSEP), known to be rate-limiting for hepatobiliary bile acid secretion (39). The liver-selective T-0681 was found to promote bile acid production and biliary sterol secretion in different mouse models. There was a marked increase in hepatic CYP7A1 and increased expression of hepatic ATP-binding cassette sub-family G members 5 and 8 (ABCG5 and ABCG8), which are known to promote biliary sterol secretion upon dimerization. Additionally, mice treated with T-0681 displayed reduced intestinal absorption of dietary sterols, most likely as a result of competition with sterols of biliary origin (34). Baxter and colleagues reported that individuals treated with eprotirome displayed an increase in plasma 7α-hydroxy-4-cholesten-3-one, a surrogate marker of bile acid synthesis (40). Thus, the promotion of bile acid synthesis and biliary sterol secretion represents an inherent pharmacological principle of selective thyromimetics.

THYROMIMETICS PROMOTE REVERSE CHOLESTEROL TRANSPORT

Ideally, a lipid-lowering agent would not only decrease LDL cholesterol levels but also promote RCT via HDL. Both sobetirome and T-0681 were shown to increase hepatic expression of the HDL receptor (scavenger receptor class B member 1, SR-BI) in mice and rabbits (32-34). SR-BI is known to mediate the selective uptake of cholesterol from HDL into hepatocytes, without affecting HDL particle count (41). Moreover, expression of SR-BI was associated with increased biliary excretion of cholesterol (42-44). Biliary excretion of cholesterol, in turn, was recently shown to be crucial for adequate RCT (45).

Upregulation of hepatic SR-BI, together with the induction of bile acid production and secretion, should promote the reverse transport of cholesterol from lipid-laden macrophages back to the liver, and ultimately its fecal excretion. The hypothesis that thyromimetics promote RCT was tested by measuring cholesterol transport from

macrophages to feces in mice treated with T-0681 (34), according to the method developed by Rader and colleagues (46). After a period of 48 h following the i.p. injection of cholesterol-loaded [^{3}H]-labeled J774 macrophages, T-0681-treated animals displayed a significant increase in both fecal [^{3}H]-bile acid and [^{3}H]-cholesterol levels (34).

In humans, cholesterol from plaque macrophages can be transported to the liver either directly via HDL particles or (after transfer to VLDL and LDL mediated by the cholesteryl ester transfer protein, CETP) via apoB-containing lipoproteins (47). In contrast, mice do not express CETP, and the majority of plasma cholesterol is transported via HDL particles. To overcome this difference between rodents and humans, further studies were performed in mice overexpressing human *CETP* (*CETP* transgenic, Tg) under the control of its own promoter (48). Interestingly, in *CETP* Tg mice T-0681 increased hepatic SR-BI and LDL receptor, but had no effect on hepatic ABCG5/G8 and CYP7A1. Moreover, the plasma CETP concentration was decreased (34). Although there was functional receptor-mediated cholesterol uptake in livers of *CETP* Tg mice, the decrease of plasma [^{3}H]-cholesterol by T-0681 in the RCT study was not associated with increased fecal output of [^{3}H]-sterols. Previously, Rader and coworkers clearly showed that in *CETP* Tg mice a considerable amount of macrophage-derived [^{3}H]-cholesterol is transferred from HDL to apoB-containing lipoproteins by CETP, and subsequently cleared by the hepatic LDL receptor (49). Taken together, both decreased plasma CETP concentrations and the unaffected biliary sterol metabolism may have impaired RCT in T-0681-treated *CETP* Tg mice. Interestingly, in our previous study in rabbits, we found no influence of the thyromimetic on plasma CETP activity (33); thus, the first data on CETP function from the ongoing clinical trials with thyromimetics are eagerly awaited.

THYROMIMETICS INFLUENCE CHOLESTEROL EFFLUX FROM MACROPHAGES

In our experiments in *Apoe* knockout mice, short-term treatment with T-0681 significantly decreased cholesterol efflux from macrophages to mouse serum (34). The macrophages displayed a dose-dependent increase in SR-BI upon thyromimetic treatment. SR-BI mediates either cholesterol uptake or efflux to serum HDL, depending on the cholesterol gradient between the cell and the HDL particle (41). We thus speculate that at an early time point during treatment, cholesterol-rich HDL particles may have promoted cholesterol reuptake into macrophages rather than net efflux. On the other hand, prolonged treatment with T-0681 appeared to have remodeled plasma HDL particles (primarily through cholesterol depletion), which restored the efflux capacity, comparable to that of untreated animals. These findings suggest that, probably due to an unfavorable plasma lipoprotein composition, macrophages within the arterial wall may become overloaded with cholesterol via SR-BI at an early treatment stage. We speculate that this potentially negative effect of thyromimetics may have resolved over time most likely due to HDL remodeling.

THYROMIMETICS PROTECT FROM ATHEROSCLEROSIS IN DIFFERENT ANIMAL MODELS

Animal models of atherosclerosis develop lesions either spontaneously or by intervention such as dietary cholesterol supplementation. We reported that the liver-selective thyromimetic T-0681 reduced the atherosclerotic lesion area by 80% in cholesterol-fed NZW rabbits (33). A follow-study in *Apoe* knockout mice on a Western-type diet showed that prolonged treatment with T-0681 also decreased the circulating levels of proatherogenic apoB-containing lipoproteins in rodents, strongly inhibiting the progression of atherosclerotic lesions (34). We believe that the inhibition of lipid deposition in the vasculature may well be due to a functional interplay between promotion of RCT, the LDL receptor as crucial gateway to the liver and enhanced biliary sterol secretion (Fig. 2).

The advantages of rabbits include ease of handling and short disease induction times. An important disadvantage of the cholesterol-fed rabbit is the extreme hyperlipidemia, and subsequent lipid overload, required to produce lesions. This results in a cholesterol storage disease affecting the heart, kidneys, liver and lungs, which

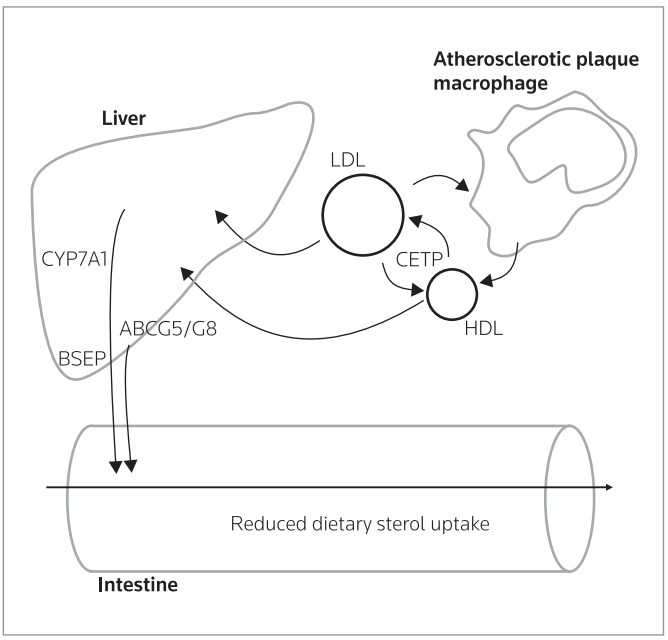

Figure 2. How selective thyromimetics protect from atherosclerosis. One main mechanism of action is the upregulation of the LDL receptor in the liver, which leads to a strong reduction in plasma LDL particles, associated with a significant reduction in plasma total cholesterol. The second main atheroprotective mechanism is the promotion of so-called reverse cholesterol transport, which describes the transport of cholesterol from extrahepatic tissues, e.g., plaque macrophages, back to the liver for fecal excretion. Selective thyromimetics increase hepatic expression of the HDL receptor scavenger receptor class B member 1 (SR-BI), which increases the clearance of HDL cholesterol without affecting HDL particle number, thus promoting the delivery of HDL cholesterol derived from atherosclerotic macrophages. In addition, in humans, HDL cholesterol can be transferred to LDL particles via cholesteryl ester transfer protein (CETP) and cleared through the hepatic LDL receptor. Biliary sterol excretion: hepatic cholesterol, in turn, is excreted into the bile either directly via the transporters ABCG5 and ABCG8 (ABCG5/G8) or after conversion to bile acids by cytochrome P450 7A1 (CYP7A1) via the bile salt export pump (BSEP), both mechanisms promoted by selective thyromimetics. Finally, thyromimetics reduce intestinal absorption of dietary sterols, most likely due to competition with sterols of biliary origin.

does not typically occur in humans. The resulting lesions are early stage, highly lipid filled and –in contrast to humans– occur predominantly in the aortic arch and ascending aorta. Similarly, *Apoe* knockout mice on a Western-type diet display a strong increase in VLDL cholesterol as a result of their inability to clear chylomicrons from plasma. Again, a disadvantage of this atherosclerosis model is the extreme hyperlipidemia and the associated whole-body lipid overload. Therefore, results from the mentioned animal studies can be extrapolated to humans only with caution.

CLINICAL TRIALS

Data from the first clinical trial with eprotirome in patients with hypercholesterolemia were published in 2008 (40), results from a phase I trial with sobetirome in euthyroid men were recently presented at a scientific meeting (50), and Metabasis Therapeutics announced the successful completion of a phase Ib trial with MB-07811 in healthy volunteers with elevated LDL cholesterol levels prior to suspending the development of this compound in 2009 (press releases no longer available online). In summary, the trial results demonstrated that the tested thyromimetics significantly and dose-dependently reduced plasma LDL cholesterol and TG levels by up to 40% in both normolipidemic and hyperlipidemic individuals, without inducing severe adverse events (24).

As statins represent the clinical care standard, any new therapy should have adjunctive activity when administered in combination with statins (28). To answer this question, Ladenson and Angelin conducted a randomized, placebo-controlled, double-blind phase II trial at 15 sites including 184 patients who had been treated with statins for at least 3 months before entry into the study (mean LDL cholesterol between 138 and 144 mg/dL under statin treatment). After a 4-week dietary lead-in phase, patients were randomly assigned to eprotirome (25, 50 or 100 µg once daily) or placebo. At week 12, serum LDL cholesterol levels in the eprotirome groups were 113, 99 and 94 mg/dL, respectively, corresponding to a dose-dependent decrease of 22%, 28% and 32%, respectively, from baseline (51). These effects were associated with a significant, dose-dependent 20-30% decrease in serum apoB levels. Serum TG levels fell 16-33% compared with an increase of 5% with placebo. Also, levels of serum Lp(a) decreased with the addition of eprotirome to statins; the median baseline values were between 27 and 36 mg/dL, and the values at 12 weeks were 42, 20, 23 and 15 mg/dL (mean reductions from baseline = 10%, 27%, 32% and 43%), respectively, in the placebo group and the low-dose, medium-dose and high-dose eprotirome groups.

In humans, neither eprotirome nor sobetirome elicited harmful effects (24, 51). There were no changes in heart rate or electrocardiogram and echocardiography readings with any dose of the compounds tested. Increases in the levels and activity of serum liver enzymes were reported upon eprotirome treatment (51). However, the increase was mild and reversed despite continued treatment.

Selective thyroid hormone analogues have been repeatedly shown to reduce serum thyroxine levels in animals (25, 26, 33), which has been mainly attributed to feedback inhibition of the thyroid and to increased conversion of thyroxine to its active form, triiodothyronine, in the liver (24). Accordingly, in both the previous phase I and the recently published phase II trial with eprotirome, dose-dependent reductions of 22-34% in levels of serum total thyroxine were observed (40, 51). However, in the study by Ladenson et al. no symptoms of overt hypothyroidism were observed (51).

CONCLUSIONS

The NIH recently recognized that an aggressive reduction of LDL cholesterol below 70 mg/dL confers more benefit than the canonical 100 mg/dL originally recommended in 2001 (52). With statin therapy it is now possible to significantly lower LDL cholesterol; however, many patients do not reach the recommended goals. Thyromimetics such as sobetirome or eprotirome may be useful in treating patients who do not adequately respond to statin treatment. Particularly in view of their potent effect in lowering levels of apoB and TG, thyromimetics may represent a useful treatment for combined hyperlipidemia associated with a major cardiovascular risk. Thyromimetics might prove useful in combination not only with statins, but also with HDL-elevating drugs such as fibrates or nicotinic acid. As a novel therapeutic strategy, they may not simply lower LDL cholesterol, but may also reduce preexisting plaques through promotion of reverse cholesterol transport.

DISCLOSURES

The authors state no conflicts of interest.

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