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Review Article

Thyroid hormone analogues: their role in treatment of hyperlipidemia

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Abstract

Thyroid hormones are central regulators of lipid metabolism and energy homeostasis, which primarily act through Thyroid Hormone Receptors (TRs). Selective Thyroid Hormone Receptor Modulators (STRMs) are chemical analogues of thyroid hormone, designed to preferentially induce beneficial actions of thyroid hormone through specificity for TRβ (isoform specificity) and specific accumulation in liver (tissue selectivity). Although initial results from studies of TH analogs that combine TRβ and tissue selectivity were promising, producing Impressive to Dramatic reductions of serum LDLC and triglycerides in animal models and human patients, none of these compounds has progressed beyond the early clinical stage so far. While recent human trials of STRMs have consistently produced impressive improvements in serum lipid parameters, they have also revealed unexpected side effects. Although STRMs have the potential to serve as treatments for hyperlipidemia, these developments make their widespread use in the future highly uncertain.

Special Issue on

Role of Thyroid Hormone in Metabolic Homeostasis

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- MGL-3196

ABBREVIATIONS

ALT: Alanine Transaminase; AST: Aspartate Transaminase; BAT: Brown Adipose Tissue; CGH: Chorionic Gonadotropic Hormone; CNS: Central Nervous System; CRYM: Mu-crystallin homologue; DBD: DNA Binding Domain; DIO: Deiodinase; DITPA: Diiodothyropropionic Acid; FH: Familial hypercholesterolemia; HDL: High Density Lipoprotein; H-P-T: Hypothalamic-Pituitary-Thyroid; LBD: Ligand Binding Domain; LDL/C: Low Density Lipoprotein /Cholesterol; LDLR: Low Density Lipoprotein Receptor; LP: Lipoprotein; MCT: Medium Chain Triglycerides; NADP: Nicotinamide Adenine Dinucleotide; NAFLD: Nonalcoholic Fatty Liver Disease; NASH: Nonalcoholic Steatohepatitis; NEFA: Non-Esterified Fatty Acids; NTCP: Na-Taurocholate Co-transporting Polypeptide; RCT: Reverse Cholesterol Transport; RTH: Resistance to Thyroid Hormone; RXR: Retinoid X Receptor; SR-B1/SCARB1: S avenger Receptor B1; STRM: Selective thyroid hormone receptor modulators; TG: Triacylglycerides; TH: Thyroid Hormones; TRα/TRβ : Thyroid hormone receptors alpha /beta; TRH: Thyrotropin Releasing Hormone; TRIAC: Triiodothyroacetic Acid; TSH: Thyroid Stimulating Hormone; TSH: Thyroid Stimulating Hormone Receptor; UCP: Uncoupling Protein

INTRODUCTION

For several decades, Selective Thyroid Hormone Receptor Modulators (STRMs) have produced promising results for the treatment of hyperlipidemia, but none has successfully cleared the clinical trial stage. Such treatments are urgently needed, as mortality and morbidity related to obesity continue to rise [1]. Serum cholesterol and associated lipid parameters are strong predictors of obesity-related risk; hyperlipidemias, characterized by elevated LDL cholesterol and/or triglycerides, often with reduced HDL cholesterol levels, are associated with increased mortality [2,3]. Currently available Statins, dietary interventions [4,5] and lifestyle modification [5,6] offer limited benefits to patients. The modulation of Thyroid Hormone (TH) signaling with synthetic compounds offers a promising therapeutic avenue [7].

TH signaling is one of the body's most important mechanisms for regulating metabolic homeostasis, as is clearly observable from cases of naturally occurring thyroid excess or deficiency. Symptoms of hypothyroidism include weight gain, elevated cholesterol and serum lipids, hypothermia and depression, and can include cognitive deficits if it occurs during pregnancy [8,9]. Symptoms of hyperthyroidism include reduced cholesterol, tachycardia, arrhythmia, hyperthermia, weight loss, muscle catabolism, reduced bone mineralization, disruption of CNS development and mood disorders. Approaches to dissociate harmful effects of TH excess from potentially beneficial effects on cholesterol lowering could lead to powerful and useful therapeutics.

Regulation of thyroid hormone levels

Secreted THs regulate their own serum levels via a CNS negative feedback loop via the Hypothalamic-Pituitary-Thyroid (H-P-T) axis [10,11]. Thyroid Stimulating Hormone (TSH), secreted from the anterior pituitary gland, binds to its receptor (TSHR) and activates the release of THs (T4 and T3) from the follicle cells of the thyroid gland. TSH synthesis and secretion is, in turn controlled by Thyrotropin Releasing Hormone (TRH), secreted from the hypothalamus. Both TSH and TRH are repressed by TH, resulting in a negative regulatory feedback mechanism that maintains serum TH levels at a consistent level.

The activity of TH is also regulated at multiple steps within specific tissues. TH is converted to its primary active form (T3, Figure 1) through the actions of Deiodinases (DIO). DIO 1 and 2 convert thyroxine to the active form through the removal of iodine from its outer ring, while DIO3 causes inactivation through removal of iodine from the inner ring [12]. Cellular uptake of TH is mediated by membrane transporters, including Monocarboxylate Transporters (MCTs) 8 and 10 and organic anion transporter protein 1c1 (OATP1C1) which are differentially expressed and vary in their substrate preference [13]. Within the cell, THs can be sequestered in inactive pools within the cytoplasm of certain tissues, including liver and kidney, through its interaction with Mu-crystallin, an NADP-regulated TH binding protein encoded by the CRYM gene [14]. Thus, levels and activity of THs are regulated at multiple levels, which enable a finely-tuned homeostasis of TH signaling and coordination of tissue specific biological processes throughout the body [12,13].

Regulation of gene transcription by thyroid hormone

Most physiological effects of TH are mediated by TH receptors (TRs alpha and beta), conditional transcription factors in the nuclear hormone receptor superfamily [10]. TRα and TRβ exhibit distinct patterns of expression in tissues (e.g. TRβ is the predominant form in live [15]. TRα and TRβ are encoded by separate genes, each of which has several splice variants. TRα encodes a single T3-binding variant, TRA1, which is expressed in brain, heart and skeletal muscle, along with non-binding variants, TRA2 and TRA3. TRβ encodes three major T3-binding variants, TRβ1, which is widely expressed in tissues, including liver, as well as TRβ2, which is expressed in hypothalamus and pituitary, retina and inner ear cells and TRβ3, expressed in kidney, liver and lung.

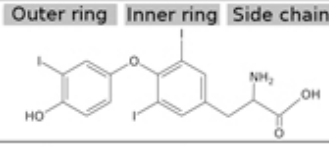
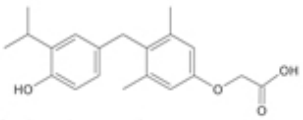
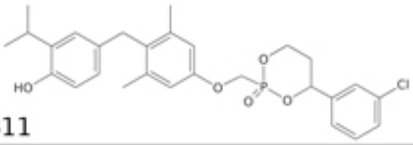
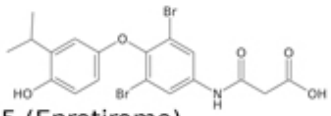
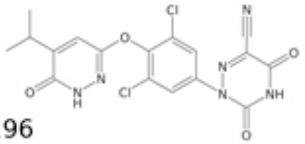
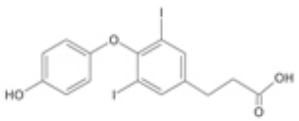
Compound	Indications	Trials
Outer ring / Inner ring / Side chain  T3	Endogenous hormone	
 GC-1 (Sobetirome)	Dyslipidemias; Hypercholesterolemia; Obesity; NAFLD	Phase Ia: ↓LDLC
 MB07811	Dyslipidemias; Hypercholesterolemia	Phase 1b: ↓LDLC ↓TG
 KB-2115 (Eprotirome)	Dyslipidemias; Hypercholesterolemia; FH	Phase II: ↓LDLC ↓LPA ↓TG Statin synergy
 MGL3196	Dyslipidemias; Hypercholesterolemia; NAFLD; FH	Phase 1b: ↓LDLC ↓TG
 DITPA	Dyslipidemias; Hypercholesterolemia Heart Failure	Phase Ib: ↓LDLC Statin synergy

Figure 1 Structures, indications and findings from human trials of Selective Thyroid Hormone Receptor Modulators (STRMs).
Note: Endogenous thyroid hormone (T_3) has been included for reference. Compound structures are aligned by region, according to standard nomenclature ("Outer ring", "Inner ring" and "Side chain").

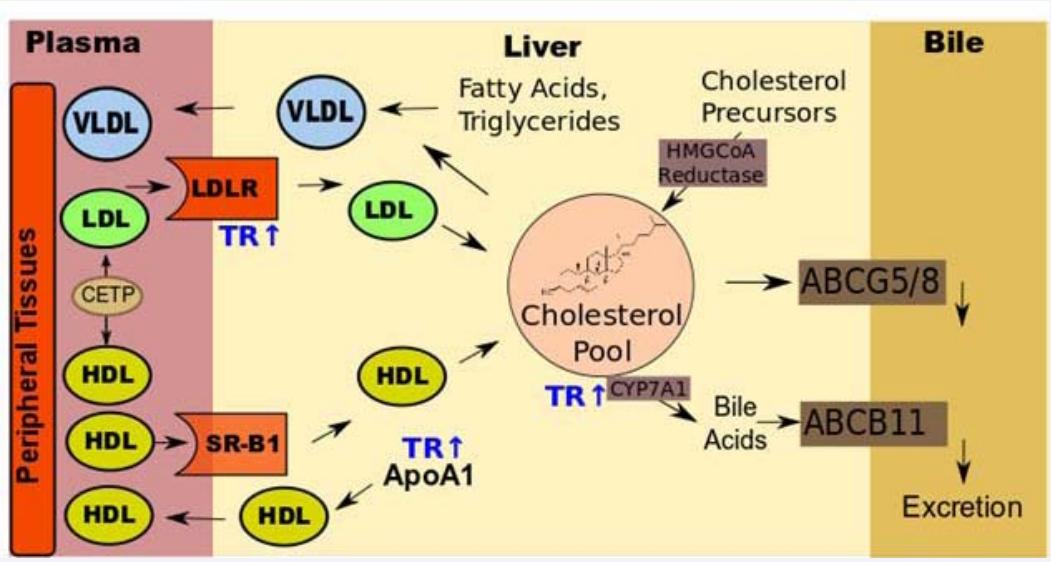


Figure 2 Summary of defined mechanisms of lipid regulation by hepatic actions of Thyroid Hormone (TH) and thyromimetics. TH activate the uptake of serum Low-Density Lipoprotein-Associated Cholesterol (LDLC) through activation of the ApoE receptor LDLR. Internalized LDL particles are metabolized and their cholesterol component becomes part of the intracellular cholesterol pool. TH also regulates the direct depletion of this pool, through activation of cholesterol metabolism into bile acids through the activation of CYP7A1 expression. TH also activates cholesterol uptake, independent of LDLR expression, through the regulation of alternative pathways. TH activates the expression of HDL components, including ApoA1, which may enhance the rate of HDL-mediated Reverse Cholesterol Transport (RCT).

Like other nuclear hormone receptors, TRs activate transcription by binding to conserved hormone response elements in proximity to target genes through DNA binding domains and recruiting coregulators in response to hormone binding to the ligand binding domain. TRs exhibit constitutive binding to response elements, as heterodimers with the Retinoid X Receptor (RXR [16]. TRs conform to the general domain organization of nuclear hormone receptors, consisting of an N-terminal Activation Function (AF1), followed by a DNA Binding Domain (DBD), containing a conserved Zn finger binding motif, connected by a flexible domain to the C-terminal Ligand Binding Domain (LBD), containing a ligand-dependent Activation Function (AF2). Ligand binding to the LBD triggers conformational changes, specifically in helix 12, resulting in the exchange of corepressors for coactivators, which mediate gene activation [17].

TH have also been found to activate effects independent of TR binding [18], in some cases mediated by TH metabolites, which typically exhibit rapid kinetics and are activated by distinct ligand classes. An example of this is the activation of processes in vascular endothelial cells [19]. Although physiologically important, these appear to be infrequent mediators of TH action, as evidenced by the results of mutational analysis of TR actions [15].

Several studies have characterized the genome-wide regulatory patterns of TRs in various cell models. Two recent studies examined gene expression at a single time point [20] or multiple time point [21] following T3 treatment in HepG2 cell lines engineered to express either TRα1 or TRβ1. The studies suggested a high degree of overlap in regulatory targets between these receptors, with very few TR subtype-specific targets. A separate study examined genome-wide binding of TRβ1 in HepG2 cells, and revealed large numbers of binding events outside of known genes, suggesting long-range regulation of target genes by distant binding events. Another study of TRα and TRβ binding in neuronal cells using a ChAP-seq methodology that enabled specific observation of long-range binding events found these to be a common regulatory mechanism [22]. As described below, these studies have not only provided insight into the mechanisms of TR regulation, but also revealed novel patterns of hepatic gene regulation.

THE MECHANISMS OF CHOLESTEROL REGULATION BY TH

Studies of gene regulation by TRs suggest that they control lipid parameters through the modulation of multiple, interrelated pathways, which include classical, LDLR-dependent cholesterol reabsorption, as well as LDLR-independent pathways (Figure 2). TRβ promotes LDL cholesterol uptake by activating the hepatic expression of the LDLR gene, directly [23,24] as well as indirectly, through regulation of transcriptional regulators such as SREBP2 [25]. LDLR acts as a membrane transporter of lipoproteins that contain Apolipoprotein (Apo) A and ApoE, allowing the removal of LDL particles from serum. Its influence upon serum cholesterol levels is illustrated by dramatic hypercholesterolemia in LDLR-/- mice [26], and in human Familial Hypercholesterolemia (FH), caused by inherited mutations in the LDLR gene. It has also recently been found that TH receptor activation can promote reduction of serum cholesterol in an LDLR-/- mouse model [27,28]. Consistent with this, the thyromimetic KB2115 was observed to promote further lowering of serum LDL levels in patients treated with statins [29], drugs which primarily act through enhancement of LDLR-mediated uptake [26,30-32]. These observations suggest that TH also regulates cholesterol through one or more LDLR-independent mechanisms; studies

have already revealed pathways (bile acid synthesis and reverse cholesterol transport) capable of mediating these actions.

TH has been found to indirectly activate cholesterol uptake through the activation of bile acid synthesis, a process which depletes hepatic cholesterol pools. TRβ activates transcription of the cholesterol metabolizing enzyme cholesterol 7-a-hydroxylase (CYP7A1) in mice [33]. This enzyme performs the first, rate-limiting step in bile acid synthesis, promoting the conversion of cholesterol into bile acid and intestinal excretion [34,35], and is a mediator of reverse cholesterol transport [36]. Adenovirus-mediated over-expression of CYP7A1 in livers of LDLR-/- mice promotes the lowering of serum LDL cholesterol [37], presumably through an LDLR-independent pathway, suggesting the idea that regulation of CYP7A1 represents an alternative pathway of reverse cholesterol transport. Early studies of CYP7A1 regulation did not find transcriptional regulation of by TH [38]. However, regulation of CYP7A1 in TRB-expressing HepG2 cells has recently been observed [39] and increased levels of a CYP7A1 metabolite [40] were found in clinical trials of the thyromimetic KB2115 [36]. The relative contribution of these pathways in mediating the effects of TH on serum lipid parameters is not known, but studies in this area continue to provide new insight [41].

TH and thyromimetics also enhance the rate of reverse cholesterol transport [42], the process by which cholesterol is removed from the periphery by hepatic reabsorption of High Density Lipoprotein (HDL) particles and eliminated from the body by subsequent conversion to bile acids and excretion [43]. In preclinical models of metabolic processes, TRβ1 activates hepatic genes with known roles in this process. As mentioned, TH induces ApoA1 [44], which is the major protein component of HDL and required for re-absorption of HDL particles into the liver [44]. and STRMs also induce the hepatic HDL receptor SR-B1 [41]. Together, these observations may imply that THs enhance both HDL particle synthesis and reabsorption and thus, the overall flux of cholesterol through the HDL pathway.

STRMs: toward selective activation

The first modern TH analog development efforts began in the 1980s. Without the complete understanding that molecular and structural biology would eventually provide, these primarily focused on developing tissue-selective compounds, which targeted TRs in liver. These efforts were successful in producing compounds with beneficial effects on lipid metabolism (reviewed in [45]). Two notable compounds were L-9490 [46] and a Ciba-Geigy compound, CGS23425, which was subsequently confirmed as a TRβ-selective compound [47]. Both compounds lowered serum cholesterol without detrimental effects on the heart. CGS23425 also lowered total serum and LDL cholesterol and increased ApoA1 synthesis, the major protein component of High-Density Lipoproteins (HDL). Additionally, some naturally-occurring forms of active TH were observed to have beneficial effects on serum lipid parameters. DITPA and the naturally occurring analog Triac were found to be weakly TRβ selective and could lower cholesterol without effects on heart [48-50]. These early efforts were significant in confirming the viability of STRMs as an effective means to improve serum lipid parameters without inducing negative effects on heart or other tissues [49].

Modern efforts: targeting TRβ

Modern development of STRMs has often targeted TRβ, based on observations from patients with mutations in the TRβ1 gene and from animal models of TRβ ablation which have suggested that TRβ is the critical mediator of metabolic regulation, through its primary expression in liver, while TRα mediates many of TH's undesirable side effects in heart.

The development of molecular cloning techniques in the 1980s enabled the direct study of TR isoforms in physiological models. The cloning of TRα and TRβ was a major breakthrough and led to the realization that these two closely related TRs have distinctly different biological functions and tissue distribution [51]. The introduction of mutations in TRα and TRβ in mice allowed further understanding of the mechanisms mediating the physiological actions of T3 and has confirmed a major role for TRβ in the regulation of serum lipid parameters, including cholesterol and triglyceride levels.

Studies of patients with mutations in the TRβ gene provided a unique perspective on actions of TR isoforms in humans. These patients exhibit Resistance to TH (RTH), characterized by high serum TH levels and frequent tachycardia [52]. Elevated serum TH levels are due to reduced TRβ2 activity in the hypothalamus and pituitary, which results in defective negative feedback of TH signaling through the H-P-T axis. While higher than normal Serum TH levels are thought to rescue activities of mutant TRβ1 in the periphery, tachycardia is thought to result from hyperactivation of wild type TRα in heart.

Together, these findings suggested that TRβ-selective ligands could improve serum cholesterol and triglyceride levels without inducing the harmful effects on extra-hepatic parameters observed with natural TH, such as tachycardia and arrhythmias [53]. Consequently, a number of TRβ: selective compounds were developed, (Figure 1), including GC-1 (5-10 fold selective [54], the GC-1 derivative, GC-24 (40-100 fold selective [55]), KB141 (14 fold selective [56]), KB2115 (TRβ selectivity not disclose [41]). More recent development efforts have specifically focused on selective activation of TRβ without activation of TRα, development of MGL-3196 employed a coactivator interaction screen to select compounds based on their ability to enhance TRβ versus TRα activity as well as TRβ selective binding (28 fold selective [57]).

Molecular Mechanisms of TRβ selectivity

The results of these structural and molecular biology studies have made it possible to derive models of TR selectivity. Structural studies of TRs in the late 90s [58-60] found that the LBDs of TRα and β share highly similar structural conformations as well as sequences, with only 32 substituted residues out of 237 and only one (ser277α/asn331β) which directly contacts ligands. TRβ selective binding has been attributed to three factors: i) side chain interactions, ii) helical displacement and iii) entropic contribution. The first factor explains the selectivity of compounds such as GC-1 and KB141 [54,56], which specifically interact with a conserved pocket arginine, forming a stable hydrogen bond network with arg282 of TRβ, while forming a much weaker bond with arg228 of TRα, which flips between interacting and non-interacting conformations [17,61]. Chemical

modification of GC-1's side-chain confirmed that this charged group is required for selectivity [62]. The second model provides insight into the selectivity of compounds with large outer ring extensions, such as GC-24 (Figure 1). These extensions directly contact residues near the surface of the binding pocket, leading to large helical displacement [63], which appear to be greater in the case of TRβ, due to the greater stability of this region in TRα because of global structural influence [64,65]. The third model provides insight into the mode of Triac selectivity, and compounds with similar negatively-charged carboxylate side chain groups [66]. TRβ selective expansion of the binding pocket near the ligand carboxylate group allows more water molecules to enter TRβ's ligand binding cavity. These ligand-water interactions allow for increased mobility of the Triac carboxylate group, allowing greater ligand mobility, and this increased entropic contribution favors binding to TRβ [66]. Based on these studies, side chain groups and 3' extensions appear to be readily targetable sites moieties in the design of selective analogs. The precise mechanisms mediating selectivity of compounds such as MGL-3196 have yet to be determined, but it is likely that the pyridazinone substituent plays an important role in mediating selectivity. TRβ specificity is an important component of STRM development, as well as tissue selectivity, discussed below.

TISSUE-SELECTIVE STRMS

Tissue selectivity has been an important consideration in the earliest STRM development efforts, and research in this field over the past decades has enabled us to attribute tissue selectivity to: i) first-pass metabolism, in the case of liver ii) active uptake by specific transporters and iii) binding to cellular proteins. Since most of the observed beneficial effects depend on the activation of target genes in liver, liver-targeted STRMs would be expected to exhibit desirable clinical outcomes, absent the side effects resulting from activation of target genes in heart or other tissues. As mentioned above, CGH-509A was a liver-selective compound generated by Ciba-Geigy in the 1980s through the conjugation of L-T3 with cholic acid to promote liver uptake [7,67]. More recently, Metabasis developed the 'HepDirect' pro-drug MB07811, which undergoes first-pass hepatic extraction and cleavage by cytochrome P450, to generate the free methylphosphonic acid, MB07344, an active thyromimetic [68]. MB07344 is excreted in from the liver in bile and escapes enterohepatic recirculation. It has also been observed that MCT8, a major cellular transporter of T3 is unable to recognize MB07344 [68]. Together, these observations explain why MB07811 exhibits a high degree of liver specificity.

The cloning of several specific TH transporters in the last decade has provided a new model for tissue selectivity. Recent analysis has found that in several cases, these transporters exhibit transport activity for specific STRMs. Recently, Theo Visser observed that a hepatic luminal bile acid transporter SLC10A1 (NTCP) transported KB211 [69], while exhibiting no activity for T4, T3 and other thyromimetics (Triprop, DITPA, Tetrac, TRIAC), although these did competitively inhibit transport. Previous characterization of this gene found it to be exclusively expressed in liver, suggesting that this represents a unique, liver-specific mechanism of STRM transport.

While contemporary efforts have largely focused on the development of TRβ-selective agonists, many modern TRβ-selective STRMs (such as GC-1, KB2115 and MB07344) also display unexpected liver selectivity as well. Characterization of KB2115 has demonstrated that it is a highly liver-selective TH analogue [66]. In fact, of TRβ selective ligands, only KB141 exhibits a wider tissue distribution pattern that more closely resembled that of T3, as determined by mass spectroscopic analysis of tissue extract [53]. MB07344, the active product of the liver targeted prodrug MB07811 is more than ten-fold TRβ selectivity [70]. These results suggest that liver selectivity is a common feature of STRMs, and that their physiological effects may be largely explained by targeting of common hepatic gene regulation.

TRβ-specificity and liver-selectivity may be viewed as achieving largely similar outcomes. This is supported by results from recently developed hepatocyte models mentioned above, in which TR isoform expression has been maintained at physiologically relevant levels. Expression array studies suggest that TRα and TRβ regulate similar genes when expressed at the same level in the same hepatic cell model [20,21,52]. Based on this, observed differences in the phenotypes regulated by each receptor appear to be due to their expression in distinct tissues, rather than large scale inherent differences in their activities in liver cells, and targeting of TRβ is largely a means to target TRβ-expressing tissues. The TRβ-specificity and tissue-selectivity of STRMs may coincide, both resulting in hepatic gene activation. For instance, the observation that GC-1 lowers cholesterol without affecting heart parameters may be due to selective accumulation in liver or specific activation of TRβ, which is predominantly expressed in liver.

Since both TRβ-specificity and tissue selectivity are predicted to produce overlapping beneficial effects on serum lipid profiles, it is difficult to determine which factor is more important in determining the effectiveness of STRMs, while differences in binding affinity and pharmacokinetics would further complicate such an analysis. While GC-1 binds TRβ with approximately equal affinity to T3 [54], many other STRMs exhibit reduced binding affinity other STRMs display lower affinity (GC-24 exhibits 0.5 fold affinity of T3[63]; MB07344 0.5 fold of T3 [68,70]; KB141 1/6 fold of T3 [56]. Although the various STRM studies currently available allows us to make general conclusions on this issue, differences in their affinity and activation complicate even direct comparisons in the same model.

Effects of STRMs on Lipid Metabolism in Animals

Several TRβ-selective TH analogs have been investigated through preclinical studies in animal models of metabolic disease, including the compounds listed in Figure 1. These early studies revealed dramatic improvements in a metabolic parameters [66,71]; several studies observed that STRMs reduced total serum cholesterol in rodents [68,72-74]. Treatment of mice with GC-1 and KB-141 reduced cholesterol levels and LDL cholesterol, L (a) and produced body weight-loss. MB07811 reduced lipids in rats and obese mice and also reduced serum triglycerides and NEFA in hamsters and rabbits [75]. GC-1, KB-141 and MB07811 were found to reduce serum LDL cholesterol in primates, as well as L(a) levels [75], an atherogenic lipoprotein, specific to humans and primates [76], which is an independent risk factor

for the development of atherosclerosis. These were rapid effects, induced after 1-2 weeks of treatment.

Beneficial effects on serum lipids described above were obtained at doses that were much lower than those required to cause problematic effects on heart, muscle or bone, suggesting that it is possible to obtain these effects in a manner that is highly selective and avoids harmful side-effect [53,56,68,77,78]. GC-1 and KB141 both exhibited a 30-fold therapeutic window between the induction of cholesterol reduction and the induction of effects on heart rate in rodent [7,77,78]. MB07344 exhibited an even larger safety window between cholesterol-lowering effects and off-target effects in rodent models [79]. The weight loss observed in GC-1 treatment was also found to spare lean muscle mass [79] and similar effects were observed for GC-24, based on analysis of soleus and extensor digitorium muscle fibers [55]. Similarly, neither GC-1 nor GC-24 affected bone mass, measured by dual-energy X-ray absorptiometry [80].

A concern in the use of STRMs is their effects on endogenous TH signaling mechanisms through the H-P-T axis. Since TRβ mediates this negative feedback mechanism through its repression of TSH and TRH transcription in the hypothalamus and pituitary, we would predict that TRβ-selective STRMs which reach those parts of the CNS could suppress endogenous TH levels, leading to a specific form of selective hypothyroidism in tissues that are not targeted by the STRM. All of the STRM studies mentioned here have included measurements of endogenous TH levels, and these have found varying degrees of TH suppression, especially at higher doses [7]. The highly liver-selective MB07811 exhibited substantially less effects on TH levels than other STRMs, probably owing to its enhanced liver targeting, although it did reduce serum T4 levels [68]. The long-term outcomes of endogenous TH suppression are unknown. We may expect that mild suppression of TH levels would result in relatively benign outcomes, which could actually offset some of the risks of STRM treatment. However, the form of TH suppression seen with STRM treatment would likely resemble TRα-specific suppression, the nature of which would depend on the tissue distribution of the STRM in use, and it is therefore impossible to predict the outcome.

STRMs may offer a viable treatment for Nonalcoholic Fatty Liver Disease (NAFLD) and related Nonalcoholic Steatohepatitis (NASH). GC-1 was found to prevent and even reverse NAFLD in a choline/methionine rat mode [81]. MB07811 also prevented steatosis in normal and metabolically challenged mouse models with greater potency than T3 [82]. The basis of these effects could be increased hepatic mitochondrial respiration and increased lipid oxidation in treated animals. Additionally, TR's recently discovered regulation of autophagy could provide an additional pathway for the clearance of hepatic lipids and treatment of NAFLD [83]. Currently, limited treatments exist for NAFLD, often limited to lifestyle changes and neutraceuticals such as Vitamin E and Omega 3 Fatty Acids. STRMs could provide a viable treatment for such diseases.

Effectiveness of TRβ/Liver Selective STRMs for treatment of metabolic parameters

It is impossible to ignore the influence of overall metabolic status in the treatment of hyperlipidemias, and results of studies with STRMs have found them to be extremely effective in weight loss and related parameters. GC-1 and KB141 have been observed to induce weight loss through the specific reduction of body fat in various animal models, including Ob/Ob mice, Zucker rats, and mice with diet induced obesity, as well as lean rats and primates without effects on lean muscle or bone [73,79]. Doses required to induce these effects are higher than those used for cholesterol reduction, but still fall safely below doses that induce effects on hear [7,84]. Weight loss is less pronounced in the most hepato-selective STRMS, such as MB07811 [68], suggesting that extra-hepatic effects are required for pronounced effects on weight loss.

The weight loss observed with some STRMs may be due to their direct activation of thermogenesis in extra-hepatic tissues including Brown Adipose (BAT) or beige adipose. BAT has been found to be an important mediator of energy expenditure in humans, mediated by the actions of uncoupling proteins, which decouple mitochondrial electron transport from glucose and lipid metabolism, resulting in heat production. TH is known to regulate thermogenesis in BAT, an effect which seems to involve TRβ as well as TR [85,86], and GC-1 and GC-24 have been found to activate thermogenesis in Brown Adipose Tissue (BAT) through the induction of uncoupling protein 1 (UCP1) transcription [79,87]. TH has also been found to act on beige adipose, white adipose tissue which has acquired some of the thermogenic properties of BAT, including increased mitochondrial numbers and elevated UCP expression, converting it to an energy consuming tissue [88]. TH has been found to elevate mitochondrial numbers in adipose tissue [89], and generation of beige adipose may explain weight loss from STRMs. Although historically, weight loss has been regarded as an elective goal with a consequently high standard of safety, the realization of obesity as an illness associated with other morbidities [90] and the integral relationship between metabolic status and serum lipid parameters may serve as catalysts for development of STRMs that specifically promote weight loss.

HUMAN CLINICAL TRIALS

KB2115, GC-1, MB07811 and MGL-3196 have reached clinical trials in human patients for treatment of dyslipidemias and have produced impressive results [7,29,41,57,84,91]. However, development of GC-1 and MB07811 has been discontinued after early trials, and recent results of KB2115 trials make it unlikely that it will be introduced into use in human patients. Whether STRM development efforts are able to overcome these hurdles will depend on whether they represent properties of specific compounds or inherent properties of thyroid analogs in general.

KB211 (Eprotirome)

Early development of KB2115 (KaroBio; Eprotirome) produced extremely promising results in human patient studies, however, results of recent studies of this drug have raised significant concerns over its continued development. KB2115 produced reductions in LDL cholesterol without effects on HDL levels or suppression of the H-P-T axis [41]. A 12 week phase II study, including 99 patients with high cholesterol levels observed significant cholesterol reduction without effects on biomarkers for off-target effects in heart, bone, muscle or other organs. In a

phase IIb study, 189 patients treated with up to 100ug KB2115 per day for 12 weeks, combined with statin therapy showed reductions in excess of statin therapy alone. These patients also exhibited reductions in triglycerides and L (a). Although patients had mild reductions of T4 levels, no other disruptions of H-P-T were observed [29].

Despite its initial promise, KB2115 development was stopped after a parallel 12-month dosing study in dogs revealed adverse effects on cartilage, a result which may cast a broader shadow on STRM development in general. Following this, Phase III trials of KB2115 were discontinued as well. The results of the KB2115 trial in dogs may have implications beyond this compound, in that they seem to illustrate a previously uncharacterized role of TH signaling. It is difficult to understand why this liver-selective compound would have effects on bone catabolism and cartilage maintenance. As discussed above, recent case studies of patients with TRα mutations reveal that disruption of TRα signaling results in profound disruptions in bone formation and analogous mouse models with various TRα mutations support the notion that TRα mediates effects of TH in bone and cartilage. While these studies provide insight into the role of TH in bone maintenance and formation (Bassett and Williams 2009; Bassett et al. 2008), the effects on cartilage are not as well understood, although previous studies have suggested linked subclinical hypothyroidism to cartilage defects (McLean and Podell 1995).

Though the results of the KB2115 trial remain unpublished, we may speculate three potential hypotheses: i) KB2115 acts directly on TRα in bone. Although these effects were not observed in previous in vitro or patient studies, the use of dogs in this long-duration study provide a superior model for observation of effects on bone or cartilage ii) KB2115 acts on the H-P-T regulatory access to generate hypothyroidism. Subtle effects on serum T4/T3 ratio were observed in prior clinical studies (Ladenson et al.), and the influence of this is uncertain. iii) KB2115's strong activity in liver influences cartilage indirectly through the transcription of hepatic targets, such as DIO3, which could result in global hypothyroidism through TH inactivation. A key to attributing the mechanism of these effects will be to precisely describe the nature of the defects observed in this case. However, one interpretation of these results is that they revealed an aspect of TH signaling that is only observable after long-term treatment of an ideal model for bone and cartilage formation. This implies that further development of STRMs may require similar long-term studies for this type of effect, representing a new barrier to the introduction of STRMs into clinical use.

Subsequent published results with KB2115 in humans have led to further concerns about safety. A 12 week double-blind, placebo-controlled, randomized, parallel-group Phase III trial in patients with Heterozygous Familial Hypercholesterolaemia (FH) was initiated in 2011 to assess effectiveness for treatment of this disease, but was discontinued. More recently, a trial of 236 Homozygous FH patients, treated with 50ug or 100ug of eprotirome for 6 weeks reported cholesterol reductions of 12 and 22% in each group, but this was accompanied by reductions of T3 levels by 19 and 27%, as well as elevated levels of liver toxicity, AST, ALT, and gamma glutamyltranspeptidase (86). These results make it less likely that development of KB2115 will continue.

GC-1 (Sobetirome)

Results of Phase I trials with GC-1 have also yielded impressive outcomes for serum lipid parameter [7]. Two Phase I trials have been performed with GC-1 (QuatRx). Dramatic lipid lowering was observed in both single and multiple dose trials, both Phase I double-blind, randomized, controlled. Single dose treatments of 32 subjects induced reductions of LDL cholesterol of up to 22%, compared to 2% with placebo. In a multiple dose study of 24 individuals, up to 41% reductions in LDL cholesterol were observed after treatment with 100micrograms, as compared to 5% in placebo. In both studies, no effects were observed in other tissues, including heart [7,72]. Currently, no efforts are under way to continue clinical development of GC-1

MB07811

MB07811 has also produced impressive reductions of serum cholesterol in Phase I studies. A phase 1a trial, conducted in 2006, showed a single dose of MB07811 to be safe and well-tolerate [68]. A subsequent multiple-dose phase 1b study, including 56 subjects, administered doses ranging from 0.25 mg to 40mg for 14 days found significant reductions in serum LDL cholesterol and triglycerides, as well as an absence of serious side effects, and absence of effects on heart rate, rhythm and blood pressure [70]. Despite this, no further efforts to develop MB07811 are under way.

T2 Analogs (DITPA (3, 5-diiodothyropropionic acid))

The T2 analog DITPA is a low-affinity TR agonist, slightly selective for TRβ, originally proposed as a therapy for heart failure due to its improvement of left ventricular function in animal models. Although it was not found to improve cardiac parameters in human trials, a 24-week trial in statin-treated patients showed 30% reductions in LDL cholesterol and reduced serum triglycerides. Although weight loss was reported, the tissue responsible for this was not determined. There were also increases in markers of bone metabolism, and the treatment was poorly tolerated for unspecified reason [29,92]. A recent phase 1 study of the synthetic T2 analog TRC150094 in patients at increased cardiometabolic risk also failed to report improvement of cardiac parameter [93]. Based on these findings it is uncertain whether T2 analogs will provide valuable therapeutic options for patients at risk for cardiovascular disease.

MGL-3196

The most recent STRM to enter human trials is MGL-3196, and this has shown impressive results in the treatment of dyslipidemia. Preclinical development efforts focused on TRβ specificity, and this compound was also found to exhibit a high degree of liver selectivity compared to other STRMs. A phase 1 ascending dose study conducted in 9 healthy dose cohorts found an absence of extra-hepatic effects and no induction of hepatic toxicity markers. A subsequent phase 1b study in healthy volunteers used multiple ascending doses (50-200mg per day), and found up to 30% reduction in LDLC, as well as 24% reduction in ApoB (the primary lipoprotein of LDL cholesterol) and 60% reduction of TG, without effects on heart or the H-P-T loop [53]. These results suggest that specific targeting of TRβ and liver is a viable way to produce positive outcomes on serum lipid

parameters without side effects, and it will be of great interest whether continued investigation in larger groups support these findings.

Based on the results of reported STRM studies in human patients, it appears that TRβ specificity and liver selectivity are the most viable option for targeting the beneficial effects of TH signaling. Although the use of human subjects precludes detailed examination of tissue accumulation of STRMs, it appears that liver-specific activation provides a viable way to avoid H-P-T axis suppression, bone catabolism and overall tolerability.

THE FUTURE OF STRMS IN TREATMENT OF HYPERLIPIDEMIA

Development of STRMs to treat dyslipidemias has had a long history, but in spite of many promising results, no STRMs are currently licensed for human use. Although development of STRMs to treat metabolic disease continues, these efforts will continue to meet a special set of challenges, based on i) the deleterious effects associated with hyperthyritic states, including known effects on heart, which resulted in patient deaths in early studies as well as hitherto unknown effects, such as those observed on cartilage maintenance in recent animal studies ii) the long development time-line required for metabolic drug development, which can limit patent lifespan and financial incentives iii) the perceived banality of metabolic disease, which sets an extremely high standard for safety and efficacy which may be unreachable. Though none of these is a condemnation of research in this field, they largely explain why no STRMs have currently completely undergone licensing in the US and why these efforts will continue to face challenges.

It is unlikely that STRMs will be available for human use in the near future, due to the reasons outlined above. Despite promising initial results, no new trials are planned for either GC-1 or MB07344. Trials with MGL-3196 have also produced extremely promising results, and it will be interesting to see whether continued development of this compound produces a viable drug for the treatment of hyperlipidemia and related disorders. However, continued development and testing will require a high standard of safety, in light of KB2115's recently observed effects on bone and cartilage.

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