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Review Article

Pharmacological Profile of the Thyroid Hormone Receptor β Selective Agonist KB-141 for Treatment of Metabolic Syndrome

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Abstract

Thyroid hormone receptor (TR) agonists have long held promise for treating multiple diseases including atherosclerosis, diabetes and obesity. Endogenous TR agonists are effective at lowering cholesterol and adiposity, but they are nonspecific and have unacceptable side effects, particularly cardiac acceleration. TRs exist in two isoforms, α, which is predominant in the heart while TRβ is predominant in liver. Therefore, TR selective agonists may have anti-obesity and cholesterol lowering effects without cardiac side effects. Structure activity work identified TRβ agonists with greater than 10-fold selectivity for TRβ. KB-141 has 14-fold TRβ selectivity. *In vivo* studies show that KB-141 reduces cholesterol and increases metabolic rate slightly without tachycardia in rats and primates. KB-141 increases insulin sensitivity and reduces adiposity in *ob/ob* mice. Further improvements in TR selectivity may lead to a clinically important therapeutic agent.

Keywords: *Thyroid Hormones; Cholesterol; Obesity; Diabetes; KB -141*

Abbreviations

HR: Heart Rate; LDL-C: LDL Cholesterol; Lp(a): Lipoprotein a; MVO_2: Oxygen Consumption; SAR: Structure Activity Relationship; T_4: Thyroxine; TR: Thyroid Hormone Receptors; T_3: Triiodothyronine

Introduction

Great strides have been made in therapeutic and surgical treatment of cardiovascular disease and metabolic syndrome. While reduction in LDL cholesterol (LDL-C) with statins is beneficial, they are not optimal and cardiovascular disease continues to be the leading cause of mortality in the USA [1-3]. Obesity and diabetes rates continue to soar worldwide and optimal treatments still defy us [2,3]. Thyroid receptor (TR) hormone agonists have long held great appeal to researchers and clinicians for their ability to lower lipids, reduce adiposity, and increase insulin sensitivity, but their wide diversity of actions, while attractive, have historically been their downfall [3]. In this brief review, we will describe one of several approaches, the TR agonist, KB-141.

The thyroid hormone thyroxine (T_4) and its more active form, triiodothyronine (T_3), activate nuclear hormone receptors which increase or repress transcription of proteins involving energy metabolism (lipid and glucose metabolism), normal growth, fetal development, mood, bone metabolism, and a variety of other physiological actions including tachycardia and positive inotropic activity [3-5]. Two TR isoforms (TR α/β) exist, each with two splice variants and the α_1 and β_1 splice variant being the active forms [3]. While ubiquitously expressed, TRβ predominates in the liver while TRα predominates in the heart. T_3 binds to both with similar affinity (see review 3). TR agonists reduce LDL cholesterol (LDL-C) via increased excretion and reduced synthesis while increasing heart rate (HR) through TRα activation. They increase metabolic rate and alter glucose metabolism through stimulation of both subtypes [3-8]. TRα and β subtypes are highly conserved and this similarity, along with being intracellular receptors, make development of selective, therapeutically useful TR agonists extremely difficult as we will show below. We must point out that the wide number of TR effects which make them so attractive to researchers are also what makes them so hard to develop as therapeutics.

Experiments were performed by nature showing that hypothyroidism causes weight gain, high cholesterol, reduced energy metabolism and an increased propensity for cardiac disease while hyperthyroidism causes weight loss, tachycardia, and reduced plasma lipids [3]. Neither T_3 nor T_4 can be used clinically due to poor selectivity. Nevertheless, TR agonists have great appeal as potential therapeutics for obesity, atherosclerosis, and diabetes. Early studies with agonist metabolites such as triiodoacetic acid (triac) with slightly greater TRβ selectivity did show reduction in plasma lipids, but the cardiac side effects were too profound for clinical benefit [3]. Nevertheless, triac has great appeal to professional body builders looking to increase muscle definition.

Development of KB-141

Recent work has shown the potential for TRb selective agonists and in this brief review, we will describe the TRb agonist KB-141. TR selectivity is difficult to achieve and efforts have yielded compounds with TRβ selectivity of 10 - 40 fold [3,4,9]. The Structure-Activity-Relationship (SAR) of a series of analogs, based on *L*-T_3 (1) (Figure 1), revealed that increasing R_1-chain length had a profound effect on affinity for $TR\alpha_1$ and $TR\beta_1$. Affinity increased in the order formic < acetic < propionic acid, while $TR\beta_1$-selectivity was highest when the R_1-position was substituted with acetic acid. Furthermore, when the iodine atoms at the R_3 and R_5-positions were substituted with chlorine or bromine, $TR\beta_1$-selectivity was increased even further. This gave KB-092 (2a) and KB-141 (2b) (Figure 1) that were found to reveal the most promising *in vitro* data based on isoform selectivity (9- and 14-fold, respectively). In Chinese Hamster ovary (CHO) cells expressing human $TR\alpha_1$ or $TR\beta_1$, KB-141 was a full agonist for both $TR\beta_1$ and $TR\alpha_1$, being essentially equipotent to *L*-T_3 for $TR\beta_1$, but less potent for $TR\alpha_1$. The reason for the $TR\beta_1$-selectivity of KB-141 was realized to be due to the single amino acid difference in the ligand binding pocket (Ser277 in $TR\alpha_1$ and Asn331 in $TR\beta_1$), which created one extra bifurcated salt-bridge for the terminal carboxylate in $TR\beta_1$ [9].

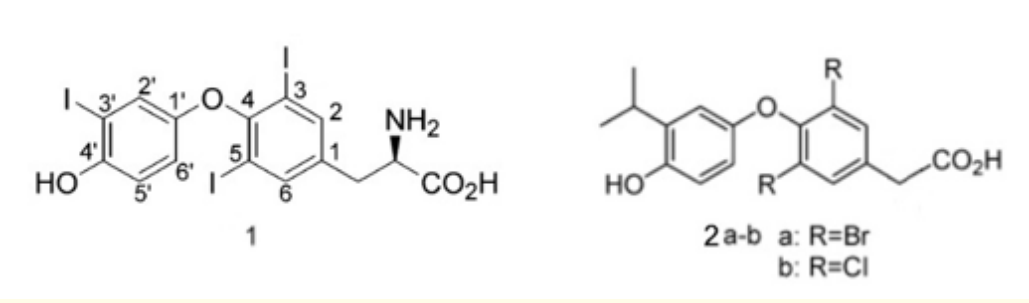

Figure 1: *Chemical structures of L-T3 (1) including ring-numbering, and KB-092 (2a) and KB-141 (2b).*

In vivo characterization of KB-141

Testing of efficacy of KB-141 was done in rats, cynomolgus monkeys, and *ob/ob* mice. We first tested KB-141 in rats. In order to show selectivity, we simultaneously measured cholesterol, HR, oxygen consumption (MVO_2), and TSH [4]. In order to show selectivity, we tested multiple doses over a week and compared dose ratios and compared with T_3 in order to determine whether cholesterol reduction and slight increases (5%, perhaps enough to cause weight reduction) in MVO_2 could be achieved without tachycardia. MVO2 is our surrogate marker for possible anti-obesity effects. As shown in figure 2, cholesterol was reduced in a dose dependent manner by both compounds, but with less potency for KB-141, consistent with its lower TRβ potency. T_3 caused a dose dependent increase in HR, while KB-141 had little effect. KB-141 reduced cholesterol with a -27-fold selectivity compared with tachycardia. T_3 also caused a steep, dose dependent increase in MVO_2, while KB-141 caused modest (up to 5%) increases at the doses that also caused cholesterol reduction. MVO_2 was only slightly increased such that the selectivity of 5% increase vs tachycardia was approximately 10-fold. There was no difference in selectivity for TSH reduction between KB-141 and T_3 (this will be discussed below). No differences in tissue distribution between T_3 and KB-141 were observed, suggesting that TR selectivity explained the physiological selectivity of KB-141.

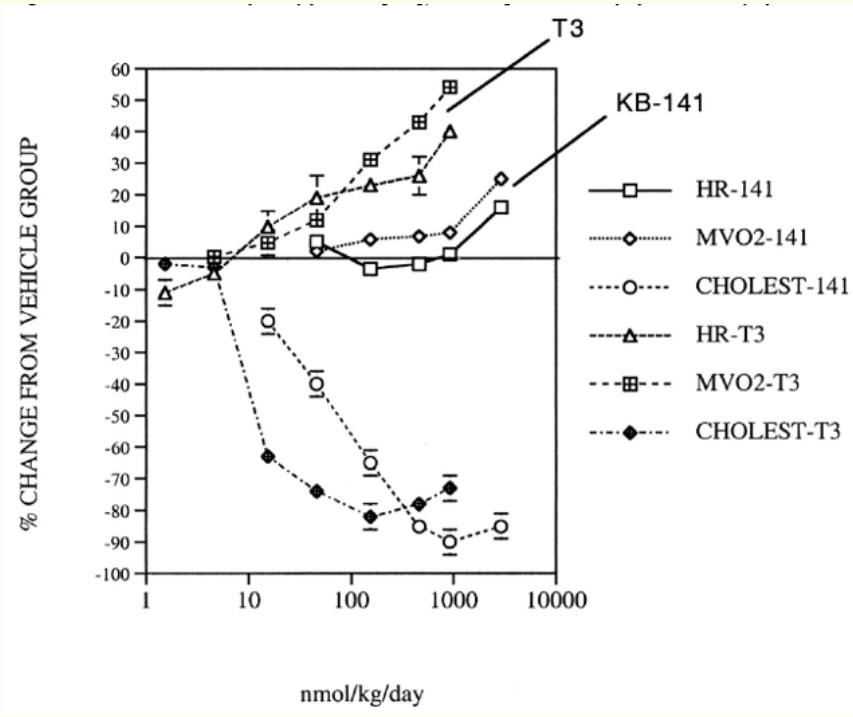

Figure 2: *The effect of increasing doses of T3 and KB-141 on serum cholesterol, heart rate (HR) and total oxygen consumption (MVO2) in cholesterol fed rats. Doses were administered for one week. T3 caused steep dose-dependent increase in HR, MVO2 and cholesterol. By comparison, KB-141 had a similar reduction in cholesterol while have minimal effects on HR and increasing MVO2 by around 5% over a broad dose range. These data suggest the possibility of weight reduction and lipid lowering without cardiac acceleration.*

These data suggest a therapeutic window is possible for cholesterol reduction and weight reduction without tachycardia. As primates are similar to man in cholesterol homeostasis, we determine the effect of KB-141 in cynomolgus monkeys [4]. We saw dose dependent reductions in cholesterol and lipoprotein (a) (Lp(a)) with KB-141 (Figure 3). Significant body weight reduction was also seen at these doses without tachycardia or other toxic effects. Further studies were in *ob/ob* mice to determine the effect of KB-141 on adiposity, diabetes and lipids [6]. KB-1141 reduced adiposity and body weight while improving glucose and insulin tolerance. In this study, KB-141 also reduced cholesterol and triglycerides. No tachycardia caused by the doses of KB-141 used in this study.

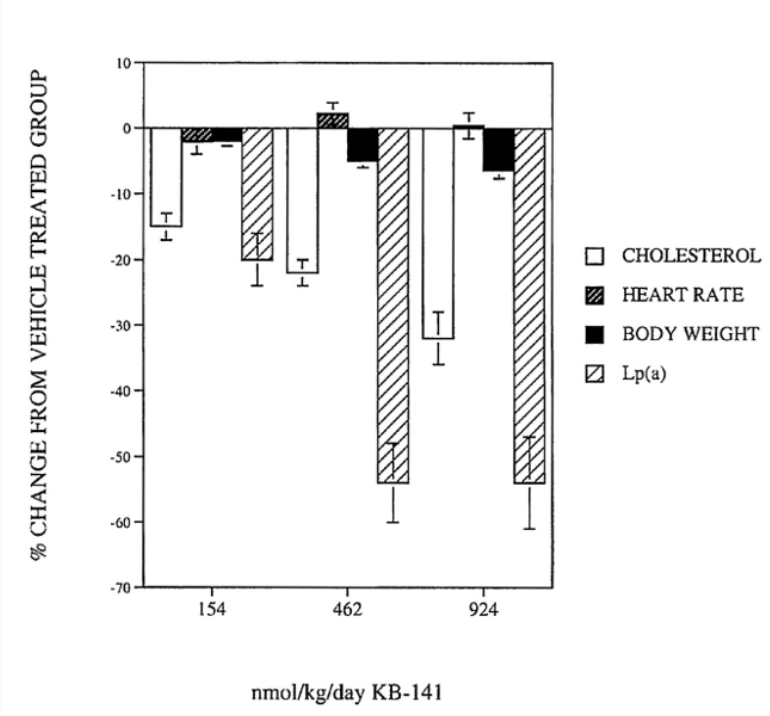

Figure 3: *Dose response (7 days treatment) of KB-141 on cholesterol, heart rate, body weight and lipoprotein (a) (Lp(a) in cynomolgus monkeys. KB-141reduced cholesterol, body weight and Lp(a) in a dose dependent manner while having no effect on heart rate.*

Conclusions and Summary

TR agonists have been of interest for treating metabolic syndrome for decades. Selectivity allowing for a sufficient therapeutic window has unfortunately been hard to achieve. Two approaches have been tried, TRβ selectivity or selective tissue uptake [3,4,7]. Compounds such as GC-1 are TRβ selective, but also show some specific tissue selectivity [8], but this compound is not being clinically developed. An interesting approach was a liver specific prodrug of MB07811 which did reduce cholesterol and triglycerides at doses that did not have cardiac liability [7]. While this a novel approach for cholesterol reduction, liver selectivity most likely precludes efficacy for obesity and diabetes. It may be necessary to develop specific TR agonists for diabetes, obesity and lipid reduction, but the idea of developing one agent with sufficient selectivity to treat all of these conditions is indeed alluring, if not practical.

It is presently unclear whether TR selective agonists have sufficient therapeutic window to be an effective therapeutic in man. KB-141 does reduce the severity of diabetes and reduces adiposity as well as lipid lowering, which may make such compounds more desirable

than MB07811. On the other hand, attempting to achieve selectivity suitable for this array of diseases may be difficult at best. Selective tissue uptake of TR agonists may be possible, but the tissue targets for obesity and diabetes are not as clear as liver metabolism of cholesterol and triglycerides, so screening for tissue selectivity may have to be done *in vivo*, which is challenging. At KaroBio and Bristol Myers Squibb, we were able to develop SAR in a rapid *in vivo* rat model and these are to be published. Another potential disadvantage for TRβ selective agonists is their tendency to reduce TSH which may cause some tissues such as brain to become hypothyroid as they will reduce secretion of pituitary TSH and therefore reduce production of pituitary T_4/T_3.

Bibliography

1. Waters DD., *et al.* "Are we aggressive enough in lowering cholesterol?" *The American Journal of Cardiology* 88 (2001): 5F-10F.
2. Hruby A and Hu FB. "The epidemiology of obesity: a big picture". *Pharmaco Economics* 33 (2014): 673-689.
3. Shoemaker TJ., *et al.* "Thyroid hormone analogues for the treatment of metabolic disorders: new potential for unmet clinical needs". *Endocrine Practice* 18 (2012): 954-964.
4. Grover GJ., *et al.* "Selective thyroid hormone receptor-β activation: A strategy for reduction of weight, cholesterol, and lipoprotein (a) with reduced cardiovascular liability". *Proceedings of the National Academy of Sciences* 100(2003): 10067-10072.
5. Boelaert K., *et al.* "Thyroid hormones in health and disease". *Journal of Endocrinology* 187 (2005): 1-15.
6. Bryzgalova G., *et al.* "Anti-obesity, anti-diabetic, and lipid lowering effects of the thyroid receptor b subtype selective agonist KB-141". *The Journal of Steroid Biochemistry and Molecular Biology* 111 (2008): 262-267.
7. Erion MD., *et al.* "Targeting thyroid hormone receptor-β agonists to the liver reduces cholesterol and triglycerides and improves the therapeutic index". *Proceedings of the National Academy of Sciences of the United States of America* 104 (2007): 15490-15495.
8. Trost SU., *et al.* "The thyroid hormone receptor-beta selective agonist GC-1 differentially affects plasma lipids and cardiac activity". *Journal of Endocrinology* (2000): 3057-3064.
9. Ye L. "Thyroid receptor ligands 1. Agonist ligands selective for the thyroid receptor beta1". *Journal of Medicinal Chemistry* 46 (2003): 15580-1585.

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