Introduction

Thyroid hormones act by binding to nuclear thyroid hormone receptors(TRs)α and β.Both TRα and TRβ are expressed in most tissues,but their relative levels of expression vary among organs;TRα is particularly abundant in brain,kidney,gonads,muscle,and heart,whereas TRβ expression is relatively high in the pituitary and liver.Both receptors are variably spliced to form unique isoforms.The TRβ2 isoform,which has a unique amino terminus,is selectively expressed in the hypothalamus and pituitary,where it plays a role in feedback control of the thyroid axis.The TRα2 isoform contains a unique carboxy terminus that prevents thyroid hormone binding;it may function to block the action of other TR isoforms **(Weetman A and Jameson J, 2005).**

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 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 analogues that are capable of uncoupling beneficial effects from deleterious effects have been developed. Such drugs could serve as powerful new tools to address two of the largest medical problems in developed countries--atherosclerosis and obesity **(Baxter J and Webb P, 2009).**

Selective thyroid hormone receptor subtype-beta (TRbeta) agonists have received attention as potential treatments for hypercholesterolemia and obesity, but have received less attention as

treatments for diabetes, partly because this condition is not improved in thyroid hormone excess states. The TRbeta selective agonist KB-141 induces 5-10% increases in metabolic rate and lowering of plasma cholesterol levels without tachycardia in lean rats, unlike the major active thyroid hormone, T3. In the current study, we determined whether KB-141 promotes weight loss in obese animals and whether it exhibits anti-diabetogenic effects. Thus, KB-141 elicits anti-obesity, lipid lowering and anti-diabetic effects without tachycardia suggesting that selective TRbeta activation may be useful strategy to attenuate features of the metabolic syndrome. **(Bryzgalova G et al., 2008).**

Thyroid hormone has the unique properties of lowering cholesterol in hypothyroid individuals and improving cardiac performance. Beginning in the 1950s, extensive efforts were made to develop thyroid hormone analogs that could utilize the cholesterol-lowering property in euthyroid individuals without affecting the heart. These efforts culminated in the development of analogs that selectively bind to beta1-type nuclear thyroid hormone receptors (TRs), which are responsible for cholesterol-lowering activity, without activating alpha1-type receptors in the heart. Beta1-Selective compounds may be useful in lowering cholesterol in euthyroid individuals who are intolerant to treatment with 'statins'. Screening of compounds for those that might be suitable for improving cardiac performance in heart failure led to the identification of 3, 5-diiodothyropropionic acid (DITPA). DITPA binds to both alpha- and beta-type TRs with relatively low affinity. In postinfarction models of heart failure and in a pilot clinical study, DITPA increased cardiac performance without affecting heart rate. This compound also lowers cholesterol and may be a useful adjunct to standard heart failure therapy. Although there is both experimental and

clinical evidence indicating that thyroid analogs act differently than thyroid hormones, the details of their mechanism of action have not been completely elucidated.Clinical trials for thyroid hormone analogues are in prospect **(Morkin E et al., 2004).**

Thyroid hormones regulate cholesterol and lipoprotein metabolism, but cardiac effects restrict their use as hypolipidemic drugs. TRbeta is the predominant isoform in liver, whereas T3 effects on heart rate are mediated mostly by TRalpha. Drugs that target TRbeta or exhibit tissue-selective uptake may improve plasma lipid levels while sparing the heart. Here, we asked how the TRbeta- and liver uptake-selective agonist GC-1 influences cholesterol and triglyceride metabolism in euthyroid mice. GC-1 treatment reduced serum cholesterol levels by 25% and serum triglycerides by 75% in chow-fed mice and also attenuated diet-induced hypercholesterolemia. GC-1 reduced plasma high-density lipoprotein cholesterol levels; increased expression of the hepatic high-density lipoprotein receptor, and increased fecal excretion of bile acids. Collectively, these results suggest that GC-1 stimulates important steps in reverse cholesterol transport. Use of TRbeta and uptake selective agonists such as GC-1 should be further explored as a strategy to improve lipid metabolism in dyslipoproteinemia **(Johansson L et al., 2005).**