Summary

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 **(Weetman A and Jameson J, 2005).**

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 **(Baxter J and Webb P, 2009).**

Extensive efforts were made to develop thyroid hormone analogues that could utilize the cholesterol-lowering property in euthyroid individuals without affecting the heart. These efforts culminated in the development of analogues 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 **(Morkin E et al., 2004).**

The thyroid hormone agonist, called GC1, has selective actions on TRβ. In animals, GC1 reduced serum cholesterol and serum triglycerides, probably by stimulation important steps in reverse cholesterol transport. Other selective thyromimetic, KB- 2115 and KB - 141 have similar effects **(Tancevski I et al., 2005).**

Interestingly, GC-1, a TRβ1 agonist with no effect on cardiac rhythm, has been shown to have a proangiogenic action that is initiated at

the plasma membrane and requires the activation of MAPK signaling **(Mousa S et al., 2005).**

KB-141 is another TRβ1 agonist thought to be suitable for treating obesity, hyperlipidemia, and diabetes **(Grover G et al., 2007).**

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). It has also been that DITPA can lower cholesterol and improve cardiac performance without affecting heart rate **(Morkin E et al., 2004).**

DITPA **(Morkin E et al., 2002)** and Eprotirome (KB2115)**(Berkenstam A et al., 2008)**, respectively, showed TR b 1-selective thyromimetics to lower plasma LDL cholesterol and triglycerides also in humans, without untoward cardiac effects **(Tancevski I et al., 2007).**

In summary, the past 20 years saw the development of either organ-selective or TR b 1-selective TH analogues, all of which lowered plasma cholesterol without deleterious effects on the heart **(Moreno et al. 2008**).

However, current studies do not provide sufficient data on the central question as to whether the observed relative hypothyroidism may have deleterious effects on the human organism. Thus, further studies on the mechanism of negative feedback on the thyroid axis induced by both TR b 1-selective and organ-selective TH analogues, are needed **(Tancevski I et al., 2008).**It is not currently possible to assess

whether selective thyromimetics will reduce cardiovascular morbidity and mortality in humans when used long term **(Tancevski I et al., 2010).**