Introduction

Thyroid hormones are important modulators of lipid homeostasis and metabolism. Overthyroidism in humans is associated with elevated low density lipoprotein (LDL) cholesterol and apolipoprotein B due to decreased clearance of LDL, resulting in part from reduced expression of hepatic LDL receptors. Conversely, in hypothyroidism there is an increased excretion of cholesterol and increased turnover of liver-derived total and LDL cholesterol (reviewed by Dunn and Ibetea, 2012). Apolipoprotein B is the main structural surface protein found on all beta lipoproteins (Chylomicrons, LDL, VLDL, and IDL) and can function to traffic cholesterol into the arterial wall. Lipoprotein(a) [Lp(a)] is a type of low density lipoprotein and is covalently bound to apolipoprotein B by a disulfide bridge (Steyer et al. 1994). Lp(a) interacts with fibrinolysis by competing with plasminogen binding to molecules and cells. In addition, Lp(a) tends to macropathies via a high-affinity receptor that promotes foam cell formation and the depopulation of cholesterol in atherosclerotic plaques (Zioncheck et al. 1991). The association of Lp(a) with cardiovascular disease has been shown in several studies, including a meta-analysis of over 120,000 subjects which concluded that Lp(a) was particularly involved in cardiovascular outcomes such as CHD and stroke (Engrum et al. 2009).

Hypothesis

The thyroid hormone receptor isozyme beta-1 (TRβ-1) is a nuclear receptor that is responsible for the effects of T3 on cholesterol, triglycerides, and bile acid metabolism. Cholesterol excretion in the bile as well as hepatic hepatic expression of LDL and HDL receptors is stimulated through binding to TRβ (reviewed by Angeli and Rudling 2010). These characteristics suggest potential promising therapeutic effects in settings where elevated lipids contribute to long-term cardiovascular risks.

In animals, VK2809 has demonstrated potent reductions of plasma cholesterol, triglycerides, and liver fat content.

Reduction of atherogenic lipoprotein (a) and apolipoprotein B in humans with the selective thyroid receptor beta agonist VK2809

Steven L. Schoenfeld1, Brian Lian1, Rochelle Hanley1, Ken Homer2

1Viking Therapeutics, San Diego, CA, 2Integrium, LLC, New Jersey

Reduction in atherogenic protein levels could be important for patients with elevated markers of CV risk such as Lp(a)/Apo B. A proof of concept study is underway to evaluate the effects of VK2809 on atherogenic (p) and liver fat content in patients with hypercholesterolemia and fatty liver disease.

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