Institutionen för Medicin

Studies on the effects of thyroid hormone on cholesterol and lipoprotein metabolism

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i föreläsningssal B64, Karolinska Universitetssjukhuset, Huddinge

Fredagen den 14 december, 2012, kl 12.00

av

Ylva Bonde
Fil. mag.

Huvudhandledare:
Professor Mats Rudling
Karolinska Institutet
Institutionen för Medicin

Bihandledare:
Professor Bo Angelin
Karolinska Institutet
Institutionen för Medicin

Doktor Cecilia Gälman
Karolinska Institutet
Institutionen för klinisk kemi

Fakultetsopponent:
Professor Jan Oscarsson
Göteborgs Universitet
Institutionen för Neurovetenskap och Fysiologi

Betygsnämnd:
Professor Gunilla Olivecrona
Umeå Universitet
Institutionen för Fysiologisk Kemi

Docent Jens Mittag
Karolinska Institutet
Institutionen för Cell- och Molekylärbiologi

Professor Joseph Rafter
Karolinska Institutet
Institutionen för Biovetenskaper och Näringslära

Stockholm 2012
ABSTRACT

Elevated plasma lipids, particularly cholesterol within low density lipoproteins, is an important risk factor for developing atherosclerosis which can cause angina pectoris, myocardial infarction, and stroke. Thyroid hormone (TH) has a strong influence on lipid metabolism and the aim of this thesis was to gain more insight into how TH modulates cholesterol and lipoprotein metabolism.

In contrast to normal rats, plasma cholesterol increases in hypophysectomized (Hx) rats upon cholesterol feeding. In paper I, it was found that the increased plasma cholesterol in Hx rats in response to cholesterol feeding is partly caused by an increased intestinal absorption of dietary cholesterol. TH was found to normalize the increased absorption of cholesterol in Hx rats. The changes in intestinal absorption of dietary cholesterol induced by hypophysectomy and TH could not be explained by changes in the intestinal gene expressions of sterol transporters ABCG5/G8 and NPC1L1. However, hepatic gene expressions of ABCG5/G8 were found to be diminished in Hx rats and strongly stimulated by TH, associated with a markedly reduced and stimulated biliary secretion of cholesterol, respectively, that may influence the absorption of dietary cholesterol.

The sterol transporter ABCG5/G8 is of major importance in the biliary secretion of cholesterol. However, alternative pathways that promote biliary cholesterol secretion have been proposed. TH stimulates both biliary cholesterol secretion and the hepatic gene expression of ABCG5/G8. In paper II, it was investigated if the TH-induced secretion of cholesterol into bile is mediated by ABCG5/G8, or if other pathways are involved. TH-induced secretion of cholesterol into bile was found to be largely dependent on the ABCG5/G8 transporter. It was also found that nuclear hormone receptor LXRα, reported to be positively regulated by TH and to have a stimulatory effect on ABCG5/G8 gene expression, is not critical for the TH-induced effect on ABCG5/G8 gene expression or on biliary cholesterol secretion.

In paper III, the responses to hyperthyroidism in humans were studied and compared to those of healthy subjects treated with the liver-specific thyromimetic eprotirome. Hyperthyroidism lowered VLDL-, LDL-, and HDL-cholesterol, apoB, Lp(a), and serum PCSK9. Bile acid synthesis was increased and serum FGF19 reduced. Cholesterol synthesis was unaltered while intestinal absorption of dietary cholesterol was reduced. Serum free fatty acids and glycerol were increased, while insulin, glucose, and FGF21 were unaltered. Eprotirome treatment resulted in similar reductions in lipoprotein cholesterol, apoB, Lp(a), and PCSK9. In contrast to hyperthyroidism, eprotirome reduced plasma triglycerides. There were no effects on bile acid synthesis, FGF19, or cholesterol absorption, in response to liver-selective stimulation of TH receptors by eprotirome.