Karolinska Institutet

Institutionen för Medicin, Huddinge

Studies on cholesterol and lipoprotein metabolism – emphasis on diabetes and sugar

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Föreläsningssal B64 (Barngatan 4, plan 6), Karolinska Universitetssjukhuset, Huddinge

Fredagen den 29 maj, 2015, kl 09.15

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Stockholm 2015

ABSTRACT

Cholesterol has important functions in the body; as a precursor in the synthesis of steroid hormones and bile acids (BAs), and as a component of cellular membranes. However, an elevated level of plasma cholesterol, transported in low density lipoprotein (LDL) particles, is one of the major risk factors and causes for cardiovascular disease. Therefore its metabolism is tightly regulated, from synthesis to excretion. Cholesterol can be excreted from the liver into the bile, directly or after conversion into BAs. By modulation of cholesterol and BA metabolism, carbohydrate and triglyceride (TG) metabolism can also be affected, and vice versa. The main focus of this thesis was to further characterize these relationships.

In **Paper I**, the effects of inhibiting the ileal bile acid transporter (IBAT; also known as apical sodium dependent bile acid transporter [ASBT]) on TG and glucose metabolism were studied. This was studied in IBAT-deficient mice fed a sucrose-enriched diet and in *ob/ob* mice treated with an IBAT inhibitor. Liver TG was reduced in the first model and plasma TG and blood glucose was reduced in the second. IBAT inhibition could therefore be a promising therapeutic agent. An unexpected finding was that BA synthesis was reduced by the sucrose-enriched diet.

This was further studied in **Paper II** in which rats were fed two different sucrose-enriched diets. The first one, with increased sucrose content and concomitantly reduced contents of fibers and fats, reduced BA synthesis. However, the second more controlled high-sucrose diet, in where the complex carbohydrates were replaced by sucrose, did not affect BA synthesis. It was therefore concluded that it was not sucrose *per se* in the first diet that reduced BA synthesis. Both high-sucrose diets induced a very strong reduction in the hepatic expression of the cholesterol transporters ATP-binding cassette sub-family G members 5 and 8 (Abcg5/8).

In **Paper III**, the effect of growth hormone (GH) on circulating levels of fibroblast growth factor 21 (FGF21) was investigated in three human studies with administration of different doses of GH, and for various durations. It was concluded that GH is not crucial for maintaining basal FGF21 levels and does not increase FGF21 levels acutely or after long-term administration of physiological doses. However, prolonged administration of supraphysiological doses increases FGF21.

In **Paper IV**, type 2 diabetic patients were shown to have lower levels of LDL cholesterol in interstitial fluid than healthy controls, when related to their serum levels. This was unexpected as it was hypothesized that these patients would have higher LDL levels in interstitial fluid and that this could explain their increased risk of cardiovascular disease. However, the reduced level may mirror an increased cellular uptake of apoB-containing lipoproteins from the interstitial fluid.

In conclusion, this thesis has further characterized the interactions between the metabolism of cholesterol and BAs, with that of TGs and glucose. It is shown that interruption of the enterohepatic circulation of BAs may be a promising drug target for improving glucose and TG metabolism. Furthermore, dietary sucrose may reduce the secretion of cholesterol into bile, however, this needs to be confirmed. It is shown that the hormone-like protein FGF21 can be elevated by high GH levels in humans. Lastly, type 2 diabetic patients have unexpectedly low LDL cholesterol levels in interstitial fluid, presumably reflecting their increased propensity to develop atherosclerosis.

ISBN 978-91-7549-870-6