Göteborg, 2021

Lipoproteins in the postprandial state

- studies on the metabolism of triglyceride-rich lipoproteins using multicompartmental models

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i Sahlgrens aula Blå stråket 5, den 10 juni 2021, klockan 13.00
av Elias Björnson

Fakultetsopponent:

Professor Bo Angelin

Karolinska Institutet, Sverige

Avhandlingen baseras på följande delarbeten

I. Björnson, E., Packard, C. J., Adiels, M., Andersson, L., Matikainen, N., Söderlund, S., ... & Borén, J. (2019). **Investigation of human apoB48 metabolism using a new, integrated non-steady-state model of apoB48 and apoB100 kinetics**. *Journal of internal medicine*, *285*(5), 562-577.

II. Björnson, E., Packard, C. J., Adiels, M., Andersson, L., Matikainen, N., Söderlund, S., ... & Borén, J. (2020). **Apolipoprotein B48 metabolism in chylomicrons and very low-density lipoproteins and its role in triglyceride transport in normo-and hypertriglyceridemic human subjects**. *Journal of internal medicine*, *288*(4), 422-438.

III. Taskinen, M. R., Björnson, E., Matikainen, N., Söderlund, S., Pietiläinen, K. H., Ainola, M., ... & Borén, J. (2021). **Effects of liraglutide on the metabolism of triglyceride-rich lipoproteins in type 2 diabetes**. *Diabetes, Obesity and Metabolism*.

IV. Taskinen, M. R., Björnson, E., Kahri, J., Söderlund, S., Matikainen, N., Porthan, K., ... & Borén, J. (2020). **Effects of Evolocumab on the Postprandial Kinetics of Apo (Apolipoprotein) B100-and B48-Containing Lipoproteins in Subjects With Type 2 Diabetes**. *Arteriosclerosis, Thrombosis, and Vascular Biology*, ATVBAHA-120.

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Abstract

Lipoproteins are lipid-containing spherical particles that circulate in the human blood stream. The reason for their intense study over the decades is their ability to cause atherosclerosis[1]. Atherosclerotic cardiovascular disease (ASCVD) remains as the single largest cause of death worldwide; and here in Sweden, around a third of all deaths can be attributed to the category: *diseases of the circulatory system*[2]. The strength of evidence that low-density lipoproteins (LDL) cause ASCVD is very high. In recent years evidence has emerged indicating that so-called triglyceride-rich lipoproteins (TRLs) also contribute causally to atherosclerosis[3]. The two sources of TRLs in the human circulation are the liver – which produces lipoproteins continuously, and the intestine – which produces lipoproteins in response to a meal. The liver-derived particles contain a structural surface protein called apolipoprotein B100 (apoB100) whereas particles from the intestine contain apolipoprotein B48 (apoB48). TRLs can also be further classified based on density into the following fractions: intermediate-density lipoprotein (IDL), very low-density lipoprotein 2 (VLDL2), very low-density lipoprotein 1 (VLDL1) and lastly the chylomicron (CM) fraction. Lipoproteins are studied in many ways, both in humans and in model organisms. In the current thesis I, study human lipoproteins *in vivo* with the help of multicompartmental modelling in conjunction with specifically designed metabolic studies involving stable isotopes. This enables quantification of the *fluxes* of lipoproteins as opposed to quantification of concentrations only. I developed a model able to study the postprandial, non-steady state, metabolism of both apoB48- and apoB100 containing lipoproteins. The model was primarily designed to study TRLs but was later adapted to also encompass LDL. After developing the model, it was first implemented for the purpose of studying whether the metabolism of TRLs differed across the range of subjects with low-to-high TRL levels. ApoB48 was found to track the metabolism of apoB100 which revealed a more complex picture of the state of hypertriglyceridemia (high levels of TRLs) with postprandial excursions of particles overlayered on a baseline steady-state level. Second, the model was implemented to study the effects of the antidiabetic drug liraglutide. We found that chylomicron secretion was specifically affected by liraglutide, an effect that was likely independent from the improvements in insulin sensitivity induced by the drug. Lastly, we implemented the expanded model to study the effects of the LDL-cholesterol lowering drug evolocumab. We found that evolocumab mostly affected apoB100-containing lipoproteins. Particles in the VLDL1 fraction remained unaffected but VLDL2, IDL and LDL concentrations were decreased with the largest effect size seen for LDL (around 80 % reduction). We further found evidence for the existence of two distinct LDL species with differing kinetic properties, that were differentially affected by evolocumab. In conclusion, here I present a new comprehensive multicompartmental model of lipoprotein metabolism. The model is designed to study apoB100- and apoB48 containing lipoproteins in the postprandial state. The model is used in the current thesis to study TRLs in hypertriglyceridemia and to study the effect of drugs on both TRLs and LDLs. The higher purpose for these studies is to add to the body of evidence for the role of lipoproteins in heart disease.

Keywords: Lipoproteins, kinetic studies, apoB48, apoB100, postprandial

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