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Title of project: The role of the apolipoprotein A-IV in metabolic health

ABSTRACT

Elevated fasting plasma insulin, glucose and triacylglycerol levels are key components in insulin resistance and the metabolic syndrome, and liver fat accumulation appears to be central in glucose homeostasis dysregulation and dyslipidemia. Within this postdoctoral project, it will be investigated whether the apolipoprotein A-IV (apoA-IV) may be a linking molecule. Our novel observations indicate a strong connection between dietary carbohydrate and fat availability, circulating apoA-IV levels and hepatic insulin sensitivity, but the causal relationship is unknown.

The aim of this research is to clarify the regulation and function of apoA-IV. More specifically, the impact of dietary carbohydrate and fat intake on liver fat and apoA-IV levels, and the role of apoA-IV in regulation of insulin and glucose homeostasis by the liver and lipid clearance from the blood will be investigated. Human dietary studies, and mouse studies with recombinant apoAIV protein will be applied to uncover the mechanistic and functional underpinning. ApoA-IV may thus be a promising target in the treatment of glucose intolerance and dyslipidemia. Moreover, apoA-IV has the potential advantage to be modulated and impact on metabolic regulation via changes in dietary intake. As part of the project, the molecular imprint of insulin-resistant versus insulin-sensitive liver will be subject for investigation, which potentially can provide new understanding to obesity-induced insulin resistance.

ABSTRAKT

Forhøjede niveauer af faste insulin, glukose og triacylglycerol i blodet udgør vigtige komponenter i det metaboliske syndrom samt insulin resistens. En øget fedtakkumulering i leveren spiller desuden en central rolle i dysguleret glukose homeostase samt dyslipidæmi. I dette projekt vil der blive forsket i hvorvidt apolipoprotein A-IV (apoA-IV) kan være et koblende molekyle. Vores nylige observationer indikerer en stærk sammenhæng mellem kostens kulhydrat- og fedttilgængelighed, cirkulerende niveauer af apoAIV og leverens insulinfølsomhed, men den kausale sammenhæng er ukendt.

Formålet med dette forskningsprojektet er derfor at klarlægge regulering samt funktion af apoA-IV. Mere specifikt søges det at afdække betydningen af kulhydrat- og fedtindtagelse for regulering af apoA-IV og leverens fedtindhold, samt betydningen af apoA-IV for leverens regulering af insulin og glukose homeostase, og den perifere fjernelse af fedt fra blodet. Humane koststudier, samt musestudier med rekombinant apoA-IV protein vil bidrage til at afdække mekanistiske og funktionelle sammenhænge. ApoA-IV kan således være et loverende reguleringspunkt i glukose tolerance og fedtmetabolisme. Som del af projektet vil den molekylære signatur af henholdsvis

insulin resistent versus insulin sensitiv lever metabolisme undersøges, hvilket kan bidrage til ny viden og forståelse i fedme-induceret insulinresistens.