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Title of project: Understanding the mechanisms underpinning metabolic flexibility

ABSTRACT

I have just returned from a 13 months research stay in the lab of David James in Sydney, Australia, and will during this two year DDA-financed postdoc be working at Molecular Physiology Group at Department of Nutrition, Exercise and Sports at University of Copenhagen and in the lab of Matthias Tschöp at Institute for Diabetes and Obesity, Helmholtz Diabetes Center in Munich. In this project I am interested in understanding the molecular mechanisms that are responsible for regulating *metabolic flexibility*. Human metabolism needs to be able to cope with irregularities of both supply and demand for energy. This requires the ability to readily switch between carbohydrate and lipid utilization which is termed metabolic flexibility. Conversely, the inability to adapt to different energy sources (termed metabolic *inflexibility*) is a hallmark dysfunction of a cluster of diseases called the metabolic syndrome. The reason for this metabolic inflexibility has been proposed to primarily be a function of decreased mitochondrial function in skeletal muscle, but the actual molecular mechanisms that promote metabolic flexibility, or conversely that are impaired to trigger metabolic inflexibility, have not been elucidated**.** Together with researchers at the pharmaceutical company, Novo Nordisk, and a research group in Munich, we will take advantage of our recently developed model to study metabolic flexibility, in which fatty acid oxidation is pharmacologically inhibited in mice. This induces a shift to increased glucose uptake and utilization in various peripheral tissues such as skeletal muscle. In this model, we will by use of transgenic mouse models and pharmacological inhibitors investigate proposed molecular mechanisms in e.g. skeletal muscle that are responsible for increasing glucose uptake during inhibition of fatty acid oxidation. Especially, we are interested in investigating the role of a protein, fibroblast growth factor 21 (FGF21) that are massively increased in the circulation and in the liver during inhibition of fatty acid oxidation and may be involved in this phenomenon.

ABSTRAKT

Jeg er netop hjemvendt fra et 13 måneders forskningsophold i David James' laboratorie i Sydney, Australien og vil under dette 2 års DDA-finansierede postdoc arbejde i Molekylær Fysiologisk Sektion på Institut for Idræt og Ernæring på København Universitet samt i Matthias Tschöps laboratorie på Instititut for Diabetes and Obesity, Helmholtz Diabetes Center i München. Jeg er i dette projekt interesseret i at forstå de molekylære mekanismer, der er ansvarlige for reguleringen af *metabolisk fleksibilitet*. Menneskets stofskifte skal hele tiden imødekomme ændringer i tilgængeligheden af energi og et varierende energiforbrug. Dette kræver evnen til hurtigt at skifte mellem forbrænding af kulhydrat og fedt, der er kaldt metabolisk fleksibilitet. En manglende evne til at adaptere til forskellige energisubstrater (kaldet metabolisk infleksibilitet) er derimod en central dysfunktion i en række sygdomme samlet under betegnelsen metabolisk syndrom. Årsagen til denne manglende metaboliske fleksibilitet er foreslået primært at være forårsaget af nedsat

mitokondriefunktion i skeletmusklen, men de reelle molekylære mekanismer der sikrer metabolisk fleksibilitet, eller som omvendt er dysreguleret i metabolisk infleksibilitet, er ikke kendte. Sammen med forskere i medicinalfirmaet, Novo Nordisk, samt en forskningsgruppe i München, vil vi udnytte vores nyligt udviklede model til at studere metabolisk fleksibilitet, hvor fedtoxidationen i mus er hæmmet farmakologisk. Dette medfører en større optagelse og forbrænding af glukose (kulhydrat) i forskellige perifere væv, herunder skeletmusklen. I denne model vil vi anvende transgene musemodeller og farmakologiske hæmmere af proteiner til at undersøge molekylære mekanismer i f.eks. skeletmusklen, som er ansvarlige for at øge glukoseoptagelsen under hæmning af fedtoxidationen. Især er vi interesserede i at undersøge betydningen af et bestemt protein, *fibroblast growth factor 21* (FGF21), som vi har fundet er massivt forøget i blodet og i leveren under hæmning af fedtoxidationen, og som måske er involveret i dette fænomen.