Theme 2: Disentangling insulin resistance

1. ‘Defining the Human Insulin Resistance Molecular Network; SIGNATURE’, DKK 59,961,322 over 6 years

Main applicant: Jørgen Wojtaszewski, Depart. of Nutrition, Exercise and Sports, University of Copenhagen

Co-applicants:
David James, School of Life and Environmental Sciences and School of Medical Sciences, University of Sydney

Claudia Langenberg, Precision Healthcare University Research Institute, Queen Mary University of London

Brief description:
Human insulin sensitivity is markedly variable even among healthy, young well-matched individuals. This poses a major challenge in identifying key molecular mechanisms behind insulin resistance. Studies attempting to explain this individual variation by genetic differences have been inconclusive due to insufficient genetic effect sizes, relative to the comparatively strong influence of environmental factors. A lack of highly controlled experimental conditions further contributes to the difficulty in unravelling mechanisms of insulin resistance.
The project will expose healthy individuals to a series of short-term well-controlled environmental exposures with extensive phenotyping and tissue sampling. It will couple the deep phenotyping at baseline and after each intervention to multi-omics analyses of obtained tissues, to discover machine learning based signatures that accurately predict discrete features of the insulin resistance network. These signatures will then be used for genetic mapping of distinct insulin resistance classes in larger already available human cohorts.
Finally, the project will provide human validation and establish mechanistic causalities for identified molecular signatures or specific targets. These signatures and the associated genetic variants will be invaluable for diagnostic and therapeutic purposes, enabling individualized strategies to prevent the onset of metabolic disease.

2. 'Disentangling the effect of Brain Insulin Resistance on Brain Health: The BIR-BrainHealth Project', DKK 59,999,991 over 6 years

Main applicant: Henrik Larsson, Department of clinical physiology and nuclear medicine, Rigshospitalet

Co-applicants:
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Brief description:
Brain insulin resistance (BIR) is linked to cognitive decline in both type 1 and type 2 diabetes, yet the underlying mechanisms are largely unexplored. The project will characterize human BIR, delineate underlying mechanisms, and uncover its clinical impact.
The project will start with metabolic and cognitive phenotyping of 600 persons with diabetes using novel methods to quantify the BIR by magnetic resonance imaging (MRI) combined with intranasal insulin administration. It will use advanced MRI to examine blood-brain barrier integrity, cerebrovascular regulation, glucose metabolism, and glycolysis, scrutinizing insulin's influence on the neurovascular and neurometabolic function. The transport of insulin into the brain and its role in regulating brain metabolism using position emission tomography (PET) neuroimaging will be investigated. Utilizing radiolabelled insulin as a PET-tracer will reveal new insights into the neural distribution of insulin and its action on energy metabolism. Finally, a multi-omics approach will be employed, anticipating the discovery of unique biomarkers sets indicative of brain insulin action. The potential biomarkers will be cross-referenced with extensive clinical data on cognitive function, the type of diabetes and risk-factors and treatments, and additional phenotypical traits of the patient population. The proposed study could reshape our understanding of BIR and its connection to cognitive decline and dementia in individuals with diabetes. Disentangling where and how BIR occurs will facilitate the development of personalized treatment for patients with diabetes with distinct phenotypes.