Studies on microcirculation on insulin resistance

Akademisk avhandling

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av

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III. Josefin Olausson, Reza Mobini, Per Fogelstrand, Karin Mossberg, Emanuel Fryk, Lena Strindberg, Lillemor Mattsson Hultén, Per-Anders Jansson. Delivery of insulin to subcutaneous adipose tissue and skeletal muscle in type 2 diabetes patients and healthy controls – A microdialysis study. Manuscript


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ABSTRACT

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The overall aim of this thesis was to investigate the microcirculation in insulin resistance, with focus on the expression of endothelin-1, through a translational approach.

Specific aims: 1) Investigate if circulating endothelin-1 levels predict incident coronary heart disease events. 2) To assess if sex differences modify endothelin-1 as a predictor of type 2 diabetes. 3) To investigate if microvascular insulin resistance impairs insulin delivery to the subcutaneous adipose tissue and skeletal muscle. 4) To investigate if acute administration of the PDE-5 inhibitor tadalafil induces positive vascular, metabolic and anti-inflammatory effects in type 2 diabetes. 5) To further elucidate the molecular action of tadalafil in tumour necrosis factor-α (TNF-α) stimulated human endothelial cells.

Principal findings: The population-based cohort in Vara-Skövde was investigated for paper I-II. During baseline cardiovascular risk factors and endothelin-1 were assessed and incident coronary heart disease (CHD) was followed-up during a 10-year period (paper I). Endothelin-1 levels had a predictive value for incident CHD in women, but not in men. A randomly selected subgroup was investigated in a follow-up after 10 years, and impaired glucose tolerance (IGT) and T2D was documented for paper II. Here, higher quartiles of endothelin-1 at baseline were associated with IGT/T2D at follow-up in women. Paper III investigates microvascular aspects of insulin resistance using microdialysis; participants with T2D and age-matched healthy controls were studied after an oral glucose load. Participants with T2D had decreased delivery of insulin to adipose tissue, and a blunted subcutaneous adipose tissue blood flow compared with controls. In paper IV, T2D participants received either placebo or tadalafil (20 mg) before a mixed meal in a randomized controlled trial. Tadalafil increased forearm blood flow, glucose uptake and capillary recruitment, and blunted a postprandial increase of endothelin-1. In paper V, the effects of tadalafil were studied in an experimental setting using TNF-α stimulated endothelial cells. Tadalafil treatment decreased expression of c-Jun N-terminal kinase (JNK) phosphorylation as well as reduced gene expression and secretion of endothelin-1.

Conclusions: This thesis shows that (i) endothelial dysfunction precedes IGT/T2D and CHD, and that endothelin-1 may pose as a risk factor for women, (ii) delivery of insulin from the circulation to subcutaneous adipose tissue is impaired in participants with T2D, and that participants with T2D exhibit a blunted postprandial blood flow response, (iii) acute administration of tadalafil induces positive vascular and metabolic effects in the postprandial state in T2D, and tadalafil decrease gene expression of endothelin-1 in cultured endothelial cells by decreasing activation of JNK.

Keywords: endothelin 1, coronary heart disease, type 2 diabetes, phosphodiesterase 5 inhibition, tadalafil, insulin resistance, endothelial dysfunction, c-Jun N-terminal kinase, nitric oxide, microdialysis.