Endothelin-1 in the regulation of vascular function and glucose metabolism in insulin resistance

AKADEMISK AVHANDLING

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av

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Insulin resistance plays a major role in the pathogenesis of type 2 diabetes and is an important risk factor for cardiovascular disease. Endothelial dysfunction, characterized by reduced bioactivity of nitric oxide and increased activity of the vasoconstrictor and pro-inflammatory peptide endothelin-1 (ET-1), is present in insulin-resistant states and is an important factor promoting the development of cardiovascular complications in patients with insulin resistance. The aim of the thesis was to explore the mechanisms linking insulin resistance to endothelial dysfunction. The hypothesis was that ET-1 via activation of its receptors, ETA and ETB, contributes to endothelial dysfunction and reduced insulin sensitivity in subjects with type 2 diabetes mellitus and insulin resistance.

Study I
The effect of the blockade of ET receptors on endothelium-dependent vasodilatation was studied in 12 individuals with insulin resistance without any history of diabetes or cardiovascular disease. Local intra-arterial dual ETA/ETB receptor blockade, but not selective ETA blockade, enhanced forearm endothelium-dependent vasodilatation.

Study II
The importance of endogenous ET-1 for the regulation of total body glucose uptake and insulin sensitivity was studied in 7 patients with insulin resistance and coronary artery disease. Intravenous dual ETA/ETB receptor blockade, but not selective ETA blockade, enhanced insulin sensitivity in this patient group.

Study III
We studied if ET-1 regulates skeletal muscle glucose uptake in 11 insulin resistant subjects in vivo and in cultured human skeletal muscle cells. Intra-arterial dual ETA/ETB receptor blockade enhanced basal and insulin-stimulated forearm glucose uptake in insulin resistant subjects. ET-1 directly impaired glucose uptake in skeletal muscle cells via a receptor-dependent mechanism.

Study IV
The effect of exogenous ET-1 on basal forearm glucose uptake was studied in 9 subjects with insulin resistance and in cultured human skeletal muscle cells. Intra-arterial ET-1 infusion not only induced vascular dysfunction, but also acutely impaired forearm glucose uptake in individuals with insulin resistance and in skeletal muscle cells from type 2 diabetic subjects. The mechanism seems to be related to signaling downstream of IRS1 Ser636.

Collectively, the obtained data suggest that ET-1 is of pathophysiological importance for the development of endothelial dysfunction and contributes to glucometabolic perturbations in subjects with insulin resistance. Dual ETA/ETB receptor blockade may be a potential therapeutic target in order to improve endothelial function and insulin sensitivity in this patient group.