

ABSTRACT

Vascular and metabolic effects of selective PDE-5 inhibition

Clinical and experimental studies

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Key words: Type 2 diabetes, phosphodiesterase-5 inhibition, inflammation, endothelial cells, HUVEC.
TNF α , ICAM-1, VCAM-1, E-Selectin, JNK, MAPK

Background: Type 2 diabetes (T2D) patients show impaired glucose metabolism, endothelial dysfunction, chronic low-grade inflammation as well as an increased risk of cardiovascular disease. Phosphodiesterase-5 (PDE-5) inhibition amplifies nitric oxide (NO) signaling within the cell and has emerged as a novel treatment option against microvascular insulin resistance and subclinical inflammation. However, very little is known about metabolic effects induced by PDE-5 inhibition in T2D patients.

The overall aim of this thesis was to investigate whether the selective PDE-5 inhibitor tadalafil demonstrate any positive effect on glucose uptake, vascular function and inflammatory markers in T2D patients, and whether any molecular mechanism could be linked to the tadalafil effect in cultured endothelial cells (HUVEC).

Methods and results Paper I-III

Paper I: 17 female T2D patients and healthy controls were recruited and investigated with muscle microdialysis, plethysmography and sampling from an artery and a deep vein in the forearm, to study acute effects of 20 mg tadalafil compared with placebo in a double-blind, randomized controlled trial (RCT). We found that tadalafil treatment resulted in increased capillary recruitment and glucose uptake in forearm muscle.

Paper II: Twenty-six T2D patients of both gender were included in a RCT with parallel groups. Tadalafil 20 mg or placebo were administered before a mixed meal and participants were investigated with muscle microdialysis, plethysmography and blood sampling from an artery and a deep vein in the forearm. In a post hoc analysis we showed positive microvascular, macrovascular and metabolic effects and decreased circulating levels of the vasoconstricting peptide endothelin-1.

Paper III: We studied the effect of tadalafil on inflammatory signaling in HUVEC using Western blot, ELISA and RT-PCR. The results showed that tadalafil reduced gene expression of inflammatory markers and reduced secretion of endothelin-1. Moreover, tadalafil attenuated TNF α -induced phosphorylation of c-Jun N-terminal Kinase (JNK).

Conclusions: Acute administration of the PDE-5 inhibitor tadalafil induced positive metabolic and vascular effects in T2D patients. Furthermore, tadalafil reduced expression of endothelin-1 via a mechanism involving JNK.

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Avhandlingen baseras på följande arbeten:

- I** **Tadalafil increases muscle capillary recruitment and forearm glucose uptake in women with type 2 diabetes.** Per-Anders Jansson, Giuseppe Murdolo, Lovisa Sjögren, Britta Nyström, Mikaela Sjöstrand, Lena Strindberg, Peter Lönnroth, *Diabetologia*. 2010; 53(10):2205-8
- II** **Postprandial Effects of the Phosphodiesterase-5 Inhibitor Tadalafil in Type 2 Diabetes Patients – A Randomized Controlled Trial**
Lovisa Sjögren, Josefin Olausson, Lena Strindberg, Reza Mobini, Per Fogelstrand, Lillemor Mattsson Hultén, Per-Anders Jansson *Submitted to J Clin Endocrinol Metabol*
- III** **Tadalafil Decreases Expression of Endothelin-1 In TNF- α -Activated Human Endothelial Cells – Possible Role of The c-Jun N-terminal Kinase Pathway**
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