Abstract: P159

Vascular endothelial growth factor receptor 2 inhibition improves endothelial function in type 2 diabetic rats: a link to purinergic signalling?

Authors:
A Mahdi¹, Y Tratsiakovich¹, J Yang¹, C-G Ostenson², JAH Danser³, J Pernow¹, Z Zhou¹, ¹Karolinska Institute, Unit of Cardiology, Department of Medicine - Stockholm - Sweden, ²Karolinska Institute, Endocrinology and Diabetology, Department of Molecular Medicine and Surgery - Stockholm - Sweden, ³Erasmus Medical Center, Division of Vascular Medicine and Pharmacology, Department of Internal Medicine - Rotterdam - Netherlands,

Topic(s):
Vascular Tone, Permeability, Microcirculation

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S42

Funding Acknowledgements:
Swedish Heart and Lung Foundation & Sigurt and Elsa Goljes Memorial Foundation

Introduction: Both vascular endothelial growth factor receptor (VEGFR) 2 and purinergic signalling are dysregulated in type 2 diabetes (T2D). Previous studies showed that VEGFR2 inhibition increases insulin sensitivity and reduces glucose level suggesting a therapeutic potential in T2D. A novel dinucleotide Up4A, biosynthesized by activation of VEGFR2, enhances vascular contraction in renal arteries in T2D via purinergic P2 receptor and by decreasing nitric oxide (NO) bioavailability. However, the functional role of VEGFR2 and purinergic signalling in T2D-mediated endothelial dysfunction remain elusive.

Purpose: To test the hypothesis that VEGFR2 and purinergic P2 receptor inhibition improve endothelial function in T2D, and that Up4A-activated purinergic signalling may serve as putative downstream mechanism of VEGFR2.

Methods: Aortae were isolated from Goto Kakizaki (GK) rats, a model with spontaneously developed T2D, and age matched control rats (15-16 weeks). Protein levels of VEGFR2 were determined by Western blot. Endothelium-dependent (EDR) and -independent relaxations (EIR) were evaluated with acetylcholine and sodium nitroprusside (10⁻⁹ - 10⁻⁵ M), respectively, using wire myograph in the absence or presence of the selective VEGFR2 inhibitor SU1498 (1 µM) or the combination of SU1498 and NO synthase inhibitor L-NAME (100 µM), and the non-selective P2 receptor antagonist PPADS (10 µM). Moreover, Up4A-induced vasoconstrictor response was determined with and without the selective P2X7 receptor antagonist A438079 (10 µM). EDR was also assessed in aortae isolated from GK rats treated with vehicle or the tyrosine kinase inhibitor sunitinib (2 mg/kg/day, by gavage), non-selectively targeting VEGFR2, for 6 weeks.

Results: VEGFR2 levels were 4.4 fold higher in aortae from GK rats compared to control (p<0.001). EDR but not EIR was impaired in aortae isolated from GK rats (EDR Emax 43±6.4) compared to control (75±7.8 p=0.05), indicating endothelial dysfunction. Both SU1498 and PPADS normalized EDR in aortae from GK rats. L-NAME fully attenuated EDR in aortae of GK rats, both with and without SU1498. Moreover, Up4A-induced contraction was enhanced in aortae from GK rats (Emax 41±4.4) compared to control (Emax 16±2.8, p<0.05), an effect that was reversed by A438079. Finally, 6 weeks treatment with sunitinib markedly improved EDR (Emax 94±2.1 in sunitinib-treated vs. 51±6.5 in vehicle-treated p<0.0001) in aortae of GK rats.

Conclusions: VEGFR2 and purinergic P2 receptor inhibition improve endothelial function in T2D. The beneficial effect of VEGFR2 inhibition is likely through increased NO bioavailability. Up4A enhances vascular contraction in T2D through P2X7 receptor, which may serve as putative link to VEGFR2. Targeting VEGFR2 and
purinergic signalling may provide a novel therapeutic tool for treatment of endothelial dysfunction in T2D.