Visfatin reduces gap junction mediated cell-to-cell communication in proximal tubule-derived epithelial cells

Hills CE, Kerr M, Wall M, Squires PE.
School of Life Sciences, University of Warwick, Coventry, CV4 7AL, UK

Aim: Associated with obesity, visfatin may have a role in the pathogenesis of diabetic nephropathy in type II diabetes. This study identifies a link between the visfatin, TGF-β1 and reduced cell-to-cell coupling in proximal tubule derived epithelial cells.

Methods: Western blot analysis confirmed changes in expression of connexins Cx26, Cx40 and Cx43 in HK2-cells +/- visfatin &/or TGF-β1. Visfatin evoked increases in TGF-β1 secretion were determined by ELISA, and functional intercellular communication assessed via Lucifer yellow dye transfer and paired-whole cell patch clamp electrophysiology.

Results: Visfatin (10, 100 and 200ng/mL) decreased expression of Cx26 to 58±11%, 40± 3% and 21±2% and Cx43 to 73±5%, 44± 4% and 29±6% as compared to control at 48hrs (n=3; $P<0.01$). The effects were not dependent on changes in membrane integrity, cytotoxicity or cell viability as assessed by MTT, crystal-violet and lactate-dehydrogenase assays. Expression of Cx40 was unaffected by the adipocytokine. Visfatin (200ng/ml) increased TGF-β1 secretion by 154% of control ($n=3$; $p<0.01$). Visfatin-evoked changes in Cx26 and Cx43 expression were mimicked by exogenous application of TGF-β1 (2-10ng/ml, $p<0.001$ n=3). Visfatin reduced dye transfer between coupled-cells and decreased functional conductance by 63% as compared to control (n=6; $p<0.01$).

Conclusions: Visfatin reduced connexin expression in HK2-cells, an effect mirrored by a loss in functional conductance between coupled cells. Visfatin increased TGF-β secretion and the pattern of change for connexin expression was mimicked by exogenous application of the pro-fibrotic cytokine. These data suggest that visfatin reduces connexin-mediated intercellular communication in proximal tubule-derived epithelial cells via a TGF-β dependent pathway.

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