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Hyperosmolarity-enhanced cox-2 expression contributes to high glucose-induced microangiopathy

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Aim: Diabetic hyperglycemia increases plasma osmolarity, leading to adaptive cellular responses. Cyclooxygenase-2 (COX-2) plays a role in angiogenesis and plaque stability. We tested whether glucose-induced hyperosmolarity promotes angiogenesis through activation of COX-2 expression.

Methods: Human aortic endothelial cells (HAEC) and dermal microvascular endothelial cells (HMVEC) were incubated with 5.5 mmol/L glucose (normoglycemia), high glucose (HG, at 12.5, 25 and 45 mmol/L), or equimolar concentrations of the hyperosmolar control mannitol (HM).

Results: Both HG and HM increased the expression of the water channel aquaporin-1 (AQP1) and of COX-2. HG and HM for 1 h increased the nuclear accumulation of Tonicity enhancer binding protein (TonEBP) and its binding to Tonicity enhancer element at electrophoretic mobility shift assay. HG and HM induced endothelial migration at a fluorimetric assay, and tubulization in Matrigel. Targeting the osmosignaling pathway with small interfering RNAs to AQP1 and to TonEBP both reverted the inducing effects of HG and HM on COX-2 expression, as well as angiogenic activities. Finally, compared with age- and sex-matched C57BL6 control mice (N=5 wild type, WT), the retina of Ins2 Akita diabetic mice (N=5, male, 1 year-old mice) showed higher vascular density as visualized with CD31 staining (Figure, panel A-B; legend: ONL, outer nuclear layers; OPL, outer plexiform layers; INL, inner nuclear layers; IPL, inner plexiform layers), and increased expression of AQP1 and COX-2 (panel C-E) (**p<0.01 by ANOVA and t-test).

Conclusion/Interpretation: By activating the water channels AQP1 and TonEBP, hyperosmolarity caused by HG or HM induces COX-2 expression and angiogenesis in human endothelial cells, which may be relevant for microvascular complications of diabetes.