

Hyperglycemia alters renal cell responsiveness to pressure in a model of malignant hypertension.

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Objective: Poor glycemic control contributes to development of diabetic nephropathy. However, for a majority of clinical situations, the mechanisms responsible for high glucose-induced aggravation of renal tissue injury are not fully elucidated. We investigated responsiveness to pressure of various renal cell subsets subjected to hyperglycemic environment, in an in vitro model of malignant hypertension.

Methods: Rat renal mesangium, epithelium (KNRK) and endothelium (HUVEC) were exposed to high glucose-containing medium for 10 days and then subjected to high hydrostatic pressure for 1h, to simulate the incidence of malignant hypertension. In some cultures, renin-angiotensin system (RAS) was experimentally suppressed prior to pressure application. Proliferation, apoptosis, intrarenal p53, H₂O₂ and Angiotensin-II synthesis were subsequently assessed.

Results: By contrast to cultures not exposed to high glucose, in all hyperglycemic cells p53 expression, Angiotensin-II synthesis and apoptosis were increased, while proliferation depressed, irrespective of pressure enforcement. H₂O₂ release was enhanced by high pressure per se, and increased further following exposure to high

glucose. In all diabetic cultures, inhibition of p53 by a specific inhibitor pifithrin concomitantly significantly decreased apoptosis.

Conclusions: Hyperglycemic environment alters responsiveness of renal cells to in vitro simulation of malignant hypertension. The main consequence of either malignant hypertension or hyperglycemia is exaggerated apoptosis. However, the operating mechanisms differ: a) Malignant hypertension stimulates renal cell apoptosis via increased Angiotensin-II, while hyperglycemia elicits apoptosis via augmented p53. b) By contrast to pressure-induced excessive proliferation of normoglycemic cells, hyperglycemia prohibits elevated proliferation in response to pressure. c) Angiotensin-II production is maximally augmented by hyperglycemic environment and is not stimulated further by pressure application.