Involvement of the endothelin system in the pathogenesis of renal ischemic damage in an experimental diabetic rat model

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Introduction: Ischemic acute renal failure (iARF) in diabetes mellitus (DM) is associated with a rapid deterioration in kidney function, more than in non-diabetic subjects. Since diabetes and iARF are characterized by increased production of the vasoconstrictor endothelin (ET)-1, it is appealing to investigate whether this system plays a role in the enhanced sensitivity of the diabetic kidney to ischemic injury compared with the non-diabetic kidney.

Aims: To compare the effects of renal ischemia on kidney function in diabetic compare to non-diabetic rats, and to investigate the involvement of ET system in the vulnerability of diabetic kidney to ischemic damage.

Methods: Diabetes was induced by a single injection of Streptozotocin (65 mg/kg body weight, ip). iARF was induced by clamping the left renal artery for 30 min followed by reperfusion in both diabetic and non diabetic rats. Right intact kidney served as control. 48 hrs following ischemia, clearance protocols were applied to determine renal function including urinary flow (V), sodium excretion (UNaV) and glomerular filtration rate (GFR) in both ischemic and non-ischemic kidneys. The role of ET system on kidney function in these models was evaluated using the ET_A and ET_B receptor antagonists (RA), ABT-627 or A192621.1 (10 mg/kg, p.o), respectively.

Results: Diabetic rats exhibited increased V and reduced UNaV as compared with non-diabetic animals, but comparable GFR (1.17±0.056 vs.1.16±0.04 ml/min). Induction of iARF in non-diabetic and diabetic rats caused significant reduction in V, UNaV, and GFR (0.43±0.10 and 0.026±0.010 ml/min, respectively), suggesting that the deleterious renal effects of iARF are greater in diabetic than non-diabetic rats. While ET_A RA did not affect GFR of normal kidney in diabetic rats (1.23±0.08 vs. 1.17±0.05 ml/min), it enhanced the GFR in ischemic kidney of diabetic animals by 2 folds (0.026±0.010 vs. 0.058±0.030 ml/min), suggesting that ET_A receptor mediates renal vasoconstriction and subsequently impairs GFR in iARF diabetic kidney.

ET_B RA decreased V in the ischemic kidney of diabetic rats (1.5±0.4 vs. 0.30±0.09 µl/min), as compared with non-ischemic kidney (19.6±1.6 vs. 15.6±2.9 µl/min). ET_B RA decreased UNaV in ischemic kidney (0.093±0.026 µEq/min to 0.015±0.004 µEq/min), without significant effect in normal kidney of diabetic rats (0.65±0.26 µEq/min vs. 0.68±0.21 µEq/min). In contrast to ET_A RA, ET_B blockade decreased GFR both in non-ischemic (0.83±0.08 vs. 1.17±0.05 ml/min), and ischemic diabetic kidneys (0.01±0.005 vs. 0.026±0.01 ml/min).

Conclusions: Ischemic diabetic kidney is more susceptible to ET-1 action than non-ischemic kidney. Excessive vasoconstrictor effects of ET-1 via ET_A may be responsible for the impaired recovery of renal function in the early post-ischemic phase of diabetic rats.