Metabolic alterations following renal ischemia reperfusion in rats

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Background
Acute kidney injury (AKI) is a major health issue, associated with high morbidity, mortality, fibrosis and CKD. Ischemia reperfusion (IR) injury during surgical procedures such as coronary artery bypass grafting or transplantation can cause AKI. In this study, we sought to characterize the time course of molecular and cellular pathophysiological consequences of ischemia reperfusion kidney injury in the rat.

Methods
Sprague-Dawley rats underwent 45-minute bilateral renal ischemia followed by reperfusion for 30 minutes, 4, 8, 12, 24, 48, 72 hours or 14 days. Renal injury was characterized by plasma and urine biomarker measurements at all time points. Tubular injury was defined as presence of tubular necrosis and casts in parallel to initiation of repair mechanisms. Je67 proximal tubular cells. Early injury occurred within 15 minutes of reperfusion for some rats, progressing through 24-72 hours, and was sustained at 14 days. Endothelial injury was evident by reduced Vegf with a concomitant increase in VEGFA inhibitor. Adm1 as early as 4 hours post reperfusion. The IR was established by 14 days post reperfusion, mediated by early transcriptional increases in Igef2 and Celp2 as well as collagen deposition (Trichrome staining, black arrow) in the kidney.

Study design
Termination times post reperfusion

Kinetic profile of Acute Kidney Injury biomarkers

(A) Plasma biomarkers creatinine and NGAL were peaked at 24 hours, whereas the peak of BUN was at 48 hours. (B) Urinary biomarkers Ngal and KIM-1 had similar time-dependent profiles peaking at 24-48 hours. (C) Urinary FABP-1 excretion peaked at 4 hours followed by rapid decline. The rat Nephrocheck equivalent was consistent with human data, with an increase from 4-24 hours (Koshari, et al., Crit Care. 2013).

Early induction of tubular and endothelial injury leads to a late fibrotic response

(C) Tubular injury denoted by presence of tubular necrosis and casts in parallel to initiation of repair mechanisms denoted by Je67 proximal tubular cells. Early injury occurred within 15 minutes of reperfusion for some rats, progressing through 24-72 hours, and was sustained at 14 days. Endothelial injury was evident by reduced Vegf with a concomitant increase in VEGFA inhibitor. Adm1 as early as 4 hours post reperfusion. The IR was established by 14 days post reperfusion, mediated by early transcriptional increases in Igef2 and Celp2 as well as collagen deposition (Trichrome staining, black arrow) in the kidney.

Nephrocheck Equivalent

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Gene expression analysis reveals persistent dysregulation of mitochondrial homeostasis, fatty acid oxidation, glucose utilization and anti-oxidant handling in IR-AKI

In the renal cortex, reduced gene expression of (I) Apal, Ucp1, Fpn1 & Ppargc1a indicate sustained reduction of mitochondrial homeostasis. Decreased expression of renal cell type specific genes (II) Apg5, Apg2 & Nphp1 suggest loss of proximal, distal tubular cells, and podocytes, respectively. An increase in glycolytic flux is indicated by upregulation of (III) Hk2 and Ldhα, leading to reduced Mct1 expression, suggesting reduced transport of Acetyl-CoA into the mitochondria. (IV) Cpt1a, fat mass transport mediator, and the gene responsible for fatty acid oxidation Acadv1, are reduced, as are key genes involved in the regulation of the antioxidant response, (N) Cat and Glc.

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