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Proximal Tubule Megalin Inhibition Prevents Acute Kidney Injury Due To Rhabdomyolysis in Mice

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Abstract

Introduction

Destruction of skeletal muscle (rhabdomyolysis) releases myoglobin, causing rhabdomyolysis-induced acute renal injury (rhAKI). As rhAKI commonly occurs in austere environments such as earthquakes and armed conflict, supportive care is challenging. Specific therapy would be a significant advance. Since myoglobin is taken into renal tubular cells via the renal cortex-specific transporter megalin (LRP2), we hypothesized that interfering with megalin would ameliorate rhAKI.

Methods

We bred inducible, proximal tubule-specific megalin knockout mice (LRP2 fl/fl, Ndrg1CreERT2, iMegKO). Glomerular filtration rate (GFR) was measured at baseline and 24 hours and urine was collected for 24 hours before and after experiments. Male mice received 8mL/kg 50% glycerol intramuscularly. 24h later, plasma and urine myoglobin, and myoglobin clearance were quantified. Kidney sections were imaged for pathology, injury markers (KIM-1 and caspase-3), and megalin and myoglobin. C57BL/6 mice then received cilastatin, a pharmacologic megalin inhibitor, or vehicle, simultaneously with glycerol injection, and were similarly evaluated.

Results

Tamoxifen treatment induced cre recombinase, causing deletion of megalin in the renal cortex of iMegKO mice but not cre- littermates (controls). After glycerol injection, controls demonstrated GFR 22.4± 0.3 % of baseline, oliguria, and severe histologic injury. In iMegKO mice GFR was 92.8 ± 5.9 % of baseline ($p<0.001$, n=4-5), and urine output was 5.3±0.9 mL/24h ($p=0.008$, n=4-5). In wild-type mice cilastatin preserved GFR (526±125 vs.67±31 µl/min/100g, $p=0.03$, n=4/gr), urine output (1.8 ±0.3 vs. 0.4±0.1, $p=0.01$, n=4/gr), and histology. KIM-1 and cleaved caspase-3 were reduced by megalin interference and cilastatin treatment. Pharmacologic or genetic interference with myoglobin increased

myoglobin clearance (5-16x) over controls and redistributed intrarenal myoglobin toward the cortex.

Conclusion

Renal megalin deletion ameliorates rhAKI by increasing clearance of myoglobin. The FDA-approved megalin inhibitor cilastatin ameliorates rhAKI similarly. There is potential for rapid translation, enabling change in disaster and trauma medicine. Additional translational study is imperative.