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ACUTE KIDNEY INJURY

Loss of PKC-ε protects against IRI

Sudden, temporary interruption of renal blood flow induces ischaemia–reperfusion injury (IRI), a major cause of acute renal failure. A new study conducted by Grazyna Nowak and colleagues shows that deletion of protein kinase C-ε (PKC-ε) prevents IRI-induced changes in mitochondrial function, kidney morphology and renal function.

The researchers previously showed that blocking the hypoxia or oxidant-induced activation of PKC-ε, which mediates mitochondrial dysfunction, in renal proximal tubular cells *in vitro* protected them from oxidative stress and hypoxic injury. These findings suggested that PKC-ε inhibition could protect against IRI *in vivo*.

To test this hypothesis, the researchers have now assessed renal and mitochondrial function after 24 h of ischaemia in PKC-ε-deficent mice. PKC-ε deletion reduced ischaemia-induced proximal tubular necrosis, cast formation, inflammatory cell number and brush border loss compared with wild-type controls. Genetic ablation of PKC-ε also reduced the IRI-induced increase in serum creatinine levels by 50% and improved survival after IRI from 86% to 100%.

In wild-type mice, 24 h of ischaemia induced a 44% and 27% reduction in mitochondrial complex I and complex II-coupled state 3 respirations, respectively, a 50% decrease in the respiratory control ratio coupled to glutamate and malate oxidation, and decreases in the activity of complexes I, III, and IV (by 59%, 89%, and 61%). By contrast, aside from increased complex II-coupled state 3 respiration, these parameters were unchanged after ischaemia in PKC-ε-deficient mice. PKC-ε deletion also reduced the production of oxidant in the kidney cortex and altered the proteomic response to ischaemia.

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“The protective effect of PKC-ε deletion on mitochondrial function after ischaemia is due, in part, to increased protein levels of crucial subunits of mitochondrial respiratory complexes and ATP synthase,” says Nowak. Future studies will address whether therapies that block or decrease PKC-ε activity can prevent ischaemia-induced acute kidney injury.

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