

Isoflurane mediates protection from renal ischemia-reperfusion injury via sphingosine kinase and sphingosine-1-phosphate-dependent pathways.

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The inhalational anesthetic isoflurane has been shown to protect against renal ischemia-reperfusion (IR) injury. Previous studies demonstrated that isoflurane modulates sphingolipid metabolism in renal proximal tubule cells. We sought to determine whether isoflurane stimulates sphingosine kinase (SK) activity and synthesis of sphingosine-1-phosphate (S1P) in renal proximal tubule cells to mediate renal protection via the S1P signaling pathway. Isoflurane anesthesia reduced the degree of renal failure and necrosis in a murine model of renal IR injury. This protection with isoflurane was reversed by SK inhibitors (DMS and SKI-II) as well as an S1P(1) receptor antagonist (VPC23019). In addition, mice deficient in SK1 enzyme were not protected from IR injury with isoflurane. SK activity as well as SK1 mRNA expression increased in both cultured human proximal tubule cells (HK-2) and mouse kidneys after exposure to isoflurane. Finally, isoflurane increased the generation of S1P in HK-2 cells. Taken together, our findings indicate that isoflurane activates SK in renal tubule cells and initiates S1P-->S1P(1) receptor signaling to mediate the renal protective effects. Our findings may help to unravel the cellular signaling pathways of volatile anesthetic-mediated renal protection and lead to new therapeutic applications of inhalational anesthetics during the perioperative period.

PMID: 17898040 [PubMed - in process]