Carnitine Pretreatment Reduces Apoptosis and Prevents Ischemic Acute Renal Failure.

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Background: Acute Renal Failure (ARF) from Ischemia-Reperfusion Injury (IRI) is mediated at least in part via renal tubule cell apoptosis due to ATP depletion. The purpose of our study was to determine if pre-treatment with carnitine, a fatty-acid transporter required for mitochondrial ATP production would prevent activation of apoptotic pathways and thus renal failure following IRI.

Methods: Mice (control, ischemic, and carnitine pre-treated, 5 animals in each group) underwent bilateral renal artery clamping for 30 minutes and were sacrificed at 24hrs of reperfusion. Kidney tissues samples were taken and Tunel Assay was used to detect apoptosis. ATP levels in the kidney were determined fluorometrically, and kidney function measured using a colorimetric assay for serum creatinine. Immunohistochemistry was used to determine which apoptotic pathway was affected by carnitine. Western Blotting was used to determine expression of key mitochondrial apoptotic regulators (BCL-2, BCL-XL).

Results: Carnitine pretreatment decreased apoptosis, ameliorated the rise in serum creatinine, and increased ATP levels in 24hr. IRI kidney tissues. It was further determined by immunohistochemistry that carnitine pre-treatment affects the mitochondrial pathway and more specifically, prevents Bax activation and cytochrome c release from the mitochondria. Carnitine, however, showed no effects on extrinsic pathway factors Fas or FADD. Western Blotting technique revealed that carnitine pre-treatment up-regulates anti-apoptotic factors BCL-2 and BCL-XL. Both factors are members of the BCL-2 family of proteins and work to prevent Bax activation.

Conclusion: The Results indicate that pre-treatment with carnitine will reduce apoptosis and thus prevent IRI-induced ARF. Further, it was determined that carnitine regulates the mitochondrial pathway by increasing levels of anti-apoptotic factors BCL-2 and BCL-XL. These factors can inhibit Bax activation and cytochrome C release, thus preventing apoptosis. Finally, serum creatinine levels were shown to decrease close to normal levels in carnitine pre-treated animals, demonstrating the protective role of carnitine on kidney function following IRI.