Dietary, Surgical, and Genetic Treatments Prevent Cyclosporin A-Induced Hydroxyl Radical Production in the Rat

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Cyclosporin A (CsA) increases free radical formation in the kidney. These studies used a variety of interventions that decrease free radical formation to elucidate mechanistic features of CsA nephrotoxicity. CsA treatment (25 mg/kg, i.g.) decreased glomerular filtration rates, caused vasoconstriction and increased hydroxyl radical formation in the kidney as expected. 4-Hydroxynonenal, a product of lipid peroxidation, accumulated in proximal and distal tubules after CsA treatment. Dietary glycine (5%), which causes vasodilatation and prevents CsA renal toxicity, minimized hypoxia and blocked free radical production. CsA infusion for 30 min increased efferent renal nerve activity 2-fold. Dietary glycine totally blocked this phenomenon, indicating that glycine most likely prevents CsA nephrotoxicity by blocking renal nerve firing, vasoconstriction and subsequent hypoxia-reperfusion injury. Renal denervation also significantly decreased free radical adduct concentrations in the urine, further confirming the role of vasoconstriction in CsA nephrotoxicity. Polyphenols from *Camellia sinenesis* are potent free radical and singlet oxygen scavengers. Dietary polyphenols (0.1%) blunted the increases in hydroxyl radical adducts in urine and minimized nephrotoxicity caused by CsA. Adenovirus transfection of the gene for Cu/Zn-superoxide dismutase also decreased free radical production. Taken together, these results support the hypothesis that CsA increases hydroxyl radical formation by increasing renal nerve activity that results in vasoconstriction and hypoxia-reoxygenation. CsA nephrotoxicity can be decreased by blocking its effect on the renal nerve with glycine, by minimizing free radical production with antioxidant enzymes like SOD, or by including antioxidants in the diet.