Mechanisms of Cyclosporin Nephrotoxicity

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Cyclosporine (CsA) has improved allograft survival in organ transplantation. More recently CsA has also been advocated as a promising therapeutic agent for the autoimmune diseases. However, this drug has major side effects that considerably limit its use in humans, maily because of liver and renal toxicity. CsA treatment is associated with an early reversible impairment in renal function, that is likely a consequence of the toxic effects of CsA on vascular endothelium, followed by a chronic form of renal toxicity leading to interstitial fibrosis, glomerular obsolescence, and renal failure.

Several experiments in animals have consistently found that, in the acute setting, CsA enhances renovascular resistances and decreases renal blood flow and glomerular filtration rate (GFR). Very similar findings have been obtained in studies in humans. We previously reported that renal transplant recipients receiving CsA have remarkably hypoperfused kidneys at regular intervals each time the drug is administered. Thus, each single oral administration of CsA is followed consistently by a reduction in GFR and renal plasma flow (RPF) that occurs a few hours after the peak level of the drug is reached. Micropuncture studies in rats have shown that this phenomenon is hemodynamic in nature. Actually, CsA administration causes a reduction in single-nephron (SN) GFR associated with a decrease in afferent arteriolar plasma flow (Qa) and in the ultrafiltration coefficient (Kf). GFR reduction is partially prevented by calcium (Ca) channel blockade. In line with these and other experimental data, the transient depression in GFR has been almost completely prevented also in humans by concomitant administration of the Ca channel blocker lacidipine. Based on this and a number of subsequent studies that convincingly documented the effect of Ca channel blockers of protecting transplanted kidneys from CsA-induced hypoperfusion, administering these drugs in the early post-transplantation period is now common in medical practice.

To elucidate the mechanism of CsA toxicity and protective effect of Ca channel blockers, we evaluated glomerular ultrafiltration determinants during acute CsA administration in the rat. Micropuncture measurements in CsA-treated animals showed that a reduction in GFR is associated with a significant increase in glomerular capillary pressure and efferent arteriolar resistence, whereas single-nephron (SN) GFR and Kf are both importantly reduced. Lacidipine partially prevented SNGFR and Kf decline despite the presence of elevated Pgc. This study further documents that Ca channel blockade has favorable effects on CsA-induced acute renal dysfunction. The mechanisms of protection includes the prevention of glomerular hemodynamic changes induced by CsA, mainly GFR decline and reduction in glomerular Kf.

The most recent evidences on the effect of CsA on glomerular structure and function allows to understand in more details the mechanisms by which this therapy is toxic to the kidney and allow to limit or prevent these deleterious effects in the clinical practice.