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Pathophysiological Role of 20-HETE a Cytochrome P450 Metabolite of Arachidonic Acid

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Cyclosporine A (CsA) is a potent immunosuppressant drug for organ transplantation and autoimmune diseases, but its use is limited by its nephrotoxicity. Chronic treatment with CsA has been associated with renal histological lesions including renal interstitial fibrosis and tubular atrophy. Several investigators have reported that CsA-induced nephrotoxicity is associated with an increase in renal production of prostaglandins, thromboxane, endothelin-I, and angiotensin II. However, the exact mechanism by which CsA causes renal damage is still unknown.

It has long been well-known that cyclooxygenase and lipoxygenase enzymes catalyze arachidonic acid (AA) metabolism in the kidney and the metabolites formed regulate both renal vascular tone and tubular function. However, in the last 15 years, a new pathway for the renal metabolism of AA has been discovered (1). AA is primarily metabolized by cytochrome P450 (CYP) enzymes to 20-hydroxyeicosatetraenoic acid (20-HETE) and epoxyeicosatrienoic acids (EETs). It is quite apparent that these eicosanoids play an important role in the regulation of renal vascular tone and tubular function. Especially, 20-HETE is a potent vasoconstrictor eicosanoid that activates L-type Ca2+ channels, leading to vasoconstriction of renal afferent arterioles (2). 20-HETE also inhibits Na+-K+-ATPase activity in the proximal tubule by enhancing protein kinase C-induced phosphorylation of the α-subunit of the Na+-K+-ATPase (3).

A recent paper by Seki et al. (4) revealed the possible involvement of 20-HETE in CsA-induced nephrotoxicity. The authors clearly showed that urinary excretion of 20-HETE increases in rats treated with CsA. In the previous study, Nakamura et al. (5) have indicated that protein expression of CYP4A2, which is the one of 20-HETE synthesizing enzymes, and the activity of omega-hydroxylation of AA are up-regulated in the kidney from CsA-treated rats. Seki et al. (4) have extended the previous finding because they have demonstrated that increased levels of 20-HETE in urine is associated with the strong expression of CYP4A protein in the proximal tubule. Excitingly, the authors have also shown that the elevated urinary excretion of 20-HETE highly correlates with the increase in blood urea nitrogen, serum creatinine, and urine volume. These observations suggest that 20-HETE may play an important role in the pathophysiology of CsA-induced nephrotoxicity. However, it is unclear at present whether this increase in urinary excretion of 20-HETE is a cause or result during the progression of nephrotoxicity induced by CsA.

Recently, Miyata et al. have discovered HET0016, a potent and selective inhibitor of 20-HETE synthesizing enzyme (6). HET0016 potently inhibits the formation of 20-HETE in rat renal microsomes and recombinant CYP4A11 and CYP4F2 proteins without affecting CYP2C9, CYP2D6, or CYP3A4 (6, 7). If the authors examined the effect of the 20-HETE enzyme inhibitor on the abnormal renal function including renal blood flow, glomerular filtration rate, and urine flow in CsA-induced nephrotoxic rats, they would be able to address the precise role of 20-HETE in CsA-induced nephrotoxicity and might provide a new therapeutic approach for CsA-induced nephrotoxicity.

The role of 20-HETE in the regulation of cardiovascular function is a rapidly expanding field in relation to renal (8), cerebral (9), and coronary circulation (10). In this respect, changes in levels of 20-HETE have been recently reported after subarachnoid hemorrhage in rats (7) and ischemia-reperfusion injury in canine myocardium (10). An inhibitor of 20-HETE syntheses reduces the acute fall in cerebral blood flow and myo-

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cardiac infarct size, respectively. These observations indicate that 20-HETE may be a key important mediator in the regulation of cardiovascular systems under pathological conditions.

References