F-D5

싸이클로스포린 투여 쥐에서 클로라이드 션트의 분자학적 기전

한양대학교 의과대학 내과학교실

이창화 · 김수아 · 강종명 · 김근호

The Molecular Basis of Chloride Shunt in Cyclosporine-Treated Rats

Chang Hwa Lee, Sua Kim, Chong Myung Kang, Gheun-Ho Kim

Department of Internal Medicine, Hanyang University College of Medicine

Purpose : An increased permeability for chloride in the distal cortical nephron (chloride shunt) has been proposed as a mechanism responsible for the hyperkalemia and distal renal tubular acidosis (type 4) associated with cyclosporine nephrotoxicity. Two molecular mechanisms are conceivable to explain chloride shunt: 1) the transcellular pathway mediated by the thiazide-sensitive Na-Cl cotransporter (NCC) in the distal convoluted tubule and 2) the paracellular pathway mediated by the tight junction in the cortical collecting duct. This study was undertaken to investigate whether the expression of distal renal tight junction proteins are altered for the mechanism of chloride shunt in cyclosporine-treated rats.

Methods : Cyclosporine was subcutaneously administered to male Sprague-Dawley rats at a daily dose of 7.5 mg/kg (n=6) for 6 weeks. Control rats (n=6) received a daily subcutaneous injection of the vehicle solution only. All rats were placed on regular rat chow not on a low-salt diet. At the end of the animal experiment, kidneys were harvested for semiquantitative immunoblotting and immunohistochemistry.

Results : Urine pH was significantly lowered in cyclosporine-treated rats compared with vehicle-treated rats, but arterial blood gas analyses revealed no significant differences between the two groups. With cyclosporine treatment, urinary excretion of sodium and chloride showed a reducing tendency, but urinary potassium excretion was not affected. In renal cortical homogenates, the NCC protein abundance was significantly decreased by cyclosporine treatment (68±4 vs. 100±4%, $p<0.005$), but plasma aldosterone level was not altered. Consistent with the downregulation of the NCC, the abundance of WNK4 protein was increased in both cortex (160±9 vs. 100±17%, $p<0.05$) and medulla (158±17 vs. 100±16%, $p<0.05$). The expression of occludin, the tight junction protein colocalizing with the WNK4, was also increased by cyclosporine treatment in both cortex (152±13 vs. 100±5%, $p<0.01$) and medulla (207±16 vs. 100±23%, $p<0.05$).

Conclusion : The tight junction proteins, WNK4 and occludin, may be upregulated by long-term cyclosporine treatment, enhancing urinary acidification by reducing the backleak of acid from lumen to blood. The transcellular chloride transport by the NCC does not seem to contribute to the chloride shunt, but the paracellular pathway mediated by the tight junction proteins such as WNK4 and occludin would have a major role.