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싸이클로스포린 투여 쥐에서 요농축능의 변화

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Urinary Concentration Defect in Cyclosporine-Treated Rats

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Background : Urinary concentration defect is one of the major features of cyclosporine nephrotoxicity. However, the mechanisms by which impaired urinary concentration occurs are not clearly defined. In cyclosporine- treated rats, whether water or osmotic diuresis occurs is not clear because previous animal studies reported that both water channels and sodium transporters were downregulated. Here we report important clues to the explanation of why urinary concentration is impaired in cyclosporine- treated rats.

Methods : Cyclosporine was subcutaneously injected to male Sprague- Dawley rats at a daily dose of 25 mg/kg (n=6) for 2 weeks (Experiment I) and 7.5 mg/kg (n=6) for 6 weeks (Experiment II). In each experiment, control rats (n=6) received a daily subcutaneous injection of the vehicle solution only. All rats were placed on regular rat chow and had free access to water. Physiologic parameters were measured from urine and plasma samples, and semiquantitative immunoblotting and immunohistochemistry were carried out to see if the renal expression of GLUT2 is altered by cyclosporine treatment.

Results : In Experiment I, cyclosporine treatment caused an increase in urine volume (27.2±3.1 vs. 8.9±1.7 ml/day, $p<0.001$) and a decrease in urine osmolality (1,379±478 vs. 2,831±554 mOsm/kg H_2O, $p<0.05$). However, urinary excretion of osmoles was not affected by cyclosporine treatment (31.3±4.8 vs. 25.9±6.7 mosmoles/d), and urinary excretion of glucose was remarkably elevated in cyclosporine- treated rats (12,896±3,218 vs. 7±3 mg/day, $p<0.005$). In renal cortical homogenates, the GLUT2 protein abundance was significantly decreased by cyclosporine treatment (55±6 vs. 100±3%, $p<0.005$). The result of GLUT2 immunohistochemistry was compatible with that of immunoblotting. In Experiment II, cyclosporine treatment induced an increasing tendency in urine volume (26.2±4.5 vs. 15.3±2.0 mL/day, $p=0.066$) and an increase in urinary excretion of osmoles (41.2±4.4 vs. 23.0±1.1 mosmoles/d, $p<0.01$). Urinary excretion of glucose was also remarkably elevated in cyclosporine- treated rats (29,564±6,522 vs. 22±4 mg/day, $p<0.005$), but plasma glucose was not affected (127±14 vs. 102±8 mg/dL).

Conclusion : Urinary concentration defect in cyclosporine- treated rats is derived from osmotic diuresis. Renal glycosuria is responsible for the osmotic diuresis, and downregulation of GLUT2 may have a role in producing renal glycosuria in cyclosporine- treated rats.

Key Words : 싸이클로스포린, 신독성, 다뇨
Cyclosporine, Nephrotoxicity, Polyuria