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시클로포스파미드에 의한 신장 수분축적 기전

한양의대 내과학교실[1], 경북대학교 의학전문대학원[2]

김수아[1], 최효정[2], 조철호[1], 박준성[1], 권태환[2], 김근호[1]

Intrarenal Mechanisms for Cyclophsophamide-induced Water Retention in Rat Kidney

Sua Kim[1], Hyo-Jung Choi[2], Chor Ho Jo[1], Joon-Sung Park[1]
Tae-Hwan Kwon[2], Gheun-Ho Kim[1]

Hanyang University College of Medicine[1], Kyungpook National University School of Medicine[2]

Background: Cyclophosphamide can produce hyponatremia when hypotonic fluid intake is not limited. Because cyclophosphamide-induced hyponatremia was reported to occur in central diabetes insipidus, cyclophosphamide or its metabolite may directly dysregulate the protein expression of water channels or sodium transporters in the kidney. We investigated whether the intrarenal mechanisms for urinary concentration are activated by the treatment with cyclophosphamide and 4-hydroperoxycyclophosphamide (4-HC), an active metabolite of cyclophosphamide.

Methods: After a single intraperitoneal cyclophosphamide (25 mg/kg BW) administration to male Sprague-Dawley rats, kidneys were harvested in 12 hours. Immunoblot analysis and immunohistochemistry were performed to evaluate the changes in protein expression of aquaporin-1 (AQP1), aquaporin-2 (AQP2), aquaporin-3 (AQP3) and Na-K-2Cl cotransporter type 2 (NKCC2). Real-time PCR analysis was done for AQP1, AQP2, NKCC2 and V2R mRNA quantification. Primary cultures enriched in inner medullary collecting duct (IMCD) cells prepared from pathogen-free male Sprague-Dawley rats were treated with 10 and 30 μM of 4-HC for 24 hours. Laser scanning confocal miscroscopy was used for AQP2 localization.

Results: In response to cyclophosphamide administration, urine output was reduced in cyclophosphamide-treated rats (n=6; 15.3±1.8 mL/12 h, $p< 0.05$) compared with controls (n=6; 22.5±2.4 mL/12 h), despite unchanged urine osmolality and serum sodium concentration. However, cyclophosphamide-treated rat kidneys showed significant increases in the expression of AQP2 protein (137±10% vs. 100±6%, $p<0.05$), NKCC2 protein (205±32% vs. 100±11%, $p<0.05$) and V2R mRNA (169±18% vs. 100±13%, $p<0.05$) compared with vehicle-treated controls. Immunohistochemistry for AQP2 and NKCC2 revealed compatible results with immunoblot analyses. Moreover, when primary cultured IMCD cells were treated with 4-HC at 10 μM in the absence of vasopressin stimulation, confocal laser scanning miscroscopy revealed that AQP2 targeting to the apical plasma membrane was increased.

Conclusions: In rat kidneys, cyclophosphamide may activate V2R and induce upregulation of AQP2 and NKCC2 in vivo or directly increase AQP2 trafficking in vitro in the absence of vasopressin stimulation. These results would be novel as a drug-induced nephrogenic syndrome of inappropriate antidiuresis.

Key Words: 수분통로-2, 바소프레신수용체-2, 시클로포스파미드
Aquaporin-2, Vasopressin-2 receptor, Cyclophosphamide