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Differential Effects of Cyclophsophamide on Aquaporin-2 Expression in Rat Kidney

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

Hanyang University[1], Kyungpook National University[2]

Background: Cyclophosphamide can produce hyponatremia when hypotonic fluid intake is not limited. However, the mechanism by which cyclophosphamide induces water retention in the kidney is not known. Auaporin-2 (AQP2) is the major water channel in the collecting duct to contribute to the final urinary concentration.

Methods: Male Sprague-Dawley rats were used for both in vivo animal studies and in vitro inner medullary collecting duct (IMCD) cell culture studies. Two animal protocols were given to water-loaded rats: 3 days' experiment after a single intraperitoneal cyclophosphamide 50 mg/kg BW (Protocol I) and daily oral cyclophosphamide 30 mg/kg BW for 7 days (Protocol II). Primary cultures enriched in IMCD cells were prepared and treated with 10 and 30 μM of 4-hydroperoxycyclophosphamide (4-HC), an active metabolite of cyclophosphamide, for 24 h. Immunoblot analysis was used for estimating the AQP2 protein expression.

Results: In Animal Protocol I, there were no differences in functional parameters (urine output, urine osmolality, plasma sodium, and BUN) between controls (n=7) and treated rats (n=7). However, AQP2 protein was increased in treated rat kidneys (201±26% vs. 100±13%, $p<0.01$). Na-K-2Cl cotransporter type 2 (NKCC2) was also increased in treated rat kidneys (149±12% vs. 100±19%, $p<0.05$). In Animal Protocol II, there were no differences in urine output and urine osmolality between controls (n=6) and treated rats (n=6). However, the daily amount of water intake was significantly larger in treated rats than in controls. Consistent with this, plasma sodium was lower in treated rats than in controls (146±1 mEq/L vs. 150±1 mEq/L, $p<0.01$). AQP2 protein was notably decreased in treated rat kidneys (100±16% vs. 38±8%, $p<0.01$). Primarily cultured IMCD cells also showed different results of AQP2 expression in responses to 4-HC treatment. AQP2 protein was increased (118±6% vs. 100±6%, $p<0.05$) and decreased (66±6% vs. 100±6%, $p<0.05$) at 10 μM and 30 μM, respectively.

Conclusions: AQP2 protein expression is altered by cyclophosphamide treatment in rat kidneys. Low-dose or short-term treatment may increase AQP2, whereas high-dose or long-term treatment may decrease AQP2. Dipsogenic or nephrotoxic effect of cyclophosphamide might be considered.

Key Words: Cyclophosphamide, Water, Auaporin