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Diminished Renal Expression of Aquaporin Water Channels in Rats with Experimental Bilateral Ureteral Obstruction

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Whether the postobstructive diuresis can be related to an altered regulation of aquaporin (AQP) water channels in the kidney was investigated. Male Sprague-Dawley rats were bilaterally obstructed of proximal ureters for 48 hours. The renal expression of AQP1-4 proteins was then determined by Western blot analysis and immunohistochemistry. To specify the primary impairment in the upstream pathway leading to the expression of cAMP-mediated AQP channels, the expression of Gsa as well as that of adenylyl cyclase was also determined. In some rats, the obstruction was released to collect urine samples. Following the ureteral obstruction, the urinary flow rate was increased, and the free water reabsorption decreased. In the obstructed kidney, the expression of AQP1-3 was decreased in the cortex, outer medulla, and inner medulla, while that of AQP4 was decreased only in the inner medulla. Immunoreactivities for AQP1-4 were also decreased in the obstructed kidney. The protein expression of Gsa was decreased in the cortex, outer medulla, and inner medulla, while that of adenylyl cyclase VI was decreased in the outer and inner medulla. The AVP-evoked generation of cAMP was decreased in the cortex, outer medulla, and inner medulla. The cAMP generation in response to forskolin was decreased in the outer and inner medulla, while that in response to sodium fluoride was decreased in the cortex, outer medulla, and inner medulla. These results suggest that a reduced abundance of AQP water channels in the kidney accounts in part for the postobstructive diuresis. The primary impairment in the pathway leading to the expression of cAMP-mediated AQP channels may lie at the level of G proteins and adenylyl cyclase itself.

A2

Amphotericin B decreases adenylyl cyclase activity and aquaporin-2 expression in rat kidney

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The present study was aimed at examining whether the amphotericin-induced urinary concentration defect can be related to an altered regulation of aquaporin (AQP) water channels in the kidney. Male Sprague-Dawley rats were injected with amphotericin B (6 mg/kg/day, i.p.) for 21 days. The expression of AQP1-3, Gsα, and adenylyl cyclase proteins was determined in the kidney. To further specify the primary point of derangement of AQP channels that are activated by arginine vasopressin (AVP)/cAMP pathway, different components of adenylyl cyclase complex were separately examined of their activity generating cAMP. Amphotericin-treatment resulted in a renal failure associated with decreased tubular free water reabsorption and increased urinary flow rate. The expression of AQP2 proteins was significantly decreased in the outer medulla and inner medulla, while not in the cortex. The expression of AQP2 proteins in the membrane fraction changed in parallel with that in the cytoplasmic fraction, suggesting a preserved targeting. Neither the expression of AQP1 nor that of AQP3 was significantly affected in the cortex, outer medulla, or inner medulla following the amphotericin-treatment. The cAMP generation in response to AVP or sodium fluoride was decreased following the amphotericin-treatment, while that to forskolin was not significantly altered. The expression of Gsα proteins was decreased in the inner medulla by the amphotericin-treatment, whereas that of adenylyl cyclase VI remained unaltered. These findings indicate that the amphotericin-induced urinary concentration defect may in part be causally related to a reduced abundance of AQP2 channels in the kidney. It is also suggested that the primary impairment in the pathway leading to the activation of AQP channels that are regulated by AVP/cAMP system lies at the level of G proteins.