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Treatment of Lithium-Induced Nephrogenic Diabetes Insipidus with the COX-2 Inhibitor Improves Polyuria via Upregulation of AQP2 and NKCC2

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Background : Renal prostaglandins have been suggested to play an important role in lithium-induced nephrogenic diabetes insipidus (NDI), and suppression of cyclooxygenase-2 (COX-2) may blunt lithium-induced polyuria. Because NaCl transport in the thick ascending limb (TAL) and water reabsportion in the collecting duct (CD) are the two major processes for urinary concentration, it is conceivable that treatment of NDI with the COX-2 inhibitor may relieve polyuria through upregulation of Na-K-2Cl cotransporter type 2 (NKCC2) in the TAL and aquaporin-2 (AQP2) in the CD.

Purpose and Methods : To test this hypothesis, semiquantitative immunoblotting and immunohistochemistry were carried out from the kidneys of lithium-induced NDI rats with versus without COX-2 inhibition. After feeding male Sprague-Dawley rats LiCl-containing rat diet for 3 weeks, rats were randomly divided into control and experimental groups. Lithium-containing food was offered continuously to both groups throughout the study period, but the COX-2 inhibitor, DFU (40 mg/kg/d), was simultaneously given for the last week to the experimental rats only.

Results : Treatment with the COX-2 inhibitor relieved polyuria (68±10 vs. 134±15 mL/d, $p<0.05$) and raised urine osmolality (402±51 vs. 247±40 mOsm/kg H_2O, $p<0.05$). However, urinary excretion of sodium and chloride were not affected by the treatment. Semiquantitative immunoblotting using whole-kidney homogenates revealed that COX-2 inhibition caused significant increases in the abundance of AQP2 (219±9 vs. 100±22%, $p<0.01$) and NKCC2 186±30 vs. 100±14%, $p<0.05$). Immunohistochemistry for AQP2 and NKCC2 confirmed the effects of COX-2 inhibition in lithium-induced NDI rats.

Conclusion : Treatment of lithium-Induced NDI with the COX-2 Inhibitor improves polyuria via upregulation of AQP2 and NKCC2 in the kidney. The upregulation of AQP2 and NKCC2 in response to the COX-2 inhibition may underlie the antidiuretic effect induced by the nonsteroidal anti-inflammatory drug used for the treatment of NDI.