# Therapeutic Mechanisms for Relieving Polyuria in Lithium-Induced Nephrogenic Diabetes Insipidus

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Chronic lithium therapy is known to be a major cause of nephrogenic diabetes insipidus (NDI), and down-regulation of aquaporin-2 (AQP2) is the underlying molecular basis of acquired NDI. There is no specific treatment for NDI without identifying and correcting the underlying disorder or withdrawing the offending agent. Previous clinical experiences demonstrated that in NDI diuretics and nonsteroidal antiinflammatory drugs (NSAIDs) have been useful for relieving polyuria, but their therapeutic mechanisms were not clearly defined. Recent works using the animal models of lithium-induced NDI provided us with more understanding of the therapeutic mechanisms on the basis of renal tubular transporters.

Thiazide diuretics coupled with low-sodium diet remain the mainstay of treatment of NDI. The mechanism by which thiazide diuretics produce their paradoxical antidiuretic effect in patients or animals with NDI has been poorly understood, although the widely accepted hypothesis is that mild volume depletion induces an increase in proximal sodium and water reabsorption and causes a reduction in distal delivery of sodium associated with enhanced fractional water reabsorption in the collecting duct. Recently, the possibility that thiazide diuretics can directly affect water and sodium permeability in the collecting duct epithelium was reappraised. Previous studies on Brattleboro rats have shown that the antidiuretic effect of hydrochlorothiazide (HCTZ) is secondary not only to the extracellular volume contraction but also to redistribution of body sodium and increase in papillary osmolality. *An in vitro* microperfusion study reported that HCTZ enhanced water absorption in inner medullary collecting duct from normal rats and from Brattleboro rats, and we demonstrated that HCTZ treatment partially reversed lithium-induced AQP2 down-regulation and up-regulated NaCl cotransporter (NCC) and epithelial sodium channel (ENaC) in lithium-induced NDI. Up-regulation of NCC and ENaC induced by HCTZ treatment would enhance sodium reabsorption along the distal segments of nephron. The up-regulation of NCC tends to mitigate the primary effect of the thiazide diuretic. Besides, the increased ENaC-mediated transport in response to HCTZ decreases luminal osmolality in the cortical connecting tubule and collecting duct and increases the driving force for water reabsorption.

Increased renal $PGE_2$ production has been suggested to play an important role in promoting lithium-induced polyuria. Urinary $PGE_2$ was shown to be increased in congenital NDI due to either V2 receptor or AQP2 mutation as well as in acquired NDI due to lithium treatment. Previous studies in rats indicated that indomethacin reduced both urine $PGE_2$ production and urine volume in lithium-induced NDI. We reported that selective COX-2 inhibition increased AQP2 expression in lithium-induced NDI rat kidneys in association with relieving polyuria. $PGE_2$ may therefore have impaired the vasopressin-regulated AQP2 response in the collecting duct through the inhibitory G-protein Gi to inhibit cAMP production, and inhibition of renal prostaglandin synthesis may be associated with an enhanced response to vasopressin via an increase in cAMP synthesis. However, the lithium-induced down-regulation of AQP2 was recently reported to occur independently from adenylate cyclase activity and vasopressin-induced cAMP levels.

The role of the increase in osmolality of the medullary interstitium was suggested in the antidiuretic effect of indomethacin in DI rats. Previously, an increased concentration of sodium chloride in the renal papilla has been reported when renal prostaglandin synthesis is inhibited. This increase in the renal medullary sodium chloride concentration would be expected to increase the osmotic gradient during water reabsorption across the terminal collecting duct. Consistent with this, we also showed that selective COX-2 inhibition increased NKCC2 expression in the thick ascending limb in lithium-induced NDI rat kidneys.

In conclusion, up-regulation of AQP2 and ENaC in response to thiazide diuretics and up-regulation of AQP2 and NKCC2 in response to NSAIDs may underlie the therapeutic mechanisms by which those medications enhance antidiuresis in patients with NDI. AQP2 should be involved in the therapeutic mechanisms as well as in the pathophysiology of lithium-induced NDI.