Dysregulation of Renal Aquaporins and Epithelial Sodium Channel in Lithium-Induced Nephrogenic Diabetes Insipidus

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Summary: Lithium is used commonly to treat bipolar mood disorders. In addition to its primary therapeutic effects in the central nervous system lithium has a number of side effects in the kidney. The side effects include nephrogenic diabetes insipidus with polyuria, mild sodium wasting, and changes in acid/base balance. These functional changes are associated with marked structural changes in collecting duct cell composition and morphology, likely contributing to the functional changes. Over the past few years, investigations of lithium-induced renal changes have provided novel insight into the molecular mechanisms that are responsible for the disturbances in water, sodium, and acid/base metabolism. This includes dysregulation of renal aquaporins, epithelial sodium channel, and acid/base transporters. This review focuses on these issues with the aim to present this in context with clinically relevant features.
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Lithium has been used widely for treating bipolar affective mood disorders in human patients.[1] Lithium treatment, however, is associated with a variety of renal side effects including nephrogenic diabetes insipidus (NDI) (ie, a pronounced vasopressin-resistant polyuria and an inability to concentrate urine[2-4]), increased renal sodium excretion, and distal renal tubular acidosis.[5-8] Patients who have been treated with lithium manifest a slow recovery of urinary concentrating ability when treatment is discontinued. It is estimated that 1 in 1,000 of the population receive lithium and roughly 20% to 30% of these patients develop serious side effects including polyuria and renal sodium loss, which to a major extent is attributed to severe down-regulation of aquaporin-2, aquaporin-3, and the epithelial sodium channel ENaC in the kidney collecting duct.[3,4,9,10]

Moreover, chronic lithium treatment is associated with hyperchloremic metabolic acidosis and distal renal tubular acidosis.[5-7] The underlying mechanisms for the impaired urinary acidification in the distal nephron and collecting duct after lithium treatment recently have been, at least partly, identified. The impaired acidification may be the result of the following: (1) an inability to generate a maximum pH gradient across the distal nephron for H^+ secretion (gradient defect; see Nascimento et al[6]); (2) a primary impairment of the proton pump in the collecting duct (secretory defect; see Halperin et al[11]); or (3) an unfavorable effect of lithium on the electrical gradient promoting H^+ secretion (voltage-dependent defect; see Arruda et al[12]). The molecular basis for this, including potential changes in the expression of key renal acid-base transporters, recently was ex-

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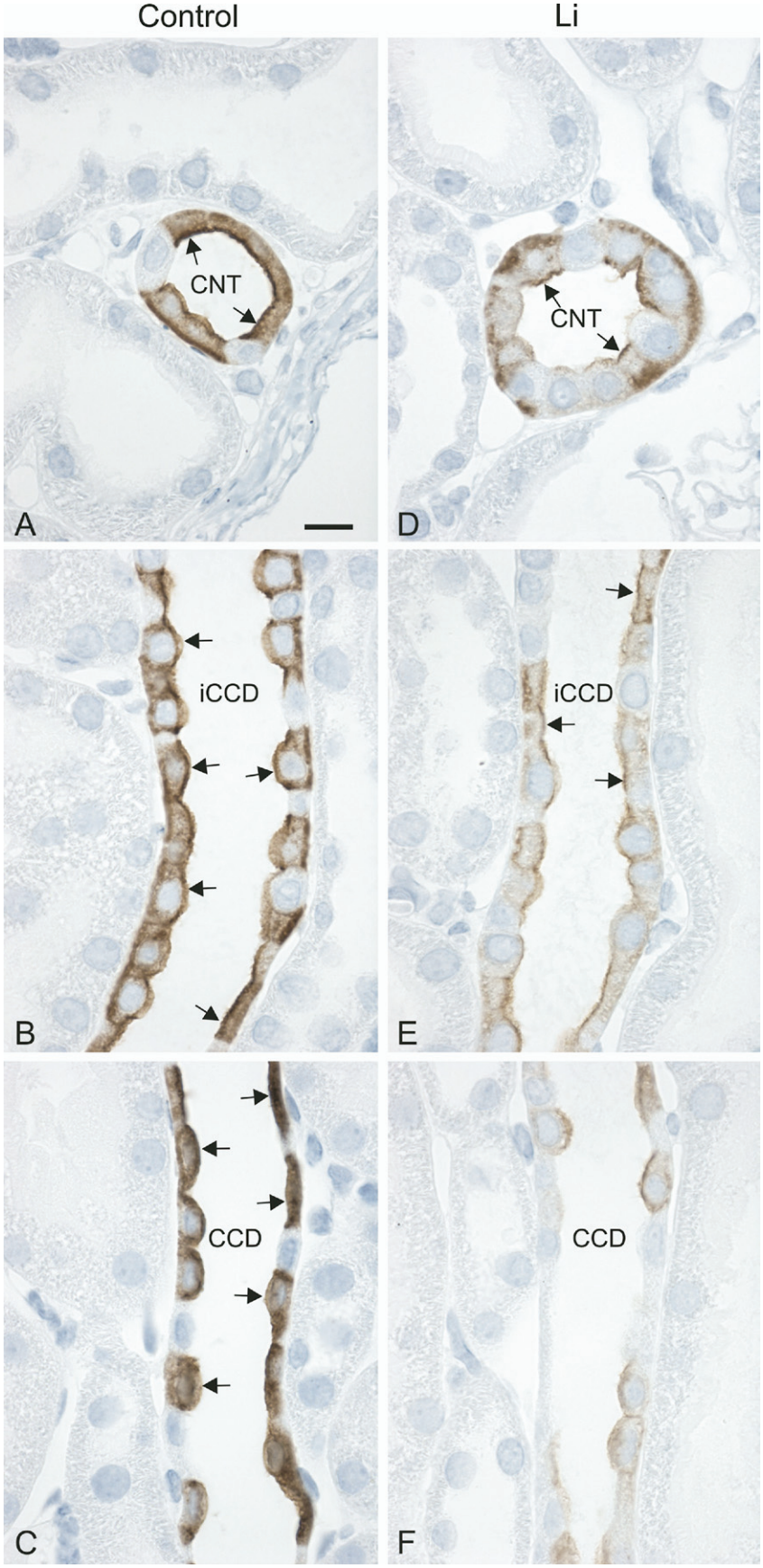
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