Analysis of channelopathy in the disorders of water and electrolyte metabolism using transgenic animals

Role of CLC-K1 chloride channel in the counter current systems of mice kidney

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CLC-K1 is a kidney-specific chloride channel exclusively present in the plasma membrane of the thin ascending limb of Henle's loop (tAL) in the inner medulla. Recently, we generated the *Clnck1*-/- mice by target gene desruption and found that the *Clcnk1*-/- mice showed nephrogenic diabetes insipidus (NDI). To investigate the pathogenesis of impaired urinary concentrating ability, we analyzed renal functions of *Clcnk1*-/- mice in details. The osmolar clearance/creatinine clearance ratio was not significantly different between *Clcnk1*+/- and *Clcnk1*+/+ mice. Fractional excretion of sodium, chloride, and urea were also not significantly affected in *Clcnk1*-/- mice compared with those of *Clcnk1*+/+ mice. These results indicate that while the loss of chloride transport in the tAL does not result in a chloride diuresis, the polyuria observed in *Clcnk1*-/- mice was water diuresis and not osmotic diuresis. The papillary osmolarity in *Clcnk1*-/- mice was significantly lower than that in *Clcnk1*+/+ mice under a hydrated condition, and it did not increase even after a 24-hour water deprivation. Sodium and chloride contents in the inner medulla in *Clcnk1*-/- mice were at about half the levels observed in *Clcnk1*-/- mice. Furthermore, the accumulation of urea was also impaired in *Clcnk1*-/- mice, suggesting that the overall countercurrent system was impaired by a defect of its single component, chloride transport in the tAL. We concluded that NDI in the *Clcnk1*-/- mice resulted from an impairment in the generation of inner medullary hypertonicity by a dysfunction of the countercurrent systems.