Hereditary chloride channelopathies of the kidney: from molecular mechanisms to pharmacological approaches

A. Liantonio, P. Imbrici, D. Conte Camerino

Section of Pharmacology, Department of Pharmacy – Drug Sciences, University of Bari, Italy

The preservation of electrolytes homeostasis and water balance is vital to our functioning. Under physiological condition, renal tubules are capable of reabsorbing 99 % of filtered sodium chloride and water. This pivotal task is accomplished by a combination of distinct and concerted activity of ion transports, channels and pumps. Genetic or acquired defects in any of these transport systems lead to distinct nephropathies (Kleta and Bockenhauer, 2006). Among these, some proteins belonging to CLC family, indicated as CLC-Ka/Kb and CLC-5, are enclosed (Planells-Cases R and Jentsch TJ 2009). Particularly, human CLC-Ka and CLC-Kb chloride channels are located in the Henle loop, distal convoluted tubule and cortical collecting ducts of the nephron where they govern chloride absorption and urine concentration (Krämer et al., 2008). Bartter syndrome (BS) type III is a rare human kidney disease characterized by severe salt wasting and hypokalemia, which is caused by mutations in CLCNKB (Simon et al, 1997). The phenotype can present either as an prenatal variant or as a classic BS initiating in early childhood. In addition to salt wasting, patients have polydipsia, polyuria due to hypokalemia, volume contraction, muscle weakness and growth retardation. BS type IV, which combines even more severe renal symptoms with congenital deafness, is either caused by mutations in the CLC-K barttin beta-subunit or by loss of function mutations in both CLC-Ka and CLC-Kb. Differently from CLC-K, CLC-5 is an electrogenic Cl-/H+ antiporter expressed in apical endosomes of proximal tubule where plays a pivotal role in endocytosis. Mutations in CLC-5 lead to Dent's disease, characterized by low molecular weight proteinuria, hypercalciuria, kidney stones and eventual renal failure. The elucidation of the role of CLC protein in kidney salt and proteins re-absorption, obtained by using mouse models, human molecular genetics, and heterologous expression systems, has brought up a growing interest toward the identification of specific ligands that allow pharmacological interventions aimed to modulate renal CLC activity. Indeed, up to date the pharmacotherapy of these disease is actually purely symptomatic, based on the use of drugs just able to alleviate symptoms. For example for BS patients indomethacin, ACE inhibitors, aldosterone antagonists, or salt replacement are currently used (Kleta and Bockenhauer, 2006; Unwin and Capasso, 2006). Moreover, CLC modulators could be of high therapeutic potential also in the treatment of the polycystic kidney disease and hypertension. By using computational modeling, molecular biology and electrophysiology, in the last few years, an extensive pharmacological characterization of CLC-K channels heterologously expressed in *Xenopus* oocytes has been performed, finally recognizing niflumic acid as a powerful activator and phenyl-benzofuran carboxylic acid analogs as inhibitors (Liantonio et al., 2006, 2008). In addition, benzofuran derivatives could represent a starting point structure for developing high affinity CLC-5 ligands. More recently, it has been demonstrated that when expressed in mammalian HEK-293 cells, a cellular system in which all regulatory pathways are preserved, CLC-K/barttin showed a different pharmacological profile (see abstract, Imbrici et al). All these findings allowed us to develop new high affinity ligands as well as to define which is the more physiological expression system allowing a more reliable translation of preclinical studies to the clinical practice (MIUR-COFIN-2009; Telethon GGP10101).

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