Activating mutation of the renal epithelial chloride channel ClC-Kb predisposing to hypertension

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The chloride channel ClC-Kb is expressed in the basolateral cell membrane of the distal nephron and participates in renal NaCl reabsorption. Loss-of-function mutations of ClC-Kb lead to classic Bartter syndrome, a rare salt-wasting disorder. Recently, we identified the ClC-Kb(T481S) polymorphism, which confers a strong gain-of-function effect on the ClC-Kb chloride channel. The present study has been performed to explore the prevalence of the mutation and its functional significance in renal salt handling and blood pressure regulation. As evident from electrophysiological analysis with the 2-electrode voltage-clamp technique, heterologous expression of ClC-Kb(T481S) in Xenopus oocytes gave rise to a current that was 7-fold larger than the current produced by wild-type ClC-Kb. The prevalence of the mutant allele was significantly higher in an African population from Ghana (22%) than in whites (12%). As tested in 1 white population, carriers of ClC-Kb(T481S) were associated with significantly higher systolic (by approximately 6.0 mm Hg) and diastolic (by approximately 4.2 mm Hg) blood pressures and significantly higher prevalence (45% versus 25%) of hypertensive (>or =140/90 mm Hg) blood pressure levels. Individuals carrying ClC-Kb(T481S) had significantly higher plasma Na+ concentrations and significantly decreased glomerular filtration rate. In conclusion, the mutation ClC-Kb(T481S) of the renal epithelial Cl-channel ClC-Kb strongly activates ClC-Kb chloride channel function in vitro and may predispose to the development of essential hypertension in vivo.

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