A new mouse model for Bartter’s syndrome

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BARTTER’S SYNDROME (BS) COMPRISкажет a heterogeneous group of hereditary diseases, characterized by salt wasting, hypokalemia, and alkalosis, due to mutations in ion transport genes: the Na\(^+\)-K\(^+\)-2Cl\(^-\) cotransporter (NKCC2) and ROMK K\(^+\) channel in the apical membrane and the ClC-KB Cl\(^-\) channel in the basolateral membrane of thick ascending limb cells. A variant associated with sensorineural deafness (type IV BS) is caused by mutations in the BSND gene encoding barttin, a regulatory subunit for ClC-KA and ClC-KB Cl\(^-\) channels. Type IV is the most severe form of BS associated with life-threatening neonatal volume depletion and chronic renal failure during infancy. However, a milder phenotype with preservation of renal function has been reported (1, 2). Knockout mice for NKCC2 (10) and ROMK (6) lead to premature lethality. However, the few surviving mice exhibit typical features of BS. By contrast, there is no mouse model for BS due to mutations of ClC-KB (ClC-K2 in the mouse).

To date, we know of only one attempt to investigate the effects of a complete disruption of barttin: knockout mice die within days after birth, and their renal function could not be investigated (9). In an issue of the American Journal of Physiology-Renal Physiology, Nomura et al. (8) present a knockin mouse model for the barttin R8L mutant (BsndR8L/R8L mice), a mutation observed in human cases of BS. Their study provides novel and stimulating insights into the physiopathology of this disease and raises a number of questions.

The authors studied in detail the subcellular localization of R8L barttin along the distal nephron and convincingly showed that membrane expression of this regulatory subunit involved in ClC-K targeting to the membrane is reduced by 50%. These results obtained in vivo qualitatively corroborate previous studies in transfected cultured cells (3, 4) that concluded to at least some reduction in cell surface expression of the complex ClC-K/R8L barttin. Unexpectedly, BsndR8L/R8L mice do not show the characteristic features of BS in basal conditions. Moreover, the transepithelial voltage measured in isolated thick ascending limbs (TAL), as well as the response to furosemide, were normal in BsndR8L/R8L mice, confirming the absence of transport defect in the TAL. In contrast, in a mouse strain generated in the process for obtaining the knockin mice, which contain both a Neo selection cassette and the R8L strain generated in the process for obtaining the knockin mice, the level of R8L barttin protein was dramatically reduced and was associated with a marked BS phenotype. Taken together, both observations indicate that the 50% reduction in surface expression of R8L barttin in BsndR8L/R8L mice is not sufficient to induce overt BS, but also that the ClC-K/R8L barttin complex is functional when it reaches the plasma membrane. Such a conclusion is hardly compatible with barttin modulating the activity of the CIC-Ks, as postulated by Fahlke et al. (2, 4) following studies in heterologous expression systems. However, in their discussion, Nomura et al. (8) propose, as an alternative explanation, that additional Cl\(^-\) pathways, including CFTR-like Cl\(^-\) channel (7) or KCl cotransport, might compensate for the reduction in the barttin/ClC-K in the TAL.

In the present study, even though the TAL functions normally, a mild salt-losing phenotype was revealed when BsndR8L/R8L mice were fed a salt-restricted diet (0.01 vs. 0.4% NaCl) (8). Since CLC-K/barttin complex expression extends to distal convoluted tubule cells and intercalated cells of the collecting duct, the authors investigated the effects of the R8L mutation on the renal response to hydrochlorothiazide administered in vivo. They observed that BsndR8L/R8L have a blunted response to thiazide and concluded that the R8L mutation reduced NaCl transport in the distal convoluted tubule. However, since intercalated cells also exhibit thiazide-sensitive NaCl absorption (5), the latter observation raises the question of the participation of intercalated cells to BS type IV phenotype.

In conclusion, the study by Nomura et al. (8) once again emphasizes the heuristic importance of mouse models reproducing human inherited disorders.

REFERENCES


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