Parvalbumin: a key protein in early distal tubule NaCl reabsorption*

Miriam Zacchia and Giovambattista Capasso

Chair of Nephrology, Department of Internal Medicine, Second University of Naples, Italy

Keywords: distal convoluted tubule; Gitelman's syndrome; Na⁺Cl⁻ cotransport; parvalbumin; thiazide diuretics

Summary of key findings

The cortical distal nephron is committed to the fine regulation of electrolytes and water balance. Several investigations have addressed the molecular mechanisms implicated in this process. The paper by Belge et al. [1] demonstrates the emerging role of parvalbumin (PV) on distal tubule NaCl reabsorption. PV is a divalent cation buffering protein, exclusively expressed in the early distal convoluted tubule (DCT1). The authors show solid data suggesting a functional relationship between PV and the thiazide-sensitive Na⁺Cl⁻ cotransporter (NCC), the main entry step for Na⁺ and Cl⁻ through the apical membrane at this nephron site. PV⁻/⁻ mice exhibit a salt-losing phenotype characterized by increased diuresis, kaliuresis and high aldosterone levels, a phenotype very similar, although not identical, to the NCC knock-out mice. Accordingly, PV⁻/⁻ mice manifest decreased expression of NCC, paralleled by no significant diuretic response to hydrochlorothiazide. Furthermore, in vitro studies performed on DCT cells show that PV may regulate NCC expression by modulating the Ca²⁺-dependent signalling pathway.

Background

This paper highlights the importance of the distal tubule in salt reabsorption. This is a very short, but complex segment. According to histological criteria, it starts with the last portion of the thick ascending limb (TAL) and ends with the branching of the cortical collecting duct (CCD). Although there are species differences [2], these segments may be identified by the sequential arrangement of well-characterized transport proteins (Figure 1): the thiazide-sensitive sodium chloride cotransporter (NCC) marks the onset and end of the distal convolute tubule (DCT); this segment may be further subdivided in an early (DCT1) and late (DCT2) portion by the co-expression, along the DCT2, with the amiloride-sensitive epithelial Na⁺ channel (ENaC) and the epithelial Ca²⁺ channel (TRPV5) [3,4]. These two latter transporters identify the connecting tubule (CNT) [5]. TRPV5 positive cells also show the expression of other proteins involved in active Ca²⁺ reabsorption, like the basolateral Na⁺/Ca²⁺ exchanger (NCX), the plasma membrane Ca²⁺-ATPase (PMCA) and the cytoplasmic calcium-binding protein calbindin D28K [2]. This last protein, confined to the DCT2 and CNT segment, is extremely important for transepithelial Ca²⁺ transport, since it facilitates the cytosolic diffusion of Ca²⁺ from the apical influx to basolateral efflux [6].

In addition to calbindin D28K, PV also belongs to the calmodulin superfamily [7]. Interestingly, PV⁻/⁻ mice show a trend to hypocalciuria at baseline and become frankly hypocalciuric following thiazide administration [1], suggesting that PV is not implicated in Ca²⁺ reabsorption, as confirmed by the absence of TRPV5 in DCT1 cells, where PV is expressed (Figure 1). The DCT is also the main segment responsible for active transcellular Mg²⁺ reabsorption [8] and it is possible that PV may be involved in this process. However, since PV⁻/⁻ mice do not manifest impaired Mg²⁺ homeostasis, at least in basal condition [1], its potential role in DCT Mg²⁺ reabsorption so far seems unlikely.

What is in it for the practising nephrologist

The paper by Belge et al. [1] is relevant since it has physiological, pharmacological and clinical implications. With respect to the first point, they have confirmed that, although DCT reabsorbs only 5% of the filtered salt load, it plays a crucial role in the overall renal handling of water and electrolytes. In this regard PV has been demonstrated to be a regulatory protein for the expression of the NCC cotransporter. The lack of a complete phenotype in the PV⁻/⁻
Clinically, the link between PV and NCC may be important to clarify the pathophysiology of distal tubulopathies, in particular Gitelman's syndrome. These patients have a highly heterogeneous phenotype and so far only mutations of SLC12A3, coding for NCC, have been described [15]. Since PV−/− mice have several clinical symptoms (urinary salt loss, secondary hyperaldosteronism, hypocalciuria and higher bone density) typical of Gitelman patients, it is possible that mutations in PV-associated gene may be responsible for those patients with as yet unidentified gene mutation [16]. This would not be unusual, since other tubulopathies are due to mutations of regulatory genes. For example, pseudohypoaldosteronism type II (also known as Gordon's syndrome) [17] is associated with mutations of members of WNK family [18] inducing upregulation of NCC, and determining a phenotype of thiazide-sensitive hypertension and hyperkalaemia, i.e. a mirror image of Gitelman's syndrome [19].

**Take home message**

The paper by Belge et al. [1] elucidates the molecular mechanism regulating Na+ handling in DCT, revealing the role of PV, a novel regulatory protein for NCC. Moreover, it emphasizes that the use of engineered mice and the studies on signal transduction pathways may help in deciphering the physiological process and in understanding the mechanism(s) of diseases.

**Acknowledgement.** This work was supported by a grant from Ministero Ricerca Scientifica (COFIN 2006).

**Conflict of interest statement.** None declared.

**References**


Received for publication: 2.11.07
Accepted in revised form: 21.11.07