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

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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 calcmodulin 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⁻/−
mice indicates that compensatory mechanisms upstream (proximal tubule) and downstream (CNT and CCD) may help to counteract the loss of function of the DCT1 segment.

The pharmacological inferences are mainly related to the mechanism of action of thiazide diuretics on Ca\(^{2+}\) excretion. It is well known that thiazide administration induces hypocalciuria, an effect that justifies its use for the treatment of hypercalciuria [9]. The molecular mechanism(s) responsible for this action is still controversial. Costanzo and Windhager demonstrated, by microperfusion experiments, that the acute application of thiazide has a direct stimulatory effect on transcellular Ca\(^{2+}\) reabsorption in the renal DCT [10]. It has been hypothesized that the hyperpolarization of the membrane voltage, induced by the inhibition of the Na\(^{+}\)-Cl\(^{-}\) cotransport by thiazide diuretics, activates the apical membrane Ca\(^{2+}\) channel thus facilitating Ca\(^{2+}\) reabsorption [11]. On the other hand, the diminished intracellular Na\(^{+}\) will ease the exchange of Na\(^{+}\) for Ca\(^{2+}\) across the basolateral membrane, resulting in increased Ca\(^{2+}\) exit from cells [12]. Overall, thiazide administration, by increasing the transepithelial Ca\(^{2+}\) calcium transport along the DCT, causes hypocalciuria. However, there are alternative explanations for the hypocalciuria observed under these conditions. It has been proposed that extracellular volume contraction, due to thiazide treatment, increases Na\(^{+}\) reabsorption in the proximal tubule and may thus enhance passive Ca\(^{2+}\) transport in the nephron site [13]. The paper by Belge et al. [1] confirms the association between NCC inhibition and increased Ca\(^{2+}\) reabsorption along the proximal tubule, as suggested by the reduced lithium clearance in PV\(^{-/-}\) mice but it also indicates the existence of an intrinsic mechanism within the DCT1 contributing in the generation of hypocalciuria since this effect persists when extracellular volume contraction is corrected. The direct action of lower doses of thiazides on the distal tubule Ca\(^{2+}\) transport has been recently demonstrated by Lee et al. [14].

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 heterogenous 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.

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References


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