Great strides in the understanding of renal magnesium and calcium reabsorption

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Introduction

In this issue Benigno et al. report their personal experience and review the literature about a rare autosomal recessive disorder called hypomagnesaemia-hypercalciuria-nephrocalcinosis [1]. Elucidation of the genetic defect in this disorder identified for the first time an essential component for the paracellular transport of magnesium and calcium in the thick ascending limb (TAL) of the loop of Henle [2] and increases substantially the understanding of the transport of these cations in this part of the nephron.

This editorial comment will be divided in three parts: mechanism of magnesium and calcium transport in TAL and distal convoluted tubule (DCT); comments about the clinical symptoms of the syndrome hypomagnesaemia-hypercalciuria-nephrocalcinosis; and finally proposals for treatment.

Transport of magnesium and calcium in TAL and DCT

In Table 1 the segmental reabsorption of sodium, magnesium and calcium is shown as revealed by micro-puncture studies in animals.

<table>
<thead>
<tr>
<th></th>
<th>Na⁺</th>
<th>Ca²⁺</th>
<th>Mg²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubule</td>
<td>40</td>
<td>48</td>
<td>80</td>
</tr>
<tr>
<td>Descending limb of Henle</td>
<td>55</td>
<td>55</td>
<td>90</td>
</tr>
<tr>
<td>Early distal tubule</td>
<td>8</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>Late distal tubule</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Urine</td>
<td>0.5</td>
<td>0.5</td>
<td>5</td>
</tr>
</tbody>
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The reabsorption of magnesium is quite different from the reabsorption of sodium and calcium. The transport of calcium in the proximal tubule is considered to be primarily passive and occurring via the paracellular pathway. The reabsorption of magnesium within the proximal tubule is likely to be transcellular indicating that the paracellular pathway in the proximal tubule has different characteristics from that in TAL.

A scheme of the transport of magnesium and calcium in TAL and DCT is shown in Figure 1 and Figure 2. As the magnesium and calcium absorption in TAL is entirely dependent on the lumen-positive transepithelial voltage the majority, if not all, of the transport of both cations occurs via the paracellular pathway.

In TAL there is a unique situation. The lumen-positive transepithelial potential difference that is only present in this part of the nephron, forms the driving force for this passive transport. A mutation in paracellin-1 located in the tight junction of TAL impairs this passive transport of magnesium and calcium [2]. Paracellin-1 is a protein of 305 aminoacids with four transmembrane domains and intracellular NH₂- and COOH-termini. It is unknown why more magnesium than calcium is transported via this pathway.

As the transepithelial voltage is lumen negative in the distal tubule with a high epithelial resistance, the magnesium and calcium transport is considered to be active and transcellular in nature [3]. In this segment the function of paracellin-1 is unclear.

Magnesium transport in the DCT remains still unresolved. Further studies in patients with isolated magnesium loss could throw light on this enigma.

More progress has recently been made in the transport mechanism of calcium. Luminal entry of calcium occurs passively via a recently cloned epithelial calcium channel [4]. Subsequently the ion binds to calbindin D28K and diffuses through the cytosol to the basolateral membranes. Here, calcium ions are extruded by a Ca²⁺-ATPase and Na⁺-Ca²⁺ exchanger. Calbindin D28K acts as a shuttle mechanism to transport Ca²⁺ from the apical to the basolateral membrane.

The influence of different hormones on the transport of magnesium and calcium both in the TAL and DCT are extensively discussed by Quamme [5].

**Symptoms of patients with hypomagnesaemia-hypercalciuria-nephrocalcinosis**

Nephrocalcinosis with progressive renal failure is the most ominous symptom of this disorder. Polyuria with polydipsia, urinary tract infections and stone passage can easily be understood. Symptoms due to hypomagnesaemia such as tetany and chondrocalcinosis are less frequent. Hypercalciuria is considered to be the cause of renal stone formation.

Calculations of the supersaturation of calcium phosphate as performed by Patzer [6] are lacking. Parathyroid hormone (PTH) levels are reported to be high even when GFR is not decreased [7]. This would contribute to increased phosphate wasting. Increased intact PTH levels in patients with renal leak hypercalciuria are observed but rare [8].

Nephrocalcinosis, together with tubulo-interstitial nephritis as it also occurs in hereditary oxalosis, is still unexplained.

The current lack of knowledge of uric acid transport in the human does not provide a frame-work to comment on the frequently associated hyperuricaemia [9].

Ophthalmological studies often reveal abnormalities in these patients, mainly myopia but also macular colobomata and chorioretinitis.

**Causes of hereditary hypomagnesaemia due to renal magnesium loss**

The diagnosis of renal magnesium loss is established by the presence of hypomagnesaemia with an inappropriately high 24 h urinary magnesium excretion. During magnesium deprivation urinary magnesium excretion can be as low as 0.2–0.4 mmol/24 h. Acquired causes of high urinary magnesium excretion such as diabetes mellitus, the use of osmotic agents, diuretics and drugs such as cyclosporin, cisplatin, ifosfamide should be excluded.

Proposal for treatment

When we accept renal stone formation as the crucial event in the pathogenesis of nephrocalcinosis and progressive decrease of the renal function, the aim of treatment should be the prevention of stone formation. The saturation of calcium phosphate (oxalate) should be lowered. This can be obtained by a decrease in urinary calcium concentration. The easiest way is to increase fluid intake. Especially during the night the urine should remain hypotonic. This will decrease the concentration of calcium by a factor of 3. The hypotonicity of the urine has to be controlled.

The reabsorption of calcium in the nephron can also be increased. At the distal tubule this can be obtained by the administration of hydrochlorothiazide. Amiloride inhibits the epithelial Na⁺ channel and has an hypocalciuric effect which is additive to that of thiazide diuretics. Thus both drugs should be used in combination. It is also possible to decrease the amount of calcium arriving at the loop of Henle by increasing the reabsorption in the proximal tubule by a limitation of salt intake. With the effect of treatment of inhibitors of cyclooxygenase in mind, in disorders such as nephrogenic diabetes insipidus, cystinosis and Bartter syndrome, a trial with indomethacin is attractive. A stimulatory effect on calcium transport in the collecting duct by indomethacin is also possible. The administration of potassium citrate and Mg salts is also recommended to prevent calcium deposition and symptoms of magnesium deficiency respectively [10].

Renal transplantation will ultimately provide definite cure, as the disorder will not recur in the transplanted kidney.

References

vitamin D

Editor’s note
See also Original Article by Benigno et al. in this issue.