The Epithelial Ca²⁺ Channel TRPV5 in Health and Disease

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The recent identification of the epithelial Ca²⁺ channel, TRPV5, in kidney represents a major step forward in our knowledge of renal Ca²⁺ handling. This membrane channel protein is the first member of a new family of Ca²⁺-selective cation channels. It consists of 6 transmembrane spanning domains, including a pore forming hydrophobic stretch between domain 5 and 6. TRPV5 constitutes the apical entry mechanism of active, transcellular Ca²⁺ reabsorption. In contrast to the paracellular route, this transcellular pathway enables the organism to actively control the net amount of Ca²⁺ reabsorption. *In vivo* studies indicated a specific regulation of TRPV5 by calcitriol, oestrogens and dietary Ca²⁺. The central role of TRPV5 in active Ca²⁺ reabsorption makes it a prime target for pharmacological manipulation and several disorders related to Ca²⁺ homeostasis could benefit from such developments. This review highlights the identification, characteristics and the clinical impact of the epithelial calcium channel, TRPV5.

Key words: active Ca²⁺ transport, channel (in)activation, kidney, oestrogens, trafficking, TRP regulation, vitamin D

IMPORTANCE OF CA²⁺ HOMEOSTASIS

The maintenance of the Ca²⁺ balance within the physiological range is pivotal for life. Ca²⁺ is the most abundant cation in the human body where it is essential for many physiological functions, such as synaptic transmission in neurons, muscle contraction, blood clotting, fertilization and bone mineralization. The extracellular Ca²⁺ concentration should, therefore, be tightly regulated. Hypercalcemia reduces membrane excitability causing lethargy, fatigue and memory loss, whereas hypocalcemia causes muscle cramps, convulsions and other symptoms of increased neuromuscular excitability[1]. Ca²⁺ homeostasis in humans is achieved through hormonal control that concerts three physiological functions: intestinal Ca²⁺ absorption, renal Ca²⁺ reabsorption and Ca²⁺ exchange of the bone mass[2]. In this physiological process the kidneys play an important role because they determine the final excretion of Ca²⁺ in the urine.

ACTIVE RENAL TRANSPORT TO FINE-TUNING THE EXCRETION OF CA²⁺

In the kidney, ~8 g Ca²⁺ is filtered at the glomerulus on a daily basis, of which less than 2% is excreted into the urine. There are two pathways for Ca²⁺ to pass through renal epithelial tissues and reach the blood compartment. The major one is by passive paracellular transport together with Na⁺ in the proximal tubules and the second is by active transcellular Ca²⁺ transport in the distal convoluted (DCT) and connecting (CNT) tubules[3-5] (Fig. 1A). Even though the distal part of the nephron realizes only ~15% of total renal Ca²⁺ reabsorption, it is generally regarded as the site for fine-tuning of the urinary Ca²⁺ excretion. Active Ca²⁺ transport allows the body to regulate Ca²⁺ reabsorption independently of the Na⁺ balance and thus the organism can respond immediately to dietary fluctuations of nutritional Ca²⁺, while it can also adapt to the body's demand during long-lasting situations like growth, development and aging[6,7].

MOLECULAR DETERMINANTS OF TRANSCELLULAR TRANSPORT IN RENAL EPITHELIAL CELLS

At the cellular level, active Ca²⁺ reabsorption is generally envisaged as a 3-step process (Fig. 1B) consisting of passive entry of Ca²⁺ across the luminal or apical membrane, cytosolic diffusion of Ca²⁺ bound to vitamin D₃-sensitive Ca²⁺-binding proteins (calbindin-D₂₈ₖ and/or calbindin-