The following full text is a publisher's version.

For additional information about this publication click this link.
http://hdl.handle.net/2066/57575

Please be advised that this information was generated on 2020-03-30 and may be subject to change.
The Epithelial Ca\textsuperscript{2+} Channel TRPV5 in Health and Disease

Dimitra Gkika, Joost G.J. Hoenderop, and René J.M. Bindels

Department of Physiology, Nijmegen Centre for Molecular Life Sciences, Radboud University Nijmegen Medical Centre, The Netherlands

The recent identification of the epithelial Ca\textsuperscript{2+} channel, TRPV5, in kidney represents a major step forward in our knowledge of renal Ca\textsuperscript{2+} handling. This membrane channel protein is the first member of a new family of Ca\textsuperscript{2+}-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 Ca\textsuperscript{2+} reabsorption. In contrast to the paracellular route, this transcellular pathway enables the organism to actively control the net amount of Ca\textsuperscript{2+} reabsorption. In vivo studies indicated a specific regulation of TRPV5 by calcitriol, oestrogens and dietary Ca\textsuperscript{2+}. The central role of TRPV5 in active Ca\textsuperscript{2+} reabsorption makes it a prime target for pharmacological manipulation and several disorders related to Ca\textsuperscript{2+} 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 Ca\textsuperscript{2+} transport, channel (in)activation, kidney, oestrogens, trafficking, TRP regulation, vitamin D

IMPORTANCE OF CA\textsuperscript{2+} HOMEOSTASIS

The maintenance of the Ca\textsuperscript{2+} balance within the physiological range is pivotal for life. Ca\textsuperscript{2+} 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 Ca\textsuperscript{2+} 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\textsuperscript{1}. Ca\textsuperscript{2+} homeostasis in humans is achieved through hormonal control that concert three physiological functions: intestinal Ca\textsuperscript{2+} absorption, renal Ca\textsuperscript{2+} reabsorption and Ca\textsuperscript{2+} exchange of the bone mass\textsuperscript{2}. In this physiological process the kidneys play an important role because they determine the final excretion of Ca\textsuperscript{2+} in the urine.

ACTIVE RENAL TRANSPORT TO FINE-TUNING THE EXCRETION OF CA\textsuperscript{2+}

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

MOLECULAR DETERMINANTS OF TRANSCELLULAR TRANSPORT IN RENAL EPITHELIAL CELLS

At the cellular level, active Ca\textsuperscript{2+} reabsorption is generally envisaged as a 3-step process (Fig. 1B) consisting of passive entry of Ca\textsuperscript{2+} across the luminal or apical membrane, cytosolic diffusion of Ca\textsuperscript{2+} bound to vitamin D\textsubscript{3}-sensitive Ca\textsuperscript{2+}-binding proteins (calbindin-D\textsubscript{28K} and/or calbindin-