Role of the Calcium-Sensing Receptor in Reducing the Risk for Calcium Stones

Kirsten Y. Renkema,*† René J.M. Bindels,* and Joost G.J. Hoenderop*

Summary
The tight control of blood Ca\(^{2+}\) levels within a narrow range is essential for the performance of vital physiologic functions. Muscle contraction, neuronal excitation, and intracellular signaling processes acquisitively require Ca\(^{2+}\). It is the concerted action of intestine, bone, and kidney that controls the Ca\(^{2+}\) balance through the regulation of intestinal absorption, bone (de)mineralization, and renal excretion of Ca\(^{2+}\), respectively. Along the nephron, fine-tuning of blood Ca\(^{2+}\) levels takes place by Ca\(^{2+}\) reabsorption. The calciotropic hormones regulate Ca\(^{2+}\) transport processes, leading to whole-body Ca\(^{2+}\) homeostasis and, importantly, preserving a constant Ca\(^{2+}\) concentration in the blood. Defects in renal Ca\(^{2+}\) handling can lead to hypercalcuria, consecutive kidney stone formation, and obstructive nephropathy. Here we give an overview of the key players involved in normal Ca\(^{2+}\) management and describe the in-depth investigations on a renal hypercalcuiuric model of disease, the Trpv5 knockout mouse, which naturally displays molecular adaptations that prevent Ca\(^{2+}\) precipitation in the kidney.

Introduction
Maintenance of a normal calcium (Ca\(^{2+}\)) balance is accomplished by the concerted action of the intestine, kidney, and bone. Disturbances in the Ca\(^{2+}\) balance can result in symptoms including kidney stones, osteoporosis, and rickets. Ca\(^{2+}\) is absorbed from the diet in multiple segments of the small intestine (1). In the jejunum and ileum, passive absorption of Ca\(^{2+}\) takes place in a paracellular manner along with sodium and water uptake. Besides that, active Ca\(^{2+}\) absorption is hormonally regulated and mainly occurs in the duodenum. The transcellular Ca\(^{2+}\) uptake process involves luminal entry into the cell through the epithelial Ca\(^{2+}\) channel, transient receptor potential vanilloid member 6 (TRPV6) (2). Ca\(^{2+}\) is subsequently bound by Ca\(^{2+}\) binding proteins (calbindin-D\(_{28K}\)) and shuttled to the basolateral side of the cell. The transcellular route is fulfilled by active Ca\(^{2+}\) extrusion to the blood via the plasma membrane Ca\(^{2+}\)-ATPase (PMCA1B). In the circulation, 45% of Ca\(^{2+}\) is present as the free ionized form, while 45% is bound to proteins. The remaining 10% forms complexes with anions, including citrate, sulfate, and phosphate. The majority of Ca\(^{2+}\) is stored in the skeleton. Taking a closer look at the kidney, it is appreciated that blood Ca\(^{2+}\) is filtered at the glomerulus and thereby enters the lumen of the renal tubule. Along the course of the nephron passive, paracellular Ca\(^{2+}\) reabsorption occurs in the proximal tubule (PT) and the thick ascending limb of Henle (TALH) (1). A small (10 to 15%), highly regulated quantity of Ca\(^{2+}\) is reabsorbed in the distal convoluted tubule (DCT) and the connecting tubule (CNT) in an active transcellular transport process (3). Whether transcellular Ca\(^{2+}\) transport is taking place in the TALH as well is still questionable and needs further investigation. A three-step process, similar to the duodenal route, mediates active Ca\(^{2+}\) reabsorption in the DCT and CNT, involving cell entry via the epithelial Ca\(^{2+}\) channel TRPV5, cytosolic transport via calbindin-D\(_{28K}\), and extrusion into the peritubular capillaries by the Na\(^{+}\)-Ca\(^{2+}\)-exchanger (NCX1) and PMCA1B (1). TRPV5- and TRPV6-mediated active entry of Ca\(^{2+}\) from the lumen into the cytosol of intestinal and renal epithelial cells, respectively, is tightly controlled by a complex network of interacting proteins and calciotropics hormones, representing the rate-limiting step in transcellular Ca\(^{2+}\) (re)absorption and, thereby, fine-tuning overall body Ca\(^{2+}\) balance.

Classic Calciotropic Hormones in Control
Ca\(^{2+}\) homeostasis is preserved by the classically recognized calciotropic hormones vitamin D (1,25(OH)\(_{2}\)D\(_{3}\)), parathyroid hormone (PTH), and calcitonin (4). Central to this process is the G-protein coupled Ca\(^{2+}\)-sensing receptor (CaSR) in the parathyroid glands that detects changes in blood ionized Ca\(^{2+}\) levels (5). In response to an alteration in the blood Ca\(^{2+}\) levels, the CaSR modulates PTH release into the circulation. Specifically, the activation of the CaSR by increased circulating Ca\(^{2+}\) levels suppresses PTH release and stimulates the secretion of calcitonin from the thyroid gland. Calcitonin reduces osteoclast-mediated bone resorption and thereby promotes a decrease in blood Ca\(^{2+}\) levels (6). Gain-of-function mutations in the CASR gene lower blood PTH levels, hampering Ca\(^{2+}\) (re)absorption and thereby evoking...
hypocalcemia in humans (7). A hypocalcemic state does not activate the CaSR, leading to PTH secretion. PTH stimulates active Ca\(^{2+}\) reabsorption, thereby enabling Ca\(^{2+}\) retention in the body. Furthermore, PTH enhances Ca\(^{2+}\) mobilization from bone and the conversion of inactive vitamin D to its biologically active form—1,25(OH)\(_2\)D\(_3\)—by the renal cytochrome P450 enzyme 25-hydroxyvitamin D\(_3\)-1α-hydroxylase (1α-OHase) in the kidney. Previous studies demonstrated that 1,25(OH)\(_2\)D\(_3\) facilitates vitamin D receptor (VDR)–mediated gene transcription that evokes transcription of Ca\(^{2+}\) transporter encoding genes in Ca\(^{2+}\) transporting cells, established by the interaction of the 1,25(OH)\(_2\)D\(_3\)–VDR complex with vitamin D responsive elements (VDREs) in the promoter regions of target genes (8). Multiple intestinal and renal Ca\(^{2+}\) transporter encoding genes were shown to contain VDREs, indicating 1,25(OH)\(_2\)D\(_3\) as an important stimulator of Ca\(^{2+}\) (re)absorption (9). As a consequence, a lack of 1,25(OH)\(_2\)D\(_3\) could cause disturbances in the Ca\(^{2+}\) balance. For example, bone diseases like osteoporosis, osteomalacia, and rickets occur as a consequence of vitamin D deficiency, occurring during malnutrition, aging, and menopause. Humans with a defect in VDR function show bone abnormalities known as vitamin D–dependent rickets type II (10). In the past, genetically modified mouse models were generated in which the 1,25(OH)\(_2\)D\(_3\) endocrine system was inactivated. Two research groups independently created the 1α-OHase knockout mouse (11,12). Phenotypic analysis showed that these mice were unable to generate 1,25(OH)\(_2\)D\(_3\), leading to severe hypocalcemia, secondary hyperparathyroidism, decreased bone mineral density, rickets, and growth retardation. Intestinal and renal Ca\(^{2+}\) transporters were downregulated, whereas repletion with 1,25(OH)\(_2\)D\(_3\) led to the restoration of renal and intestinal Ca\(^{2+}\) transporter expression levels and normalization of blood Ca\(^{2+}\) levels (13). These experiments confirmed the essential role of Ca\(^{2+}\) transport proteins in 1,25(OH)\(_2\)D\(_3\)-mediated active Ca\(^{2+}\) (re)absorption. Similarly, VDR knockout mice displayed hypocalcemia, bone degradation, increased blood PTH levels, and hypervitaminosis D, due to a lack of VDR-mediated gene transcription (14). Altogether, these investigations underlined that absence of 1,25(OH)\(_2\)D\(_3\) leads to severe disturbances of the Ca\(^{2+}\) balance and that 1,25(OH)\(_2\)D\(_3\) is of crucial importance to Ca\(^{2+}\) homeostasis. Furthermore, it was previously demonstrated that inactivating CaSR gene mutations result in elevated blood PTH and Ca\(^{2+}\) levels, parathyroid hyperplasia, bone abnormalities, and retarded growth in humans (15). Mice genetically ablated for the CaSR gene demonstrated similar symptoms (16). Together, the CaSR and the calcitropic hormones are crucial for maintenance of blood Ca\(^{2+}\) levels within a narrow physiologic range.

**Novel Regulators of the Ca\(^{2+}\) Balance**

In recent years, new key factors shown to be essential for body Ca\(^{2+}\) homeostasis have been identified. Testosterone was demonstrated to inhibit Ca\(^{2+}\) reabsorption *in vitro* as well as *in vivo*, whereas estrogen, produced in the female ovaries, promotes Ca\(^{2+}\) (re)absorption and bone mineralization processes. Van Abel *et al.* revealed that estrogen exerts an effect on renal Ca\(^{2+}\) handling *via* TRPV5 upregulation at the transcriptional level in rats, independent of 1,25(OH)\(_2\)D\(_3\) (17). Furthermore, estrogen deficiency is known to result in a negative Ca\(^{2+}\) balance and bone loss in postmenopausal women (18). These results partly explain gender differences in renal Ca\(^{2+}\) handling (19). The tissue kallikrein (TK) hormone is secreted into the pro-urine by renal tubular epithelial cells. The TK knockout mouse demonstrates renal Ca\(^{2+}\) wasting (20). In 2006, Gikka *et al.* described the mechanism through which TK stimulates TRPV5-mediated active Ca\(^{2+}\) reabsorption. TK activates the bradykinin receptor, thereby stimulating the phospholipase C/1,2-diacylglycerol/protein kinase C (PLC/DAG/PKC) pathway (21). As a result, TRPV5 channels show an increased expression on the plasma membrane, probably due to an inhibition of TRPV5 endocytosis. Hence, TK regulates the Ca\(^{2+}\) balance in a positive direction and thus preserves Ca\(^{2+}\) in the body. The antiaging hormone Klotho is a transmembrane protein with an extracellular domain that is secreted into blood, urine, and cerebrospinal fluid. Chang *et al.* demonstrated a stimulatory effect of Klotho on TRPV5-mediated active Ca\(^{2+}\) transport (22). Klotho was shown to alter the Ca\(^{2+}\) permeability of the renal luminal membrane by the removal of alpha2,6-linked sialic acids (23). Thereby, Klotho can regulate the cell surface retention of functional TRPV5, substantiating the important role of Klotho in Ca\(^{2+}\) homeostasis. Moreover, the phenotypic characterization of the Klotho knockout mouse revealed hypercalciuria, hypervitaminosis D, infertility, short life span, and bone aberrations clearly overlapping with symptoms presented by Trpv5 knockout mice (24). Although large variations in Ca\(^{2+}\) intake produce only small alterations in blood Ca\(^{2+}\) levels, due to the tight control by the above-mentioned key players, previous investigations demonstrated that high Ca\(^{2+}\) intake is an important regulator of renal Ca\(^{2+}\) transport protein expression as well, specifically in a 1,25(OH)\(_2\)D\(_3\)-deficient state, thereby contributing to the maintenance of a normal body Ca\(^{2+}\) balance (13).

**Model of Renal Hypercalciuria: Trpv5 Knockout Mice**

Genetic ablation of *Trpv5* in mice allowed us to investigate the requirement of normal TRPV5 channel functioning in Ca\(^{2+}\) homeostasis. Mice lacking TRPV5 epithelial Ca\(^{2+}\) channels in the DCT/CNT segment of the nephron displayed a significant hypercalciuria, excreting 6 to 10 times more Ca\(^{2+}\) compared with control littermate mice (25). Further phenotypic characterization showed that blood 1,25(OH)\(_2\)D\(_3\) levels were significantly elevated and normocalcemia was maintained. Bone mineral density was decreased and bone thickness was diminished. Intestinal Ca\(^{2+}\) transporters were significantly upregulated, and absorption experiments, in which the mice were challenged with radioactive Ca\(^{2+}\), showed significant Ca\(^{2+}\) hyperabsorption in the *Trpv5* knockout mice. This indicated an important molecular mechanism maintaining a normal Ca\(^{2+}\) balance despite severe renal Ca\(^{2+}\) wasting in the knockout mice, possibly involving the observed hypervitaminosis D. By generating the *Trpv5*/*1α-OHase* double knockout mice, we assessed that additional gene inactiva-
The Renal CaSR

It is clear that the kidney plays a key role in the maintenance of a normal Ca\textsuperscript{2+} balance, reabsorbing more Ca\textsuperscript{2+} in a hypocalemic state, while excreting Ca\textsuperscript{2+} during hypercalcemia. The CaSR in the parathyroid glands regulates PTH release, which is crucial for Ca\textsuperscript{2+} homeostasis (5). The identification of the CaSR in the kidney indicated an important regulatory function of this receptor in renal Ca\textsuperscript{2+} handling as well (27). The CaSR is expressed at multiple sites along the nephron, and its cellular localization depends upon the region of the nephron where it is expressed. Together with the parathyroid CaSR, the renal CaSR shows to be of crucial importance for whole-body Ca\textsuperscript{2+} handling. In the proximal tubule (PT) the CaSR is activated by increased urinary Ca\textsuperscript{2+} levels, which inhibits PTH-induced phosphate transporter-retrieval from the apical membrane and results in increased phosphate reabsorption. Hereby, excess loss of phosphate into the filtrate that contains elevated Ca\textsuperscript{2+} concentrations can be avoided, eventually preventing renal Ca\textsuperscript{2+}-phosphate precipitation (28). In the TAL, approximately 20% to 25% of the filtered Ca\textsuperscript{2+} is reabsorbed (29). Since the TAL is impermeable to water, the Ca\textsuperscript{2+} concentration at the basolateral side of the TAL cells consequently rises. This evokes an increase in the reabsorption of NaCl and other solutes along the loop of Henle. The CaSR is highly expressed at the basolateral membrane of the TAL, where it senses the extracellular Ca\textsuperscript{2+} concentration (30). This permits a negative feedback mechanism of the reabsorbed Ca\textsuperscript{2+} onto the cell, attenuating Ca\textsuperscript{2+} reabsorption and preventing hypercalcemia (31).

In the CD, the CaSR is expressed at the apical membrane in principal and intercalated cells (30). We introduce a novel regulatory function of the CaSR in the collecting duct, important for the prevention of renal Ca\textsuperscript{2+} phosphate precipitation.

CaSR Activation Decreases the Risk to Renal Stone Formation by Urinary pH Regulation

Besides a robust hypercalciuria, a significant polyuria and a decrease in urinary pH were consistently demonstrated in Trpv5 knockout mice (25). Furthermore, hyperphosphaturia was present in these mice, predisposing them to an increased risk of Ca\textsuperscript{2+}-phosphate precipitation. Strikingly, no renal Ca\textsuperscript{2+}-containing stones were observed. We hypothesized that both polyuria and increased urinary acidification might promote the excretion of large amounts of Ca\textsuperscript{2+} without being precipitated in the renal collecting duct system. Further investigations provided insight into the underlying molecular mechanisms applicable in kidney stone prevention (32). The crystallization of Ca\textsuperscript{2+}-phosphate occurs via the conversion of phosphate to its divalent form (HPO\textsubscript{4}\textsuperscript{2-}) in an alkaline, rather than an acidic, environment. From this can be hypothesized that a decrease in urinary pH can prevent Ca\textsuperscript{2+}-phosphate crystal formation (33). Acid/base transport processes take place along different nephron segments to control tubular fluid pH levels (34). Final urinary pH is assessed in the intercalated cells of the renal CD, where fine-tuning of urinary acidification takes place. The vacuolar proton pump H\textsuperscript{+}-ATPase, located in the type A intercalated cells of the CD, is mainly responsible for urinary H\textsuperscript{+} excretion. In 2009, we described how the exposure to high (5.0 mM) Ca\textsuperscript{2+} concentrations significantly enhanced H\textsuperscript{+}-ATPase activity in CD cells (32). This stimulatory effect was absent in CD cells from Atp6\textsubscript{b}vlb1 knockout mice that were genetically ablated for the CD-specific B1 subunit of H\textsuperscript{+}-ATPase (35). Moreover, the CaSR agonist neomycin increased H\textsuperscript{+}-ATPase activity as well, indicating the modulation of urinary acid excretion by CaSR activation. These findings suggested that an increased luminal Ca\textsuperscript{2+} concentration, as consistently present in the renal DCT, CNT, and CD of Trpv5 knockout mice, stimulates H\textsuperscript{+}-ATPase activity via apical CaSR activation. Interestingly, additional gene ablation of Atp6\textsubscript{b}vlb1 in Trpv5 knockout mice resulted in normalization of urinary pH levels and led to the tubular precipitation of Ca\textsuperscript{2+}-phosphate in the medullary CD (Figure 1) (32). From previous studies it was known that the formation of alkaline urine increases the risk for Ca\textsuperscript{2+}-phosphate precipitation (33). Therefore, renal stones commonly occur in distal renal tubular acidosis patients, who display a urinary acidification defect and concomitant hypercalciuria (36). Furthermore, treatment with acetazolamide, a carbonic anhydrase inhibitor resulting in the alkalization of the urine, increases the risk to drug-induced renal Ca\textsuperscript{2+}-phosphate stone formation (37,38). Our observations unequivocally revealed that the naturally occurring increased urinary acidification through CaSR activation in the distal nephron in Trpv5 knockout mice is an essential adaptive mechanism preventing renal Ca\textsuperscript{2+}-phosphate precipitation in a hypercalciuric state (Figure 2).

Diluting the Urine Prevents Renal Stone Formation

Urinary concentration takes place in the CD where the vasopressin-regulated aquaporin-2 (AQP2) water channels are localized in the apical membrane of principal cells (39). Increased diuresis diminishes the risk for renal crystal precipitation by reducing urinary Ca\textsuperscript{2+} levels. A urinary concentration defect was demonstrated in Trpv5 knockout mice and was further characterized by a significant decrease in urinary osmolarity and the occurrence of polyuria, caused by downregulation of renal AQP2 expression (Figure 2). Interestingly, medullary membrane protein fractions, isolated from control and Trpv5 knockout mice, revealed a significant downregulation of AQP2 proteins in the knockouts. Sands and coworkers linked Ca\textsuperscript{2+} and wa-
ter homeostasis, suggesting an important functional role for the renal CaSR (40). The expression of the CaSR along the apical membrane of the CD cells was shown to facilitate the activation of the receptor during a hypercalciuric state. This underlines the mechanism by which CaSR-mediated downregulation of AQP2 expression evokes polyuria, assisting the excretion of large amounts of Ca\(^{2+}\). The physiologic connection between Ca\(^{2+}\) and water balance established an important mechanism by which renal stone formation is hampered during a hypercalciuric state, emphasizing the importance of sufficient hydration in people at risk for kidney stones. Given that humans are able to increase their urinary volume by an average of only 0.3 L/24 h, and given the observation that Trpv5/Atp6v1b1 double knockout mice increased their urinary volume further, adequate hydration is insufficient to prevent stone formation (41). Therefore, the initiation of additional adaptations, like increased urinary acidification, is highly important to decrease the risk to Ca\(^{2+}\)-phosphate stone formation. Furthermore, other putative target mechanisms should be studied. Urinary molecules that retard the formation of Ca\(^{2+}\)-containing stones should be of great research interest, in which citrate is already a known urinary stone inhibitor in clinical practice (42,43). Therapeutic strategies for nephrolithiasis are dependent on the type of stones occurring and the primary cause of the urinary Ca\(^{2+}\) loss. Thiazide diuretics are often prescribed, as these drugs have a Ca\(^{2+}\)-sparing effect and thereby lower the urinary Ca\(^{2+}\) levels (44). A possible concomitant positive effect of thiazide treatment on bone mineral density was proposed. However, due to contradictory research outcomes, this needs further investigation (45,46). Novel therapies hampering Ca\(^{2+}\)-phosphate stone formation could imply the stimulation of urinary acidification. Further research would be necessary to acquire insight into the possible working mechanism of such an intervention in humans.

**Hypercalciuria and Nephrolithiasis: A Socioeconomic Problem**

Hypercalciuria forms the main risk factor for renal stone formation (47). Bound to urinary solutes like phosphate and oxalate, Ca\(^{2+}\) can precipitate in the urine and the renal tissue once sufficiently supersaturated. Most renal stones contain Ca\(^{2+}\), with the majority classified as Ca\(^{2+}\)-oxalate stones (48). Nephrolithiasis forms a worldwide health and socioeconomic problem, occurring in every geographical, cultural, or racial group. In the United States (US), over 5% of the population develops a clinically significant episode of kidney stone disease during life, with a large economic impact (49). Underlying causal factors for nephrolithiasis
include genetic predisposition, dietary habits, urinary tract infection, and disorders characterized by a disturbance in body ion handling (50). Patients suffering from renal stone disease experience renal colic (severe pain), obstruction of urine flow, hematuria, and slowly progressing tissue damage, whereas kidney stones form a risk factor for chronic kidney disease (51). New advances in treatment technologies are under current investigation, although shock-wave lithotripsy and surgery are the common therapies at the moment, depending on the size of the kidney stone. The chance for recurrence is 60% to 75% and, therefore, pharmacologic treatment, lifestyle, and dietary modifications are implemented in individuals at risk. Further investigations are necessary to elucidate the genetic and environmental risk factors for hypercalciuria-related nephrolithiasis and will permit the fine-tuning of therapeutic strategies that are currently employed.

**Genetic Susceptibility to Renal Stone Formation**

Individuals with a positive family history have an increased risk for the development of kidney stones (52). This strongly suggests that genetic factors are involved in the pathogenesis of hypercalciuria (50). As there are a myriad of potential disturbances in the Ca\(^{2+}\) balance that can cause hypercalciuria, with many genes encoding proteins involved in Ca\(^{2+}\) homeostasis, hypercalciuria is very heterogeneous. Thus, many candidate genes were hypothesized to be involved in the pathogenesis of hypercalciuria. TRPV5, as well as TRPV6, gene ablation in mice leads to hypercalciuria and, thus, these epithelial Ca\(^{2+}\) channels are important candidate genes possibly involved in the pathogenesis of hypercalciuria. To date, mutation analysis of the human TRPV5 gene has not revealed a primary role for defects in this epithelial Ca\(^{2+}\) channel in idiopathic hypercalciuria (53). However, the involvement of TRPV5 or TRPV6 gene defects in hypercalciuria has not been definitively excluded. Specific single nucleotide polymorphisms (SNPs) or haplotypes of the encoding genes may modulate channel activity and might therefore be responsible for altered renal Ca\(^{2+}\) excretion. Unusual haplotype differences were identified in the TRPV6 gene among worldwide populations (54). It was suggested that a specific TRPV6 haplotype comprising three nonsynonymous SNPs (C157R, M378V, and M681T) resulted in a selective advantage during human history. This might indicate a different genetic composition across populations that are currently employed.

**Future Directions**

The investigations described here demonstrate that normal renal Ca\(^{2+}\) handling is fundamental in the prevention of disturbances in the Ca\(^{2+}\) balance, greatly underlined by characterization of the unique hypercalciuric Trpv5 knockout mouse model. Interestingly, the underlying mechanisms that explained polyuria and increased urinary acidification were established in these mice, revealing a crucial role for the renal CaSR in prevention of Ca\(^{2+}\)-phosphate stone formation. In humans, the effects of hypercalciuria on urinary volume and pH remain to be elucidated, providing important knowledge for the development of novel therapeutic strategies and screening possibilities for the benefit of kidney stone patients. Investigations should focus on local therapeutic targets like Ca\(^{2+}\), acid/base and water transporting proteins, and the renal CaSR. Future therapeutic strategies that modulate urinary volume and pH might involve calcimimetic compounds that locally activate the CaSR in the collecting duct. Additionally, pH-sensing receptors were recently identified in the kidney (58). Via these proton sensors, alterations in urinary and blood pH are monitored, after which downstream signaling evokes a tight regulation of body pH. As urinary pH is an important parameter for renal stone formation, these pH sensors might be important therapeutic targets in the prevention of kidney stones as well. Whether urinary pH modulation can influence Ca\(^{2+}\)-oxalate stone formation has been debatable so far. Previous investigations suggested that an acidic environment stimulates Ca\(^{2+}\)-oxalate precipitation, whereas others showed no effect of pH (48). Altogether, these investigations are very important for the understanding of the processes that take place in the body during a hypercalciuric state and also raise new issues concerning applicability in clinical practice that require follow-up.

**Disclosures**

None.

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