

Calcium Transport across Plasma Membrane in Early Stages of Chronic Kidney Disease – Impact of Vitamin D₃ Supplementation

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Abstract

Mini review summarizes the results of studies focused on elucidating pathophysiological mechanisms of altered intracellular calcium homeostasis in the peripheral blood mononuclear cells of patients with early stages of chronic kidney disease. The basic mechanisms of calcium entry as well as those of its removal are impaired by the disease. These disturbances cause an increase concentration of free cytosolic calcium which can result in a change of broad range of cellular processes and expression patterns of various signaling molecules. Vitamin D₃ supplementation is the standard treatment of frequent vitamin D₃ insufficiency or deficiency in these patients. It can be assumed that vitamin D₃ through the pleiotropic effects may participate in modulation of intracellular calcium homeostasis. Vitamin D₃ supplementation resulted in a reduction of cytosolic free calcium affecting some of the transport systems involved in cell calcium entry as well as calcium exit. Normalization of the cytosolic free calcium concentration can have a beneficial effect on intracellular signaling. The mechanisms for regulating and controlling intracellular calcium homeostasis in chronic kidney disease patients are currently still under investigation.

Keywords: Cytosolic calcium; Calcium transport; Vitamin D; Chronic kidney disease

Abbreviations: CKD: Chronic Kidney Disease, PBMCs: Peripheral Blood Mononuclear Cells, [Ca²⁺]_i: Free Cytosolic Calcium Concentration, Ca²⁺: Calcium Cations, ROC: Receptor Operated Channel, VOC: Voltage Operated Channel, SMOC: Second Messenger Operated Channel, SOC: Store Operated Channel, CRAC channel: Calcium Release Activated Calcium Channel, PMCA: Plasma Membrane Ca₂⁺-ATPase, ATP: Adenosine Triphosphate, 2APB: 2-Aminoethyl-Diphenylborate, Tg : Thapsigargin

Review

Calcium cations (Ca²⁺) play an important role in the cellular signaling and in a number of physiological processes. The cell Ca²⁺ distribution is exactly regulated by transport systems which maintain low free cytosolic calcium concentration ([Ca²⁺]_i) (50-100 nmol/l) in comparison with Ca²⁺ concentration in extracellular space (about 1.3 mmol/l). The plasma membrane possesses several types of channels which control the Ca²⁺ entry into the cells, and systems that extrude it. Calcium enters the cell by any of the general classes of channels, including voltage-operated channels (VOC), second messenger-operated channels (SMOC), store-operated channels (SOC) and receptor operated-channels (ROC). Calcium release from the cells is regulated principally by Ca²⁺ - ATPase, and Na⁺ exchanger (Figure 1). Plasma membrane is responsible for the 10,000-fold gradient of Ca²⁺ normally measured between the extracellular space and the cytoplasm. The very large gradient of Ca²⁺ across the plasma membrane not only ensures full availability of the cation, but it is also dynamically beneficial, since even minor changes in the Ca²⁺ permeability of the plasma membrane provides significant fluctuations in the [Ca²⁺]_i. Passing Ca²⁺ through the plasma membrane triggers a cascade of events that are vital for cellular activities. Calcium cation is an important ubiquitous messenger, controlling a broad range of cellular processes. It has a direct role in controlling the expression patterns of its signaling systems that are constantly being remodelled in both, health and disease.

Chronic kidney disease (CKD) is associated with a significant elevation in the [Ca²⁺]_i which is toxic to the cells and may be responsible for multiple organ dysfunction [1,2]. Knowledge of the relationship between CKD and cellular calcium homeostasis, as well as regulation

mechanisms of calcium signaling especially in the early stages of the disease are missing.

Mini review summarizes the results of our studies focused on elucidating pathophysiological mechanisms of altered intracellular calcium homeostasis in the peripheral blood mononuclear cells (PBMCs) of CKD patients. Moreover, vitamin D deficiency or insufficiency is highly prevalent in CKD patients, and under current guidelines, the therapeutic strategies include supplementation of native vitamin D (ergocalciferol or cholecalciferol) [3]. The critical role of the vitamin D endocrine system in disease prevention extends beyond the classic regulation of calcium and phosphorus homeostasis and skeletal integrity, to its pleiotropic effects on extramineral metabolism [4,5]. Vitamin D is an important modulator of cellular proliferation, differentiation, inflammation and immunity. Vitamin D attenuates kidney injury by suppressing fibrosis, inflammation, and apoptosis [6,7]. Therefore, the effect of vitamin D₃ supplementation on the major mechanisms involved in maintaining cell calcium homeostasis was examined in patients with early stages of CKD.

Free intracellular calcium

Elevation of free cytosolic calcium concentration ([Ca²⁺]_i) is a highly versatile signal, that operates over a wide temporal range to regulate many different cellular processes. Ca²⁺ signals control many cellular functions, ranging from short-term responses such as contraction and secretion, to longer term regulation of cell growth and proliferation.

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On the other hand, Ca^{2+} signal may induce apoptosis or less specific necrosis under special conditions. $[Ca^{2+}]_i$ is controlled by mechanisms that regulate Ca^{2+} entry from the extracellular space and Ca^{2+} release from intracellular stores, and by the activity of ATP-dependent Ca^{2+} -ATPases and antiporters that move Ca^{2+} back into stores or out of cells [8-10]. Previous studies on the metabolic profile of various cells have shown, that chronic renal failure already in early stages is associated with a significant elevation in $[Ca^{2+}]_i$ (Figure 2) [11], which may be responsible for the multiple organ dysfunction in haemodialysed patients [12]. Most of the intracellular calcium is either sequestered in the endoplasmic reticulum and mitochondria, or bound to cytoplasmic proteins and other ligands. More and more evidence suggests that intracellular Ca^{2+} stores might be critical for some physiological processes [9].

For determination of intracellular Ca^{2+} stores, thapsigargin (Tg), the specific inhibitor of endoplasmic reticulum Ca^{2+} -ATPase, is used (Figure 3A). The effect of Tg in the absence of extracellular calcium strongly indicates that intracellular Tg sensitive calcium reserves in PBMCs of CKD patients (stage 2-3) are significantly higher in comparison with

healthy volunteers (Figure 3B). Vitamin D_3 supplementation returned the elevated $[Ca^{2+}]_i$ in CKD patients to values comparable with healthy subjects (Figure 2), but did not affect intracellular calcium reserves (Figure 3B) [11,13].

Calcium entry

Calcium release activated calcium channels: Calcium enters into the cells by calcium/cation channels. In nonexcitable cells, like PBMCs, the predominant Ca^{2+} entry pathway is the store-operated one, in which the emptying of intracellular Ca^{2+} stores activates the Ca^{2+} influx to the cell (Figure 1). This type of the channel is in PBMCs known as the calcium release activated calcium (CRAC) channel. The calcium entry through CRAC channels activates certain transcription factors which regulate the gene expression for cytokines responsible for immune responses [14,15]. Dysregulation of Ca^{2+} homeostasis involving the endoplasmic reticulum and store-operated calcium channels has been manifested in neurodegenerative disorders, in patients with immunodeficiency, acute pancreatitis, polycystic kidney disease and cardiac hypertrophy [14-21].

In PBMCs of non-diabetic CKD patients, CRAC channels are activated indirectly by intracellular Ca^{2+} store depletion using Tg, the specific inhibitor of endoplasmic reticulum Ca^{2+} -ATPase. When

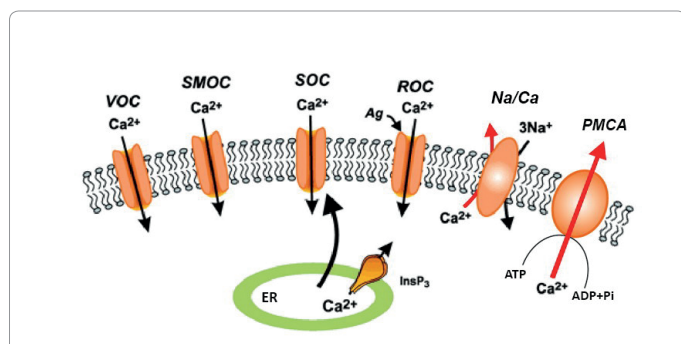


Figure 1: Basic mechanisms of calcium transport across plasma [9]. Calcium entry: ROC - receptor operated channel, VOC - voltage operated channel, SMOC -second messenger operated channel, SOC - store operated channel. Calcium removal: PMCA - plasma membrane Ca^{2+} -ATPase, Na/Ca - Na^+/Ca^{2+} exchanger. Ag - agonist, IP_3 - inositol triphosphate, ATP - adenosine triphosphate, ADP - adenosine diphosphate, Pi - inorganic phosphate, ER - endoplasmic reticulum

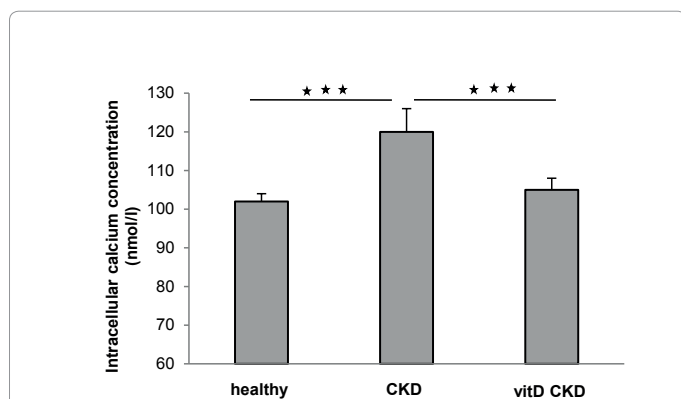


Figure 2: Measurements of free cytosolic calcium concentration [11]. Cytosolic Ca^{2+} measurements were performed by Fluo-3 fluorimetry in isolated PBMCs of healthy volunteers and CKD patients before and after vitamin D_3 supplementation (***) $P < 0.001$.

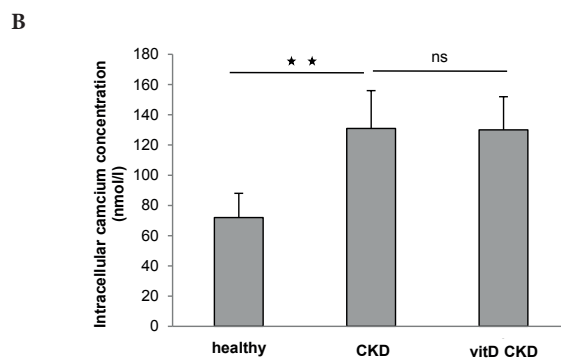
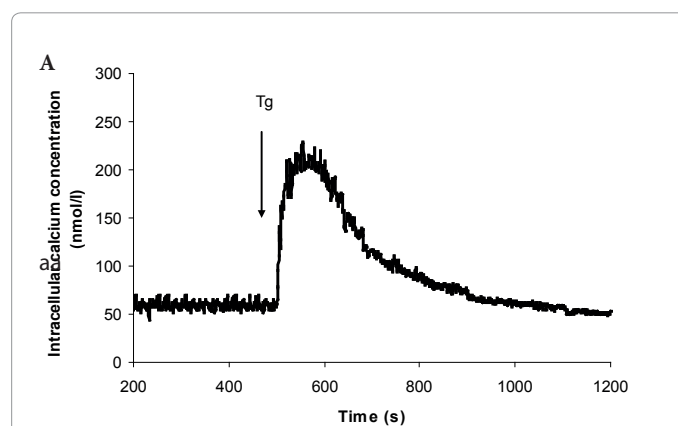


Figure 3: Determination of intracellular calcium concentration of Tg-sensitive stores [11].

(A) Typical effect of Tg (the specific inhibitor of endoplasmic reticulum Ca^{2+} -ATPase) in a Ca^{2+} free physiological salt solution and in the presence of extracellular Ca^{2+} chelator (EGTA, pH=7).

(B) Comparison of intracellular calcium concentration of Tg-sensitive stores in PBMCs of healthy subjects, CKD patients at baseline and CKD patients after 12-month vitamin D_3 supplementation (** $P < 0.01$).

the reliable inhibitor of these channels 2-aminoethyl-diphenylborate (2APB) was applied during the sustained phase of Tg effect, it evoked a decrease in $[Ca^{2+}]_i$, which represents particularly the Ca^{2+} influx through CRAC channels (Figure 4A). In early stages of CKD, the calcium entry via CRAC channels was significantly increased when compared with healthy individuals. After the treatment with vitamin D₃, the enhanced Ca^{2+} entry through these types of channels was significantly decreased (Figure 4B) [13].

L-type calcium channels: Many of previous studies have implicated L-type Ca^{2+} channels in Ca^{2+} influx during T-lymphocyte activation and proliferation [22]. Nonexcitable cells express Ca^{2+} channels that share common structural features with voltage-dependent Ca^{2+} channels of excitable cells, but are not solely gated by changes in membrane potential. However, Kotturi et al. presented both, molecular and pharmacological evidence for the presence of L-type Ca^{2+} channels in the plasma membrane of resting lymphocytes in 2003 [23].

Despite of this knowledge, in PBMCs of early-stage CKD patients, calcium influx via L-type Ca^{2+} channels was not increased in comparison with healthy subjects [11]. Stimulation PBMCs by 1,25(OH)₂D₃, an active metabolite of vitamin D, does not induce calcium response through L-type calcium channels in healthy subjects [24]. In accordance with this finding, the calcium influx through L-type calcium channels was not observed after supplementation of vitamin D₃.

P2X₇ receptors: At the present time, purinergic signaling is accepted as a crucial component of diseases and was found to mediate a vast array of biological processes [25-27]. Until today, seven subtypes

of P2X receptors have been identified. P2X₁-P2X₆ are predominantly expressed by neurons and some excitable cells. The P2X₇ receptors are expressed primarily on cells of hemopoietic origin, where they participate in immune responses, cell proliferation, cell death, bone formation and resorption [25]. The P2X₇ receptor is a bifunctional purinoreceptor, that either opens a non-selective cation channel, or forms a large, cytolytic pore. ATP binding leads to opening of cation channel that permits K⁺ efflux and both Ca^{2+} and Na⁺ influx into the cells. This causes major disturbances of the ionic gradient across the plasma membrane that raises calcium influx into the cell, thus triggering several intracellular signaling cascades, including mediation of inflammatory responses and modulation of cell turnover. A key factor of P2X₇-dependent cytotoxicity is the massive intracellular Ca^{2+} increase triggered by its activation. It may result in membrane blebbing and cell death by apoptosis or necrosis. There is an increasing body of evidence implicating P2X₇ receptor in various pathological conditions [28-31]. The most recent advances provide compelling evidence for P2X receptors, playing a key role in regulating cell physiological and pathophysiological processes and are involved in the disrupted cell calcium homeostasis in CKD patients [32,33].

In PBMCs of non-diabetic CKD patients Ca^{2+} entry via P2X₇ channels and pores has been increased and also the permeability of P2X₇ pores was higher, in comparison with healthy subjects. In addition, the function of P2X₇ channels and pores was altered [13,34]. It is known, that 1,25(OH)₂D₃, an active metabolite of vitamin D, prevents Ca^{2+} increase through P2X₇ channels and reduces the plasma membrane permeability through P2X₇ pores in human PBMCs of healthy subjects [24]. 1,25(OH)₂D₃ can also up or downregulate the expression of several genes in many cell types. To our knowledge, the effect of 1,25(OH)₂D₃ on P2X₇ receptor expression has not been studied. Our study disclosed that vitamin D₃ supplementation reduced Ca^{2+} influx through P2X₇ channels and affected their functionality. Moreover, the supplementation had no effect on permeability of P2X₇ pores, and the differences in responses to stimulation or inhibition were not found [13]. Different effects of vitamin D₃ on P2X₇ channels and pores in CKD patients may have been made due to different sensitivity to these channels and pores. It is known, that various agonists and antagonists of P2X₇ receptors may have a distinct effect on the function of P2X₇ channels and/or pores [35]. Not only the function, but also the expression of P2X₇ receptors may be altered in some pathological conditions [26,36-38]. We found a 1.5-fold increase in the expression of surface P2X₇ receptors on PBMCs from non-diabetic CKD patients when compared to healthy subjects (Figure 5A) [39]. In our recent study, the flow cytometric measurement revealed, that vitamin D₃ decreased the expression of P2X₇ receptors by 45% (Figure 5B) [13].

Calcium removal

Plasma membrane Ca^{2+} -ATPase: The plasma membrane possesses two systems that extrude Ca^{2+} : a high-affinity, low-capacity Ca^{2+} -ATPase, and a lower affinity, large-capacity Na⁺/ Ca^{2+} exchanger which is particularly active in excitable cells. The plasma membrane Ca^{2+} -ATPase (PMCA) is critical for the maintenance of resting $[Ca^{2+}]_i$ in non-excitable cells and may be the last gatekeeper for the control of low $[Ca^{2+}]_i$.

PMCA activity of non-diabetic CKD patients is reduced by 34% against healthy subjects [40]. This finding is consistent with other studies and points out that the PMCA activity decreases with kidney disease progression [41]. The decline in PMCA activity may be caused by numerous factors, such as calmodulin deficiency, an activity of other endogenous protein regulators, and inhibition of mitochondrial or

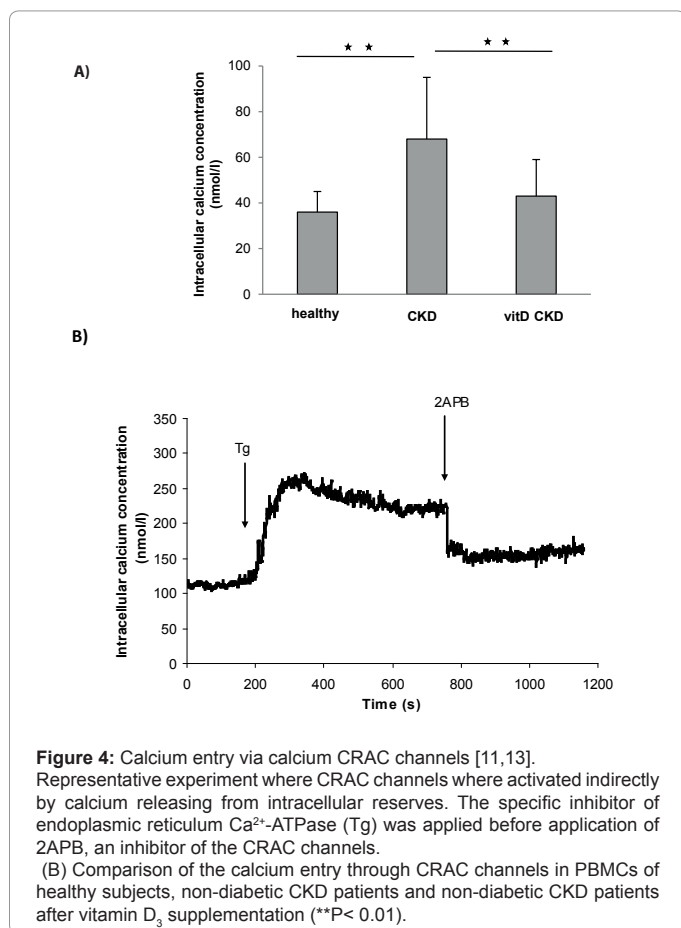


Figure 4: Calcium entry via calcium CRAC channels [11,13].

Representative experiment where CRAC channels were activated indirectly by calcium releasing from intracellular reserves. The specific inhibitor of endoplasmic reticulum Ca^{2+} -ATPase (Tg) was applied before application of 2APB, an inhibitor of the CRAC channels.

(B) Comparison of the calcium entry through CRAC channels in PBMCs of healthy subjects, non-diabetic CKD patients and non-diabetic CKD patients after vitamin D₃ supplementation (**P < 0.01).

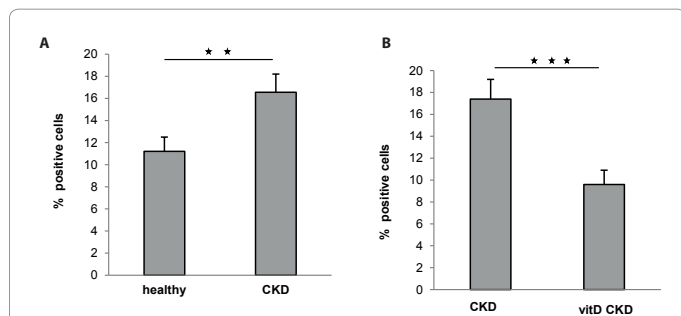


Figure 5. The expression of cell surface P2X7 receptors [13,34]. The expression of P2X₇ receptors was measured by flow cytometry using primary antibody for the extracellular domain of the P2X₇ receptor (anti-P2X₇, extracellular) antibody. (A) Expression of P2X₇ receptors on PBMCs of healthy subjects and early stages non-diabetic CKD patients (**P<0.01). (B) Expression of surface P2X₇ receptors before and after 6-month vitamin D3 supplementation (***P<0.001).

glycolytic metabolism [42]. The Ca²⁺ influx through CRAC channels is also an important regulator of PMCA activity, and an altered communication between them may be another cause of PMCA malfunction [43,44]. Several experimental studies have observed direct and/or indirect effects of 1,25(OH)₂D₃ and/or 24,25(OH)₂D₃ on activity and expression of PMCA in different cells, but the effects of 25(OH)D₃ itself, have not been studied. The studies targeting at the effects of native vitamin D₃ supplementation on cell calcium homeostasis in patients with early stages of CKD are missing. In our study the impact of 6 month vitamin D₃ (cholecalciferol) supplementation on the PMCA activity was investigated [40]. After the treatment, no changes in PMCA activity were detected. However, the concentration of plasma membrane proteins was increased by 47%. Therefore, the possibility of increased expression of PMCA cannot be excluded [13,40].

Conclusions

Our studies contribute to elucidation of pathophysiological mechanisms of altered intracellular calcium homeostasis in PBMCs of patients with CKD. Already in early stages of CKD, cytosolic free calcium concentration and calcium concentration of intracellular stores are significantly increased mainly due to increased activity of CRAC channels and P2X₇ receptors activation and expression. This disturbed calcium balance can activate aberrant inflammatory and vascular pathways participating in renal injury, which may contribute to progression of renal disease [27,45]. Pharmacological blockade of P2X₇ receptor protect agonist antibody-mediated glomerular inflammation and hypertensive renal injury in rodent [45]. Renoprotection is associated with reduced numbers of renal macrophages and has been attributed to direct anti-inflammatory effect of P2X₇ antagonism. Similarly, pharmacological suppression of CRAC channel activity reduces pro-inflammatory cytokine expression [46]. Thus, P2X₇ receptor and CRAC channel blockade may have broad therapeutic value not only in renal disease. Vitamin D₃ supplementation in CKD patients causes reduction in calcium influx through CRAC channels and P2X₇ receptors and downregulation of P2X₇ receptors expression. These effects of vitamin D₃ may be involved in anti-inflammatory and immunoregulatory effects of vitamin D₃ in CKD patients and can contribute to its renoprotective effect in general.

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