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The influence of extracellular and intracellular calcium on the secretion of renin

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Abstract

Changes in plasma, extracellular and intracellular calcium can affect renin secretion from the renal juxtaglomerular (JG) cells. Elevated intracellular calcium directly inhibits renin release from JG cells by decreasing the dominant second messenger intracellular cyclic adenosine monophosphate (cAMP) *via* actions on calcium-inhibitable adenylyl cyclases and calcium-activated phosphodiesterases. Increased extracellular calcium also directly inhibits renin release by stimulating the calcium-sensing receptor (CaSR) on JG cells, resulting in parallel changes in the intracellular environment and decreasing intracellular cAMP. *In vivo*, acutely elevated plasma calcium inhibits plasma renin activity (PRA) *via* parathyroid hormone-mediated elevations in renal cortical interstitial calcium that stimulate the JG cell CaSR. However, chronically elevated plasma calcium or CaSR activation may actually stimulate PRA. This elevation in PRA may be a compensatory mechanism resulting from calcium-mediated polyuria. Thus, changing the extracellular calcium *in vitro* or *in vivo* results in inversely related acute changes in cAMP, and therefore renin release, but chronic changes in calcium may result in more complex interactions dependent upon the duration of changes and the integration of the body's response to these changes.

Keywords

calcium sensing receptor; hypercalcemia; parathyroid hormone; cAMP; juxtaglomerular cell; adenylyl cyclase

Calcium

The ubiquitous cation calcium has an important role in signal transduction pathways as a second messenger involved in a variety of cellular functions in almost all mammalian cells. Calcium also acts as critical cofactor for most enzymes, as well as the process of secretion [82]. Extracellular calcium, and particularly the plasma level of calcium is closely regulated with a normal concentration of 2.2–2.6 mM of total calcium (complexing with various other ions and binding to plasma proteins), and an ionized free calcium of 1.1–1.4 mM. These

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levels are normally maintained within a tight range and rarely fluctuate more than 5% over time.

Within most cells, the concentration of ionized calcium is roughly 100 nM, but can increase as much as 1–2 orders of magnitude as part of a stimulation of a cell signaling cascade. Thus, the intracellular calcium concentrations are five orders of magnitude less than that of the extracellular concentration, creating a steep diffusion gradient which is maintained by limited permeability, calcium extrusion pumps and efficient binding by intracellular stores [82].

Juxtaglomerular cells and the calcium paradox. *In vitro* studies

While increased calcium usually a positive factor in secretory processes [82], there are two cells in which increased extracellular calcium has be characterized as a negative regulator. These include the chief cells of the parathyroid gland [83] in which increased circulating calcium suppresses parathyroid hormone (PTH) secretion, and the renin-containing juxtaglomerular (JG) cells [90] at the glomerular pole of the afferent arteriole of the kidney.

Classic stimuli for the secretion of renin are mediated by various second messengers, including cAMP, cGMP and intracellular calcium [25]. However, the dominant second messenger for renin secretion is cAMP [25,31], synthesized by adenylyl cyclases within the JG cell. Activation of adenylyl cyclase is the target for all known classical stimuli for renin secretion, such as β-adrenergic activation [46,70] and macula densa-mediated PGE_2 stimulation via the EP-4 receptors [30,40,106]. The question has always been how do the other second messengers interact either directly with renin secretion (in parallel with cAMP), or perhaps by mediating the synthesis or degradation of cAMP [25]. As for cGMP, its interaction seems to be indirect, either by inhibiting phosphodiesterase-3 degradation of cAMP [11,37,40,67], or by via inhibition through cGMP-dependent protein kinase II [41,122]. The exact role of calcium as a second messenger has been more elusive. Renin secretion from the JG cells has a somewhat unique interaction with calcium, in that while in most secretory cells calcium is a regulatory co-factory for stimulation, both increased intracellular and extracellular calcium inhibits renin secretion [9,10,25,36]. It was Park and Malvin [90] who first suggested there was an inverse relationship between intracellular calcium concentration in the JG cell and its release of renin. Because of this unusual and seemingly paradoxical relationship between intracellular calcium and renin secretion, it has been referred to as the “calcium paradox” [46]. Numerous *in vitro* studies have reinforced this observation, including increasing extracellular calcium [9,24,87,107], chelating intracellular [79,85] or extracellular calcium [9], increasing intracellular calcium using calcium channel agonists [27] or various receptor-mediated hormones such as angiotensin II, endothelin and vasopressin [71,98,116] known to increase intracellular calcium, activating release of intracellular stored calcium [108], or using calcium ionophores or calcium channel blockers [24,29,38]. While the phenomenon has been observed for over 25 years, recently two laboratories presented a mechanistic explanation of how changes in intracellular calcium influenced renin secretion [45,85,86]. The first key was that manipulating intracellular calcium resulted in coincident changes in both JG cell cAMP and renin release [45,85], suggesting that the effects of calcium were “upstream” from the production of the dominant second messenger cAMP. Next, both laboratories reported multiple lines of evidence for the calcium-inhibitable isoforms of adenylyl cyclase (AC), AC-5 and/or AC-6 in their JG cells. Further, while AC-6 is generally regarded as a cell membrane-bound isoform fluorescent immunohistochemistry of AC-5 found it co-localized on the renin containing granules within the JG cell cytoplasm [85,86]. Interestingly, while the mechanism for either isoform is presumably similar, the laboratories in Regensburg find both AC-5 and AC-6 in their JG cells, with a dominant role for AC-6 [6,45], while the

laboratories in Detroit did not find AC-6 in their JG cells, and could account for the inhibitory effect of intracellular calcium completely through AC-5 [86]. So, what is the resolution to this discrepancy? Both laboratories used a similar technique with isolated JG cells in primary culture from mice. While it has not yet been tested, it is highly likely that these differences are due to the huge variability in the phenotype of mice as a laboratory animal, even in similar strains [35]. Regardless of the isoform(s), the key to the calcium paradox seems to be that when calcium increases, the activity of calcium-inhibited adenylyl cyclase is reduced, attenuating the basal or stimulated synthesis of the second messenger cAMP, resulting in decreased renin secretion. This pathway is illustrated in figure 1. It should be noted that while the predominance of the literature suggests renin secretion is highly cAMP dependent, at least one study [66] suggests under certain circumstances renin may be released without changes in cAMP.

Calcium and phosphodiesterase

In addition to the inhibition of cAMP synthesis by calcium, it has also been reported that the JG cells contain the calcium-activated phosphodiesterase (PDE) isoform, PDE-1C [87]; the only calcium-stimulated PDE-1 isoform that targets cAMP. These studies suggested that at normal extracellular calcium concentrations, this PDE was relatively dormant. However, as extracellular (and intracellular) calcium concentrations increased, its degradation of cAMP became more prominent. Such an interaction between calcium-inhibited AC and calcium-stimulated PDE-1 are usually found co localized in the same tissues. PDE1c has been localized in various tissues, including brain [21], testis [127] and smooth muscle [101] in association with calcium inhibitable adenylyl cyclases, isoforms 5 and 6 [44]. These data would suggest that with increases in intracellular calcium, there is a symbiotic interaction between decreased synthesis (via AC) and increased degradation (via PDE) of cAMP, and thus an amplified inhibition of the signal for renin secretion.

Calcium-calmodulin

Cyclic nucleotide hydrolysis by the PDE1 family is calcium-calmodulin dependent [44]. The isoforms of the PDE1 family are characterized as the “calcium- and calmodulin-dependent phosphodiesterases” [22]. Their activity is regulated by binding with the calcium-calmodulin complex. Calcium-calmodulin binding stimulates the PDE1 activity by increasing its *V*max [57]. The calcium calmodulin complex may actually inactivate an inhibitory domain on the PDE, increasing its activity [21,109], and there is a [intracellular] calcium threshold at which this activation may be initiated. Calcium-mediated inhibition of renin secretion has been shown to be calmodulin-dependent. Inhibitors of calmodulin increase renin release [9,28,65,91,108] *in vitro*, and reverse high extracellular calcium-mediated inhibition of renin [9]. However, how calmodulin fits into the calcium-mediated inhibition of renin has remained unclear. The Ca-calmodulin dependent PDE1 family comprises three isoforms; PDE1A, PDE1B and PDE1C {44]. PDE1 is regulated by calcium, and is tightly associated with calmodulin. Calmodulin inhibitors do not change basal cAMP content in JG cells [65,87]. However, either activating the CaSR or increasing extracellular calcium lead to a rise in intracellular calcium, and reduces both JG cell cAMP content and renin release [87], in part by increasing PDE1 activity. This is consistent with the activating threshold of calcium-calmodulin activation of PDE1. The PDE1A and PDE1B isoforms have a high affinity for cGMP, while PDE1C has an equally high affinity for both cAMP and cGMP [44]. In isolated JG cells in primary culture, both calmodulin inhibition and PDE1 inhibition reversed the suppression of cAMP formation and renin release in response to increased intracellular or media calcium. The similar reversals of calmodulin or PDE1 inhibition of renin were not additive suggesting PDE1 and calmodulin work in concert in the JG cell, as in other cell types [44].

The calcium-sensing receptor

If changes in the extracellular calcium concentration do effect similar changes in the cytosolic calcium concentration in order to influence calcium-sensitive AC's and PDE's, how might such a signal be transmitted? Similar to the parathyroid gland [99], the JG cells have been found to have calcium-sensing receptors (CaSR); G protein-coupled receptor whose activation increases intracellular calcium by activating phospholipase C (PLC) *via* G_q [117]. These membrane-bound receptors sense and translate micromolar changes in the extracellular calcium into parallel changes in intracellular calcium [99]. The half-maximal effective calcium concentration (EC_{50}) for the CaSR is 1.2 mM, which is the normal concentration of interstitial free ionized calcium in the renal cortical interstitium [5,66]. Ortiz-Capisano et al [84] identified CaSR in primary cultures and freshly isolated mouse JG cells. They found that either increased extracellular calcium or activation of the CaSR using the calcimimetic Cinacalcet-HCl significantly decreased both JG cell cyclic AMP formation and renin release by approximately 45%. They concluded that JG cells express CaSR, and CaSR respond to changes in extracellular calcium to modify or activate calcium-mediated intracellular signaling [84] that regulates the secretion of renin. Their results have been corroborated by both *in vitro* [78] and *in vivo* [8,78] studies.

If the changes in intracellular calcium in the JG cells are linked to the activation of the CaSR, then what is the post-receptor signaling cascade? While the actual pathway from CaSR to renin secretion in the JG cell has not been described, in the parathyroid gland activation of the CaSR activates phospholipase C [16], with the generation of receptor inositol trisphosphate (IP_3) and diacylglycerol. Subsequent activation of the IP_3 on the endoplasmic reticulum causes release of calcium into the cytosol, and the depletion of endoplasmic reticulum calcium then stimulates store operated calcium channels [95]. Intracellular calcium is buffered by mitochondrial uptake and calcium sequestration in the endoplasmic reticulum [10]. Changes in cytoplasmic calcium can come from calcium release from sequestered intracellular stores or from the extracellular fluid through opening of calcium channels. Numerous studies of juxtaglomerular renin release in various preparations of renal cortical tissue have identified possible pathways which might lead to increased intracellular calcium, including activation of store-operated calcium entry channels [107,108], mobilization of calcium from intracellular stores in the endoplasmic reticulum [29,31,33], and activation of voltage-gated L-type calcium channels [24,26,27,38]. Renin secretion is coupled to the electrical potential of the JG cell, such that depolarization inhibits renin release [24,26] and hyperpolarization increases renin release. Numerous studies *in vitro* have shown KCl depolarization inhibit renin release [10,56], while patch-clamp studies [38] have shown renin release is characterized by changes in JG cell electrical potential [105]. Activation of these channels inhibits cAMP induced renin secretion [38]. Inhibition of the L-type voltage-gated calcium channels has been repeatedly shown to stimulate renin release [24,26,27]. Thus, either release of stored intracellular calcium, opening of store-operated calcium channels, or the opening of voltage gated calcium channels are all possible pathways which could be triggered by activation of the CaSR on the JG cell, but which of these is actually coupled to the CaSR has yet to be definitively shown.

Vasoconstrictors such as Angiotensin II and Endothelin [3,50,73] stimulate arteriolar contraction via the AT1 receptor or ETB receptor (3), respectively. In JG cells these G-protein coupled receptors stimulate calcium influx or the release of calcium from intracellular stores, increase cytosolic calcium and inhibit renin release (24,79,112). The membrane potential of the JG cell is a critical factor in regulating renin secretion. Vasoconstriction of the afferent arteriole is associated with JG cell depolarization [18,19] and the inhibition of renin secretion, and there is significant electrical coupling between JG

cells and the afferent arteriolar smooth muscle cells (18,72,100). *In vitro*, potassium-induced depolarization of the JG cells also suppresses renin release [10,24,26,56,68]. The JG cells have calcium-activated chloride channels [20,55,72] that, when activated shift the chloride equilibrium potential of the JG cell to a depolarized state, inhibiting of renin release [72]. Patch-clamp studies have shown renin release is coupled to changes in JG cell electrical potential [38,102]. Numerous studies in various preparations of renal cortical tissue have identified possible pathways which might lead to increased intracellular calcium, including activation of store-operated calcium entry channels [107,108], mobilization of calcium from intracellular stores in the endoplasmic reticulum [29,31,33], and activation of voltage-gated L-type calcium channels [24,26,27,38]. JG cell depolarization may induce opening of L-type voltage-gated calcium channels, and these channels have been confirmed in JG cells [39], and a number of studies have shown blocking these channels results in increased renin release [24,26,40]. Scholz and Kurtz (104) reported that afferent vascular smooth muscle cells differed as they approached the JGA. While both populations contained angiotensin AT-1 receptors and calcium-activated chloride channels, in afferent smooth muscle cells distant from the JG cells, intracellular calcium was increased via voltage-gated channels, but in those closer to the JG cells (presumably more similar in phenotype), the increase in cytosolic calcium takes place through mobilization of intracellular stores. Consistent with this, recent studies have suggested the magnitude of depolarization needed to induce voltage-gated channels in JG cells is too great, and have suggested alternatively receptor-mediated activation of store-operated calcium channels may be the predominant pathway for increasing intracellular calcium [45,72,128] under normal physiologic conditions. All of these studies of calcium-mediated regulation of renin require the presence of extracellular calcium, suggesting ultimately the result of any pathway involves calcium entry. It is not clear, however, if the inhibition of renin secretion by vasoconstriction or depolarization is mediated just by increasing intracellular calcium, as additional indirect pathways are probably also involved, especially *in vivo.*

In contrast, vasodilation results in JG cell hyperpolarization and stimulates renin secretion. *In vitro*, potassium-induced JG cell hyperpolarization or chloride channel inhibition stimulates renin release [26,34,39,50,54,80]. *In vitro*, furosemide inhibition of the Na.K/2Cl co-transporter NKCC1 results in JG cell hyperpolarization and stimulates renin release from isolated JG cells [20]. Presumably, this works in the opposite direction as depolarization, reversing calcium-mediated renin inhibition. *In vivo*, this would work in concert with furosemide inhibition of NKCC2, provoking macula densa stimulation of renin secretion via PGE_2 targeting the JG cell adenylyl cyclase. *In vivo*, the integration of the multiple signals associated with the hemodynamic changes (contraction, dilation) obviously extend well beyond a simple calcium-mediated signaling pathway in the JG cell. It is important to consider that the calcium effect in the JG cell appears to modify the activity of the target enzymes (AC 5/6 and PDE1), modifying the renin response to the typical renin-stimulating pathways (renal baroreceptor, macula densa or sympathetic stimulation) rather than directly causing renin secretion or inhibition.

Propagation of a calcium wave

An alternative calcium-mediated pathway involves the initiation and propagation of calcium waves through the juxtaglomerular region. JG cells contain gap junctions linking them to the adjacent endothelial cells, and these intercellular channels have been suggested as possible conduit pathways for propagating a calcium-mediated signal through the endothelium and into JG cells [64,113,128]. Connexins are transmembrane proteins that combine to form hemichannels in the plasma membranes of the gap junction, linking the cytoplasm of two cells. The sizes of these channels are large enough to permit the diffusional movement of calcium. Mechanical distortion of a renal endothelial monolayer was found to generate a

wave of increased intracellular calcium which was mediated by connexin 40 [113], a major connexin involved in the JG cells [121]. Wagner et al [121] found connexin 40 deletion eliminated the calcium-mediated negative feedback response of renin to both angiotensin and renal baroreceptor inhibition of renin by increased renal perfusion. Peti-Peterdi [94] found that changing tubular flow rate lead to propagation of a calcium wave, which increased intracellular calcium in the JG cells. These data suggest Cx40-dependent gap junctions of the JG cells may mediate inhibition of renin by calcium-dependent factors such as angiotensin and renal perfusion, and possibly the macula densa *via* a unique endothelial transmitted pathway [64,121]. The end result would be a separate integrated pathway in the juxtaglomerular apparatus to influence the intracellular calcium in the JG cell, independent of the signaling through the CaSR. Importantly, this pathway would be characterized by a cell-to-cell, intracellular signal derived from the endothelium, perhaps in response to some initiating mechanical transmission. It is also possible that the direction of the transmission is not to the JG cell, but originating from the JG cell, secondary to the CaSR initiating changes in intracellular calcium

Summary, *in vitro* studies

Overall, the mystery of the calcium paradox in the JG cell has at least one tenable explanation, in that changes in calcium concentration of the extracellular environment can be transmitted to similar changes in the intracellular compartment *via* the CaSR. An increase in intracellular calcium, possibly mediated through any number of channels or stores, results in diminished activity of the calcium-inhibitable isoforms of adenylyl cyclase, AC-5 (and AC-6), as schematically summarized in figure 1. This results in decreased synthesis of the positive second messenger cAMP, and consequently diminished renin release. This response is supplemented by calcium activation of PDE1C to enhance cAMP degradation in concert with diminished synthesis. Changes in intracellular calcium can also be initiated by any number of receptor-mediated factors (such as angiotensin) that also stimulate increased intracellular calcium concentrations, or through calcium waves initiated by hemodynamic or tubular signals, propagated *via* the connexins in the gap junctions. The changes in intracellular calcium alter the activity of these regulatory enzymes, influencing both basal renin release as well as the classical renin stimuli that target activation of adenylyl cyclases. But in the whole kidney, what are the conditions that mimic the changes in extracellular calcium suggested by these many *in vitro* studies? The following section will address the extrapolation of this cellular regulatory pathway into the whole animal, and provide some perspective on how it may be important in clinical and pathological conditions.

Calcium and renin secretion *In Vivo*

Similar to its well-studied *in vitro* effects, calcium also has many effects on renin *in vivo*. Both acute and chronic changes in plasma calcium can affect renin. Chronic elevations in plasma calcium due to hyperparathyroidism or hypercalcemia of malignancy are encountered more often clinically, but acute changes in plasma calcium are also seen in rhabdomyolysis-related acute renal failure. We will review and describe the effects of acute and chronic experimental elevations of plasma calcium on renin and their assorted clinical correlates.

The acute *in vivo* effects of calcium on renin

The acute effects of calcium on renin *in vivo* are generally similar to those seen *in vitro*: calcium inhibits renin secretion. A strong body of literature demonstrates that acutely increasing plasma calcium inhibits plasma renin activity or renin secretion in rats, dogs and humans [1,7,8,51,61,62 121,124,125,126,130]. The literature is not completely unanimous, as some studies have shown equivocal or negligible effects of acute calcium changes on

renin secretion [29,52,75]. The reasons for these discrepancies are not entirely clear, but it may pertain to the basal renin levels from these experiments. The acute *in vivo* inhibitory effects of calcium on renin are much stronger in studies that have renin secretion stimulated by sodium restriction or other means [7,58,92,125,126]. One could argue this illustrates that calcium acts as a brake on the traditional stimulatory pathways of renin secretion, rather than a major inhibitory pathway in its own right. Irrespectively, the amount of evidence demonstrating an inhibitory effect of acutely increased plasma calcium on renin greatly outnumbers those suggesting otherwise.

After initial studies demonstrated that acutely elevated plasma calcium inhibited renin secretion, research into a mechanistic explanation for this response failed to progress. However, this changed with the discovery and cloning of the calcium-sensing receptor (CaSR) [16]. The CaSR is a 7-transmembrane domain, G-protein-coupled receptor that transmits changes in plasma calcium into intracellular signaling [17]. While originally discovered in the parathyroid gland [16], the CaSR was also strongly detected in the kidney [96]. Based on this, Ortiz et al. [84] discovered that the CaSR was functionally expressed in primary cultures of mouse, renin-secreting JG cells. The expression of the CaSR in mouse JG cell primary cultures suggested that it could be the receptor responsible for the acute inhibitory effects of elevated plasma calcium on renin secretion.

Because of this, two separate groups tested whether the CaSR could inhibit renin *in vivo*. The group of Maillard et al. [78], tested whether stimulating the CaSR with pharmacological agonists could inhibit plasma renin activity (PRA) *in vivo*. They found that the acute administration of the calcimimetic (allosteric CaSR agonist) R-568 decreased isoproterenol-, enlapril- or furosemide-stimulated PRA in conscious rats. Similarly, Atchison et al. [8] tested whether the CaSR was expressed in JG cells *in vivo* and whether pharmacologically stimulating the CaSR could decrease PRA. In slices of renal cortex fixed *in vivo*, they demonstrated positive immunofluorescent staining of the CaSR in the renin-containing afferent arteriole. Pharmacologically stimulating the CaSR with intravenous calcimimetics acutely decreased both basal and furosemide-stimulated PRA in anesthetized rats. When combined with the *in vitro* data presented in the first part of this review, these data suggest that activation of the JG cell-expressed CaSR inhibits renin secretion *in vivo*.

The results from the preceding data led to the obvious question: is there a calcium paradox *in vivo*? If the CaSR is functionally expressed *in vivo*, can it regulate the inhibitory effects of acutely elevated plasma calcium on renin secretion? It has now been shown that pharmacologically inhibiting the CaSR *in vivo* completely eliminated the hypercalcemia-mediated inhibition of PRA, confirming that the CaSR regulates the inhibition of renin by high plasma calcium [7]. Additionally, PTH appears to permissively regulate the inhibition of PRA by hypercalcemia. Hypercalcemia results in acutely increased renal interstitial (extracellular) calcium, driven by PTH *via* the TRPV5 calcium transporter in the distal tubule, activating the CaSR, resulting in acute inhibition of PRA [7]. A schematic for the proposed pathway from PTH-mediated calcium reabsorption to renin secretion acute hypercalcemia on PRA is summarized in figure 1.

Further research questions on the inhibitory effects of renal cortical interstitial calcium on renin remain. Based on previous results, the TRPV5 knockout mouse should have an impaired inhibitory response of calcium on renin [48]. However, another possibility could be claudin-16, which is a tight-junction protein in the thick ascending limb of the loop of Henle, where it regulates the paracellular reabsorption of cations [49]. Genetic deletion of claudin-16 leads to hypomagnesaemia and hypercalciuria, suggesting that claudin-16 could also regulate interstitial calcium levels [13].

Finally, the acute inhibitory effect of elevated plasma calcium on renin secretion may have clinical implications as well. While pathologies with chronically elevated plasma calcium arise more often, acute changes in plasma Ca can occur in acute renal failure associated with rhabdomyolysis [4]. Concomitant and inverse changes in PRA occur with these changes in plasma Ca [114], but whether the changes in plasma Ca actually influence PRA is unknown.

Chronic effects of calcium on renin *in vivo*

Chronic changes in plasma calcium also affect renin. Plasma calcium is chronically manipulated *via* dietary means or by hormonal changes seen in various neoplastic syndromes. Chronically elevated plasma calcium tends to stimulate renin secretion. However, the effects of plasma calcium on renin in hypercalcemia models may be due to the specific way in which changes (or the extent of change) in plasma calcium are induced.

Increased Dietary calcium consumption

Chronically increasing dietary consumption of calcium does not affect PRA under normal conditions [60], but dietary $CaCl_2$ decreases PRA stimulated by NaCl restriction [62]. However, this is likely due to chloride replenishment, as chronic calcium gluconate consumption has no effect on PRA stimulated by NaCl restriction [60]. This is consistent with the inhibitory effect of chloride at the macula densa [77]. Thus, outside of chloride-specific effects, changes in dietary calcium do not affect renin. It should be noted that plasma calcium did not change with the increase in dietary consumption. Thus, increased dietary calcium may not affect PRA because plasma calcium levels are very tightly controlled, and do not change much with increased dietary calcium intake.

Vitamin D-induced hypercalcemia

To test the effects of chronically elevated plasma calcium on PRA, some groups have employed models of vitamin D-induced toxicity and hypercalcemia. Spangler et al. [111] found that vitamin D-induced hypercalcemia significantly increased PRA as well as JG cell hypertrophy and hyperplasia. Peterson [93] found that Vitamin D-induced hypercalcemia caused polyuria with no changes in PRA, except when Vitamin D-treated rats were pair-watered with controls. Under these conditions, PRA increased slightly. Levi et al. [75] found that Vitamin D-induced hypercalcemia and polyuria had no effect on PRA. Thus, while the effects of Vitamin D-induced hypercalcemia on renin are somewhat ambiguous, the current data suggest that chronic, vitamin D-induced hypercalcemia may mildly stimulate PRA as a protective mechanism against hypercalcemia-induced polyuria and dehydration [93].

The likely reason these three studies found differing effects on PRA was that different levels of hypercalcemia were induced in each. Spangler induced a 60% increase in plasma calcium with their Vitamin D treatment, and this correlated with a 3-fold increase in PRA [111]. Peterson affected a 38% increase in plasma calcium, which caused a 51% increase in PRA in pair-watered rats [93]. Levi increased plasma calcium by 28%, and this had no effect on PRA [75]. Thus, Vitamin D-induced hypercalcemia may dose-dependently stimulate PRA.

Leydig cell tumor-induced hypercalcemia

Sowers et al.[83] tested the effects of Leydig cell tumor transplantation on PRA and plasma calcium in the Fischer rat. Leydig cell tumor transplantation significantly increased both PRA and plasma calcium. Whether the increase in plasma calcium contributed to the increase in PRA is unknown. However, tumorous Leydig cells express renin [89]. Whether the renin expressed in Leydig cells is contributing to the elevation in PRA is unknown.

Chronic CaSR stimulation

As previously mentioned, the CaSR mediates the inhibitory effects of acute hypercalcemia on renin. However, whether chronic CaSR stimulation affects renin is less clear. It has been shown that the oral administration of calcimimetics (CaSR agonists) did not affect either basal or stimulated PRA in rats [8]. This is in contrast to patients with type-V Bartter Syndrome, a heterogeneous disorder, defined by impaired NaCl reabsorption, hypokalemic metabolic acidosis and hyperreninemia [59]. Type-V Bartter syndrome is due to an extremely potent activating mutation of the CaSR [118,124]. Patients with type-V Bartter syndrome also have elevated PRA [90,91,96]. The elevated PRA in these patients is likely due to the severity of the activating mutation, as the CaSR is near maximally stimulated at physiological (1.0 mM) concentrations of ionized calcium in these patients [118,124]. Thus, similar to the dose-dependent effects of Vitamin D-induced hypercalcemia on renin, the ability of chronic CaSR stimulation to increase PRA is likely due to the strength of stimulation (or the severity of the activating mutation) of the CaSR. Since a large percentage of these patients develop renal dysfunction, further studies clarifying the role of renin in these patients are necessary [118,124].

Interestingly, the potential side effects of aminoglycoside antibiotic therapy include the development of transient hypoparathyroidism, hypocalcaemia and hypercalciuria, similar to a type V Bartter Syndrome phenotype [23]. These symptoms are presumably due to an aminoglycoside-induced stimulation of the CaSR [123]. Chou et al.[24] highlighted in a literature review that the “type-V Bartter-like” syndrome led to elevated PRA in some, but not all patients treated with aminoglycosides. Whether other CaSR agonists can stimulate renin chronically remains to be determined.

Primary hyperparathyroidism

The effects of primary hyperparathyroidism on renin are controversial. Some studies suggest that patients with primary hyperparathyroidism have elevated PRA [14,15,42,63,81,97] while other studies find no relationship [10,12,115]. The reason for this discrepancy is not clear. One possibility, similar to the effects of Vitamin D-induced hypercalcemia and CaSR activating mutations, is that the effects of hyperparathyroidism on renin could be dose dependant. Whether these proposed increases in PRA contribute to the elevated renal and cardiovascular morbidity rates in these patients is unknown [129]. Similarly, the effects of chronic parathyroid hormone-related protein (PTHrP) administration on renin are unknown. PTHrP is one of the causative factors of hypercalcemia of malignancy and acts on the same receptor as PTH to exert its hypercalcemic effects [2]. While it is known to acutely stimulate renin is isolated-perfused kidneys [103], it is not known if it stimulates renin secretion chronically *in vivo*. Further research is needed to determine if experimentally-induced hyperparathyroidism or related hypercalcemic, neoplastic syndromes stimulate PRA.

Conclusions

Calcium has a dichotomous relationship with renin *in vivo*. Acutely elevated plasma calcium inhibits renin *via* increasing the (extracellular) renal cortical interstitial calcium, consistent with the pathways described in the extensive *in vitro* literature. However, chronically elevated calcium appears to (indirectly) stimulate renin secretion. While we now have a better understanding of acute inhibitory mechanisms of calcium on renin, the explanation or resolution of the renin-stimulating pathway of chronically elevated plasma calcium remain to be determined. These are likely influenced by a plethora of chronic changes associated with elevated calcium that may influence renin indirectly. Future research should also

determine whether elevations in renin activity cause or contribute to cardiorenal disease in these patients.

Overall, calcium acts as an inhibitory second messenger by directly influencing the activity of the enzymes that control the synthesis and degradation of the primary second messenger cAMP within the JG cell. Thus, it acts as a regulator “upstream” from cAMP. Importantly, while calcium can directly influence the basal release of renin, it also modifies the activity and therefore the magnitude of the response of adenylyl cyclase which is the target for the classical stimulatory pathways for renin, such as β-adrenergic innervation, the macula densa pathway and the renal baroreceptor (10).

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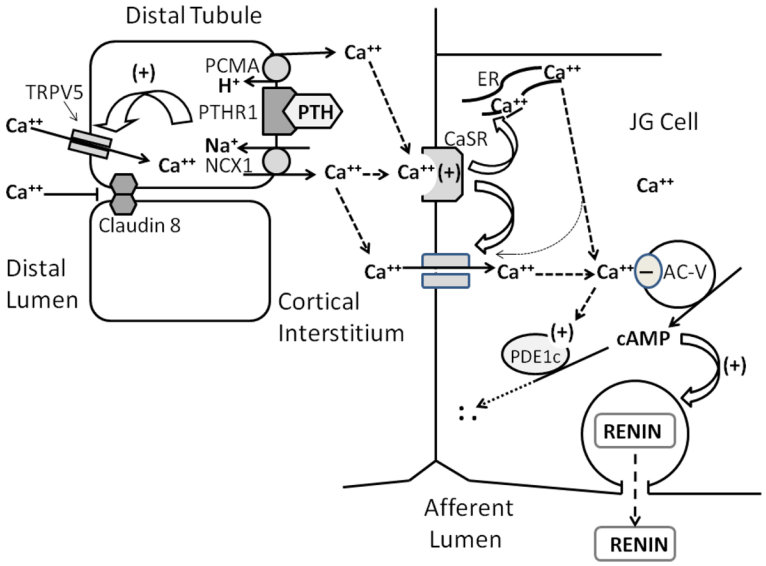

Figure 1.

Schematic summary of the calcium-regulated pathway from PTH-mediated calcium reabsorption in the distal tubule to cAMP-regulated renin secretion into the afferent arteriolar lumen. *Abbreviations and acronyms*: AC-V = adenylyl cyclase isoform 5, Ca^{++} = (ionized free) calcium, cAMP = cyclic adenine monophosphate, CaSR = calcium-sensing receptor, ER = endoplasmic reticulum, H^+ = hydrogen ion, JG = juxtaglomerular, NCX1= sodium/calcium exchanger- member 1, PMCA= plasma membrane Ca^{++} ATPase, PTH = Parathyroid hormone, PTH-R1 = parathyroid hormone type 1 receptor, PDE1c = phosphodiesterase isoform 1c, TRPV5= Transient receptor potential cation channel subfamily V member 5, **(+)** = stimulatory, and **(−)** = inhibitory action.