

The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the renin-angiotensin system

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Ferder M, Inserra F, Manucha W, Ferder L. The world pandemic of vitamin D deficiency could possibly be explained by cellular inflammatory response activity induced by the renin-angiotensin system. *Am J Physiol Cell Physiol* 304: C1027–C1039, 2013. First published January 30, 2013; doi:10.1152/ajpcell.00403.2011.— This review attempts to show that there may be a relationship between inflammatory processes induced by chronic overstimulation of the renin-angiotensin system (RAS) and the worldwide deficiency of vitamin D (VitD) and that both disorders are probably associated with environmental factors. Low VitD levels represent a risk factor for several apparently different diseases, such as infectious, autoimmune, neurodegenerative, and cardiovascular diseases, as well as diabetes, osteoporosis, and cancer. Moreover, VitD insufficiency seems to predispose to hypertension, metabolic syndrome, left ventricular hypertrophy, heart failure, and chronic vascular inflammation. On the other hand, inappropriate stimulation of the RAS has also been associated with the pathogenesis of hypertension, heart attack, stroke, and hypertrophy of the left ventricle and vascular smooth muscle cells. Because VitD receptors (VDRs) and RAS receptors are almost distributed in the same tissues, a possible link between VitD and the RAS is even more plausible. Furthermore, from an evolutionary point of view, both systems were developed simultaneously, actively participating in the regulation of inflammatory and immunological mechanisms. Changes in RAS activity and activation of the VDR seem to be inversely related; thus any changes in one of these systems would have a completely opposite effect on the other, making it possible to speculate that the two systems could have a feedback relationship. In fact, the pandemic of VitD deficiency could be the other face of increased RAS activity, which probably causes lower activity or lower levels of VitD. Finally, from a therapeutic point of view, the combination of RAS blockade and VDR stimulation appears to be more effective than either RAS blockade or VDR stimulation individually.

oxidative stress; mitochondria; cardiovascular disease; angiotensin receptor blocker; vitamin D receptor

VITAMIN D (VitD) deficiency is pandemic. Our hypothesis maintains that this deficiency is probably due to environmental factors, such as diet, sun exposure, sedentary life style, and stress.¹ Recent studies suggest that, in addition to its importance in bone metabolism, VitD plays a central role in such basic cell functions as multiplication, differentiation, and metabolism. This may explain why low VitD levels represent a risk factor for several apparently different diseases, such as infective, autoimmune, neurodegenerative, and cardiovascular diseases, as well as diabetes, osteoporosis, and cancer. Accumulating evidence suggests that an adequate intake of VitD may significantly decrease the prevalence and improve the

clinical outcomes of these diseases (42, 60, 92, 146). Moreover, VitD insufficiency seems to predispose to hypertension, diabetes, metabolic syndrome, left ventricular hypertrophy, heart failure, and chronic vascular inflammation (57, 99, 107, 181).

The relationship between baseline VitD status, dose of VitD supplements, and cardiovascular events remains to be investigated by ongoing randomized trials; however, increasing evidence suggests that the provision of a simple, well-tolerated, and inexpensive correction of VitD insufficiency favorably affects the morbidity and mortality of cardiovascular disease and prevents the most common chronic degenerative diseases (104).

Evolution

The photosynthesis of VitD evolved over 750 million years ago; the phytoplankton coccolithophor *Emeliani huxleii* is an early example (55). Nevertheless, the exact role of VitD in

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early plants and animal forms is unknown. From an evolutionary standpoint, a fascinating example is an ancient vertebrate lacking a calcified skeleton and teeth, the lamprey (*Petromyzon marinus*), in which a type of VitD receptor (VDR) has been described (131). In this jawless fish, several noncalcemic roles for VitD, including its action as a sensor for endogenous or exogenous toxins and as an inducer of cytochrome *P*-450 (CYP) enzymes, have been proposed. More interestingly, VitD plays a role in the regulation of the lamprey's primitive immune function (172). Lamprey studies provide valuable insight into the evolution of the adaptive immune system, as these ancient vertebrates possess a convergently evolved adaptive immunity with cells that function like the T cells and B cells in higher vertebrates (141). This could have implications for the anti-inflammatory effect of VitD, which is described later in this review.

Because VitD can be synthesized via a photochemical process only, early vertebrates that ventured onto land had to ingest foods that contained VitD or had to be exposed to sunlight to photosynthesize VitD in their skin to satisfy their bodies' VitD requirements (54).

Also, the renin-angiotensin system (RAS) is found in animals as primitive as the jellyfish, the lamprey, and the crab,

among others. However, none of these animals has a closed circulatory system (109). What function does the RAS serve in these animals if they do not have the necessity of retaining sodium and there is no pressure to maintain? Why would the members of these species have a RAS? The RAS is also a system of self-defense. ANG II regulates the synthesis of proinflammatory substances, and inflammation is the most basic mechanism found in any living organism, allowing them to defend themselves against any aggressor (136, 139).

Finally, it could be proposed that VitD and RAS evolved in nature in a similar and parallel way (Fig. 1).

Sources and Synthesis of VitD

Two main sources of VitD are available to humans: sunlight (exposure to solar UV-B radiation) and food (including dietary supplements). VitD exists in two forms: VitD₂ (ergocalciferol) and VitD₃ (cholecalciferol). VitD₂, found in plants, is the product of UV-B (290–315 nm) irradiation of ergosterol and can be consumed as a supplement or in fortified foods (57). VitD₃, a product of UV-B irradiation of 7-dehydrocholesterol, is synthesized in the human epidermis or is found in oily fish, fortified foods, and supplements.

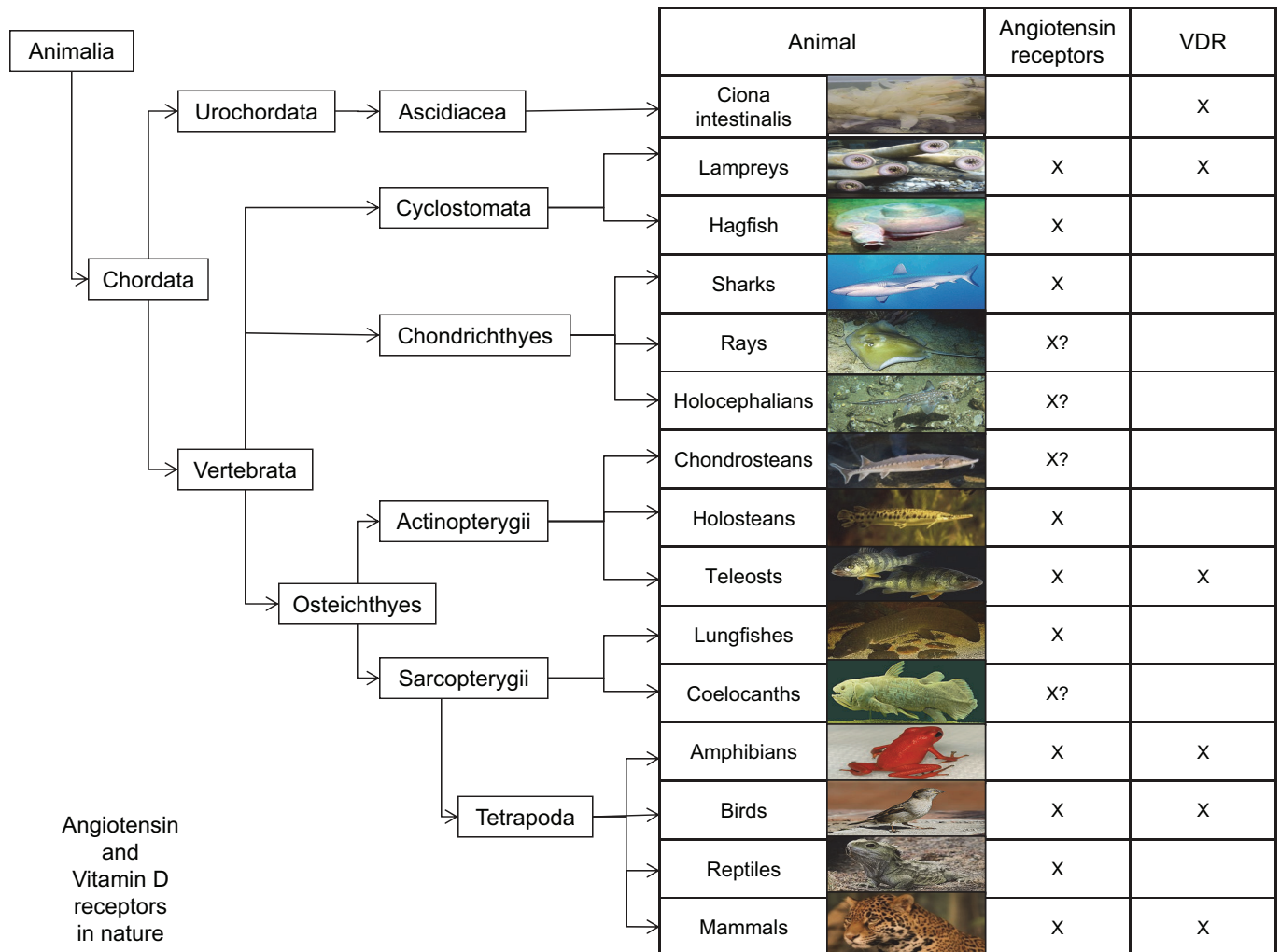


Fig. 1. Occurrence of angiotensin receptors and vitamin D (VitD) receptors (VDRs) in nature.

VitD is converted in the liver to 25-hydroxyvitamin D [25(OH)D], which is the major circulating metabolite of VitD. Serum 25(OH)D concentrations, which reflect VitD intake and endogenous production, should be measured to clinically assess VitD status (57). In the kidney, 25(OH)D is converted by 1 α -hydroxylase to its active form, 1,25-dihydroxyvitamin D [1,25(OH)₂D]. VitD in the form of 1,25(OH)₂D is a hormone, because it is produced primarily in one organ (the kidney) and then circulates throughout the body, where it exerts wide-ranging effects. Extrarenal synthesis of 1,25(OH)₂D occurs through cytokine stimulation (175) and is locally important in the paracrine regulation of cell growth, differentiation, and function (101). This may explain why VitD deficiency has been associated with type 1 diabetes, cancer, and multiple sclerosis (92).

It is now recognized that most cells in the body have a VDR, and they also have the ability to produce 1,25-dihydroxyvitamin D₃ [1,25(OH)₂D₃], which in turn is capable of regulating a wide variety of genes that have important functions in regulating cell growth, modulating immune function, and promoting cardiovascular health (59).

VitD Deficiency

VitD deficiency and VitD insufficiency are prevalent in most of the world's population (41, 57, 114). Although a consensus regarding the optimal level of serum 25(OH)D has not been established, most experts define VitD deficiency as a 25(OH)D level of <20 ng/ml (50 nmol/l) and VitD insufficiency as 21–29 ng/ml. For all studied end points to date, the optimal concentration of 25(OH)D is \geq 30 ng/ml (14). A rapidly evolving knowledge base indicates that VitD deficiency is much more prevalent than has previously been recognized and is present in up to 50% of young adults (154) and apparently healthy children (57). The Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative cross-sectional survey of the noninstitutionalized population in the United States carried out from 1988 to 1994, reported the prevalence of VitD deficiency in the United States to be 25–57% of adults (95).

Racial differences in the adequacy of VitD stores have been shown (48). VitD deficiency is seen frequently in African Americans, who also present a high prevalence of hypertension (112). In addition, VitD deficiency throughout life from its earliest phases may adversely affect the microvasculature in African Americans, thereby playing a major role in the genesis and maintenance of hypertension (135). This is probably due to skin pigmentation with melanin, which is a limiting factor in the cutaneous synthesis of VitD. Melanin acts as an effective natural sunscreen; therefore, increased skin pigment can reduce the solar UV-B-mediated cutaneous synthesis of VitD₃ by as much as 99% (18).

Epidemiological studies have also recently linked VitD deficiency with an increased risk of major adverse cardiovascular events (169). Accordingly, data from NHANES III show an elevated risk of cardiovascular death (coronary heart disease, heart failure, and stroke) in adults with 25(OH)D serum levels in the lowest quartile (mean = 13.9 ng/ml) compared with those in the three higher quartiles (mean = 21.6, 28.4, and 41.6 ng/ml) (36).

Relationship Between VitD and the RAS

Three decades ago, an original early work suggested a possible link between VitD and the RAS (68).

The RAS is a regulatory cascade that plays a critical role in the regulation of blood pressure and electrolyte and plasma volume homeostasis. Inappropriate stimulation of the RAS has been associated with hypertension, heart attack, stroke, and hypertrophy of the left ventricle and vascular smooth muscle cells (181).

It is well established that renin secretion is regulated by renal perfusion pressure, renal sympathetic nerve activity, and tubular sodium load (8, 49). It is also stimulated by factors such as prostaglandins, nitric oxide (NO), and adrenomedullin and inhibited by other factors, including ANG II (feedback), endothelin, vasopressin, and adenosine (8, 49). These stimulations of renin secretion are often mediated by an increase in intracellular cAMP and are accompanied by increases in renin gene transcription (134). Recent studies have significantly enhanced our knowledge of the regulation of gene expression encoding for renin production on a cellular basis (7, 116, 121). It is interesting to note that, to regulate gene expression, 1,25(OH)₂D₃ can act as a negative regulator of specific DNA sequences [VitD response element (VDRE)] in the promoter of target genes [inhibition of other transcriptional complexes by the VDR-retinoid X receptor (RXR) heterodimers or the VDR homodimers, interaction of the VDR-RXR heterodimers with corepressors, and binding of the VDR to a negative VDRE]. Therefore, 1,25(OH)₂D₃ can suppress renin gene expression through a *cis*-DNA element(s) in the renin gene promoter. The finding that 1,25(OH)₂D₃ suppresses the expression of renin's gene is of utmost interest, although the exact molecular mechanism has not been elucidated (88). However, one important mechanism underlying this action is transrepression of renin gene transcription by 1,25(OH)₂D₃ by targeting the cAMP-PKA pathway (174) (Fig. 2).

Several mechanisms have been proposed to explain the relationship between VitD and blood pressure (124). Some of these relationships show that VitD downregulates renin gene expression and inhibits renin synthesis, thereby suppressing the RAS (87, 88, 143, 174).

In VitD-deficient animals, there is an increased incidence of hypertension, left ventricular hypertrophy, and atherosclerosis (143). In normal mice, VitD deficiency stimulates renin expression, whereas injection of 1,25(OH)₂D₃ reduces renin synthesis. In cell cultures, 1,25(OH)₂D directly suppresses renin gene transcription by a VDR-dependent mechanism. Mice lacking the VDR gene develop hyperreninemia, resulting in elevated production of ANG II, leading to hypertension, cardiac hypertrophy, and increased water intake (75, 88, 173).

The increased levels of renin can also act through the prorenin/renin receptor (108) and may, independently of ANG II, cause renal and/or cardiovascular damage (166).

Recent studies show that diabetic VDR-null mice developed more severe nephropathy than did wild-type mice, suggesting that VitD protects against hyperglycemia-induced renal injury by regulating the RAS. It has been further suggested that 1,25(OH)₂D₃ suppresses hyperglycemia-induced AGT expression in the kidney by blocking NF- κ B activation of AGT gene transcription. A functional NF- κ B binding site in the AGT gene promoter was bound by the p65/p50 heterodimer in the

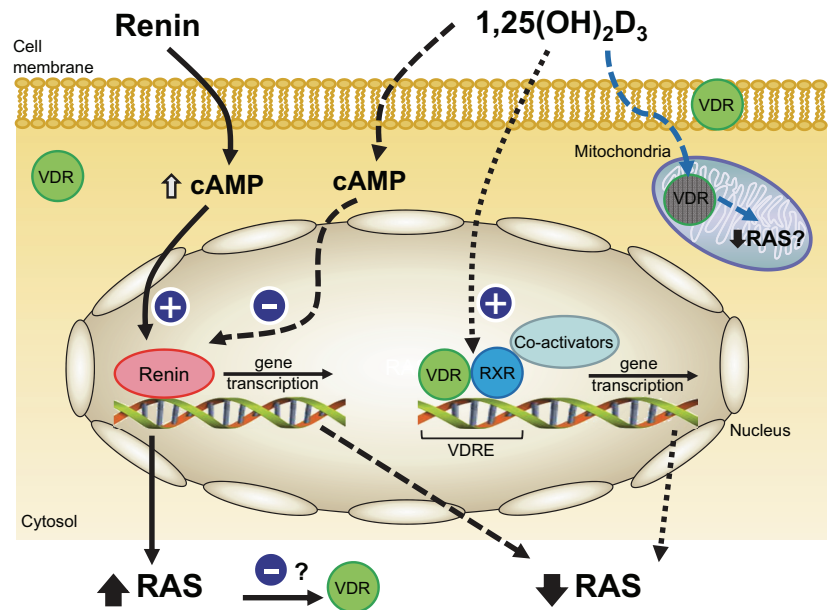


Fig. 2. Cellular interactions of angiotensin and VitD receptors. RXR, retinoid X receptor; RAS, renin-angiotensin system; VDRE, VitD response element; 1,25(OH)₂D₃, 1,25-dihydroxyvitamin D₃.

presence of high glucose, in association with the induction of the promoter activity (177).

VitD's suppression of renin expression is independent of calcium metabolism, the volume- and salt-sensing mechanisms, and ANG II feedback regulation (88, 89).

Using a transgenic mouse model with mice overexpressing the human VDR in renin-producing cells, Kong et al. (76) demonstrated that suppression of renin expression by 1,25(OH)₂D in vivo is independent of parathyroid hormone and calcium.

Clinical studies conducted over the last two decades have shown an inverse association between plasma 1,25(OH)₂D₃ concentration and blood pressure and/or plasma renin activity in normotensive men and patients with essential hypertension (17, 78, 90, 132). In accordance with the aforementioned data, other studies have shown a reduction in blood pressure in patients with primary hypertension who were receiving VitD₃ supplements (123), as well as a reduction in blood pressure, plasma renin, and ANG II concentration in patients with secondary hyperparathyroidism (73, 118).

In a study of subjects exposed to UV-B radiation in a tanning bed three times per week for 3 mo, Krause et al. (77) reported a 180% increase in 25(OH)D levels and a 6-mmHg reduction in systolic and diastolic blood pressure. A small, randomized, placebo-controlled study of patients with type 2 diabetes and low baseline 25(OH)D levels showed that a single dose of 100,000 IU of VitD₂ reduced systolic blood pressure by a mean of 14 mmHg and significantly improved endothelial function as measured by forearm blood flow (146). In the NHANES III study, the mean systolic blood pressure was ~3 mmHg lower in individuals in the highest quintile of serum 25(OH)D levels than those in the lowest quintile (137).

Receptors

VDRs. Even though bone, small intestine, and kidneys are the primary organs responsive to VitD, the effects of VitD in the body are more far-reaching. Increasing experimental data have revealed a broad range of biological actions for the VDR, including induction of cell differentiation (19, 61), inhibition of

cell growth (82), immunomodulation (93, 110), and control of other hormonal systems (87, 128). The VDR has been identified in many tissues and organs, including those not typically associated with calcium homeostasis and bone metabolism (58). It is present in a large variety of cell types, including myocytes, cardiomyocytes, pancreatic beta cells, vascular endothelial cells, neurons, immune cells, osteoblasts, and chondrocytes (57, 181) (Table 1).

The VDR is a steroid hormone nuclear receptor that binds to 1,25(OH)₂D with high affinity and mediates transcriptional gene regulation (56). 1,25(OH)₂D regulates >200 genes, including those involved in renin production in the kidney, insulin production in the pancreas, release of cytokines from lymphocytes, production of cathelicidin in macrophages, and growth and proliferation of vascular smooth muscle cells and cardiomyocytes (57).

The extranuclear receptor localization is still controversial. Several reports indicate a subcellular distribution in the cytoplasm, in discrete regions of the nucleus, and along the nuclear envelope (10), whereas the membrane-initiated effects are attributed to a plasma membrane-associated receptor (106); in fact, the VDR has been found in caveolae-enriched plasma membrane (62). Moreover, microscopy studies have revealed that the VDR has mitochondrial, membrane-based, cytosolic, and perinuclear localizations (43). Silvagno et al. (142) found that human platelets express the VDR, which is mainly located in the mitochondrial compartment. The anucleated platelets are a good model in which to study the extranuclear VDR localization involved in the nongenomic response to VitD. In agreement with the intracellular distribution suggested by Western blot analysis, an anti-VDR antibody revealed the presence of the VDR in the mitochondrial structures and in the cytosol, without significant labeling of other platelet structures. In their work, they report not only the presence of the VDR in human platelets but also, most interestingly, its mitochondrial localization.

In a recent study, Gonzalez-Pardo et al. (43) also described a mitochondrial VDR. Indeed, fractionation studies demon-

Table 1. *Systems where VitD and RAS receptors are localized*

System	VitD	RAS
Endocrine	Thyroid	Thyroid
	Parathyroid	Adrenal
	Pancreatic beta cells	Pancreatic beta cells Posterior pituitary
Cardiovascular	Vascular smooth muscle cells	Vascular smooth muscle cells
	Myocardium	Myocardium and myocardial mitochondria
		Endothelium Connective tissue
Musculoskeletal	Striated muscle	Striated muscle
	Osteoblasts	
	Chondrocytes	
Gastrointestinal	Intestine	Intestine
	Stomach	Stomach
	Esophagus	
		Salivary glands
Hepatic	Pancreas	Pancreas
	Colon	Colon
	Liver	Liver
Urinary	Kidney (tubules, juxtaglomerular apparatus, podocytes)	Kidney (tubule, juxtaglomerular apparatus, podocytes, mesangial cells)
		Bladder
Reproductive	Testis	Testis
	Ovary	Ovary
	Uterus	Uterus
	Spermatozoa	Spermatozoa
	Prostate	Prostate
Immune	Leukocytes	Leukocytes
	Bone marrow	Bone marrow
	Platelets	Platelets Spleen
Respiratory	Thymus	
	Lung	Lung
Integumentary	Epidermis	Epidermis
	Dermis	Dermis
Nervous system	Brain	Brain
	Sensory neurons	Sensory neurons
Other	White and brown adipose tissue	White and brown adipose tissue
	Placenta	Placenta
	Mitochondria	Mitochondria

VitD, vitamin D; RAS, renin-angiotensin system. Data are from Refs. 5, 16, 30, 31, 44, 119, 140, 147, and 167.

strated the presence of the receptor in the mitochondrial compartment, and the observation was confirmed by immunoelectron microscopy analysis of platelets. In agreement and moreover, a recent study from our laboratory showed that low mitochondrial VDR expression was associated with increased ANG II type 1 (AT₁) receptor expression in the course of RAS upregulation in an animal experimental model, whereas VDR induction by paricalcitol [19-nor-1,25(OH)₂D₂, a VDR activator (VDRA)] treatment conditioned a minor AT₁ receptor expression linked to VDR upregulation. These results suggest a cytoprotective effect of paricalcitol, revealing for the first time a possible AT₁ receptor-dependent protective effect that occurs at the mitochondrial level (39).

Again, the presence of the VDR in several tissues (Table 1) supports the assumption that the VitD endocrine system is in-

involved in various physiological functions beyond calcium-phosphate balance. This notion is additionally confirmed by the presence of CYP27A and CYP27B, the enzymes that catalyze conversion of 25(OH)D to 1,25(OH)₂D₃ in these tissues (60, 144).

VitD signaling is dependent on the availability and turnover of the active VDR ligand 1,25(OH)₂D₃ and on the efficiency of VDR transactivation. Transactivation of the VDR depends on the correct molecular structure, effective nuclear translocation, and presence of the unliganded heterodimer partner RXR and other nuclear cofactors (32). In most cases in which 1,25(OH)₂D₃ acts as a positive regulator, the liganded VDR heterodimerizes with the RXR and binds to specific DNA sequences (VDRE) in the promoter of target genes to regulate gene expression. On the other hand, 1,25(OH)₂D₃ can also act as a negative regulator, but the mechanism of the negative regulation is more complicated and only partially understood (88).

Finally, the mitochondrial localization of the VDR, which has been recently confirmed (142), suggests a mitochondrial nongenomic activity. Therefore, we suggest that this effect could be associated with the RAS, since kidney mitochondrial injury is attenuated by AT₁ receptor blockade in experimental models (25).

RAS receptors. Components of the RAS [renin, angiotensin-converting enzyme (ACE), angiotensinogen, ANG I, and ANG II] receptors have been found in many areas, including kidney and adrenal tissues, blood vessels, and discrete regions of the brain (22) (Table 1). Distribution of AT₁ and ANG II type 2 (AT₂) receptors has been mapped by in vitro autoradiography throughout most tissues of many mammals, including humans. The AT₁ receptor occurs in sites known to be targets for the physiological actions of angiotensin, such as the adrenal cortex and medulla, renal glomeruli and proximal tubules, vascular and cardiac muscle, and brain circumventricular organs (Table 1). In addition, many new sites of action have been demonstrated. In the kidney, the AT₁ receptor occurs in high density in renal medullary interstitial cells. In the heart, the highest densities of the AT₁ receptor occur in association with the conduction system and vagal ganglia. In the central nervous system, high AT₁ receptor densities occur in many regions behind the blood-brain barrier, supporting a role for neurally derived angiotensin as a neuromodulator (2). The AT₁ receptor is also found in hepatocytes and bile duct epithelial cells (64, 84, 115, 170). The AT₂ receptor also has a characteristic pattern of distribution in several tissues, including the adrenal gland, heart, and brain. The role of this receptor in physiology is still being elucidated, but it appears to involve inhibition of proliferation and participation in development (2).

ANG II also stimulates mitochondrial oxidant release, leading to energy metabolism depression. By lowering mitochondrial oxidant production, ANG II inhibition enhances energy production and protects mitochondrial structure. This seems to be one of the mechanisms underlying the benefits of ANG II inhibition in hypertension, diabetes, and aging rodent models (28).

Hence, some cellular mechanisms responsible for the protective actions of RAS inhibitors were previously discussed in recent reviews by us (26–28). Moreover, and as mentioned above, we found high levels of mitochondrial AT₁ receptor mRNA expression in renal cortexes from rats (39). Some mitochondria were increased in size and contained dilated crests and larger-than-normal spaces in their interiors. These changes were not present with paricalcitol treatment.

The existence of intramitochondrial AT₁ and AT₂ receptors and a functional RAS has been subsequently corroborated by Abadir et al. (1). How these receptors are transported to the mitochondria is still controversial. Interestingly, disruption of the AT₁ receptor was associated with an increased number of mitochondria and upregulation of the prosurvival genes nicotinamide phosphoribosyltransferase (*Nampt*) and sirtuin 3 (*Sirt3*) in the kidney, leading to a marked prolongation of the lifespan of mice (12).

Finally, the RAS appears to be much more complicated than it was thought to be a few years ago. Thus, ANG II-(1-7) exhibits direct and indirect effects, the latter resulting from the ANG II-(1-7)-dependent formation of NO and vasodilatory prostaglandins. ANG II-(1-7) potentiates the hypotensive effect of bradykinin and also plays a major role in control of hydroelectrolytic balance. It possesses its own receptors, AT₁, AT₂, AT₃, AT₄, AT₅, AT₆, and AT₇, which are recognizable by [Sar¹-Thr⁸]ANG II or sarthran (24). Also, ANG II and its derivatives, ANG III, ANG IV, and ANG-(1-7), alter vascular contractility with different mechanisms of action (158). New evidence has accumulated showing the existence of several novel receptor-interacting proteins and various ANG II receptor activation mechanisms, such as dimerization and mechanical stretch-induced activation, which differ from classical ANG II receptor signaling. These findings may provide new potent therapeutic targets for the treatment of cardiovascular disease (102).

Finally, it should be noted that the VDR and AT₁ receptor are distributed in almost the same tissues (Table 1).

Mechanisms in Which VitD and RAS Interact

RAS activity and VitD levels could be related in several ways. In this review we focus on inflammatory response, oxidative stress, and atherosclerosis.

Inflammatory Response

Association of VitD deficiency with markers of inflammation (such as tumor necrosis factor- α) (122) is evidenced by elevated levels of C-reactive protein and IL-10 (181). Furthermore, administration of 1,25(OH)₂D to VitD-deficient individuals downregulated inflammatory markers (e.g., C-reactive protein) and conferred an antiproliferative effect (138). VitD is known to have immune-modulating effects (94). There are four potential ways by which serum VitD can influence T cell function: 1) direct effects on T cells mediated via systemic VitD, 2) indirect effects on antigen presentation to T cells and the intracrine synthesis of VitD, 3) direct effects of VitD on T cells following synthesis of the active form of VitD, a paracrine mechanism, and 4) intracrine conversion of 25(OH)D to VitD by T cells (51). In addition, VitD is required for the development of invariant natural killer T cells and CD8 $\alpha\alpha$ T cells. The selective requirement for VitD and the VDR in the development of these two populations of regulatory T cells, and not conventional T cell development, suggests that there may be some common mechanism (113).

The recent finding by Isakova et al. (66) that IL-6 is a potential mediator of the association between low levels of VitD and albuminuria is congruent with prior reports.

Hypertension and proteinuria are the two major factors that induce many inflammatory and mitogenic mediators such as

transforming growth factor- β (13). In renal proximal tubular cells, 1,25(OH)₂D₃ stimulates expression of transforming growth factor- β 1, a growth factor with anti-inflammatory and profibrotic actions that plays an important role in the development and progression of nephrosclerosis (171).

The RAS has a fundamental role in the mechanisms of inflammation (161) and defense for the different cells and tissues of organisms. This last function is fulfilled by regulation of oxidative stress at the cytoplasmic and mitochondrial levels. This phenomenon was also shown to be associated with the metabolic syndrome (34), as well as the initiation of renal fibrogenesis during unilateral ureteral obstruction (96).

ANG II induces proinflammatory genes and other proinflammatory substances and increases oxidative stress, which could damage endothelium, myocardium, and renal tissue. Chronic activation of NF- κ B (a protein complex that controls the transcription of DNA) and chronic activation of NAD(P)H oxidase are fundamental steps in these proinflammatory mechanisms in which intramitochondrial oxidative stress could play a critical role (34, 127). In this way, NF- κ B is a potent inducer of proinflammatory cytokines and oxidative stress in cardiovascular disease (71). Also this chronic stimulus is a well-known event in many other proinflammatory diseases (53).

This sequence of events might explain why reduction of ANG II synthesis by angiotensin-converting enzyme inhibitors and angiotensin receptor blockers has a protective effect against cardiovascular disease (34). From an evolutionary standpoint, this occurred before its role as a regulator of arterial pressure. If we were to consider cardiovascular disease as being inflammatory, then beyond its antihypertensive effect, blockade by the RAS could be seen as an etiological treatment of cardiovascular disease (139).

NF- κ B activation leads first to a proinflammatory immune response and then to a VitD-dependent anti-inflammatory response. Binding of the active metabolite 1,25(OH)₂D₃ to the VDR yields a transcription factor that represses NF- κ B activation and, additionally, modulates and downregulates adaptive, but enhances innate immune, responses and improves redox balance, thus counterbalancing inflammation on multiple levels. However, these built-in late counterbalances against inflammation work only when stores of calcium and 25(OH)D₃ are abundant (53). Therefore, a connection between lowered VitD metabolism and persistent NF- κ B activation can be postulated. Consistent with this notion, it has been reported that the VDR reduces NF- κ B activation by interference with NF- κ B p65 and p105 (40).

Knowledge about the impact of VitD deficiency on chronic NF- κ B activation is growing (53).

Oxidative Stress

Oxidative stress and free radicals result from an increase in production and/or a decrease in clearance. An excess of free radicals is detrimental to cell function [including function of beta cells (50, 52, 70), endothelial cells (4), fat cells (157), muscle cells (120), and nerve cells (20)]. Decreasing production or increasing clearance should reduce the net amount of free radicals and cell damage. Different patients (98) (or the organs, tissues, or cells of an individual patient) may be more or less sensitive to free radicals and have different susceptibility to oxidants or greater antioxidant defenses (3, 6, 33, 129).

The same level of oxidative stress may be more or less deleterious, depending on the protective antioxidant enzyme defense system and reparative process.

It is clear that the increased generation of cellular reactive oxygen species (ROS) and the activation of redox-sensitive signaling cascades are critical events involved in ANG II actions (163). After binding to its AT₁ receptor, ANG II triggers intracellular superoxide production (46, 72, 103). ANG II also enhances NO generation (126), and since the reaction of NO with superoxide generates peroxynitrite, it can promote the production of ROS and reactive nitrogen species and reduce NO availability (103, 160). Under normal physiological conditions, ANG II-mediated ROS and reactive nitrogen species production and the resulting stimulation of redox-sensitive signaling pathways are closely regulated (160). However, under conditions associated with RAS overactivation, such as hypertension, diabetes (133, 162), and normal aging (11, 47, 156, 168), ANG II-dependent oxidant generation becomes a significant contributor to cell oxidation and tissue damage (28, 117).

Oxidative stress linked to VitD metabolism was initially discussed in 1988 (21). These experiments suggested that an increase in mitochondrial membrane lipid hyperperoxide production resulted in a loss of 1 α - and 24-hydroxylase activity in proximal tubule cells (21).

Chang et al. (23) found, in monocytes and vascular smooth muscle cells, that 1,25(OH)₂D₃ inhibits NO synthase (NOS), which in turn reduces NO and free radical production.

Recently, it has been demonstrated that ANG II upregulation stimulates NOX4-derived ROS via the AT₁ receptor (45), that NOX4 is the major isoform expressed in renal cells, and that the VDR attenuates obstructive renal injury, at least in part, by suppressing the RAS (176). More recently, our group showed that paricalcitol has an antioxidant effect in the myocardium, aorta, and kidney tissue (63), as well as in mitochondrial fractions from renal cortexes of obstructed kidneys (39).

Treatment with a VDRA has survival benefits that are probably related to its effects beyond its traditional role in mineral metabolism. Recently, Tanaka et al. (152) showed that VDRA reduces oxidative stress in hemodialysis patients. After 4 wk of treatment with calcitriol (1.5 μ g/wk iv), Tanaka et al. reported no significant changes in serum intact parathyroid hormone, calcium, or phosphorus levels; however, the ratio of oxidized to unoxidized albumin was markedly decreased. Furthermore, after calcitriol treatment, the radical scavenging activity of albumin was greater than that of untreated albumin (152). Their data suggest that intravenous calcitriol treatment reduces oxidative stress and strengthens antioxidant defenses by inhibiting albumin oxidation.

Atherosclerosis

VitD can inhibit various aspects of inflammation leading to intimal and medial calcification (167).

It is also well known that the immune system actively participates in the inflammatory process. T lymphocytes and macrophages are known stimulators of intimal thickening and plaque formation in arteries that are susceptible to atherosclerosis. Th1 lymphocytes secrete IFN- γ , which is a potent macrophage activator and a Th2 lymphocyte suppressor. Th2 lymphocytes, in turn, are antiatherogenic (through the produc-

tion of IL-10, which inhibits macrophage activation) (86). The development of CD4⁺ T cells into T helper (Th) type 1 (Th1) or Th type 2 (Th2) cells determines the outcome of an immune response and is primarily directed by cytokines. VDRA has potential ameliorating effects on the development of atherosclerosis, acting on several mechanisms. First, they directly affect naive CD4⁺ T cells by enhancing the development of Th2 lymphocytes (through IL-4 production) (15). Furthermore, treatment with VDRA inhibits the transcription of IFN- γ , which is required for Th1 development or is a product of Th1 cells (15, 145). Moreover, human and mouse naive CD4⁺ cells differentiate into IL-10-producing T cells after treatment with VDRA and dexamethasone (9). Through these mechanisms, VDRA may change the Th1-Th2 balance and influence the production of anti-inflammatory mediators.

The stimuli of ANG II not only regulate vascular tone and sodium balance but also activate immune cells and promote cell infiltration into target organs (105).

Moreover, increased proinflammatory cytokines in the vessel wall contribute to immune cell recruitment and modified LDL cholesterol deposition by increasing scavenger receptor expression and cholesteryl ester synthesis and by decreasing cholesterol efflux (155). Active VitD metabolites [1,25(OH)₂D₃ or its analogs] promote monocyte-macrophage differentiation and diminish proinflammatory cytokine release by immune mononuclear cells, suggesting that 1,25(OH)₂D₃ signaling may regulate monocyte vascular infiltration and macrophage cholesterol retention in the vessel walls (42, 74).

Foam cells are the result of accumulated oxidized LDL within the macrophages (then phagocytes) and, finally, form the fatty streaks of the atheroma plaques. Oh et al. (111) cultured macrophages in VitD-deficient or -supplemented media and exposed them to modified LDL cholesterol. They found that 1,25(OH)₂D₃ suppressed foam cell formation by reducing acetylated or oxidized LDL cholesterol uptake. Conversely, deletion of the VDR in macrophages accelerated foam cell formation induced by modified LDL. Their results suggest that reduced VDR signaling is a potential mechanism underlying increased foam cell formation and accelerated cardiovascular disease.

Also dysfunctional mitochondria seem to contribute to the pathophysiology of atherosclerosis. As mentioned above, at the mitochondrial level, RAS overactivation plays a critical role (34).

Recently, in a model of apolipoprotein E-deficient atherosclerotic mice, our group showed that treatment with paricalcitol and enalapril, alone or in combination, ameliorates inflammatory and oxidative aortic injury in atherosclerotic mice by decreasing monocyte chemoattractant protein-1, TNF- α , cyclooxygenase-2, NADPH oxidase subunit p22 phox, Mn-SOD and inducible NOS protein expression and malondialdehyde levels and by restoring GSH levels and CuZn-SOD and endothelial NOS protein expression. Therefore, atherosclerotic processes can be countered more effectively with the combined use of drugs that act on the VDR (paricalcitol) and RAS receptor (enalapril) (63).

Since the RAS is involved in the pathogenesis of atherosclerosis and is downregulated by VitD, the interaction of paricalcitol and enalapril likely enhances the protective effect against atherosclerosis lesions, probably by means of a more effective amelioration of vascular inflammatory and oxidative injury to the renal and cardiovascular endothelium (63).

Clinical and Epidemiological Studies

Several clinical and epidemiological studies have shown that there may be an association between hypertension and VitD. Scragg et al. (137) recently reported the relationship between serum 25(OH)D concentration and blood pressure. In their study of data from NHANES III, they found a significant inverse association between serum 25(OH)D concentration and blood pressure that was evident even after adjustment for variables including age, gender, ethnicity, and physical activity. Judd et al. (69) also analyzed the NHANES III survey data and determined that there was a statistically significant inverse association between circulating 25(OH)D concentrations and systolic blood pressure. Martins et al. (97) found that a low VitD level was associated with a higher risk of hypertension.

A possible mechanism underlying these findings was studied in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study (159). This work was aimed at documenting a potential association between 25(OH)D, 1,25(OH)₂D, and the circulating RAS in a large cohort of patients that had been referred (n = 3,316) for coronary angiography. After measuring 25(OH)D, 1,25(OH)₂D, plasma renin, and ANG II concentration, the investigators showed an independent association between them. Their data showed, for the first time in humans, that lower 25(OH)D and 1,25(OH)₂D values are independently related to an upregulated circulating RAS (159).

Hypotheses

It seems very possible that a functional interaction between VitD and the RAS exists.

From the evolutionary point of view, both systems developed simultaneously and in parallel, both actively participating in the regulation of inflammatory and immunological mechanisms (Figs. 1 and 3). ANG II is a proinflammatory hormone, and VitD seems to have anti-inflammatory effects. From this, we can speculate that an increased proinflammatory response, generated by various stimuli accompanying diverse pathologies, such as the metabolic syndrome and cardiovascular diseases, could inhibit VitD, that is, an increase in proinflammatory tissue tone that facilitates the development of atherosclerotic (cardiovascular) disease. This would help explain why, in the process of enculturation, humans happened to be the only mammal that developed cardiovascular disease (an inflammatory disease), which also is the number-one cause of mortality in the modern world.

In this review we hypothesize that increased RAS activity and lower activation of the VDR can be complementary situations (Figs. 2 and 3), probably underlying a causal relationship. Furthermore, intervening in one factor seems to change, in the opposite direction, the other. It appears quite clear that the RAS can be regulated by VitD, but in turn our novel proposal is that increased ANG II or AT₁ receptor may regulate the levels of VitD.

This relationship is also evident in other pathologies that are not discussed in this review but have been very well documented, such as hypertension (73, 91, 118, 123, 124, 143, 173, 180, 181), aging (27, 35, 65, 67, 79–81, 83, 100, 153, 164, 165), diabetes and obesity (29, 37, 38, 76, 85, 88, 125, 148, 151, 174, 176, 178, 179), and chronic kidney disease (66, 130, 149, 150, 176).

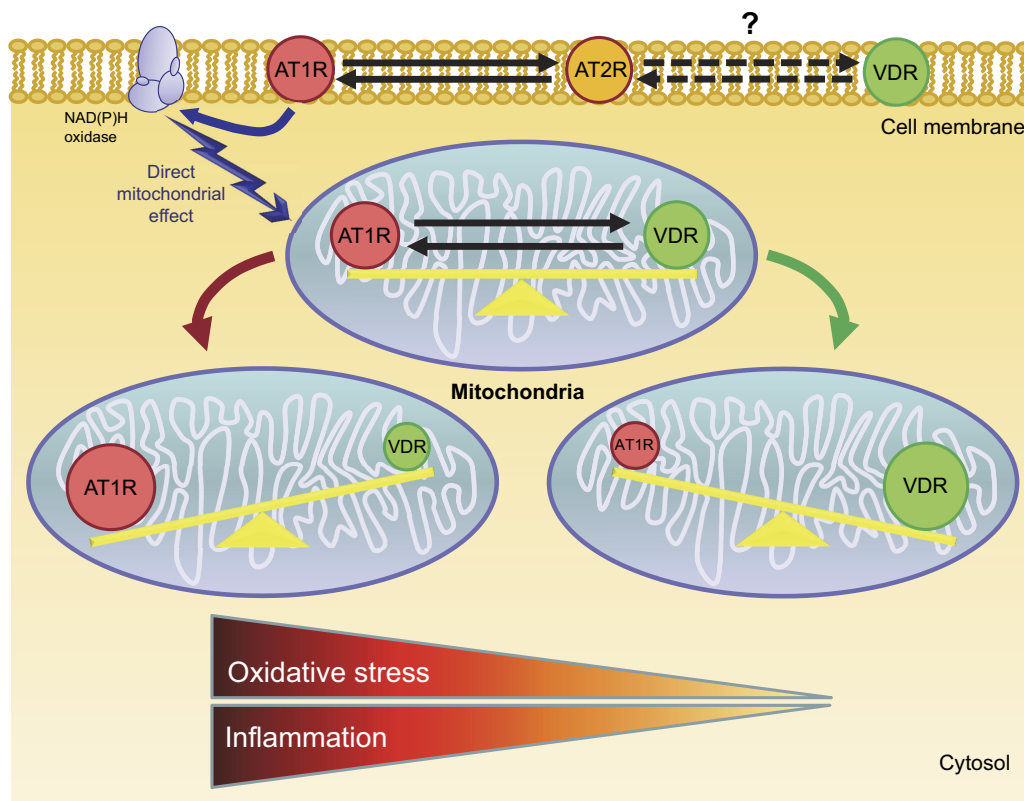


Fig. 3. Potential interaction between RAS receptor and VDR, with focus on oxidative stress and inflammatory balance (1, 39). Proposed interaction between angiotensin type 1 receptor (AT₁R), angiotensin type 2 receptor (AT₂R), and VDR may occur throughout the cell.

In fact, the pandemic of VitD deficiency could be the other face of increased RAS activity, which probably causes lower activity or lower levels of VitD. To make this more likely, a close spatial interaction between the two systems would be necessary. We have shown that almost all tissues that express the VDR also express ANG II receptors (Table 1). This coexpression appears to be present in mitochondria as well, which is basically where cellular energy is generated and where cell signals are triggered, resulting in the oxidative changes associated with chronic inflammatory processes, especially in the cardiovascular and renal systems (Fig. 3). A RAS blockade or VDR stimulation produces similar changes in these oxidative inflammatory disorders.

Finally, at a cellular and mitochondrial level, we have seen that increased ANG II produced a decrease of the VDRs.

In other words, the pandemic of human VitD insufficiency could be seen as an inflammation marker.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

M.F., F.I., and L.F. are responsible for conception and design of the review; M.F. prepared the figures; M.F., F.I., W.M., and L.F. drafted the manuscript; M.F., F.I., W.M., and L.F. edited and revised the manuscript; M.F., F.I., and L.F. approved the final version of the manuscript.

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