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MOLECULAR MECHANISM OF VITAMIN D IN THE CARDIOVASCULAR SYSTEM

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Abstract

Vitamin D deficiency is a global health problem that has various adverse consequences. Vitamin D is mainly synthesized in the skin by sunlight (UV light) irradiation; therefore, the vitamin D status is influenced by geographic locations, seasonal changes and skin pigmentations. The kidney is involved in the biosynthesis of 1,25-dihydroxyvitamin D and the reuptake of filtered 25-hydroxyvitamin D from the proximal tubules, thus vitamin D-deficiency is highly prevalent in patients with kidney disease who suffer renal insufficiency. There is a growing body of epidemiological and clinical evidence in the literature that links vitamin D deficiency to cardiovascular disease. The discovery of the vitamin D hormone functioning as an endocrine inhibitor of the renin-angiotensin system provides an explanation for this association. This review will discuss the mechanism underlying the connection between vitamin D and cardiovascular disease and its physiological and therapeutic implications.

Introduction

Vitamin D deficiency is a global health problem that has various adverse consequences¹. Vitamin D is synthesized in the skin from 7-dehydrocholesterol, and this reaction requires sunlight or ultraviolet (UV) irradiation. Vitamin D is converted in the liver to 25-hydroxyvitamin D [25(OH)D], which is the main circulating vitamin D metabolite and commonly used as an indicator of vitamin D status. 1,25-dihydroxyvitamin D [1,25(OH)₂D₃], the hormonal form of vitamin D, is synthesized in the kidney. Therefore, vitamin D status is influenced by geographic locations, seasonal changes and skin pigmentations¹. In addition to 1,25(OH)₂D₃ biosynthesis, the kidney is also required for the reuptake of filtered 25(OH)D from the proximal tubules², thus vitamin D-deficiency is highly prevalent in patients with kidney disease who suffer renal insufficiency³. There is a growing body of epidemiological and clinical evidence in the literature that links vitamin D deficiency to cardiovascular disease. For example, patients with chronic kidney disease have much higher cardiovascular disease mortality at advanced stage compared to the general population⁴. The discovery of the vitamin D hormone functioning as an endocrine inhibitor of the renin-angiotensin system (RAS) provides an explanation for this association. Here I will discuss the potential mechanism underlying the connection between vitamin D and cardiovascular disease and its physiological and therapeutic implications, with a focus on the RAS.

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Association of Vitamin D Deficiency with Cardiovascular Disease

UV irradiation is required for the cutaneous synthesis of vitamin D. UV irradiation decreases with the increase in latitude, and high latitudes are correlated with high prevalence of hypertension and stroke incidents^{5, 6}. Winter season, which has low UV irradiation, is associated with high incidence of myocardial infarction⁷. Dark skin pigmentation in the black population, which blocks UV light penetration, is associated with higher blood pressure^{8, 9}. Data from the National Health and Nutrition Examination Surveys (NHANES) III showed an inverse relationship between serum 25(OH)D and blood pressure in the general population¹⁰. The NHANES III database also revealed an inverse correlation between serum 25(OH)D levels and the prevalence of cardiovascular risk factors including hypertension, diabetes, obesity and hyperlipidemia¹¹. Low vitamin D status was thought to be a contributing factor for congestive heart failure¹². A recent meta-analysis of 18 published studies confirms the inverse relationship between blood 25(OH)D levels and hypertension¹³.

Other epidemiological studies have confirmed the association between vitamin D-deficiency and increased risk of cardiovascular problems. Prospective studies with cohorts from the Health Professionals' Follow-Up Study (HPFS) and the Nurses' Health Study (NHS) showed that serum 25(OH)D levels are inversely associated with the risk of incident hypertension during 4 years of follow-up¹⁴. A nested case-control prospective study using the HPFS database also demonstrated an association of low serum 25(OH)D levels with higher risk of myocardial infarction, even after adjusting for factors known to be associated with coronary artery disease¹⁵. Low serum 25(OH)D is also associated with incident cardiovascular disease in Framingham Offspring Study participants without prior cardiovascular disease during a mean follow-up of 5.4 years, after adjustment for C-reactive protein, physical activity or vitamin use¹⁶. Therefore, vitamin D-deficiency is a risk factor for cardiovascular disease.

The Renin-Angiotensin System as a Major Target of Vitamin D

The renin-angiotensin system (RAS) is a regulatory cascade that has profound impact on the cardiovascular system. Renin is the rate-limiting step of the RAS cascade that converts angiotensinogen (AGT) to angiotensin (Ang) I. Angiotensin-converting enzyme (ACE) then converts Ang I to Ang II, the biological effector of the RAS. Systemic Ang II is a central regulator of blood pressure through increasing vasoconstriction, extracellular volume and cardiac output, and over-activation of the RAS results can lead to hypertension^{17, 18}. In addition to blood pressure control, Ang II has diverse pathological activities that promote fibrogenesis, inflammation, cell hypertrophy and proliferation¹⁹⁻²¹. Thus over-activation of the RAS is detrimental.

Recent studies have well established the RAS as a major target of vitamin D, which may in part serve the link between vitamin D-deficiency and cardiovascular disease. In fact, two early articles reported an inverse relationship between circulating 1,25(OH)₂D₃ levels and plasma renin activity in hypertensive subjects more than two decades ago^{22, 23}; however, the significance of these studies was hardly recognized until the discovery that 1,25(OH)₂D₃ is a negative endocrine regulator of renin production²⁴. This discovery stemmed from our initial observation that vitamin D receptor (VDR)-null mice, a complete vitamin D-deficient model²⁵, develop hyperreninemia due to dramatic up-regulation of renin expression in the kidney²⁴. Plasma renin activity, plasma Ang II and plasma and urinary aldosterone levels in VDR-null mice are markedly elevated, leading to development of high blood pressure, cardiac hypertrophy and polyuria^{24, 26, 27}. Interestingly, polyuria seen in VDR-null mice

appears to result from overdrinking due to up-regulation of renin in the central nerve system and activation of the brain RAS ²⁸.

The critical role of vitamin D in RAS regulation was confirmed in another genetic model of vitamin D-deficiency, the Cyp27b1-null mice. These mice lack 1 α -hydroxylase that is required for the biosynthesis of 1,25(OH)₂D₃. Similar to VDR knockout mice, Cyp27b1 knockout mice also develop hyperreninemia, hypertension and cardiac hypertrophy as a result of renin up-regulation, but these abnormalities could be corrected by exogenous 1,25(OH)₂D₃ administration ²⁹. Moreover, we have taken a transgenic approach to confirm the inhibitory role of 1,25(OH)₂D₃ in renin expression. We showed that in transgenic mice that overexpress the human VDR in the juxtaglomerular cells, renal renin mRNA levels and plasma renin activity are significantly suppressed while serum calcium and parathyroid hormone levels are normal. Furthermore, the VDR transgene is able to rescue the hyperreninemia phenotype when introduced into VDR-null mice through breeding ³⁰. We have also reported that pharmacological dose of vitamin D analogs can effectively inhibit renin expression in mice ³¹. Together these data establish the vitamin D hormone as a crucial negative endocrine regulator of the RAS.

The relevance of vitamin D regulating the RAS in humans has been confirmed in a number of recent studies. Epidemiological data from a large cohort of patients (>3000) referred for coronary angiography in the Ludwigshafen Risk and Cardiovascular Health (LURIC) study demonstrated that both serum 25(OH)D and 1,25(OH)₂D₃ levels are independently and inversely associated with plasma renin concentration and Ang II levels ³². Vitamin D analog therapy has been reported to significantly suppress plasma renin activity in patients with late stage chronic kidney disease ³³.

We have shown that 1,25(OH)₂D₃ inhibits renin gene transcription by targeting the cyclic AMP signaling pathway ³⁴, a signaling pathway that plays a critical role in renin biosynthesis and release in response to various physiological factors ³⁵. CREB and/or CREM interact with the cyclic AMP response element (CRE) in the renin gene promoter. Phosphorylation of CREB or CREM by PKA leads to recruitment of CBP/p300 to the CRE site to drive renin gene transcription. In the presence of 1,25(OH)₂D₃, ligand-activated VDR physically interacts with CREB, blocking CREB binding to the CRE and thus disrupting the formation of CREB-CBP/p300 complex on the CRE site. As a consequence, renin transcription is stopped. This is at least part of the molecular mechanism by which 1,25(OH)₂D₃ inhibits renin production. This mechanism is a basis to use vitamin D and its analogs as inhibitors to inhibit renin production.

Therapeutic Potentials of Vitamin D Analogs in Cardiovascular Disease

Because of its profound effect on the cardiovascular system, the RAS has been a major therapeutic target for prevention and intervention of cardiovascular disease. Small molecules that target the RAS, including ACE inhibitors (ACEI), Ang II type 1 receptor blockers (ARB) and renin inhibitors, are widely used anti-hypertensive drugs ³⁶⁻³⁸. The notion that 1,25(OH)₂D₃ suppresses renin biosynthesis provides a molecular basis to explore vitamin D and vitamin D analogs as novel RAS inhibitors for therapeutic purposes. Bodyak et al reported that treatment with paricalcitol (19-nor-1,25-dihydroxyvitamin D₂), an activated vitamin D analog, blocked high salt-induced cardiac hypertrophy in the Dahl salt-sensitive rat model ³⁹. Surrogate biomarkers of hypertrophy such as ANP and BNP were significantly suppressed by the treatment, together with a marked reduction of cardiac renin expression. In the rat model of chronic renal failure (5/6 nephrectomy) paricalcitol treatment significantly lowered blood pressure and suppressed the RAS in the remnant kidney ⁴⁰. In an early study, 15-weeks intravenous infusion of calcitriol (1,25(OH)₂D₃) was shown to regress

left ventricular hypertrophy in hemodialysis patients⁴¹. Interestingly, in this study the reduction in the left ventricular mass was accompanied by a significant reduction in plasma renin activity, plasma Ang II and ANP levels in these patients, consistent with the suppressive effect of 1,25(OH)₂D₃ on the RAS.

A major problem associated with the current RAS inhibitors is the compensatory increase of renin concentration⁴². As the rate-limiting step of the RAS, renin homeostasis is maintained by the negative feedback loop mediated by the AT1 receptor. Blockade of the RAS simultaneously disrupts the negative feedback loop, leading to up-regulation of renin expression. The huge increase in renin concentration and activity in the plasma and tissue interstitial space stimulates the conversion of Ang I, which can ultimately lead to the build-up of Ang I, Ang II and other angiotensin metabolites in the body, through ACE-dependent and -independent pathways (Figure 1). Ang II accumulation compromises the efficacy of RAS inhibition and may explain why the current RAS inhibitors are only clinically suboptimal.

One important application of vitamin D analogs is to block the compensatory renin increase at the transcriptional level in combination therapy with the classic RAS inhibitors⁴³ (Figure 1). The combination is expected to enhance the efficacy of RAS inhibition and achieve better therapeutic outcomes⁴⁴. Recently we demonstrated that a combination of paricalcitol or doxercalciferol (1 α -hydroxyvitamin D₂) with losartan blocks cardiac hypertrophy in spontaneously hypertensive rats much more effectively than each mono-treatment³³. Spontaneously hypertensive rats, a model of human essential hypertension, develop age-dependent left ventricular hypertrophy. The rats were treated for 2 months with losartan, paricalcitol, doxercalciferol, losartan and paricalcitol combination or losartan and doxercalciferol combination. Left ventricular mass was quantified by echocardiography, and hypertrophic markers such as ANP and BNP were also measured. While paricalcitol or doxercalciferol reduced left ventricular hypertrophy as effectively as losartan in mono-treatment, the combinations had much better therapeutic efficacy than the three mono-therapies. Indeed, the compensatory increase of renin in the kidney and heart was blocked in the combination therapy³³. Similar findings were observed with the combination therapy in models of diabetic nephropathy⁴⁵⁻⁴⁷. In humans, a recently reported large randomized clinical trial (the VITAL Study) confirmed that paricalcitol was able to reduce albuminuria and blood pressure in patients with diabetic nephropathy who were already on RAS inhibitor therapy⁴⁸. Direct renin inhibitors such as aliskiren also have the problem of inducing a huge increase in plasma renin concentration⁴⁹, and it is expected that combination of aliskiren with a vitamin D analog should also lead to blockade of the compensatory renin induction and improvement of the therapeutic efficacy of aliskiren⁴⁴ (Figure 1). Therefore, the combination of vitamin D analogs and RAS inhibitors has broad therapeutic potentials. Given the wide use of RAS inhibitors in cardiovascular disease, the combination strategy warrants further investigations in clinical settings. In fact, the ongoing PRIMO study (ClinicalTrials.gov Identifier: NCT00497146; Enrollment: 220 stage 3 and 4 CKD patients), a randomized double-blind placebo control clinical trial that investigates the effect of paricalcitol on the progression of left ventricular hypertrophy in stage 3 and 4 CKD patients who are already on RAS inhibitors, will assess the cardiac outcome of the combination of vitamin D analog and RAS inhibitors in humans.

Conclusion

The finding of the vitamin D hormone as a negative endocrine regulator of the RAS has important physiological and clinical significance. It suggests that the vitamin D endocrine system may maintain the homeostasis of the cardiovascular system through suppressing the RAS, and vitamin D-deficiency or insufficiency may lead to activation of the RAS, thus

increasing the risk of cardiovascular disease. Vitamin D analogs as novel renin inhibitors have great therapeutic potentials for cardiovascular disease. Combination therapy with vitamin D analogs and RAS inhibitors can enhance the therapeutic efficacy in the treatment of cardiovascular disease.

Abbreviations

VDR	vitamin D receptor
RAS	renin-angiotensin system
AGT	angiotensinogen
Ang	angiotensin
ACE	angiotensin-converting enzyme
1,25(OH)₂D₃	1,25-dihydroxyvitamin D ₃

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Figure 1.

Vitamin D analogs block the compensatory induction of renin in combination therapy. The homeostasis of renin production is maintained by the negative feedback loop mediated by AT1 receptor. Inhibition of the RAS by the three classes of inhibitors (renin inhibitors, ACE inhibitors and ARB) disrupts the feedback loop leading to increased renin production. Ultimately Ang II levels can be raised, which reduces the efficacy of the drugs. In combination therapy, vitamin D analogs are able to block the compensatory increase of renin by suppressing renin gene expression, and that improves the therapeutic efficacy.