Vitamin D Regulation of the Renin–Angiotensin System

Yan Chun Li*

Department of Medicine, The University of Chicago, Chicago, Illinois 60637

Abstract   The renin–angiotensin system (RAS) plays a central role in the regulation of blood pressure, electrolyte, and volume homeostasis. Epidemiological and clinical studies have long suggested an association of inadequate sunlight exposure or low serum 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$] levels with high blood pressure and/or high plasma renin activity, but the mechanism is not understood. Our recent discovery that $1,25(OH)_2D_3$ functions as a potent negative endocrine regulator of renin gene expression provides some insights into the mechanism. The concept of vitamin D regulation of blood pressure through the RAS opens a new avenue to our understanding of the physiological functions of the vitamin D endocrine system, and provides a basis for exploring the potential use of vitamin D analogues in prevention and treatment of hypertension.   J. Cell. Biochem. 88: 327–331, 2003.   © 2002 Wiley-Liss, Inc.

Key words: vitamin D receptor; angiotensin II; blood pressure; hypertension

Vitamin D is a primary regulator of calcium homeostasis, and together with the parathyroid hormone, regulates intestinal and renal calcium transport and bone mineralization [DeLuca, 1988]. However, the wide tissue distribution of the vitamin D receptor (VDR), a member of the nuclear receptor superfamily that mediates the action of 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], suggests that the vitamin D endocrine system has additional physiological functions beyond calcium homeostasis. Indeed, recent studies of gene-targeted mice lacking VDR or 25-hydroxyvitamin D_3 1α-hydroxylase, the rate-limiting enzyme for $1,25(OH)_2D_3$ biosynthesis, confirmed the essential role of the vitamin D endocrine system in calcium homeostasis. They also revealed that vitamin D and VDR play important roles in the immune system, the reproductive system, and in hair growth [Li et al., 1997; Yoshizawa et al., 1997; Dardenne et al., 2001; Panda et al., 2001]. Here I review the evidence concerning the novel physiological role of vitamin D in the regulation of the renin–angiotensin system (RAS).

VITAMIN D AND BLOOD PRESSURE

The RAS is a regulatory cascade that plays an essential role in the regulation of blood pressure, electrolyte, and volume homeostasis. The rate-limiting component of this cascade is renin, a protease synthesized and secreted predominantly by the juxtaglomerular (JG) apparatus in the nephron. The main function of renin is to cleave angiotensin (Ang) I from angiotensinogen. The decapeptide Ang I is then converted to the octapeptide Ang II by the angiotensin-converting enzyme (ACE). Ang II is the central effector of the RAS, which exerts diverse actions in multiple organs, including the brain, heart, kidney, adrenal glands, and peripheral vasculature, to regulate the blood pressure and electrolyte and extracellular volume balance [Ballermann et al., 1991]. Inappropriate stimulation of the RAS has been associated with hypertension, heart attack, and stroke. Because of its central role in the RAS, a tight regulation of renin synthesis and secretion is essential.

The renin-producing granulated cells are mainly located in the afferent glomerular arterioles in the kidney [Hackenthal et al., 1990]. It is well established that renin secretion is regulated by the renal perfusion pressure (mediated by the baroreceptor mechanism in JG cells), the renal sympathetic nerve activity (through

β-adrenergic receptors in the JG apparatus and the glomerulus), and the tubular sodium load (mediated by the macula densa) [Hackenthal et al., 1990; Ballermann et al., 1991]. Renin secretion is stimulated by factors such as prostaglandins, NO, and adrenomedullin, and inhibited by factors including Ang II (feedback), endothelin, vasopressin, and adenosine [Hackenthal et al., 1990; Ballermann et al., 1991; Bader and Ganten, 2000]. Stimulation of renin secretion is often mediated by an increase in intracellular cAMP and/or a decrease in intracellular calcium concentration, and is often accompanied by increases in renin gene transcription. In the renin gene promoter, several cAMP response elements have been identified [Bader and Ganten, 2000]. Recent studies have revealed the involvement of *LXRα*, *RAR/RXR*, *CREB/CREM*, *USF1/USF2*, and *HOX* gene family members in the activation of the murine renin gene transcription [Tamura et al., 2000; Pan et al., 2001a,b; Shi et al., 2001].

Epidemiological and clinical studies in the last two decades have suggested an inverse relationship between vitamin D and blood pressure and/or plasma renin activity. Cutaneous production of vitamin D is influenced by sunlight, seasonal changes and skin pigmentation. Data from the INTERSALT study have revealed a linear correlation between the rise in blood pressure or the prevalence of hypertension and the latitudes north or south of the equator [Rostand, 1997]. Blood pressure tends to be higher in the winter than in the summer, and is affected by variations in skin pigmentation as well. In fact, ultraviolet light has been reported to lower blood pressure in patients with mild essential hypertension [Krause et al., 1998]. Numerous studies have shown that the serum level of $1,25(OH)_2D_3$ is inversely associated with blood pressure or the plasma renin activity in normotensive and hypertensive subjects [Resnick et al., 1986; Burgess et al., 1990; Imaoka et al., 1991; Lind et al., 1995; Kristal-Boneh et al., 1997]. In clinical trials, vitamin D treatment was reported to reduce blood pressure in hypertensive or elderly patients [Lind et al., 1989; Pfeifer et al., 2001]. In several cases, $1,25(OH)_2D_3$ treatment was shown to reduce the plasma renin activity, Ang II levels, blood pressure, and myocardial hypertrophy [Kimura et al., 1999; Park et al., 1999]. These are significant observations, but the mechanism underlying the relationship between vitamin D and blood pressure and/or plasma renin activity is unclear.

VITAMIN D AS A NEGATIVE ENDOCRINE REGULATOR OF THE RENIN–ANGIOTENSIN SYSTEM

Given the critical role of the RAS in the regulation of blood pressure, especially the inverse relationship between serum vitamin D levels and the plasma renin activity observed in previous studies, we speculated that vitamin D might be a negative regulator of renin expression in vivo. If this hypothesis is correct, disruption of the vitamin D signaling pathway should lead to a deregulated elevation of renin expression, whereas an increase in serum vitamin D levels should lead to renin suppression. Our recent studies have provided strong in vivo and in vitro evidence to support this hypothesis [Li et al., 2002].

We first examined VDR(−/−) mice, reasoning that renin expression may be increased in the mutant mice due to the lack of VDR-mediated vitamin D signaling. Indeed, both renin mRNA and protein levels in the kidney, as well as the plasma Ang II production, were drastically increased in VDR(−/−) mice, whereas their angiotensinogen expression in the liver was the same as wild-type mice. Thus, the increase in plasma Ang II appeared to be mainly due to the increase in renin activity. As a consequence, VDR(−/−) mice developed hypertension, cardiac hypertrophy, and increased water intake, since Ang II is a potent vasoconstrictor and potent thirst-inducer [Fitzsimons, 1980; Ballermann et al., 1991]. These abnormalities could be corrected by captopril, an ACE inhibitor, or losartan, a AT_1 receptor antagonist, confirming that overstimulation of the RAS is indeed the cause.

Interestingly, captopril or losartan treatment resulted in a drastic up-regulation of renin expression in both wild-type and VDR(−/−) mice. Furthermore, renin expression in both wild-type and VDR(−/−) mice was also elevated by dehydration, and suppressed by a high sodium diet. In all cases VDR(−/−) mice still maintained a much higher renin expression than wild-type mice. Therefore, despite a high basal renin synthesis, the regulatory mechanisms that control renin production, including the Ang II feedback inhibition and the volume- and salt-sensing mechanisms, are intact in VDR(−/−) mice. These data also suggest that the sustained

renin up-regulation is through a different mechanism than these physiological inducers.

The suppressive role of vitamin D in renin expression in vivo was confirmed in wild-type mice. In these animals, inhibition of $1,25(OH)_2D_3$ biosynthesis with strontium [Omdahl and DeLuca, 1971] led to renin up-regulation, whereas treatment with $1,25(OH)_2D_3$ suppressed renin expression in the kidney.

VDR(−/−) mice develop hypocalcemia and secondary hyperparathyroidism [Li et al., 1997], both of which are known to influence renin production and secretion [Smith et al., 1983; Antonipillai and Horton, 1985]. A key question is whether the effect of VDR inactivation on renin expression is direct or secondary to changes in the serum calcium or PTH level. In fact, renin up-regulation was evident even in 20-day-old VDR(−/−) mice, before the hypocalcemia occurred, and persistent in normocalcemic adult VDR(−/−) mice after their blood calcium was normalized through dietary intervention. On the other hand, renin expression was normal in Gcm2(−/−) mice [Gunther et al., 2000], which were as hypocalcemic as VDR(−/−) mice. In addition, renin expression was still elevated in VDR(−/−) mice whose alopecia was rescued by targeted expression of human VDR in the skin [Kong et al., 2002]. These are very convincing evidence that vitamin D regulation of renin expression is independent of calcium metabolism and alopecia. However, the contribution of PTH to renin up-regulation in VDR(−/−) cannot be definitely excluded yet, because serum PTH starts to rise early in life before the hypocalcemia develops and cannot be completely normalized by dietary treatment, due to the lack of the VDR-mediated vitamin D inhibition of PTH biosynthesis [Silver et al., 1986].

The most direct evidence to prove that vitamin D directly suppresses renin gene expression came from in vitro studies in As4.1 cells, a JG cell-like cell line that was derived from kidney tumors of SV40 T antigen transgenic mice and maintains a high level of renin synthesis [Sigmund et al., 1990]. $1,25(OH)_2D_3$ drastically reduced renin mRNA expression in As4.1 cells transiently or stably transfected with human VDR cDNA. When the stable As4.1-hVDR cells were transfected with a luciferase reporter plasmid containing the 4.1 kb 5′-flanking sequence of the murine renin gene, $1,25(OH)_2D_3$ treatment markedly reduced the promoter activity. Thus, $1,25(OH)_2D_3$ directly and negatively regulates renin gene transcription through a VDR-mediated mechanism.

PROSPECTIVE

The discovery that vitamin D regulates renin gene expression explains the inverse relationship between vitamin D and blood pressure observed previously. Figure 1 outlines the interaction between the vitamin D endocrine system and the RAS. As a potent negative regulator, vitamin D may play a key role in preventing the detrimental over-stimulation of the RAS. Therefore, a normal level of circulating $1,25(OH)_2D_3$ is crucial not only for calcium homeostasis, but also for the homeostasis of electrolytes, volume, and blood pressure. Thus, it is predicted that mice lacking the 25-vitamin D_3 1α-hydroxylase will show a RAS phenotype similar to that of VDR(−/−) mice.

Renin synthesis and secretion are regulated by a complex network of factors at the physiological and molecular levels [Bader and Ganten, 2000; Sigmund, 2002]. Given the important role of vitamin D in the regulation of the RAS, future studies should be directed at understanding the molecular mechanism of vitamin D repression of renin gene transcription and the interaction between vitamin D and other regulatory factors. It is also important to investigate whether vitamin D is also involved in the regulation of other non-renin components of the RAS.

Finally, the notion of vitamin D suppressing renin expression and blood pressure raises the possibility of using vitamin D analogues in the prevention and intervention of hypertension in the future. Highly potent vitamin D analogues
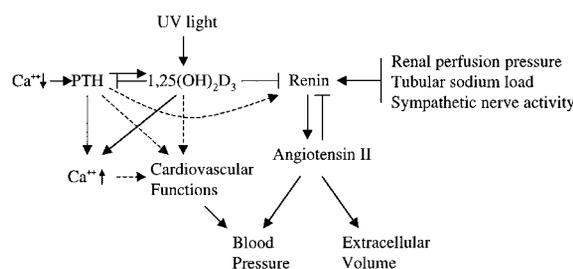

Fig. 1. Outline of the interaction between the vitamin D endocrine system and the renin–angiotensin system (RAS). Under normal physiological conditions 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) functions as an endocrine suppressor to maintain the homeostasis of renin production. Renin is also feedback suppressed by Ang II. The mechanism of PTH regulation of renin is unclear. Other studies suggest that vitamin D, PTH and calcium may also directly affect the cardiovascular functions (dashed lines).

with less calcemic effects are good candidates. By inhibiting the rate-limiting step in the renin–angiotensin cascade, vitamin D analogues might have some advantages over the ACE inhibitors and Ang II receptor blockers, which, besides side effects such as hyperkalemia, have some intrinsic problems in their efficacy. That is because Ang II can be generated through ACE-independent pathways, and one Ang II receptor antagonist cannot completely block the effects of Ang II, as Ang II has multiple receptors. In this regard, vitamin D analogues might be more effective.

REFERENCES

Antonipillai I, Horton R. 1985. Role of extra- and intracellular calcium and calmodulin in renin release from rat kidney. Endocrinology 117:601–606.

Bader M, Ganten D. 2000. Regulation of renin: New evidence from cultured cells and genetically modified mice [in process citation]. J Mol Med 78:130–139.

Ballermann BJ, Zeidel ML, Gunning ME, Brenner BM. 1991. Vasoactive peptides and the kidney. In: Brenner BM, Rector FC, editors. The kidney. Philadelphia: W.B. Saunders Company. pp 510–583.

Burgess ED, Hawkins RG, Watanabe M. 1990. Interaction of 1,25-dihydroxyvitamin D and plasma renin activity in high renin essential hypertension. Am J Hypertens 3:903–905.

Dardenne O, Prud'homme J, Arabian A, Glorieux FH, St-Arnaud R. 2001. Targeted inactivation of the 25-hydroxyvitamin D(3)-1(alpha)-hydroxylase gene (CYP27B1) creates an animal model of pseudovitamin D-deficiency rickets. Endocrinology 142:3135–3141.

DeLuca HF. 1988. The vitamin D story: A collaborative effort of basic science and clinical medicine. FASEB J 2:224–236.

Fitzsimons JT. 1980. Angiotensin stimulation of the central nervous system. Rev Physiol Biochem Pharmacol 87:117–167.

Gunther T, Chen ZF, Kim J, Priemel M, Rueger JM, Amling M, Moseley JM, Martin TJ, Anderson DJ, Karsenty G. 2000. Genetic ablation of parathyroid glands reveals another source of parathyroid hormone. Nature 406:199–203.

Hackenthal E, Paul M, Ganten D, Taugner R. 1990. Morphology, physiology, and molecular biology of renin secretion. Physiol Rev 70:1067–1116.

Imaoka M, Morimoto S, Kitano S, Fukuo F, Ogihara T. 1991. Calcium metabolism in elderly hypertensive patients: Possible participation of exaggerated sodium, calcium, and phosphate excretion. Clin Exp Pharmacol Physiol 18:631–641.

Kimura Y, Kawamura M, Owada M, Oshima T, Murooka M, Fujiwara T, Hiramori K. 1999. Effectiveness of 1,25-dihydroxyvitamin D supplementation on blood pressure reduction in a pseudohypoparathyroidism patient with high renin activity. Intern Med 38:31–35.

Kong J, Li XJ, Gavin D, Jiang Y, Li YC. 2002. Targeted expression of human vitamin D receptor in the skin promotes the initiation of postnatal hair follicular cycle and rescue the alopecia in vitamin D receptor null mice. J Invest Dermatol 118:631–638.

Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM. 1998. Ultraviolet B and blood pressure. Lancet 352:709–710.

Kristal-Boneh E, Froom P, Harari G, Ribak J. 1997. Association of calcitriol and blood pressure in normotensive men. Hypertension 30:1289–1294.

Li YC, Pirro AE, Amling M, Delling G, Baron R, Bronson R, Demay MB. 1997. Targeted ablation of the vitamin D receptor: An animal model of vitamin D-dependent rickets type II with alopecia. Proc Natl Acad Sci USA 94:9831–9835.

Li YC, Kong J, Wei M, Chen ZF, Liu SQ, Cao LP. 2002. 1,25-Dihydroxyvitamin D(3) is a negative endocrine regulator of the renin–angiotensin system. J Clin Invest 110:229–238.

Lind L, Wengle B, Wide L, Ljunghall S. 1989. Reduction of blood pressure during long-term treatment with active vitamin D (alphacalcidol) is dependent on plasma renin activity and calcium status. A double-blind, placebo-controlled study. Am J Hypertens 2:20–25.

Lind L, Hanni A, Lithell H, Hvarfner A, Sorensen OH, Ljunghall S. 1995. Vitamin D is related to blood pressure and other cardiovascular risk factors in middle-aged men. Am J Hypertens 8:894–901.

Omdahl JL, DeLuca HF. 1971. Strontium induced rickets: Metabolic basis. Science 174:949–951.

Pan L, Black TA, Shi Q, Jones CA, Petrovic N, Loudon J, Kane C, Sigmund CD, Gross KW. 2001a. Critical roles of a cyclic AMP responsive element and an E-box in regulation of mouse renin gene expression. J Biol Chem 276:45530–45538.

Pan L, Xie Y, Black TA, Jones CA, Pruitt SC, Gross KW. 2001b. An Abd-B class HOX.PBX recognition sequence is required for expression from the mouse Ren-1c gene. J Biol Chem 276:32489–32494.

Panda DK, Miao D, Tremblay ML, Sirois J, Farookhi R, Hendy GN, Goltzman D. 2001. Targeted ablation of the 25-hydroxyvitamin D 1alpha-hydroxylase enzyme: Evidence for skeletal, reproductive, and immune dysfunction. Proc Natl Acad Sci USA 98:7498–7503.

Park CW, Oh YS, Shin YS, Kim CM, Kim YS, Kim SY, Choi EJ, Chang YS, Bang BK. 1999. Intravenous calcitriol regresses myocardial hypertrophy in hemodialysis patients with secondary hyperparathyroidism. Am J Kidney Dis 33:73–81.

Pfeifer M, Begerow B, Minne HW, Nachtigall D, Hansen C. 2001. Effects of a short-term vitamin D(3) and calcium supplementation on blood pressure and parathyroid hormone levels in elderly women. J Clin Endocrinol Metab 86:1633–1637.

Resnick LM, Muller FB, Laragh JH. 1986. Calcium-regulating hormones in essential hypertension. Relation to plasma renin activity and sodium metabolism. Ann Intern Med 105:649–654.

Rostand SG. 1997. Ultraviolet light may contribute to geographic and racial blood pressure differences. Hypertension 30:150–156.

Shi Q, Gross KW, Sigmund CD. 2001. Retinoic acid-mediated activation of the mouse renin enhancer. J Biol Chem 276:3597–3603.

Sigmund CD. 2002. Regulation of renin expression and blood pressure by vitamin D(3). J Clin Invest 110:155–156.

Sigmund CD, Okuyama K, Ingelfinger J, Jones CA, Mullins JJ, Kane C, Kim U, Wu CZ, Kenny L, Rustum Y. 1990. Isolation and characterization of renin-expressing cell lines from transgenic mice containing a renin-promoter viral oncogene fusion construct. J Biol Chem 265:19916–19922.

Silver J, Naveh-many T, Mayer H, Schmeizer HJ, Popovtzer MM. 1986. Regulation by vitamin D metabolites of parathyroid hormone gene transcription in vivo in the rat. J Clin Invest 78:1296–1301.

Smith JM, Mouw DR, Vander AJ. 1983. Effect of parathyroid hormone on renin secretion. Proc Soc Exp Biol Med 172:482–487.

Tamura K, Chen YE, Horiuchi M, Chen Q, Daviet L, Yang Z, Lopez-Ilasaca M, Mu H, Pratt RE, Dzau VJ. 2000. LXRalpha functions as a cAMP-responsive transcriptional regulator of gene expression. Proc Natl Acad Sci USA 97:8513–8518.

Yoshizawa T, Handa Y, Uematsu Y, Takeda S, Sekine K, Yoshihara Y, Kawakami T, Arioka K, Sato H, Uchiyama Y, Masushige S, Fukamizu A, Matsumoto T, Kato S. 1997. Mice lacking the vitamin D receptor exhibit impaired bone formation, uterine hypoplasia, and growth retardation after weaning. Nat Genet 16:391–396.