25-hydroxyvitamin D₃ may Function via Genomic and Non-Genomic actions

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Abbreviations

25D₃: 25-hydroxyvitamin D₃; 1α,25D₃: 1α,25-dihydroxyvitamin D₃; CYP27B1: 25-hydroxyvitamin D 1α-hydroxylase; VDR: vitamin D receptor; RXR: Retinoid X receptor; VDRE: Vitamin D responsive element.

Commentary

Vitamin D₃ ingested from food or produced in the skin binds to the vitamin D binding protein (DBP) in the blood. Vitamin D₃ bound to DBP is carried to the liver and hydroxylated at position 25 by CYP2R1 or CYP27A1, belonging to the cytochrome P450 (CYP) superfamily, resulting in 25-hydroxyvitamin D₃ (25D₃). 25D₃ binds to DBP and circulates through the blood; in the kidney, it binds to megalin, is highly expressed in the renal proximal tubule, and is taken up by endocytosis [1]. 25D₃ incorporated into cells together with DBP is hydroxylated at the 1α position by CYP27B1, resulting in 1α,25-dihydroxyvitamin D₃ (1α,25D₃). 1α,25D₃ circulates through the blood and binds to vitamin D receptor (VDR) in organs with VDR expression, such as the bone, small intestine, and kidney [2]. VDR forms a dimer with retinoid X receptor (RXR) and binds to vitamin D response elements (VDRE) upstream of the target gene promoter [3,4]. As a result, vitamin D interacts with various transcription coupling factors and basic transcription factors to activate promoters and regulate gene expression [5]. 1α,25D₃ plays an important role in the maintenance of calcium homeostasis, bone formation, and differentiation of cells by genomic action, i.e., by controlling the expression of the target genes, mainly via VDR. However, in recent years, rapid, non-genomic action that does not involve protein synthesis has been reported. Specifically, 1α,25D₃ activates the intracellular signaling molecule present in the membrane via caveolae, structural functional components of the cell membrane, and membrane-associated rapid response steroid (MARRS) binding protein, and liberates a second messenger [6,7]. It has been reported that such non-genomic action leads to physiological activities, such as insulin secretion and smooth muscle cell migration. These previous findings have indicated that vitamin D exerts various physiological effects by genomic and non-genomic action.

The expression of CYP27B1, a key enzyme that makes 1α,25D₃, is suppressed by 1α,25D₃. In contrast, the enzyme CYP24A1 inactivates 1α,25D₃ and is induced by 1α,25D₃. Accordingly, the 1α,25D₃ concentration in the blood is kept fairly constant. Based on these observations, 1α,25D₃ is referred to as "active vitamin D₃" because its affinity for VDR is several hundredths that of 1α,25D₃. However, many observations cannot be explained if only 1α,25D₃ is regarded as active vitamin D₃. For example, the 1,99P mutation in CYP2R1 causes rickets [8]. The 25D₃ concentration (approximately 10 nM) in the blood of individuals who are homozygous for this mutation is markedly lower than that of healthy people (30 to 120 nM). Blood calcium and phosphorus levels are also low, and the blood alkaline phosphatase concentration is abnormally high, i.e., 10 times that of healthy people. However, the concentration of 1α,25D₃ in the blood of patients is normal, and this result is difficult to understand.

Vitamin D is deeply involved in bone metabolism, cell differentiation and proliferation, and immunity, and is closely related to various diseases, such as osteoporosis, cancer, diabetes, arteriosclerosis, and autoimmune diseases [9]. The 25D₃ concentration, but not the 1α,25D₃ concentration, in the blood is a disease indicator. The affinity of 25D₃ for VDR is remarkably low, about 1/500 times that of 1α,25D₃, but, conversely, the blood concentration is nearly 1000 times higher. These facts suggest that 25D₃ itself may act directly as a ligand for VDR. Additionally, several papers have suggested the importance of direct action of 25D₃ [10,11].
Munetsuna et al. added 25D$_3$ at a final concentration of 10 nM or 100 nM to the medium of human prostate-derived PZ-HPV-7 cells, and observed incorporation of 25D$_3$ into cells, metabolism of 25D$_3$, and intranuclear translocation of VDR and CYP24A1. Induction of the transcription of VDR target genes and cell proliferation were measured over time. They also investigated the effects of VDR and CYP27B1 using siRNA [12]. They found that the ratio of intracellular/extracellular abundance of 25D$_3$ reached an equilibrium within 10 minutes, VDR nuclear translocation was nearly complete in 90 minutes, CYP24A1 transcription was induced beginning at 120 minutes, and significant metabolism of 25D$_3$ by CYP24A1 occurred after approximately 300 minutes [13]. HPLC using tritium-labeled 25D$_3$ showed a faint peak at the elution position of 1α,25D$_3$. Even if all of these peaks are regarded as 1α,25D$_3$, the amount of 1α,25D$_3$ produced in cells is very small, and the observed phenomena are mainly attributed to 25D$_3$ itself. In addition, siRNA studies have strongly suggested that 25D$_3$ directly binds to VDR and acts almost independently of CYP27B1. Furthermore, based on a comprehensive analysis of gene expression using DNA microarray and real-time PCR approaches, cystatin D, cystatin E/M, and semaphorin 3B are each involved in the inhibitory effects of 25D$_3$ on cell proliferation. In other words, 25D$_3$ is presumed to control the expression of various genes and suppress cell proliferation by genomic action, i.e., by binding to VDR as a ligand in PZ-HPV-7 cells [13]. This suggests that in humans, the direct effect of 25D$_3$ can explain the risk of prostate cancer and the 25D$_3$ concentration in the blood shows a negative correlation with cancer risk (Figure 1).

Figure 1: Schematic effect of 25D$_3$ via genomic and non-genomic actions.

1α,25D$_3$ is not detected in the blood of Cyp27b1 knockout mouse, which exhibit an osteogenesis deficiency, uterine hypoplasia, immune dysfunction, etc. Cyp27b1 knockout mice can be treated successfully by the administration of 1α,25D$_3$, indicating that 1α,25D$_3$ plays important roles in bone formation, uterus formation, immune function, and other processes. Rowling et al. found a remarkable increase in the 25D$_3$ concentrations, blood calcium concentration, and bone density after the administration of 25D$_3$ to Cyp27b1 knockout mouse, suggesting a direct effect of 25D$_3$. However, since the weight, size, and capacity of the spinal column are considerably smaller than those of wild-type mice, they deduced that it is not possible to compensate for the effects of 1α,25D$_3$ with only 25D$_3$ [14,15]. Asano et al. reported a non-genomic action in which 25D$_3$ suppresses the expression of the sterol regulatory element-binding protein (SREBP) gene, an important transcription factor in lipid cholesterol and fatty acid biosynthesis, directly, without VDR [16]. In addition, in a comparative analysis, Hirota et al. found that hair loss observed in Vdr knockout mice was not observed in Cyp27b1 knockout mice. These results suggest that 25D$_3$ has a genomic action responsible for the maintenance of the hair cycle in the hair matrix via Vdr. Furthermore, abnormal chondrogenesis was less frequent in Vdr knockout mice than in Cyp27b1 knockout mice. Vdr knockout mouse phenotypes are thought to be explained by non-genomic effects in which 1α,25D$_3$, which does not interact with Vdr, but is abundant in the blood, directly controls the proliferation of chondrocytes [17].
Based on previous findings, Sakaki proposed that the physiological action of vitamin D is the sum of the effects of the "strong hormone 1α, 25D₃ and weak hormone 25D₃, and the contribution of both is different depending on the organ and cell" [9]. Additionally, 1α,25D₃ is a powerful hormone produced in small quantities in an emergency, assuming that 25D₃ is responsible for vitamin activity. In future vitamin D research, it is necessary to elucidate its comprehensive functions in vivo by clarifying the genomic and non-genomic actions of 25D₃.

References