

Review

The Vitamin D System in Humans and Mice: Similar but Not the Same

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Abstract: Vitamin D is synthesized in the skin from 7-dehydrocholesterol subsequently to exposure to UVB radiation or is absorbed from the diet. Vitamin D undergoes enzymatic conversion to its active form, 1,25-dihydroxyvitamin D (1,25D), a ligand to the nuclear vitamin D receptor (VDR), which activates target gene expression. The best-known role of 1,25D is to maintain healthy bones by increasing the intestinal absorption and renal reuptake of calcium. Besides bone maintenance, 1,25D has many other functions, such as the inhibition of cell proliferation, induction of cell differentiation, augmentation of innate immune functions, and reduction of inflammation. Significant amounts of data regarding the role of vitamin D, its metabolism and VDR have been provided by research performed using mice. Despite the fact that humans and mice share many similarities in their genomes, anatomy and physiology, there are also differences between these species. In particular, there are differences in composition and regulation of the *VDR* gene and its expression, which is discussed in this article.

Keywords: vitamin D; vitamin D receptor; human; murine; drug testing

1. Introduction

Different animal models have been used in biomedical research. Simple organisms, such as yeast, fruit flies, *C. elegans* and zebrafish are useful to study function of particular genes and their roles in development. However, when it comes to drug research, nothing compares to mice (*Mus musculus*). Mice are the most widely used animals for finding drugs for human diseases. This is because both mice and humans are mammals, and there is a high homology between their genomes, anatomy and physiology. In addition, mice are cheap and easy to breed, they reproduce quickly and genetic manipulations are relatively simple to conduct. However, there are also obvious and striking differences between humans and mice. Humans are approximately 2500 times larger than mice, the murine metabolic rate per gram of tissue in mice is seven times higher than that of an average man, mice preferentially consume grains and cereals, while contemporary people have plenty of meat in their diet. Mice lead a nocturnal life, while natural human behavior is diurnal, and lastly, mice are covered in fur, in contrast to humans [1].

2. Murine Model in Vitamin D Research

2.1. Short Overview of Vitamin D Physiology

Vitamin D is a derivative of cholesterol, as is similar with other steroid hormones. However, in contrast to other steroid hormones, it requires sun to be produced in the human body. In 7-dehydrocholesterol deposited in the skin, exposure to UVB radiation causes a break between C-9 and C-10 of the B ring, resulting in the formation of pre-vitamin D. Then, thermal isomerisation occurs which results in the formation of vitamin D, a biologically inert compound [2]. During the

industrialization period, when people started to live in the overcrowded cities, decreased access to the sun resulted in a massive outbreak of rickets, due to vitamin D deficiency. It has been proposed by Jędrzej Śniadecki in 1822 that the exposure of children to the sun has an antirachitic effect [3]. Nowadays, rickets is rare, but since most of the people live in the areas where the access to sun is limited for approximately half a year, and in sunny days the use of sunscreens is advised, most people are not vitamin D sufficient. Therefore, the alternative sources of vitamin D are used, such as a vitamin-D-rich diet or vitamin D supplementation. The activation of vitamin D is performed in the body by cytochrome P450 oxygenases (CYPs) and occurs in two steps, and in two organs: 25-hydroxylation by CYP2R1 or CYP27A1 in the liver, followed by 1 α -hydroxylation by CYP27B1 in the kidneys (Figure 1) [4].

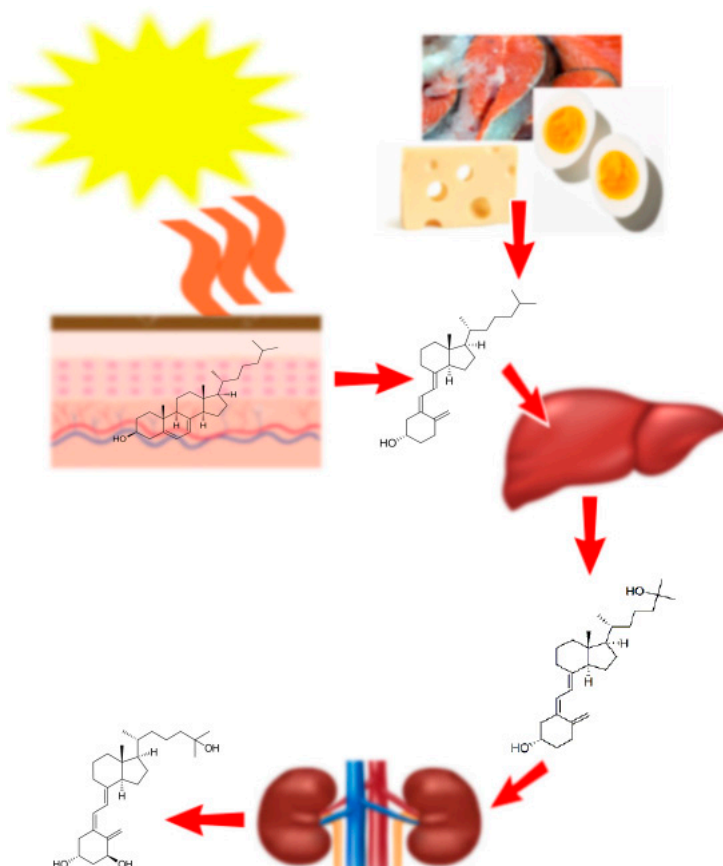


Figure 1. Outline of vitamin D metabolism. After exposure to sun, vitamin D is synthesized in the skin from 7-dehydrocholesterol. Alternatively, vitamin D may be obtained from diet. Vitamin D is converted to 25-hydroxyvitamin D in the liver, and then to 1,25-dihydroxyvitamin D in the kidneys.

Double hydroxylated vitamin D, 1,25-dihydroxyvitamin D (1,25D), is a highly active compound, whose concentration in the human body must be strictly controlled. The mechanism of this control is performed by *CYP24A1*, encoding 24-hydroxylase of 1,25D, which catabolizes 1,25D to water soluble and biologically inactive calcitric acid [4]. 1,25D, similarly to other steroid hormones, exerts its biological activity by binding to the nuclear vitamin D receptor (VDR), which forms a dimer with retinoid X receptor (RXR) after ligation. The 1,25D/VDR/RXR complex is then translocated to the cell nucleus where it acts as a ligand activated transcription factor [5]. There are hundreds of VDR-regulated genes, but the most strongly regulated one is *CYP24A1*, this way providing a negative feedback loop, which controls effective concentration of 1,25D [6]. The best known role of 1,25D is the control over calcium-phosphate homeostasis in the body [7]. However, VDR is present also in cells and tissues not implicated in calcium and phosphate regulation therefore the roles other than calcemic have been proposed for 1,25D. It has been accepted that 1,25D is important for regulation of immune system,

however the clear and precise picture of this regulation is still not available [8]. The presence of VDR in developing blood cells has also been documented, and it has been shown that in human hematopoietic stem cells (HSCs) physiological concentrations of 1,25D induce monocytic differentiation [9].

2.2. Vitamin D Analogs

VDR was found not only in normal cells, but also in many of their cancerous counterparts [10]. In some of these cancers, 1,25D is capable to induce differentiation [11,12]. Thus, a number of studies have investigated the therapeutic potential of 1,25D. However, the use of 1,25D as a drug is limited by possible development of hypercalcemia [13]. This is why numerous 1,25D analogs have been produced, which are less calcemic than 1,25D, but still capable to induce cell differentiation [14,15]. Some of 1,25D analogs have been registered as drugs for psoriasis [16] or hyperparathyroidism [17], other are still in preclinical trials. The hundreds of available analogs have been tested first for their affinity to VDR, then in in vitro cell cultures, and eventually for toxicity and calcemic effects in vivo in murine models. Some of these analogs have been rejected from further studies because of general toxicity for mice [18].

2.3. Vitamin D System in Humans and Mice

The source of vitamin D in mice is the same as in humans. Despite being covered by fur, rodents produce vitamin D from 7-dehydrocholesterol after exposure to sun [19], but due to their nocturnal life, mice have less opportunities than humans to expose themselves to sun. In addition, both species can absorb vitamin D from the diet and humans also use supplements [20]. Interestingly, vitamin D is a very common component of rodenticides, which not only kill mice and rats, but also cause accidental toxicosis in dogs and cats [21]. As reported, 600 IU of vitamin D (cholecalciferol) is enough to kill a mouse [22]. It is hard to say whether the equivalent doses of vitamin D are lethal for people, since such doses have not been attempted in humans (1,500,000 IU).

The importance of 1,25D for living organisms can be learned not only from deficient individuals, but also from those who have mutations in genes encoding proteins that are important for vitamin D actions. There are some naturally occurring mutations that affect the vitamin D system in humans. Hereditary vitamin-D-resistant rickets (HVDRR) is caused by mutations in the *VDR* gene [23]. The predominant symptoms are severe rickets, growth retardation and hypoplasia of the tooth enamel. However, in some patients, depending on the localization of mutation in *VDR* gene, hair loss (alopecia) is an accompanying symptom. Mutations in the region coding ligand-binding domain (LBD) do not affect hair growth, while missense mutations in the DNA binding domain (DBD) or mutations that interfere with RXR dimerization cause alopecia in patients [23].

Vitamin-D-dependent rickets type 1 (VDDR-I) is caused by mutations in the *CYP27B1* gene. This disease is an autosomal recessive disorder characterized by the early rickets with hypocalcemia due to inability to convert 25-hydroxyvitamin D to 1,25D [24]. In this other disease, hair growth has not been reported to be affected. The relevance of the above proteins for mice can be learnt from *VDR*-null and *CYP27B1*-null mice [25]. *VDR*-null mice develop hypocalcemia in infancy, followed by rickets, osteomalacia, growth retardation, secondary hyperparathyroidism and alopecia [26], while *CYP27B1*-null mice develop hypocalcemia, secondary hyperparathyroidism, retarded growth, and the skeletal abnormalities characteristic of rickets, but no alopecia. In addition, *CYP27B1*-null mice have enlarged lymph nodes in the vicinity of the thyroid gland and a reduced number of peripheral T lymphocytes. Female *CYP27B1*-null mice are infertile, exhibit uterine hypoplasia and absent corpora lutea [27]. The data described above, observed in patients and in mice, indicate that VDR has roles that are either ligand-dependent or ligand-independent. Regulation of hair growth does not depend on 1,25D, and most probably is caused by inhibition of transcription of certain genes by unliganded VDR [23]. Regulation of calcium-phosphate homeostasis, female reproduction and of some immune functions are 1,25D-dependent.

2.4. Vitamin D Receptor in Blood Development

It has been reported that VDR regulates transcription of around 3% of genes of human and murine genomes [25]. Among these genes, many are characteristic for blood cells' development and function [28]. Some of them encode transcription factors involved in hematopoiesis [29,30], or proteins important for function of blood cells [31]. It has been also reported that VDR is present in multiple blood cells, including hematopoietic stem cells (HSC) in humans and in mice [9,32]. In VDR knockout mice, haematopoiesis and blood cell counts are normal, as long as the mice are kept in a pathogen-free environment. Exposure of these mice to pathogens led to the blood disorder characterized by an appearance of chronic myeloid leukemia-like cells, splenomegaly, granulocytosis, thrombocytosis and reduced erythropoiesis [33]. The above data suggest that 1,25D, VDR, or both, might take part in hematopoiesis.

2.5. Vitamin D Receptor Gene in Humans and in Mice

Vitamin D is produced after exposure to sun in wide variety of organisms. Phytoplankton, zooplankton, most plants and animals, invertebrate and vertebrate, have the capacity to make vitamin D [34]. The role of 1,25D and of its receptor is well understood in case of terrestrial vertebrates who need to maintain healthy skeleton. It is less clear why vitamin D and VDR are ubiquitous also in lower organisms. One hypothesis says that the primary role of VDR was not in calcium-phosphate homeostasis, but in detoxification [35]. The VDR-LBD binds not only 1,25D, but also lithocholic acid (LCA) [36,37], which is a toxic and carcinogenic product of bile acids metabolism. There have been three rounds of whole genome duplications throughout the evolution of eukaryotes and common evolutionary path of humans and mice emerged after the second round. It is believed that before the second duplication, the functions of VDR and pregnane X receptor (PXR) have been combined in one protein. The function of PXR in humans is to detoxify xenobiotics by activating the enzyme CYP3A4 [38]. The second round of duplication gave rise to separate VDR and PXR genes and proteins with separate functions. It is noteworthy that in teleost fish, which were subjected to the third round of whole-genome duplication, there is one more copy of the VDR gene [39]. Separation of VDR and PXR allowed for the specification of VDR's function in bone maintenance.

Despite the common evolution of murine and human VDR genes, their compositions are diverse. The VDR gene in humans is located on chromosome 12 and spans about 100 kb of genomic DNA [40]. Its 5' regulatory region is very complex, and consists of seven untranslated exons (1a–1g) and three promoter regions [32]. Exon 1a is associated with a strong promoter and transcripts initiated in that site are the most common. Expression of transcripts originating in exons 1c, 1f and 1g is tissue-specific: exon 1f transcripts were detected in kidney, parathyroid adenoma tissue and in intestinal cell line LIM1863 [41], exon 1g transcripts in normal blood and in KG1 leukemic cell line [32,42], while the activity of 1c promoter was identified only in breast cancer cells [43]. Since no distinct promoter activity was recognized for the region adjacent to exons 1d and 1g, it has been postulated that a single promoter upstream of 1a [44] or overlapping regions [41] regulate transcription from these exons. Translation of human VDR protein starts from exon 2 and ends in exon 9. Due to the T to C polymorphism, which eliminates the most 5'-located ATG codon, translation starts from the second in-frame ATG codon in some individuals. As a result, two variants of the VDR protein exist, one of which is three amino-acids shorter (424 aa) than the other (427 aa) [45]. Two more isoforms of VDR protein: VDRB1 (477 aa) and VDRB2 (450 aa) can be generated by alternative splicing of transcripts originating in exon 1d, which contains an ATG translation start codon. The VDRB1 protein was shown to be expressed in several human tissues and may be functionally different from the main VDR isoform [46]. In addition to the polymorphism in exon 2, there are five more polymorphic sites located between the 8 and 9 exons [47–50] with no obvious functions. There were thousands of studies performed in order to determine associations of given polymorphisms with different phenotypes, but they produced conflicting results reviewed in [51].

The murine *Vdr* gene is located on chromosome 15 and is less complex than in humans. In the 5' regulatory region of the murine *Vdr* gene exons 1 and 2 were identified, with strong homology to human 1a and 1c, respectively [44]. Though exon 1d is well conserved (1d-like), transcripts containing this exon have not been reported in mice [52]. There is one murine VDR protein which consists of 422 aa, its translation starts from exon 3 and ends on exon 10 [53]. Since a polymorphism is a genetic variant that appears in at least 1% of the population, we cannot learn anything about murine polymorphisms, because studies on the representative groups of the murine population have not been performed. However, some differences between inbred strains of mice have been reported. Single nucleotide polymorphism located in exon 8, has been discovered in murine *Vdr* gene, which changes A to T. This polymorphism is responsible for an amino acid change at position 276. Individuals with an A allele have methionine amino acid and those with T allele have a lysine. It was proposed that mice with A allele have airway resistance (an indication of airway damage) lower than mice with T allele [54].

The regulation of VDR expression in humans is also complex. The promoter associated with the 1c exon (proximal to the coding region of VDR) was shown to be regulated by 1,25D, retinoic acid (RA), estrogens, and phytoestrogens in breast cancer cell lines [43]. The VDR transcripts originating from exon 1a in blood cells are also RA-responsive. Moreover, retinoic acid receptor α (RAR α)—as long as it is not activated by the ligand—acts as a suppressor of VDR expression [42]. Interestingly, the sequences of 1a and 1c promoters do not contain any apparent estrogen or RA response elements (ERE or RARE). However, the known positions of RAREs are highly variable—they range from over 10,000 bases upstream to about 8000 bases downstream of the 5' end of transcription start site [55], or may be located in introns [56]. In mice, *Vdr* expression is autoregulated by the 1,25D/VDR complex through binding to three conserved regions located 20, 27, and 29 kb downstream of the transcription start site [57]. In normal human hematopoietic cells, the expression of VDR is moderately upregulated (less than in leukemic cells) by RA, and not by 1,25D. In the normal murine hematopoietic cell, the expression of *Vdr* is robustly autoregulated by 1,25D, but not by RA [32].

3. Conclusions

In recent years, vitamin D and its active metabolite attracted much more attention than just as antirachitic agents. 1,25D has multiple functions, including inhibiting of cell proliferation, enhancing cell differentiation, augmentation of innate immune functions, and reduction of inflammation [28,58]. This is why 1,25D has been proposed as a drug in hyperproliferative and autoimmune diseases. A main limitation to the use of 1,25D as a drug is its calcemic action. The solution to this problem has been in the development of analogs with lowered calcemic and retained prodifferentiating activities [14,15]. Some of the analogs have been already registered for treatment of psoriasis [16,59], which is a hyperproliferative and an autoimmune disease [60]. Any new drug before being introduced to the market must undergo systematic preclinical testing, including experiments in nonhuman subjects to test efficacy, toxicity and pharmacokinetics. Usually, the first species to be used in such experiments are mice, and in fact, there is no comparable replacement to these animals. Despite humans and mice share many similarities in their genomes, anatomy and physiology, one should be aware that there are also differences. It seems that the regulation of VDR expression is one of these differences. In humans, other nuclear receptors and their ligands regulate the expression of VDR gene and as a consequence, an amount of VDR protein, while in mice, only the liganded VDR autoregulates the expression of the *Vdr* gene and level of VDR protein. The cause of this difference is difficult to assume, but the fact that humans in their natural environment were able to abundantly synthesize vitamin D in their skin, while mice covered with fur and spending days underground had this ability limited, may be important. Thus, if a certain vitamin D analog, or any combination therapy including vitamin D analogs, appears to be toxic in mice, it may be worth examination in other species.

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