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REVIEW

History of the discovery of vitamin D and its active metabolites

Hector F DeLuca

Department of Biochemistry, University of Wisconsin-Madison, Madison, WI, USA.

Before the twentieth century, it was not possible to describe the essentials of a diet that could support life, growth and reproduction of higher animals. The discovery of vitamin A by McCollum and Davis in 1913 ushered in the era of accessory food substances culminating in the achievement of that goal. It included the discovery of vitamin D and its production in skin caused by ultraviolet light. This was followed by a description of its actions at the physiological level that resulted in a healthy skeleton and beyond. To carry out these functions, vitamin D is converted to a hormone that acts through a nuclear receptor. The findings leading to this concept and their importance to biology and medicine are presented.

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Discovery of the Concept of Vitamin D

Although rickets, scurvy, beri-beri and other such diseases were known for centuries,[1] the cause of them remained elusive until the twentieth century. On the basis of the dogma put forth by the influential German chemists in the nineteenth century led by von Liebig,[2] an adequate diet consisted of 12% protein, 5% mineral, 10–30% fat and the remainder as carbohydrate. The belief that this defined an adequate diet was to survive until the early part of the twentieth century. In the meantime, several discoveries suggested that this was not true. First and foremost were the experiments carried out by Lunin,[3] Magendie,[4] Hopkins[5] and Funk.[6] These investigators fed the recommended proportions of these purified dietary components to animals and found that the animals failed to survive. Clearly, something was missing from these purified materials required for survival. In addition, other findings were in support of the existence of essential micronutrients in the diet. One of the earliest discoveries was that of Eijkman[7] who studied the high incidence of beri-beri among prisoners in the Dutch East Indies. These prisoners were fed predominantly a diet of polished rice. Eijkman found that providing the hulls of rice solved the beri-beri problem. Unfortunately, Eijkman concluded that polished rice possessed a toxin that was neutralized by a substance in the hulls. A colleague of Eijkman, that is, Grïjns, revisited the question and correctly demonstrated that hulls contained an important and required nutrient that prevented beri-beri, but the idea of a vitamin had not yet been given birth.[8]

Another discovery of a substance that prevented scurvy among sailors was made by Hoist and Frohlich.[9] They found that scurvy experienced by seamen could be prevented or cured by citrus fruits or a substance found therein. Yet, the idea of essential micronutrients of an organic type had yet to be conceived. The idea of vitamins was first suggested by Funk,[6] who envisioned that a 'vital amine' present in foods was required for health and survival. Unknown to Funk and without evidence, this would prove to be a term that would describe the accessory food factors later to be discovered.

Professor Steven Moulton Babcock at the University of Wisconsin had long been in opposition of the German chemists' view that an adequate diet could be described by correct proportions of protein, carbohydrate, fat and salts.[10] At long last, the Department of Dairy Science at the University of Wisconsin allowed Professor Babcock and his newly hired head of Agricultural Chemistry, that is, EB Hart, to carry out an experiment in the dairy herd at Wisconsin.[11] They fed four groups of dairy cattle with the exact dietary proportions suggested by the German chemists, except that the entire ration was derived from a single grain, namely corn, oats, wheat or a mixture thereof. The outcome was quite dramatic. Cows fed the corn diet did very well, reproduced and were able to produce large amounts of milk, whereas those on the wheat diet did poorly and, in fact, failed to survive. The oat diet resulted in a finding intermediate between wheat and corn. The Wisconsin group correctly concluded that there were accessory food factors yet to be discovered that were responsible for the health and well-being of those animals fed the corn diet.

This led Professor Hart, Chair of Agricultural Chemistry at the University of Wisconsin, to begin a series of experiments to test this hypothesis. Professor Elmer McCollum was allowed to use a small animal model, the white rat, to study the importance of various dietary components. In a controversial move for a

Correspondence: Professor HF DeLuca, Department of Biochemistry, University of Wisconsin-Madison, 433 Babcock Drive, Madison, WI 53706-1544, USA.
E-mail: deluca@biochem.wisc.edu

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college of agriculture, Hart and Babcock permitted and, in fact, supported the use of the rat as an experimental animal despite the opposition that rats are considered enemies of the farm and should not be allowed in a College of Agricultural and Life Sciences. With the white rat, McCollum and Davis[12] conclusively demonstrated that butter fat and cod liver oil contained a factor, which is required for the prevention of xerophthalmia, an eye disease, and to support growth. This finding attracted Osborne and Mendel[13] at Yale to carry out similar experiments, and, independently, McCollum *et al.*[14] at Wisconsin and Osbourne and Mendel[13] at Yale discovered a water-soluble factor that was responsible for preventing a neurological disease similar to beri-beri. McCollum, in consultation with Professor Harry Steenbock, who was also involved in the early, single-grain experiment, decided that they would use the idea of Funk to call these substances 'vitamins'. Vitamin A was the fat-soluble factor and vitamin B was the water-soluble factor. Soon thereafter, evidence was provided that another water-soluble factor prevented the disease scurvy and was called vitamin C.[15] The stage was set then for the discovery of the next vitamin, vitamin D.

Discovery of Vitamin D

Sir Edward Mellanby in Great Britain had been very concerned with the extremely high incidence of rickets in the United Kingdom, especially in Scotland. In fact, the disease became known as 'the English Disease'.[16] Sir Mellanby was taken by the work of McCollum and decided that rickets might be a dietary deficiency disease. He very cleverly used the diet consumed by the Scottish people (who had the highest incidence of rickets), primarily oatmeal, and fed that to dogs that he inadvertently kept indoors and away from sunlight. They developed rickets, which was identical to the human disease.[17] Sir Mellanby[17] could cure the disease by providing cod liver oil and he therefore assumed that it was possible that vitamin A was responsible for the prevention of rickets. McCollum who had since left Wisconsin and moved to Johns Hopkins University had been following this finding, and decided to test the hypothesis of whether vitamin A was responsible for healing rickets. He bubbled oxygen through cod liver oil that destroyed vitamin A and found that this preparation was no longer able to prevent xerophthalmia and vitamin A deficiency, but it still retained the ability to cure rickets.[18] McCollum *et al.*[18] correctly concluded that the factor that cures rickets is a new vitamin, which they called vitamin D.

Healing of Rickets by UV Light

In the meantime, Huldshinsky,[19] a physician in Vienna, and Chick *et al.*[20] in England found that children suffering from rickets could be cured by exposing them to summer sunlight or artificially produced UV light. Hess and Unger[21] also noted that sunlight could cure rickets. This dichotomy attracted Professor Harry Steenbock at the University of Wisconsin who had been assigned the small animal experimental work. Steenbock in 1916 had been working with goats when he found that when they were kept in summer sun outdoors, they were in positive calcium balance but when kept indoors in the winter in the absence of sunlight, they went into negative calcium balance.[22] Steenbock had then mentally made a connection between sunlight and calcium retention. With this background, Steenbock[23,24] began to irradiate rats, their food and the air in their cages with UV light. He found that irradiation of not only the rat but also their food could prevent or cure rickets. He found this activity to be associated with the non-saponifiable lipid fraction and correctly concluded that an inactive lipid in the diet and skin could be converted by UV light into an active antirachitic substance.[25] Professor Steenbock[26] patented the process, and with this patent was able to attract industry to use this discovery to eliminate rickets as a major medical problem. Hess and Weinstock[27] independently and somewhat later discovered that irradiation could prevent rickets.

Isolation and Identification of Vitamin D

Although the idea of vitamin D became very clear and it was found in a non-saponifiable fraction, the actual identification of the vitamin structure was not to take place until 1932 when Askew *et al.*[28] were able to isolate vitamin D_2 from an irradiation mixture of ergosterol. Vitamin D_1 had proved to be an artefact of an adduct between vitamin D_2 and lumisterol by Windaus and Linsert.[29] Thus, vitamin D_2 proved to be the first vitamin D to be isolated and identified.

In 1935, 7-dehydrocholesterol was isolated by Windaus *et al.*[30] and vitamin D_3 was identified in 1937 by the Windaus and Bock.[31] Vitamin D_3 is the natural form of vitamin D formed in the skin as a result of UV irradiation of 7-dehydrocholesterol. This then raised the question of whether vitamin D is a true vitamin or whether it is normally produced in the skin and is not found in natural foods. Although it was surmised that vitamin D_3 arises in skin via the irradiation of 7-dehydrocholesterol, this was not proven until 1978 when Esvelt *et al.*[32] actually isolated and identified vitamin D_3 by mass spectrometry. Before this, Holick *et al.*[33] provided evidence that previtamin D_3 is formed in the skin on UV irradiation. The actual chemistry of the irradiation process was defined by the work of Velluz *et al.*[34] and also by the contributions of Havinga.[35]

Figure 1 illustrates the conversion of 7-dehydrocholesterol to vitamin D_3 via its intermediate previtamin D_3.

Early Understanding of the Function of Vitamin D

Following these monumental discoveries, rickets disappeared as a major medical problem and the vitamin D research settled into a very quiescent state with only an occasional new discovery being made. Great strides were made, however, in the area of the water-soluble factors of vitamin B, which were then shown to be composed of several different factors, all providing different functions in the body with many assuming activated forms or coenzymes for function. Although there were attempts to describe vitamin D as a coenzyme, this proved to be a dead end.[36] Thus, it was assumed from this point on that vitamin D itself functioned without metabolic change, an idea that was to persist until 1968.[37]

The discovery of vitamin D resulted in a variety of attempts to understand how this steroid might result in the healing of rickets and its adult counterpart, osteomalacia. One of the early experiments that is often unappreciated are the studies of Shipley *et al.*[38,39] in which slices of bone taken from rachitic animals were incubated in the blood serum of vitamin D-deficient animals or in the blood serum of animals provided

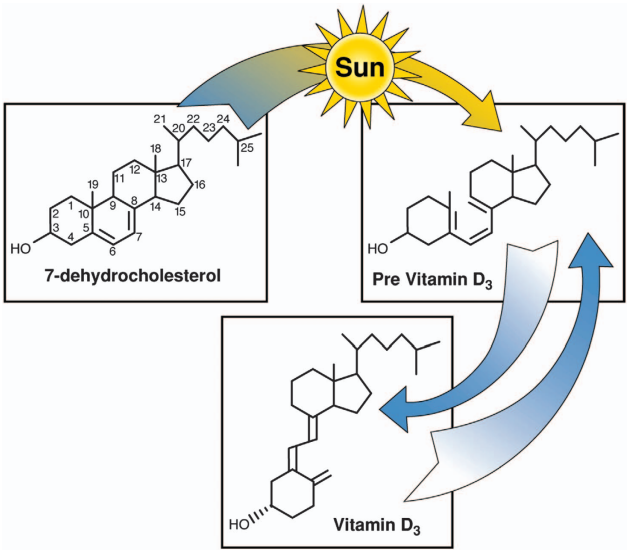

Figure 1 The conversion of 7-dehydrocholesterol to previtamin D_3 by 282–310 nm UV light and the temperature-dependent equilibrium between previtamin D_3 and vitamin D_3.

with vitamin D. The provisional deposit of calcium and phosphate was found in the case of bone slices incubated in serum of animals that had been given vitamin D. However, the addition of vitamin D to the serum of vitamin D-deficient rats did not in any way influence the deposit of mineral in the bone. Of considerable importance was that calcification of rachitic bone could be achieved by incubation in solutions that contained the same levels of calcium and phosphate as is found in the serum of animals given vitamin D. These results did not really indicate the mechanism of action of vitamin D, but it did suggest that the failure of mineralization might well be a failure of supply of calcium and phosphorus to the bone compartment in the case of vitamin D deficiency. This idea was to be left uninvestigated for some time.

The next important advance took place with the discovery by Nicolaysen *et al.*[40,41] that vitamin D increases the absorption of calcium from the small intestine. This clearly showed that vitamin D was an important factor in the utilization of dietary calcium. Nicolaysen *et al.*[41] also noted that animals on a low-calcium diet had much greater efficiency of calcium absorption than animals fed an adequate amount of calcium. In addition to the role of vitamin D in calcium absorption, Nicolaysen[41] put forth the idea of an 'endogenous' factor that would inform the intestine of the bone requirements for calcium. Thus, under circumstances of low mineralization, bone would signal the intestine that additional calcium absorption was required. The 'endogenous' factor of Nicolaysen was clearly defined with the discovery of the functional metabolism of vitamin D described later.

In 1952, a somewhat unappreciated but major discovery was made by Carlsson[42] and Bauer *et al.*,[43] who found that vitamin D, rather than directly causing a deposit of mineral in bone, actually caused the mobilization of calcium from the bone into the plasma compartment. Although this would appear to decalcify the bone, it represented an important mechanism whereby vitamin D has an important role in the maintenance of serum calcium that is required not only for mineralization of the skeleton but also for neuromuscular function. Nevertheless, this discovery defined a new way that vitamin D could cause an increase in serum calcium.

Turning back to the work of McCollum *et al.*[44] and Steenbock and Black,[25] the production of rickets in rats required not a low-calcium diet but rather a high-calcium and low-phosphorus diet. The rachitic epiphyseal plate could only be found when a high-calcium, low-phosphorus vitamin D-deficient diet was fed in the case of rats. In these animals provided vitamin D, not only was there an increase in serum calcium but also an increase in serum phosphorus.[45] It was later demonstrated that a major role of vitamin D is to increase the transport of phosphate from the lumen of the intestine to the serum, providing an increase in serum phosphorus. In a further attempt to define the mechanism of action of vitamin D at the cellular, if not molecular, level, Schachter and Rosen[46] introduced the idea of studying the transport of calcium *in vitro* using an everted sac technique. These investigators could show that vitamin D increased the active transport of calcium against a concentration gradient from the lumen of the intestine into the plasma compartment,[47] underscoring the findings of Nicolaysen and indicating that this transport is an active process; one that was later confirmed by Walling and Rothman[48] using classical electrophysiology methods. Phosphate absorption from the intestine is also an active process dependent on calcium, which is vitamin D dependent.[49,50]

Another important advance was the position taken by Lamm and Neuman[51] in their physical/chemical considerations of mineralization. Lamm and Neuman[51] provided evidence that the blood is normally supersaturated with calcium and phosphorus, and that mineralization is actually a catalyzed crystallization process. The idea then evolved that vitamin D increases serum calcium and phosphorus to supersaturating levels that are responsible for normal mineralization of the bone.[52] A final demonstration of this was carried out by Underwood and DeLuca[53] in which infusion of calcium and phosphate to maintain normal serum levels of calcium and phosphate in vitamin D-deficient rats resulted in normal mineralization. Studies then turned to an understanding of the mechanism of action of vitamin D on the intestine, bone and kidney, where calcium and phosphorus are absorbed or resorbed or mobilized. Peculiarly, rickets can be produced in rats only with a low-phosphorus, vitamin D-deficient diet, whereas a low-calcium, vitamin D-deficient diet results in a type of osteoporosis.[25,45,54] However, both low serum calcium and low serum phosphorus produce rickets in humans.[55,56]

The Functional Metabolism of Vitamin D

A study of the time course of calcium transport by the everted sac technique by the DeLuca laboratory[57] showed that a 16-h lag between dosing vitamin D_3 to vitamin D-deficient animals occurred before the active transport of calcium occurred in the intestine. The same could be said for the mobilization of calcium from the bone.[57] Thus, the lag signaled some important events were taking place before the action of vitamin D could be observed on calcium.

During the 1950 era, Professor Egon Kodicek of Cambridge became very interested in following what happens to the vitamin D_2 molecule in the course of its function.[37] Professor Kodicek laboriously prepared radiolabeled vitamin D_2 by incubating

yeast in ^{14}C containing acetate medium. He was successful in obtaining vitamin D_2 of fairly low specific activity to begin his studies on metabolism. Kodicek[37] had attempted to study metabolism without the use of radiolabels and found it laborious and difficult to interpret. After more than a decade of experimentation, Kodicek[58] concluded that vitamin D was active directly without metabolic change, as all metabolites were found without biological activity. Unfortunately, Professor Kodicek was required to use very large doses of vitamin D_2 beyond what was considered a physiologic level. As a result, his studies were primarily directed to the storage of vitamin D rather than function. To obtain evidence on the lag in vitamin D activity between the time of dosing and calcium transport, it was essential to learn whether the vitamin D actually reached the intestine as quickly as expected or whether there was some delay in transport and deposit. This required the synthesis of radiolabeled vitamin D of high specific activity, which was first achieved by the Wilzbach method,[59] and even more efficiently with a radiochemical synthesis putting the tritium in the 1 and 2 position, giving high-enough specific activity to follow a truly physiologic dose.[60] This allowed the detection of metabolites of vitamin D very quickly (within 1–2 h) after dose and long before the intestine and bone responded.[61–63] These metabolites could easily be found following Silica chromatography.[61–63] The largest metabolite fraction was termed 'peak 4,' and when this was given back to vitamin D-deficient animals it proved to be more potent and acted more quickly than vitamin D_3 in turning on intestinal calcium transport.[61,62] In the meantime, Haussler and Norman[64] published a paper using the Wilzbach-labeled vitamin D_3 and concluded that vitamin D_3 was active in the intestine without metabolic change. To generate large amounts of the peak 4 metabolite for identification, four pigs were given large doses of vitamin D_3, and their blood plasma extracted and chromatographed several times on Silica; however, even at this state of purification, mass spectrometry was not possible because of the interfering lipids. The final step on reverse-phase chromatography was devised that produced a pure metabolite, which was clearly identified by mass spectrometry, UV absorption spectrometry and nuclear magnetic resonance spectrometry as 25-hydroxyvitamin D_3 (25-OH-D_3).[65] This compound was quickly synthesized[66] and its biological effectiveness demonstrated, as well as its rapid action.[67] The synthesis of this compound from the 25-keto cholesterol material available from commercial sources could be converted to the 25-OH-D_3, which allowed for the introduction of tritium in the 26 and 27 positions by a Grignard reaction.[68] When this highly radiolabeled 25-OH-D was administered, it was rapidly metabolized to still other metabolites, of which two out of three found in the blood were identified.[69,70] However, to be certain that the metabolically active form of vitamin D was isolated and identified, the Wisconsin group used vitamin D-deficient chickens given radiolabeled vitamin D_3 in order to allow following of the metabolite. From 1600 chick intestines, a metabolite was isolated following 8 chromatographic steps to a substance, which was not yet quite pure enough for mass spectrometry.[71,72] It still contained a contaminant that interfered with identification. A final step was introduced in which all hydroxyls could be converted to a trimethylsilyl (TMS) derivative. The TMS derivative was subjected to mild acid hydrolysis, which removed the TMS from the secondary hydroxyls, leaving the 25-TMS (a tertiary hydroxyl TMS) intact. This provided a chromatographic difference between the metabolite and the contaminant, resulting in a pure 25-TMS derivative of the metabolite. By means of mass spectrometry and chemical reactions, it was identified as 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$).[71,72] This structure was reported at the Parathyroid Conference in North Carolina and was the first identification of this metabolite.[73] Subsequently, a report appeared from the Kodicek and colleagues[74] in which a 30% pure material was reputed to have been identified as 1,25-$(OH)_2D_3$, although it was not clear how that identification could take place with such an impure preparation. Still another report appeared later but did not provide the necessary information that would allow deduction of the structure.[75] The configuration of the hydroxyl on the 1 position could not be deduced until chemical synthesis was carried out, in which the 1α- and 1β-25-dihydroxyvitamin D_3 compounds could be produced.[76] By co-chromatography, it became clear that the active metabolite is 1α,25-$(OH)_2D_3$. The 1α,25-$(OH)_2D_3$ proved to be extremely potent but very short lived, and is well recognized as the metabolically active form of vitamin D in managing serum calcium, serum phosphorus and mineralization of the skeleton.[57,77] The Wisconsin group continued to isolate and identify metabolites until $\sim$30 metabolites had been identified.[78] The most notable substance that required a great deal of attention was the 24R,25-dihydroxyvitamin D_3, which was originally identified as 21,25-dihydroxyvitamin D_3[70] but was later corrected by the Wisconsin group.[79] Many claims have been made for this substance as an active metabolite and Boyle *et al.*[80] did extensive experiments in the rat to try to find a functional role for this substance. A final blow to the idea that 24,25-dihydroxyvitamin D_3 as an active form was done by the synthesis of 24,24-difluoro-25-hydroxyvitamin D_3. Animals supported for two generations on this form of vitamin D that cannot be 24-hydroxylated showed no deficiency phenotype whatsoever and, in fact, fully normal and fully able to carry out reproduction and development.[81] Thus, it became very clear that vitamin D must first be metabolized to a blood form, 25-OH-D_3, that in itself is not directly biologically active, but be further metabolized to 1,25-$(OH)_2D_3$ to carry out its functions in calcium, phosphorus and bone metabolism[57,82,83] (**Figure 2**). The active metabolites of vitamin D_2, that is, 25-hydroxyvitamin D_2 and 1,25-dihydroxyvitamin D_2, were also isolated and identified.[84,85]

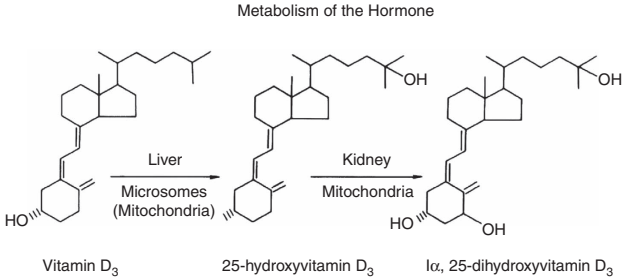

Figure 2 The functional metabolism of vitamin D_3. A CYP2R1 enzyme in the liver converts vitamin D_3 to 25-OH-D_3, the circulating form of vitamin D_3, and a CYP27B1 enzyme converts it to the 1,25-$(OH)_2D_3$ in the proximal convoluted tubule of the kidney to the final hormone, 1α,25-$(OH)_2D_3$.

The Vitamin D Endocrine System

Following identification of 25-OH-D_3, the organ responsible for the conversion of vitamin D_3 to 25-OH-D_3 was determined to be the liver because subtotal hepatectomy largely eliminated this conversion.[86] The enzyme largely responsible is the CYP2R1 as will be described in subsequent chapters.[87]

Fraser and Kodicek[88] demonstrated that the conversion of 25-OH-D_3 to what was later identified by Holick *et al.*[71,72] as 1,25-$(OH)_2D_3$ takes place in the kidney and, in particular, in the proximal convoluted tubule.[89] It was cloned as the CYP27B1 by three groups.[90–92]

With the advent of molecular biology, transcripts of the CYP27B1 have been found in several cells not previously recognized as a site of production of 1,25-$(OH)_2D_3$. Reports of the existence and the generation of 1,25-$(OH)_2D_3$ in small amounts in these tissues have suggested a paracrine/autocrine function of the vitamin D system. This is likely true but has not been firmly established by rigorous chemical methods. In any case, subsequent chapters will discuss the possible paracrine/autocrine functions of the vitamin D system.

During the course of this development, Ian Boyle in the DeLuca laboratory became very interested in the regulation of the metabolism of vitamin D. In a classical paper, it was demonstrated that when a low-calcium diet is fed a high degree of conversion of 25-OH-D_3 to 1,25-$(OH)_2D_3$ occurs, giving very high blood levels of 1,25-$(OH)_2D_3$, whereas when high-calcium diets are fed the synthesis of the active form of vitamin D is clearly suppressed producing low amounts.[93,94] The beginning of a feedback regulation system became clear. Garabedian *et al.*[95] was able to show that hypocalcemia was detected by the parathyroid glands and, in response, the parathyroid hormone (PTH) proved to be the stimulus of the 1α-hydroxylase in the kidney to produce 1,25-$(OH)_2D_3$. When the parathyroids were removed, the animal was unable to sense the hypocalcemia and interpret it by producing 1,25-$(OH)_2D_3$. Although the exact mechanism has yet to be deduced, it is clear that parathyroid acts through the G-protein mechanism to stimulate the transcription and translation of the 1α-hydroxylase enzyme to produce 1,25-$(OH)_2D_3$, and this still remains as the major regulator of synthesis of this very potent calcium-mobilizing hormone.[96] Nicolaysen's 'endogenous factor' was clearly identified as the PTH/1, 25-$(OH)_2D$ system.[52,94]

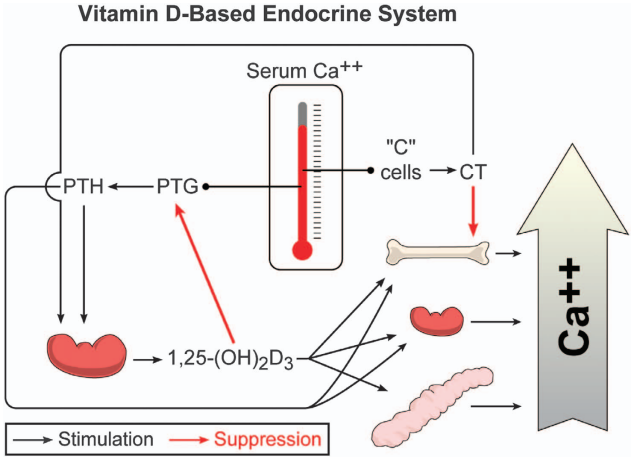

Figure 3 A diagrammatic representation of the vitamin D-based endocrine system. The calcium-sensing proteins in the parathyroid and 'C' cells are shown as a thermometer. Slight hypocalcemia causes secretion of PTH that signals the CYP27B1 to synthesize 1,25-$(OH)_2D_3$ that directs calcium mobilization in the intestine, kidney and bone. A feedback suppression of PTH synthesis and secretion, and parathyroid proliferation by 1,25-$(OH)_2D_3$ is shown. Calcitonin is secreted by the 'C' cells of the thyroid. It suppresses bone resorption.

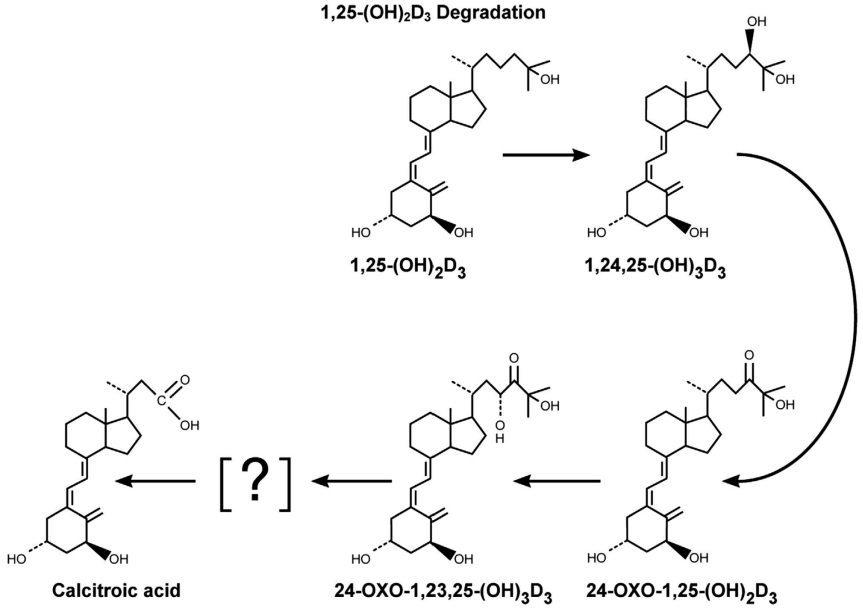

Figure 4 Degradation of 1α,25-$(OH)_2D_3$. The *CYP24A1* gene is induced by 1,25-$(OH)_2D_3$. The resulting enzyme carries out all the reactions shown to produce the biologically inactive excretion product, calcitroic acid. Presumably, a similar set of reactions takes place with 25-OH-D_3 as the substrate. Clearly, 1,25-$(OH)_2D_3$ programs its own destruction through the CYP24A1.

Attention was then focused on the 24-hydroxylase and its importance in the vitamin D endocrine system. This enzyme, which is a cytochrome P-450, is located in kidney mitochondria and in all target tissues of the vitamin D hormone.[96–99] The enzyme has been cloned and a knockout has been produced.[100] The intermediates in the metabolism of 1,25-$(OH)_2D_3$ and the final product, calcitroic acid, have clearly been identified[96,98,101] and is the primary excretory product of the active form of vitamin D. Recently, human patients have been identified with inactivating mutations of CYP24A1, elevations of serum 1,25-$(OH)_2D_3$ and idiopathic infantile hypercalcemia, further supporting a catabolic function for CYP24A1.[102] **Figure 3** illustrates the known conversion of 1,25-$(OH)_2D_3$ to its excretion product, calcitroic acid. Thus, it became clear that in vitamin D deficiency, CYP24A1 is not expressed and is induced by the vitamin D hormone acting through its receptor.[103] Thus, the active form of vitamin D induces its own destruction by turning on the synthesis of the enzyme that metabolizes it to an inactive final product. CYP24A1 also acts on 25-OH-D to produce 24,25-$(OH)_2D_3$ and is still believed to be a route of elimination of 25-OH-D. Thus far, no functional importance beyond this has been found for this important metabolite of vitamin D.

An important chapter to the vitamin D endocrine system is one that involves a feedback regulation of the parathyroid gland (**Figure 4**). The parathyroid gland has a very high concentration of the vitamin D receptor.[104] It is very clear from the work of two different groups that 1,25-$(OH)_2D_3$ through its receptor suppresses the preproparathyroid gene and diminishes the production and secretion of the PTH.[105,106] This is an important mechanism that has a striking role in the development of the disease, renal osteodystrophy. It is this target that is used to treat the secondary hyperparathyroidism of patients on dialysis, who have lost the ability to produce the vitamin D hormone. Its success in this capacity is clearly shown by not only its use to suppress secondary hyperparathyroidism but the development of at least two or three important analogs of vitamin D that are sold commercially for this purpose.[107–109] **Figure 4** puts together the vitamin D endocrine system and its regulation. In subsequent chapters, various aspects of this endocrine system will be discussed. Notably absent from this figure is the fibroblast growth factor-23 involvement with vitamin D metabolism. This discussion is beyond the scope of this historical chapter and will be covered by subsequent chapters.

From 1965 until 1975, the elements of the vitamin D endocrine system that regulate calcium and phosphorus became clear. A great deal of work remains to be done to understand how this system works, what are the many additional regulators that can be found and how does it work in regulating the transcription and suppression of target genes. These advances so far have provided a number of important forms of vitamin D for the treatment of disease and important new insights into the etiology of those diseases.

Conflict of Interest

The author declares no conflict of interest.

Acknowledgements

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