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VITAMIN D

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Summary

It is established that the classical biological actions of the nutritionally important vitamin D in mediating calcium homeostasis are supported by a complex vitamin D endocrine system which coordinates the metabolism of vitamin D_3 into $1\alpha,25(OH)_2D_3$ and $24R,25(OH)_2D_3$. The biologically inert vitamin D_3 must be converted to its daughter steroid hormone, $1\alpha,25(OH)_2D_3$, which acts in partnership with the vitamin D receptor (VDR) to mediate both genomic and rapid responses. Our updated understanding of the vitamin D endocrine system includes many more target tissues than simply the calcium-homeostasis-related intestine, bone, kidney, and parathyroid gland. It is now accepted that five previously unrecognized physiological systems respond to $1\alpha,25(OH)_2D_3$ working with VDR. These include the heart and cardiovascular system, the immune system (both innate and adaptive), muscle, pancreas, and metabolic homeostasis, and the brain. Vitamin D nutritionists and scientists in many countries agree that about half of elderly Western Europeans and North Americans and probably two-thirds of the rest of the world are not receiving enough vitamin D to maintain healthy bone. It is also agreed that the best marker of an individual's vitamin D nutritional status is the level of the serum 25(OH)D. A level of 25(OH)D of <20 ng/mL (50 nmol/L) reflects a state of vitamin D insufficiency or worse. A circulating level of 25(OH)D >30 ng/mL or 75 nmol/L is reflective of a vitamin D sufficient state. Given its recently recognized importance in important physiological systems, the fact that so many people throughout the world have much lower 25(OH)D levels is a public health challenge of major proportions.

Introduction

Background

Vitamin D is essential for life in higher animals. Classically it has been shown to be one of the most important biological regulators of calcium homeostasis. It has been established that these biological effects are only achieved as a consequence of the metabolism of vitamin D into a family of daughter metabolites, including the two key kidney-produced metabolites, $1\alpha,25(OH)_2$-vitamin D_3 [$1\alpha,25(OH)_2D_3$] and $24R,25(OH)_2$-vitamin D_3 [$24R,25(OH)_2D_3$] (see Figure 13.2). $1\alpha,25(OH)_2D_3$ is considered to be a steroid hormone and there is evidence that $24R,25(OH)_2D_3$ may also act as a steroid hormone (Feldman *et al.*, 2005).

Since the 1980s it has become increasingly apparent that $1\alpha,25(OH)_2D_3$, in addition to its role in calcium homeostasis, plays an important role in differentiation and

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proliferation of a wide variety of cells and tissues not primarily related to mineral metabolism; these include cells of the hematopoietic system, keratinocytes, and cells secreting parathyroid hormone and insulin. In addition, many types of cancer cells, including breast and prostate cancer cells, possess the vitamin D receptor (VDR) and therefore are targets of $1\alpha,25(OH)_2D_3$ action. And in the last decade, it has become clear that five new physiological roles for $1\alpha,25(OH)_2D_3$ have been added to its list of responsibilities.

The purpose of this chapter is to provide a succinct overview of our current understanding of the important nutritional substance vitamin D, the mechanisms by which its biologically active metabolite, the steroid hormone $1\alpha,25(OH)_2D_3$, mediates biological responses, and its role in several important human diseases In addition, the nutritional aspects of vitamin D are presented from the perspective that there is widespread vitamin D deficiency in all countries of the world.

Historical Review

The first scientific description of rickets, the hallmark of vitamin D deficiency, was provided by Dr Daniel Whistler in 1645 and Professor Francis Glisson in 1650 (Norman, 1979). The major breakthrough in understanding the causative factors of rickets was the development of nutrition as an experimental science, followed by the appreciation of the existence of vitamins more than two centuries later. Although vitamin D, through a historical accident, was originally classified as a vitamin, it is now known that the "D-vitamin" is produced in the skin and it is widely accepted that its biologically active form is a steroid hormone. In 1919–1920 Sir Edward Mellanby, working with dogs raised exclusively in the absence of sunlight or ultraviolet light, devised a diet which allowed him to unequivocally establish that rickets was caused by a deficiency of a trace component in the diet. In 1921 he wrote, "The action of fats in rickets is due to a vitamin or accessory food factor which they contain, probably identical with the fat-soluble vitamin." Furthermore he established that cod-liver oil was an excellent antirachitic agent, leading to the classification of the antirachitic factor as a vitamin (Norman, 1979).

The chemical structures of the D vitamins were determined in the 1930s in the laboratory of Professor A. Windaus at the University of Göttingen. Vitamin D_2, produced by ultraviolet irradiation of the plant/yeast steroid ergosterol, was chemically characterized in 1932 (Norman, 1979). Vitamin D_3, the form that is produced in the skin of vertebrate animals, was not chemically characterized until 1936 when it was shown to result from the ultraviolet irradiation of 7-dehydrocholesterol (Norman, 1979). Virtually simultaneously, the elusive antirachitic component of cod-liver oil was shown to be identical to the newly characterized vitamin D_3 (Norman, 1979). These results clearly established that the antirachitic substance vitamin D was chemically a steroid, more specifically a seco-steroid (see below).

The modern era of vitamin D began in the interval of 1965–1970 with the discovery (Haussler *et al.*, 1968) and chemical characterization of $1\alpha,25(OH)_2D_3$ (Norman *et al.*, 1971) and its nuclear receptor, the VDR (Haussler and Norman, 1969).

Chemistry of Vitamin D

The structures of vitamin D_3 (cholecalciferol) and its provitamin, 7-dehydrocholesterol, are presented in Figure 13.1. Vitamin D is a generic term and indicates a molecule of the general structure shown for rings A, B, C, and D with differing side-chain structures. The ring structure is derived from the cyclopentanoperhydrophenanthrene ring structure for steroids but with the 9,10 carbon–carbon bond of ring B broken, as indicated by the inclusion of "9,10-seco" in the official nomenclature. A discussion of the conformational shapes attainable by vitamin D is given in the legend to Figure 13.1.

Vitamin D (synonym calciferol) is named according to the revised rules of IUPAC (the International Union of Pure and Applied Chemists: IUPAC, 1960). Because it is derived from a steroid, vitamin D retains its numbering from the parent compound cholesterol (see Figure 13.1). Asymmetric centers are designated by using the R,S notation (Norman and Litwack, 1987); the configurations of the double bonds are indicated as E (*trans*) and Z (*cis*). Thus the official name of vitamin D_3 is 9,10-seco(5Z,7E)-5,7,10(19)cholestatriene-3β-ol. Vitamin D_2 differs from D_3 by virtue of the presence of a 22,23 double bond and a 24-methyl group in the side chain. The official name of vitamin D_2 is 9,10-seco(5Z,7E)-5,7,10(19),22-ergostatetraene-3β-ol. From 1940 until about 1960, vitamin D_2 was used as the food supplement to supply vitamin D activity, but since the 1970s, in the United States, vitamin D_3 has been the form of calciferol that is routinely used for food supplementation (Norman, 1979).

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