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VIEWPOINT

Vitamin D Research Frontiers

Research directed at defining the molecular mode of action of vitamin D is currently at its zenith. Evidence now implicates the essential involvement of vitamin D metabolites in a host of cellular processes, including calcium homeostasis, cell differentiation, immunology, and regulation of gene transcription. In addition, there are many examples of pathological disruption of the normal state such that a drug form of vitamin D is postulated to be a possibly useful form of treatment, e.g., renal osteodystrophy, osteoporosis, psoriasis, leukemia, and breast cancer. Detailed below is a brief enumeration of the history of vitamin D which summarizes the rather slow development of understanding of its broad biological importance.

The molecule vitamin D has been accepted as being of importance in the biological systems of higher animals since its discovery by Mellanby in 1920 [7]. It was in the interval of 1920–1930 that vitamin D officially became classified as a "vitamin" that was important, if not essential, for the normal development of the skeleton and maintenance of Ca^{2+} homeostasis. The three principal target organs were identified as being the intestine, kidney, and bone. The chemical structure of vitamin D was not deduced until 1932 [1,2] and it was only then that it was apparent that this important nutritional substance was in reality a steroid, more specifically, a seco-steroid. The chemical nomenclature term "seco" signifies that one of the rings of the cyclopentanoperhydrophenanthrene ring structure has been broken; in the case of vitamin D, it is the 9–10 carbon-carbon bond of ring B which is broken.

From 1930 to 1965 research directed towards defining the molecular mode of action of vitamin D was largely nutritional in character with an implied emphasis on the vitamin functioning as some co-factor (in a fashion analogous to the water soluble vitamins) for biological processes related to calcium metabolism [8]. In retrospect it was largely overlooked by biologists that the molecule vitamin D was a sterol, and displayed the common chemical properties characteristic of steroids, including steroid hormones. Our evolution of the understanding of the shape or conformation of vitamin D seco-steroids is summarized in the cover figure of this issue of the *Journal of Cellular Biochemistry* and its legend on the table of contents. It is now clear that the molecule vitamin D and all of its many metabolites and analogs in fact have the unique chemical property of a conformationally active A ring, a property not displayed by classic steroid hormones, such as the glucocorticoids, estrogens, androgens, progestins, etc. [5]. Thus receptors for vitamin D compounds must cope with the conformational mobility of the A ring of this steroid.

A new era of vitamin D research was initiated in approximately 1965, when researchers began to study the biological actions of vitamin D from the perspective that it was not functioning as a vitamin co-factor, but that it was in reality a steroid. In the 10-year interval 1965–1975, the vitamin D endocrine system was discovered and the molecule $1,25(OH)_2$-vitamin D_3 [$1,25(OH)_2D_3$] was accepted as being the hormonally active form of vitamin D; see references 6 and 8 for a comprehensive review. Thus the kidney is an endocrine gland which possesses a cytochrome P-450 hydroxylase which produces the steroid hormone $1,25(OH)_2D_3$. The molecule $1,25(OH)_2D_3$ is currently understood to produce biological responses both via genomic pathways [there are over 30 tissues possessing a nuclear receptor for $1,25(OH)_2D_3$] as well as by nongenomic pathways (which may involve the regulation of Ca^{2+} channels and the involvement of protein kinase A and C signal transduction pathways). The cytosolic-nuclear receptor for $1,25(OH)_2D_3$ belongs to the steroid hormone super-family of transactivating regulators of gene transcription [6]. In addition, there has emerged an astonishingly wide array of clinical application of the newer knowledge and con-

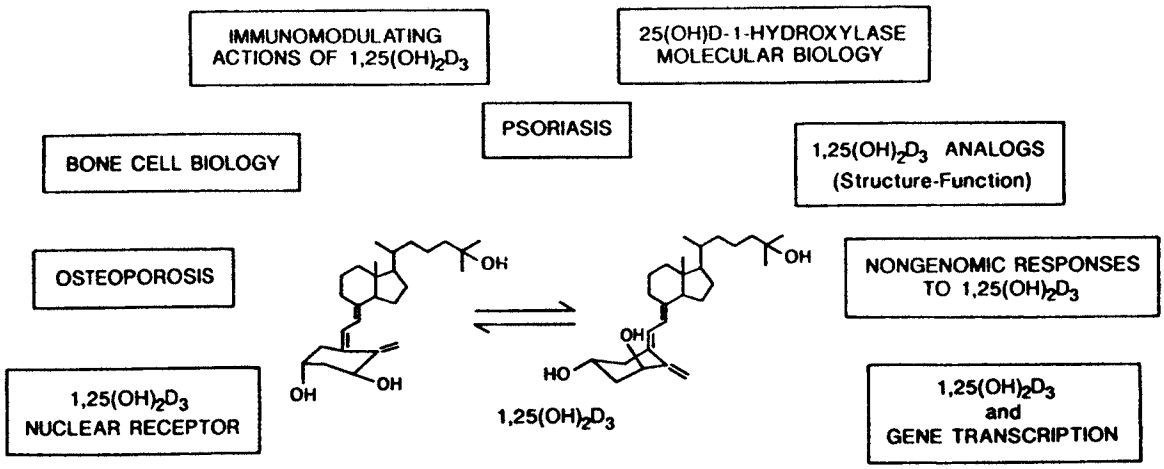

Fig. 1. Vitamin research frontiers.

cepts pertaining to the vitamin D endocrine system. Thus there are logical connections between $1,25(OH)_2D_3$ and the diseases of renal osteodystrophy, osteoporosis, diabetes, leukemia, psoriasis, and rickets, to name a few.

The extraordinary breadth of the vitamin D endocrine system then has proven to be fertile ground for research, both with the objective of defining the molecular mode of action(s) of $1,25(OH)_2D_3$, as well as elucidating how various disease states may involve aberrations in the production or actions of $1,25(OH)_2D_3$ or other metabolites.

In light of the very recent accumulation of these new biological insights it is not surprising that research on vitamin D is currently at its zenith. At the Eighth Workshop on Vitamin D, held in Paris, France, from July 5 to 10, 1991, some 605 scientists from 33 countries convened to share research findings in the arenas of chemistry, cell biology, biochemistry, molecular biology, and a wide array of clinical topics [9] related to the vitamin. As summarized in Figure 1, nine research frontiers emerged at the Workshop as being unusually productive in the sense that new insights were being gained with respect to the molecular mode of action and clinical application of $1,25(OH)_2D_3$ and the vitamin D endocrine system. It is now becoming clear that it is possible to chemically synthesize vitamin D analogs which display selective biological actions; at the Workshop the synthesis and biological properties of 20 analogs of $1,25(OH)_2D_3$ were reported. Thus, following this Viewpoint article are a series of Prospect articles, each focusing on one research frontier of vitamin D: these include structure-function relationships and chemistry of $1,25(OH)_2D_3$; bone cell biology; the biochemistry and molecular biology of the vitamin D hydroxylases; the genetics and biochemistry of the nuclear receptors for $1,25(OH)_2D_3$, including an understanding of how mutations can lead to specific genetic diseases such as vitamin D resistant rickets (VDRR); $1,25(OH)_2D_3$ receptor mediated regulation of gene transcription; new insights into the nongenomic pathways which $1,25(OH)_2D_3$ employs to generate biological responses; the role of $1,25(OH)_2D_3$ in the immune system and its potential use as a drug to mediate immunosuppression; use of drug forms of $1,25(OH)_2D_3$ for treatment of osteoporosis; and use of drug forms of $1,25(OH)_2D_3$ to treat psoriasis.

The purpose of this Viewpoint article, then, is to pique the curiosity of the reader to spend some time reading the Prospects articles and to share in the "wonderful world of vitamin D." How can a molecule as simple as vitamin D have a biology so rich and varied as that of $1,25(OH)_2$-vitamin-D_3? I hope you have an enlighting and rewarding tour of the vitamin D endocrine system.

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