A Half-century of Vitamin D: the Work of Hector F. DeLuca

25-Hydroxycholecalciferol-1-hydroxylase. Subcellular Location and Properties

Receptors of 1,25-Dihydroxycholecalciferol in Rat Intestine

1,24,25-Trihydroxyvitamin D3. A Metabolite of Vitamin D3 Effective on Intestine

Hector F. DeLuca grew up on a vegetable farm outside Pueblo, Colorado, an industrial town at the foot of the Rocky Mountains. His life on the farm allowed him to watch things grow around him, which cultivated a keen interest in the living world. His seventh grade biology class deepened this interest, and when he graduated from high school he decided to attend the University of Colorado and major in chemistry. DeLuca graduated in 1951 and went on to pursue graduate work with Harry Steenbock at the University of Wisconsin-Madison. Steenbock was a pioneer in vitamin D research and had discovered that the vitamin could be produced from exposure to sunlight and that it prevented rickets. This research had made a deep impression on DeLuca, and from the moment he arrived in Wisconsin, vitamin D became the center of his attention.

When Steenbock retired in 1955, he asked DeLuca to take over his laboratory and carry on his research. DeLuca did so, and in 1968 he isolated an active vitamin D metabolite and identified it as 25-hydroxyvitamin D3 (1). He later showed that the substance was produced in the liver. During the next several years, DeLuca, Anthony W. Norman, and E. Kodicek independently reported the existence of a second active metabolite, 1,25-dihydroxyvitamin D3, which was produced in the kidneys (2–5). From these observations it was surmised that vitamin D3 was hydroxylated in the liver to become 25-hydroxyvitamin D3, the major circulating form of the vitamin, and then converted to 1,25-dihydroxyvitamin D3 in the kidneys. This final metabolic product was the metabolically active form of vitamin D3, which carried out its functions in initiating intestinal calcium transport. An important result of these experiments was that 1,25-dihydroxyvitamin D3 was reclassified as a hormone that controlled calcium metabolism.

The three Journal of Biological Chemistry (JBC) Classics reprinted here all report on discoveries made by DeLuca after he laid this initial groundwork in vitamin D research. In the first JBC Classic, DeLuca reports on the subcellular location of the enzyme responsible for the hydroxylation of 25-hydroxyvitamin D3 to 1,25-dihydroxyvitamin D3 in the chicken kidney. Some of the properties of the hydroxylase, which DeLuca determined was located in the mitochondria, are also described in the paper.

The second JBC Classic reprinted here deals with DeLuca’s identification of the subcellular location of 1,25-dihydroxyvitamin D3 in the intestine after it is released from the kidneys. By feeding 3H-labeled 1,25-dihydroxyvitamin D3 to vitamin D-deficient rats, DeLuca was able to show that most of the vitamin derivative was located in a crude nuclear debris fraction. Of the radioactivity associated with this fraction, 30–45% was connected to chromatin whereas 50%...
appeared to be extranuclear or loosely bound to the nuclei, possibly associating with a low density protein that is rich in lipid. It was subsequently confirmed that the active vitamin D metabolite binds to a transcription factor in the nucleus of cells in the intestine. The transcription factor then regulates gene expression of transport proteins that are involved in calcium absorption in the intestine.

In the final JBC Classic reprinted here, DeLuca reports on the isolation and characterization of the vitamin D metabolite, 1,24,25-trihydroxyvitamin D$_3$. It had been found that under normal calcemia, hypercalcemia, and hyperphosphatemia conditions, the kidney limited the production of 1,25-dihydroxyvitamin D$_3$ and instead synthesized 24,25-dihydroxyvitamin D$_3$. Evidence had also indicated that this metabolite was further metabolized to a more polar compound responsible for biological responses. This suggested to DeLuca that there might be an alternate pathway for vitamin D$_3$ metabolism and that the metabolite of 24,25-dihydroxyvitamin D$_3$ might be a tissue-specific hormone that would stimulate only intestinal calcium transport. He isolated the metabolite in pure form from chicken kidney homogenates and identified it as 1,24,25-trihydroxyvitamin D$_3$.

DeLuca subsequently became interested in these tissue-specific analogues of vitamin D and their utility in the treatment of a variety of diseases including osteoporosis, vitamin D-dependent rickets, and bone disease of kidney failure. From his research, DeLuca has been able to develop several successful vitamin D-related drugs for everything from kidney failure to psoriasis. In 2001, he founded Deltanoid Pharmaceuticals, a company focused on developing therapies derived from these vitamin D-based compounds. DeLuca remains at the University of Wisconsin where he served as Chairman of the University’s biochemistry department for 30 years and is currently a Harry Steenbock Research Professor.

In recognition of his significant contributions to our understanding of vitamin D, DeLuca has received several awards and honors. These include the 1968 Meade Johnson Award from the American Institute of Nutrition, the 1973 Osborne and Mendel Award from the American Institute of Nutrition, the 1974 Gairdner Foundation Award, the 1982 William C. Rose Award from the American Society for Biochemistry and Molecular Biology, the 1983 3M Life Sciences Award from the Federation of American Societies for Experimental Biology, the 1983 Bristol-Myers Squibb/Mead Johnson Award for Distinguished Achievement in Nutrition Research, the 1985 William F. Neuman Award from the American Society for Bone and Mineral Research, and the 1993 SmithKline Beecham Clinical Assay Award. DeLuca is a member of the American Academy of Arts and Sciences and the National Academy of Sciences.

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REFERENCES