Inherited Disorders of Vitamin D Metabolism
and Action

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Summary

A key event in the activation of vitamin D is its double-stage hydroxylation to form 1,25-(OH)2D, its hormonally active metabolite. Two primary inborn errors of vitamin D metabolism are known, pseudodeficiency rickets type I and type II. Pseudodeficiency rickets type I presumably results from a defect in the final enzymatic system leading to the formation of 1,25-(OH)2D. Its clinical, radiological, and most of its biological manifestations are similar to those observed in nutritional vitamin D deficiency. Complete healing can be achieved, provided that oral treatment with pharmacological doses of vitamin D or low doses of 1,25-(OH)2D3 or analogs is given during the patient’s entire life. Pseudodeficiency rickets type II results from a nonselective tissue resistance to 1,25-(OH)2D3. Its signs are rickets refractory to high doses of vitamin D and, in half of the cases, alopecia. Its pathological manifestations, alopecia excepted, may be overcome by extremely high doses of vitamin D derivatives or, in the most severe cases, by long-term calcium infusions or ultra-high doses of oral calcium.

Introduction

Twelve years after its identification as a new form of hereditary vitamin D-resistant rickets [1], “hereditary pseudo-deficiency rickets” was recognized as the first example of inborn error of vitamin D metabolism [2]. Later on, “pseudo-deficiency rickets type II” was isolated, which is the consequence of an inherited resistance to 1,25-(OH)2D3 [3, 4], and not of an impaired formation of this vitamin D metabolite, as in type I. One hundred cases have been reported for type I but the incidence of this disorder has not been evaluated. Type II or inherited resistance to 1,25-(OH)2D3 is an extremely rare disease as only 30 families have been reported. Its description in this chapter is justified by the many clinical, biological, and radiological alterations which are common to both types of pseudodeficiency and by the difficult therapeutic problem it poses.
Formation of 1,25-(OH)\(_2\)D in the Physiological State. Vitamin D is nowadays considered to be a hormone precursor. Its hormonal form, 1,25-(OH)\(_2\)D or calcitriol, results from two successive hydroxylations [5–7]. The first one, in the liver, leads to the formation of 25-(OH)D, the major circulating vitamin D metabolite and direct precursor of the hormonal form. The second hydroxylation takes place primarily in the kidney proximal tubule, although other cells have the capacity to carry out this hydroxylation in physiological (fetoplacental unit), pathological (macrophages and lymphocytes), or in vitro culture (bone cells, keratinocytes, cells of the immune system) conditions [7–9]. Several factors control the renal synthesis of 1,25-(OH)\(_2\)D [5, 6] but in general terms and in the physiological state the 1,25-(OH)\(_2\)D synthesis depends mainly on the calcium and/or phosphorus demand from the skeleton, and is stimulated in situations where there are increased requirements (growth, pregnancy, lactation), or insufficient oral intakes of calcium and/or phosphorus.

The main physiological role of 1,25-(OH)\(_2\)D is directly to enhance intestinal absorption of calcium and phosphorus and, directly or indirectly, to facilitate skeletal mineralization through its actions on the intestine, kidney, parathyroid glands, and skeleton [6, 7]. Other actions of 1,25-(OH)\(_2\)D, unrelated to calcium and phosphorus homeostasis, are known or suspected in view of the presence of specific binding sites for 1,25-(OH)\(_2\)D\(_3\) in supposedly target cells [9, 10]. But their physiological relevance remains controversial as no significant functional abnormalities of these cells or tissues have yet been found in pathological situations where there is 1,25-(OH)\(_2\)D deficiency or resistance, apart from those presumably due to the hypocalcemia itself [1, 3, 4, 11].

The Metabolic Derangements

Primary Inherited Disorders of Vitamin D Metabolism

Apart from secondary causes, there is no known inherited pathological disorder specifically involving the formation of vitamin D in the skin, its absorption in the intestine, or its 25-hydroxylation in the liver.

In contrast, there is direct evidence in piglets [12] and indirect evidence in humans [2, 13, 14] for a specific primary defect in the renal formation of 1,25-(OH)\(_2\)D. This only known primary disorder of vitamin D metabolism is “pseudodeficiency rickets type I” (or “vitamin D dependency rickets type I”). A defect in the metabolism or degradation of 1,25-(OH)\(_2\)D has been proposed as a possible explanation for the accumulation of 1,25-(OH)\(_2\)D in the plasma of infants with hypercalcemia and an elfin facies (Williams syndrome) during the hypercalcemic phase of the disease [15], but no direct evidence for an inherited disorder of 1,25-(OH)\(_2\)D catabolism has yet been presented.