Calcium-Regulating Hormones

Vitamin D and Parathyroid Hormone

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1. INTRODUCTION

This chapter describes the structure and actions of vitamin D, which is essential for maintaining a positive calcium balance and skeletal integrity, and the parathyroid hormone (PTH), responsible for minute-to-minute maintenance of calcium homeostasis, which is critical for neuromuscular activity.

2. VITAMIN D

Vitamin D originally attracted attention because of its antirachitic properties. It is now appreciated to be a natural product of the body and is the precursor of the calcium-regulating hormone, 1,25-dihydroxyvitamin D (1,25(OH)₂D). This is produced in the kidney; is released into the circulation, and exerts its effects on mineral homeostasis by acting on intestine, bone, kidney, and the parathyroid gland. The hormone acts like a steroid hormone in the nuclei of target cells, and its production is subject to feedback regulation. Vitamin D and its metabolites form the basis of an endocrine system that interacts with the parathyroid glands and is of fundamental importance in the hormonal control of mineral metabolism.

2.1. Production and Metabolism of Vitamin D

2.1.1. CHEMICAL STRUCTURE

Vitamin D is a 9-10 secosterol with the A-ring rotated into the *cis* configuration. Although it is related to a C₂₁ steroid, it differs in structure by disruption of the bond between C-9 and C-10, opening the B-ring, and thus forms a conjugated triene structure. It also has an elongated side chain (Fig. 1). Cholecalciferol (vitamin D₃) is the natural form of the vitamin. This C₂₇ compound is produced by irradiation of the precursor 7-dehydrocholesterol. Ergocalciferol (vitamin D₂) is a synthetic C₂₈ compound originally produced by irradiation of the plant sterol, ergosterol. The side chain of vitamin D₂ differs from that of vitamin D₃ by having a double bond between C-22 and C-23 and a methyl group at C-24. Vitamins D₂ and D₃ are metabolized along similar pathways, and vitamin D written without a subscript can refer to either form of the vitamin.

2.1.2. PHOTOPRODUCTION

Normally, synthesis of vitamin D₃ in the skin can provide the body’s full requirement unless exposure to sunlight is restricted. Production of vitamin D₃ occurs by nonenzymatic photolysis of 7-dehydrocholesterol (provitamin D) in the epidermis (Fig. 2). Near-ultraviolet (UV) light with a wavelength of 290–315 nm opens the B-ring by cleaving the bond between C-9 and C-10 of 7-dehydrocholesterol, forming previtamin D₃, and rearrangement of the molecule, which is temperature dependent and favored at body temperature, yields vitamin D₃. Two other biologically inert products, lumisterol and tachysterol, are produced by photolysis of previtamin D. The skin pigment melanin can
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D–hydroxylase compensates for loss of the mitochondrial activity. An enzyme, CYP2R1, having the appropriate biochemical properties and tissue and subcellular distribution has been identified. In contrast to CYP27A1, a low-affinity, high-capacity enzyme that activates cholecalciferol but not ergocalciferol, CYP2R1 is a high-affinity, low-capacity enzyme that catalyzes hydroxylation of both vitamins D2 and D3. 25(OH)D3 is more effective than vitamin D3 in curing rickets and acts more rapidly in stimulating both intestinal calcium absorption and calcium mobilization from bone. At one time, it was believed to be the final active metabolite of vitamin D3. However, although it is not biologically active at physiologic concentrations,

Fig. 1. Structure of a C21 steroid (left) compared with a C27 secosterol (right), such as vitamin D3.

also absorb UV light and when present in large amounts competes with 7-dehydrocholesterol for this energy source. Given the same UV exposure, heavily pigmented individuals produce less vitamin D3 than lightly pigmented individuals.

Vitamin D can also be obtained from the diet either as vitamin D3 from foods that contain it naturally (e.g., liver of fatty fish) or from milk and dairy products, which are frequently fortified with either vitamin D2 or D3.

2.1.3. Metabolic Activation of Vitamin D

Biologic responses to vitamin D3 after its administration to animals are apparent only after a significant time lag. Vitamin D must undergo two hydroxylation steps before it assumes the physiologically active form, 1,25(OH)2D3. This allows it to bind to intracellular receptors in target tissues.

2.1.3.1. 25-Hydroxylation in Liver. Vitamin D3 either produced in the skin or absorbed from the small intestine rapidly accumulates in the liver, where it is hydroxylated at C-25 of the side chain to form 25-hydroxycholecalciferol (25(OH)D3), the most abundant form of the vitamin (Fig. 2). Vitamin D2 is similarly metabolized to 25-hydroxyergocalciferol (25(OH)D2). This step is obligatory for further metabolism of the sterol. The liver is the principal site of production in vivo, and total hepatectomy causes the virtual disappearance of 25(OH)D from the circulation. Hepatic 25-hydroxylase activity is associated with mitochondrial and microsomal fractions, and both activities are the result of cytochrome P-450 enzymes. The mitochondrial enzyme is CYP27A1 sterol 27-hydroxylase. Loss-of-function mutations in humans and mice manifest in markedly altered cholesterol metabolism as this enzyme catalyzes an essential step in bile acid synthesis. By contrast, vitamin D metabolism is normal, indicating that the microsomal vitamin D–hydroxylase compensates for loss of the mitochondrial activity. An enzyme, CYP2R1, having the appropriate biochemical properties and tissue and subcellular distribution has been identified. In contrast to CYP27A1, a low-affinity, high-capacity enzyme that activates cholecalciferol but not ergocalciferol, CYP2R1 is a high-affinity, low-capacity enzyme that catalyzes hydroxylation of both vitamins D2 and D3.

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Fig. 2. Metabolic pathway of vitamin D3 production and activation beginning with synthesis of previtamin D3 by UV irradiation of 7-dehydrocholesterol in skin. Rearrangement of previtamin D3 yields vitamin D3, which is metabolized to 25(OH)D3 in the liver. In the kidney, 25(OH)D3 is either metabolized to the hormonally-active 1,25(OH)2D3 or catabolized to 24R,25(OH)2D3. (Adapted from Minghetti and Norman, 1988.)