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Structural aspects of Vitamin D endocrinology

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ABSTRACT

1α,25-Dihydroxvitamin D_3 (1,25$(OH)_2D_3$) is the hormonally active form of vitamin D_3. Its synthesis and its metabolites, their transport and elimination as well as action on transcriptional regulation involves the harmonic cooperation of diverse proteins with vitamin D binding capacities such as vitamin D binding protein (DBP), cytochrome P450 enzymes or the nuclear vitamin receptor (VDR). The genomic mechanism of 1,25$(OH)_2D_3$ action involves its binding to VDR that functionally acts as a heterodimer with retinoid X receptor. The crystal structures of the most important proteins for vitamin D_3, VDR, DBP, CYP2R1 and CYP24A1, have provided identification of mechanisms of actions of these proteins and those mediating VDR-regulated transcription. This review will present the structural information on recognition of the vitamin D_3 and metabolites by CYP proteins and DBP as well as the structural basis of VDR activation by 1,25$(OH)_2D_3$ and metabolites. Additionally, we will describe, the implications of the VDR mutants associated with hereditary vitamin D-resistant rickets (HVDRR) that display impaired function.

1. Introduction

The active form of vitamin D_3, 1α,25-Dihydroxyvitamin D_3 (1,25$(OH)_2D_3$), acts as an endocrine hormone and primarily maintains calcium levels in plasma and phosphate homeostasis. In addition to endocrine hormone actions, locally produced 1,25$(OH)_2D_3$ displays paracrine/autocrine actions (Morris and Anderson, 2010) that are important for epidermal differentiation (Bikle *et al.*, 2004) or innate immune response (Liu *et al.*, 2006).

Vitamin D_3 can be obtained from dietary sources or is synthesized in the skin after sunlight exposure. The activation of vitamin D_3 is accomplished by sequential hydroxylations, 25-hydroxylation of vitamin D_3 leading to 25-hydroxyvitamin D_3, 25$(OH)D_3$, followed by the 1α-hydroxylation (Fig. 1). The first step of 25-hydroxylation occurs in the liver (Ponchon and DeLuca, 1969), and the second one occurs both in the kidney and extra-renal sites (Fraser and Kodicek, 1970; Hewison and Adams, 2011). Several cytochrome P450 enzymes, such as CYP2R1, CYP27A1, CYP3A4, CYP2D25, are able to hydroxylate at C-25. The second hydroxylation at C-1α is done by CYP27B1 (Gray *et al.*, 1972).

Catabolic desactivation pathways include a carbon-24 oxidation by CYP24A1 leading to calcitroic acid production, and a 26,23-lactone pathway for converting both 25$(OH)D_3$ and 1,25$(OH)_2D_3$ to lactone products (Prosser and Jones, 2004). All of the CYPs that are involved in vitamin D hydroxylation, catalyze single or multiple hydroxylation reactions on specific carbons of the vitamin D_3 substrate using a transient heme-bound intermediate. All CYP proteins show high conservation and exhibit a common secondary structure with multiple highly conserved helices, A to L, connected by loops and β-sheet structures. Crystal structures of CYP2R1 (Strushkevich *et al.*, 2008) and CYP24A1 (Annalora *et al.*, 2010) provided insights into the vitamin D hydroxylation mechanism.

Vitamin D_3 metabolites including 1,25$(OH)_2D_3$ are transported by a serum vitamin D binding protein (DBP), also known as GC-globulin (Daiger *et al.*, 1975). DBP also binds saturated and unsaturated fatty acids with moderate affinity, monomeric actin and is able to depolymerize filamentous actin. The crystal structures of DBP bound to 25$(OH)D_3$ (Verboven *et al.*, 2002) as well as bound to actin (Otterbein *et al.*, 2002; Head *et al.*, 2002) were solved.

Most of the biological actions of 1,25$(OH)_2D_3$ are achieved through Vitamin D Nuclear Receptor (VDR)-mediated regulation of

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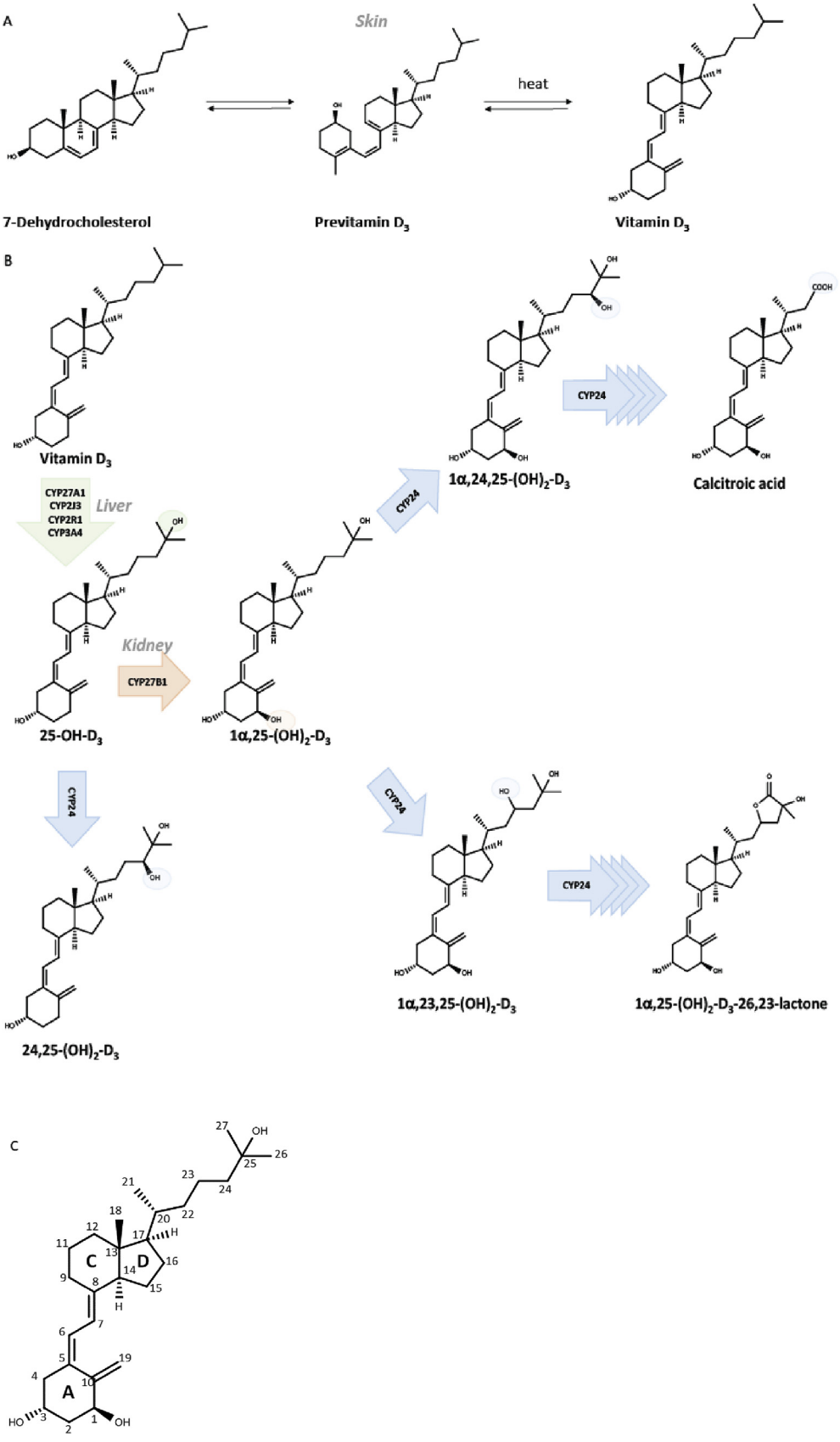

Fig. 1. (A–B) Vitamin D_3 synthesis, activation and inactivation. (C) Chemical structure and numbering of $1,25(OH)_2D_3$.