Genetic Diseases of Vitamin D Metabolizing Enzymes

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KEYWORDS

• Vitamin D metabolism • Cytochrome P450 • Rickets • Hypercalcemia

KEY POINTS

- This review presents current knowledge of the key activating and inactivating cytochrome P450 (CYP)–containing enzymes involved in vitamin D metabolism in mammals.
- The case for mutations of vitamin D_3-25-hydroxylase/CYP2R1 associated with vitamin D–dependent rickets (VDDR), type 1B, is presented.
- The case for mutations of 25-hydroxyvitamin D_3-1α-hydroxylase/CYP27B1 associated with VDDR, type 1A, is presented.
- The case for mutations of 25-hydroxyvitamin D_3-24-hydroxylase/CYP24A1 associated with idiopathic infantile hypercalcemia is presented.
- Symptoms, diagnosis, treatment, and management of VDDR and idiopathic infantile hypercalcemia are reviewed.

INTRODUCTION

The activation of vitamin D_3 is accomplished by sequential steps of 25-hydroxylation, first in the liver[1] to produce the main circulating form, 25-hydroxyvitamin D_3 [25-$(OH)D_3$], followed by 1α-hydroxylation in the kidney and extrarenal sites to produce the hormonal form, 1α,25-dihydroxyvitamin D_3 [1,25-$(OH)_2D_3$][2–4] (**Fig. 1**). Although vitamin D_2 undergoes the same hydoxylations as vitamin D_3, this article focuses on the latter because most current knowledge comes from studies of vitamin D_3. Evidence from a variety of mammalian species has revealed that several cytochrome P450 (CYP)

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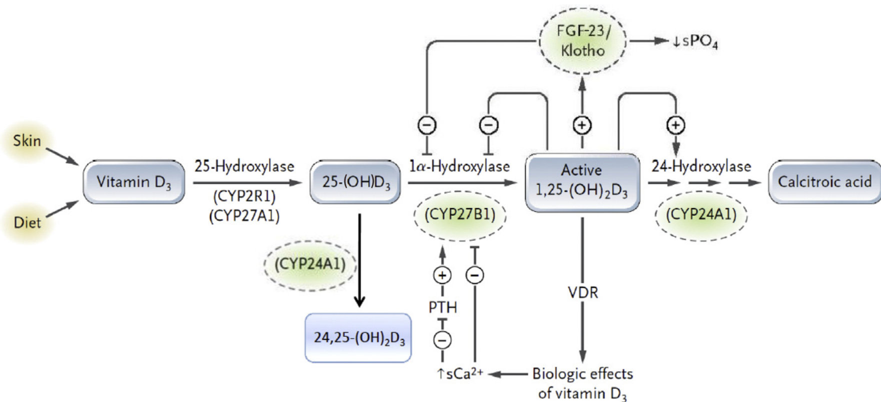

Fig. 1. Calcium and phosphate homeostasis and its close association with the enzymes involved in vitamin D metabolism. (*Adapted from* Schlingmann KP, Kaufmann M, Weber S, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. N Engl J Med 2011;365:412; with permission.)

enzymes—CYP2R1, CYP27A1, CYP3A4, CYP2D25, and perhaps others—are capable of 25-hydroxylation of vitamin D_3 and could be referred to as vitamin D_3-25-hydroxylase but that CYP2R1 is emerging as the physiologically relevant enzyme.[5] The nature of the 25-(OH)D_3-1α-hydroxylase enzyme responsible for 1α-hydroxylation as CYP27B1 is undisputed.[6,7] The third enzyme under focus is the vitamin D inactivating enzyme, 25-(OH)D_3-24-hydroxylase, known as CYP24A1, which is responsible for the side chain hydroxylation of both 25-(OH)D_3 and 1,25-$(OH)_2D_3$.[8]

CYPs are classified into 2 main subtypes based on their subcellular location: microsomal or mitochondrial; vitamin D metabolism features both subtypes.[9] Both microsomal and mitochondrial CYP subtypes are components of electron transport chains; the microsomal CYPs (eg CYP2R1) require a single general purpose protein NADPH-CYP reductase, whereas mitochondrial vitamin D–related CYPs (eg CYP27A1, CYP27B1, and CYP24A1) require the assistance of 2 additional electron-transporting proteins consisting of a general purpose ferredoxin reductase, a general purpose ferredoxin, and a highly specific CYP.[8] Most of the vitamin D–related CYPs catalyze single or multiple hydroxylation reactions on specific carbons of the vitamin D substrate using a transient Fe-O intermediate. The exact site of hydroxylation, termed *regioselectivity*, can be somewhat variable with vitamin D–related CYPs; human CYP24A1 is documented to hydroxylate at C23, C24, or C26.

All vitamin D–related CYP proteins possess approximately 500 amino acids, which makes them 50 kDa to 55 kDa, featuring abundant highly conserved residues that suggest a common secondary structure with multiple highly conserved helices (designated A–L) connected by loops and β-sheet structures.[9] CYPs possess a cysteine residue and 2 other residues near to the C-terminus, which covalently bind and align the heme group, in addition to several other domains for interaction with the electron transferring machinery, such as ferredoxin or NADPH-CYP reductase. The N-terminus inserts into the endoplasmic reticular membrane for microsomal CYPs or the inner mitochondrial membrane for mitochondrial CYPs. The substrate-binding pocket is formed by several secondary structures folded around the distal face of the heme-group so that substrate can be brought to within 3.2 Å of the iron atom for hydroxylation.

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