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Interplay between Vitamin D and the Drug Metabolizing Enzyme CYP3A4

Zhican Wang[1], **Erin G. Schuetz**[2], **Yang Xu**[1,3], and **Kenneth E. Thummel**[1]

[1]Departments of Pharmaceutics, University of Washington, Seattle, WA

[2]Department of Pharmaceutical Sciences, St. Jude Children's Research Hospital, Memphis, TN

[3]Department of Pharmacokinetics and Drug Metabolism, Amgen Inc, Thousand Oaks, CA

Abstract

Cytochrome P450 3A4 (CYP3A4) is a multifunctional enzyme involved in both xenobiotic and endobiotic metabolism. This review focuses on two aspects: regulation of *CYP3A4* expression by vitamin D and metabolism of vitamin D by CYP3A4. Enterohepatic circulation of vitamin D metabolites and their conjugates will be also discussed. The interplay between vitamin D and CYP3A4 provides new insights into our understanding of how enzyme induction can contribute to vitamin D deficiency.

Keywords

Cytochrome P450 3A4; Vitamin D; Drug metabolism; Enterohepatic circulation; Osteomalacia

1. Vitamin D as a Hormone

Vitamin D consists of two isoforms, vitamin D_2 and vitamin D_3. Vitamin D_3 is the major source of the hormone in humans and is essential for the proper maintenance of calcium and phosphate homeostasis [1]. Once synthesized in skin after sunlight exposure, or absorbed in the gut from an oral diet, vitamin D_3 is delivered to the liver where it undergoes 25-hydroxylation by CYP2R1 and CYP27A1 (and other enzymes) to form 25-hydroxyvitamin D_3 ($25OHD_3$). Although $25OHD_3$ is the major circulating form of vitamin D_3, it must be further oxidized at the 1α position by the enzyme CYP27B1 to 1α,25-dihydroxyvitamin D_3 [1α,$25(OH)_2D_3$] to become fully active at regulating gene transcription and cell function. 1α,$25(OH)_2D_3$ initiates or suppresses gene transcription by binding to the vitamin D receptor (VDR) [2]. Binding to VDR triggers hetero-dimerization of VDR with retinoid X receptor (RXR). The heterodimer then translocates to the nucleus where the complex binds to vitamin D response elements and alters gene transcription. In addition to this classical pathway of controlling cell function, several "non-genomic" pathways of cell regulation have also been proposed, involving extranuclear 1α,$25(OH)_2D_3$ and multiple growth factors [3].

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Corresponding author: Kenneth E. Thummel, Ph.D., Department of Pharmaceutics, Box 357610 University of Washington, Seattle, WA 98195. Phone: 206-543-0819. Fax: 206-543-3204, thummel@u.washington.edu.

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CYP3A4 is considered to be the most important of the family of drug-metabolizing cytochrome P450 enzyme, contributing importantly to the clearance of perhaps half of therapeutic agents that undergo metabolic biotransformation [4]. It is highly expressed in the liver and small intestine [5] and several transcription factors interacting with multiple transcriptional elements regulate its expression. The induction of *CYP3A4* gene expression in the liver and small intestine is mainly regulated through activation of the pregnane X receptor (PXR) and, in the case of the liver, also by the constitutive androstane receptor [6]. However, it has been demonstrated that $1\alpha,25(OH)_2D_3$ can also enhance the transcription of *CYP3A4* by a VDR-mediated pathway. Treatment of Caco-2 cells [7–9], LS180 cells [10, 11], HepG2 cells [12], and human hepatocytes [13] with $1\alpha,25(OH)_2D_3$ results in increased *CYP3A4* mRNA levels and accumulation of the encoded, functional enzyme. In addition, treatment of rats with $1\alpha,25(OH)_2D_3$ increases intestinal *CYP3A23* (a homolog of *CYP3A4*) expression and CYP3A metabolic activity [14, 15].

CYP3A4 transcription is induced by $1\alpha,25(OH)_2D_3$ through the binding of ligand-VDR-RXR heterodimer to the same proximal ER6 (−169/−152), distal DR3 (−7733/−7719) and DR4 (−7618/−7603) response elements to which a ligand-PXR-RXR complex binds [16–18]. VDR also functions as a receptor for the secondary bile acid lithocholic acid (LCA) and binds (as an activated heterodimer) to the same *CYP3A4* ER6 and DR3 response elements as does the $1\alpha,25(OH)_2D_3$-VDR-RXR complex [19]. Moreover, activation of VDR by LCA can induce CYP3A expression *in vivo* indicating that LCA may also contribute to CYP3A4 induction in the enteric system [20]. Finally, C-jun-N-terminal kinase has been suggested to be another mediator of $1\alpha,25(OH)_2D_3$-induced *CYP3A4* expression, presumably without involvement of VDR [8, 21].

The primary sites of CYP3A4 expression are the liver and mucosa of the small intestine. Thus, it has been suggested that VDR helps regulate CYP3A4 enzyme content at these tissue sites [16, 22]. While this is clearly plausible for intestinal expression, it has been noted that the expression of VDR in human liver is much lower than that found in the small intestine and kidney [23]. Indeed, an immunohistochemical analysis of cross-sections of the human liver indicated that VDR is essentially absent from hepatocytes, but instead expressed in selective hepatic cell populations such as Kupffer, stellate and endothelial cells [24]. Therefore, considering the cellular composition of the liver, induction of hepatic *CYP3A4* expression via VDR in non-parenchymal cells may not be that relevant to overall hepatic drug clearance [25], although additional work is needed to clarify this important regulatory issue.

Induction of CYP3A4 by $1\alpha,25(OH)_2D_3$ appears to affect the systemic exposure of orally administered drugs that are substrates of CYP3A4 (Figure 1). Humans taking vitamin D supplementation show an increased clearance of atorvastatin, a substrate of CYP3A4 [26]. In addition, blood levels of CYP3A substrates, tacrolimus and sirolimus, showed cyclic variation throughout the year that correlated with ultraviolet light exposure and serum levels of vitamin D, whereas no significant difference was observed for mycophenolic acid, a non-substrate of CYP3A4 [27]. Similarly, Thirumaran et al [25] reported that intestinal *CYP3A4* expression *in vivo* varied seasonally, correlating with seasonal vitamin D levels. It is known that intestinal CYP3A4 contributes to the first-pass metabolism of many orally administered drugs [28]. Thus, intra- and inter-individual differences in circulating vitamin D levels and associated intestinal CYP3A4 activity may contribute to variability in oral drug bioavailability.

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2. Enterohepatic Circulation of Vitamin D

Delivery of $1\alpha,25(OH)_2D_3$ to the intestinal mucosa can in theory occur by both vascular and biliary routes [29]. In the absence of active uptake across the basolateral membrane of intestinal enterocytes, one would expect unbound intracellular $1\alpha,25(OH)_2D_3$ concentrations to be the same as that found in plasma, driving transcriptional activation of VDR gene targets such as *CYP3A4,* transient receptor potential cation channel, subfamily V, member 6 (*TRPV6*) and calbindin D9K. However, studies utilizing radiolabeled $1\alpha,25(OH)_2D_3$ in humans [30, 31] and animals [32] have revealed biliary excretion and intestinal reabsorption of $1\alpha,25(OH)_2D_3$ (or its polar conjugate), suggesting the possibility of functionally significant enterohepatic cycling of $1\alpha,25(OH)_2D_3$ (Figure 1). Although biliary vitamin D metabolites have not been fully characterized, chromatography indicates small amounts of $1\alpha,25(OH)_2D_3$ and larger amounts of its more polar metabolites [31, 33]. Similar findings have been observed in man [34] and rats [35] after administration with radiolabeled $25OHD_3$. A considerable portion of the radiolabeled $1\alpha,25(OH)_2D_3$ and $25OHD_3$ dose found in the bile is subsequently absorbed from the intestine and presumably delivered back to the liver [32, 34]. Thus, although biliary excretion may not be an efficient pathway of vitamin D clearance, it may still expose enterocytes to higher unbound concentrations of active hormone (through vectoral transport through the enterocytes) than would otherwise occur by vascular delivery and represent an important element of gene regulation [34, 36].

A key initial step in enterohepatic cycling of $1\alpha,25(OH)_2D_3$ and $25OHD_3$ is conversion to a polar metabolite suitable for canalicular excretion. Glucuronidation of different vitamin D species has been reported [37–41]. In humans, the conjugation of $1\alpha,25(OH)_2D_3$ is catalyzed primarily by UGT1A4 and to a much lesser extent by UGT2B4 and UGT2B7 [41]. Three isomers are produced, with the 25-O-glucuronide isomer being the dominant product. Delivery of 25-O-glucuronide of $1\alpha,25(OH)_2D_3$ stimulates gene expression in mouse duodenum and colon tissues [42]. Glucuronides deposited in the gastrointestinal lumen are presumably subject to hydrolysis by β-glucuronidases (human epithelial or bacterial) after being secreted from the liver into the bile. Intraluminal release of $1\alpha,25(OH)_2D_3$ and $25OHD_3$ and subsequent reabsorption may serve as a critical tissue-specific hormone delivery pathway, giving explanation for a similar pattern of preferential expression of *CYP3A4* [28], *TRPV6* and calbindin D9K (Figure 2) in proximal sections of the small intestine, compared to more distal regions.

3. Biotransformation of Vitamin D by CYP3A4

The bioactivation of $25OHD_3$ involves 1α-hydroxylation, a reaction catalyzed primarily by CYP27B1 in the renal tubular epithelium [43]. The renal production of $1\alpha,25(OH)_2D_3$ is tightly regulated by other hormones such as parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF23), which up- and down-regulate expression of the *CYP27B1* gene, respectively [44]. Furthermore, a variety of cell types in different organs of the human body contain the enzyme CYP27B1 and have the capacity to synthesize $1\alpha,25(OH)_2D_3$. It has been shown that local production of $1\alpha,25(OH)_2D_3$ within nonrenal tissues is regulated in a manner different from that seen in the kidney, and thus, $1\alpha,25(OH)_2D_3$ production and action can be cell specific [45, 46]. Hydroxylation at the alkyl side chain of $1\alpha,25(OH)_2D_3$ or $25OHD_3$ is considered to be a critical first step in the hormone inactivation pathway [47] (Figure 3). Mitochondrial CYP24A1 is recognized as a key enzyme for hydroxylation at the C-24 and C-23 positions of both $25OHD_3$ and $1\alpha,25(OH)_2D_3$ [48, 49] and is found in kidney, intestine, lymphocytes, fibroblasts, bone, skin, macrophages and possibly other tissues where $1\alpha,25(OH)_2D_3$ exerts its biological effects [50]. However, Gupta et al [51, 52] reported that CYP3A4 exhibits significant 24- and 25-hydroxylation activities for 1α-

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OHD_3, 1α-OHD_2 and vitamin D_2, after screening 16 major human hepatic P450s expressed in baculovirus infected insect cells. Moreover, Xu et al [53] reported that CYP3A4 can catalyze the 23- and 24-hydroxylation of 1α,25$(OH)_2D_3$ in the human liver and small intestine. In addition, it was recently shown that CYP3A4 can catalyze 25OHD_3 monohydroxylation, generating nine different isomeric metabolites [54]. Interestingly, the major product generated by CYP3A4, 4β,25$(OH)_2D_3$, was detected in human plasma at concentrations comparable to that of 1α,25$(OH)_2D_3$ and its formation was induced by rifampin [54, 55]. Thus, intestinal and hepatic CYP3A4 may also contribute to the metabolic clearance of 1α,25$(OH)_2D_3$ and 25OHD_3, particularly under conditions of induced *CYP3A4* expression.

4. Potential Clinical Implications

Osteomalacia can be a serious, debilitating side effect from certain drug therapies. It has been associated most strongly with chronic administration of anti-epileptic drugs, such as phenobarbital, carbamazepine, phenytoin and valproic acid [56–58], as well as the antimicrobial drug rifampin [59, 60]. Although the molecular mechanism underlying this event is not fully understood, a number of theories have been proposed to explain why anti-epileptic drugs affect bone; this includes reduced levels of vitamin D metabolites, reduced calcium absorption, inhibition of the cellular response to PTH, hyperparathyroidism, vitamin K deficiency and calcitonin deficiency [61]. Among them, vitamin D deficiency is thought to be the principal pathway to drug-induced osteomalacia [62, 63]. For example, daily administration of rifampin to healthy volunteers lowered the plasma concentration of 25OHD_3 by 70% [60, 64]. Similar effects were also described for patients receiving phenobarbital and phenytoin for the treatment of epilepsy [65]. It has been suggested that alterations in vitamin D metabolism result mainly from induction of hepatic P450 enzymes [66, 67]. Pascussi et al [68] proposed that induction of CYP24A1 accelerates vitamin D catabolism, and that PXR is responsible for the regulation of CYP24A1 enzyme. In contrast, Zhou et al [69] reported that CYP3A4, and not CYP24A1, is the dominant enzyme catalyzing hydroxylation of 1α,25$(OH)_2D_3$ in human liver and small intestine. Thus, the relative contribution of these two enzymes to vitamin D catabolism may be tissue-specific. In the healthy kidney, CYP24A1 activity likely dominates 1α,25$(OH)_2D_3$ and 25OHD_3 catabolism; while in the liver and small intestine, CYP3A4 activity most likely dominates vitamin D catabolism because of a much greater level of basal and induced enzyme expression [69]. This interpretation is supported by the observation that treatment of healthy volunteers with rifampin causes preferential increases in human duodenal *CYP3A4*, but not *CYP24A1*, mRNA content [69]. Importantly, induction of CYP3A4 in the small intestine could cause local tissue vitamin D deficiency and possibly directly affect intestinal calcium absorption [11, 70]. On the other hand, induction of hepatic CYP3A4 may alter systemic circulating levels of 25OHD_3 through activation of the 4β-hydroxylation pathway [54]. Therefore, inhibition of *CYP3A4* activity in the enterohepatic circuit may constitute a viable therapeutic approach for prevention or reversal of drug-induced osteomalacia in at-risk patients.

Liver function is crucial for physiological vitamin D metabolism. Patients with chronic liver disease and cirrhosis have very high prevalence of vitamin D deficiency and insufficiency [71]. Low vitamin D levels in these patients are possibly due to limited sunlight exposure, impaired intestinal absorption and decreased hepatic 25-hydroxylation activity [71]. Given the correlation between plasma levels of vitamin D metabolites and intestinal CYP3A4 content/activity, low levels of vitamin D metabolites in patients with cirrhosis might result in a reduction in CYP3A protein expression. Indeed, it has been noted that intestinal CYP3A4 expression and function are reduced in patients with cirrhosis [72]. Although reduced metabolism of drugs is typically attributed to decreased liver function, decreased

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intestinal CYP3A activity may also contribute to greater drug exposure in these patients. Whether vitamin D supplementation could rescue intestinal CYP3A expression in these patients is something to be considered.

5. Concluding remarks

Hormonal control of *CYP3A4* expression by vitamin D represents the foundation of a potentially important interplay between xenobiotic and vitamin D metabolism. Enterohepatic cycling of vitamin D could be a functionally important pathway for delivery of active hormone to the upper intestine, resulting in preferentially higher levels of expression of VDR target genes, such as *TRPV6*, calbindin D9K and *CYP3A4*, in the duodenum and jejunum, in comparison to the ileum and colon. Intra- and inter-individual differences in vitamin D levels may contribute to the considerable variability in intestinal CYP3A4 content that affects drug disposition and pharmacological response. Interestingly, CYP3A4 catalyzes vitamin D biotransformation down pathways that appear catabolic in nature. Certain drugs, such as anti-epileptic drugs, that can induce *CYP3A4* expression in the liver and small intestine, accelerate vitamin D catabolism and may contribute to vitamin D deficiency, although a causal mechanistic link between CYP3A4 induction and vitamin D deficiency requires further evaluation.

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References

1. Plum LA, DeLuca HF. Vitamin D, disease and therapeutic opportunities. Nat Rev Drug Discov. 2010; 9(12):941–955. [PubMed: 21119732]
2. Haussler MR, Whitfield GK, Haussler CA, Hsieh JC, Thompson PD, Selznick SH, Dominguez CE, Jurutka PW. The nuclear vitamin D receptor: biological and molecular regulatory properties revealed. J Bone Miner Res. 1998; 13(3):325–349. [PubMed: 9525333]
3. Haussler MR, Jurutka PW, Mizwicki M, Norman AW. Vitamin D receptor (VDR)-mediated actions of 1alpha,25(OH)(2)vitamin D(3): genomic and non-genomic mechanisms. Best Pract Res Clin Endocrinol Metab. 2011; 25(4):543–559. [PubMed: 21872797]
4. Guengerich FP. Cytochrome P-450 3A4: regulation and role in drug metabolism. Annu Rev Pharmacol Toxicol. 1999; 39:1–17. [PubMed: 10331074]
5. Watkins PB, Wrighton SA, Schuetz EG, Molowa DT, Guzelian PS. Identification of glucocorticoid-inducible cytochromes P-450 in the intestinal mucosa of rats and man. J Clin Invest. 1987; 80(4): 1029–1036. [PubMed: 3654968]
6. Lin JH. CYP induction-mediated drug interactions: in vitro assessment and clinical implications. Pharm Res. 2006; 23(6):1089–1116. [PubMed: 16718615]
7. Schmiedlin-Ren P, Thummel KE, Fisher JM, Paine MF, Lown KS, Watkins PB. Expression of enzymatically active CYP3A4 by Caco-2 cells grown on extracellular matrix-coated permeable supports in the presence of 1alpha,25-dihydroxyvitamin D3. Mol Pharmacol. 1997; 51(5):741–754. [PubMed: 9145912]
8. Hara H, Yasunami Y, Adachi T. Alteration of cellular phosphorylation state affects vitamin D receptor-mediated CYP3A4 mRNA induction in Caco-2 cells. Biochem Biophys Res Commun. 2002; 296(1):182–188. [PubMed: 12147248]
9. Fan J, Liu S, Du Y, Morrison J, Shipman R, Pang KS. Up-regulation of transporters and enzymes by the vitamin D receptor ligands, 1alpha,25-dihydroxyvitamin D3 and vitamin D analogs, in the Caco-2 cell monolayer. J Pharmacol Exp Ther. 2009; 330(2):389–402. [PubMed: 19414624]

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10. Fukumori S, Murata T, Taguchi M, Hashimoto Y. Rapid and drastic induction of CYP3A4 mRNA expression via vitamin D receptor in human intestinal LS180 cells. Drug Metab Pharmacokinet. 2007; 22(5):377–381. [PubMed: 17965521]
11. Zheng XE, Wang Z, Liao MZ, Lin YS, Shuhart MC, Schuetz EG, Thummel KE. Human PXR-mediated induction of intestinal CYP3A4 attenuates 1alpha,25-dihydroxyvitamin D(3) function in human colon adenocarcinoma LS180 cells. Biochem Pharmacol. 2012; 84(3):391–401. [PubMed: 22562045]
12. Elizondo G, Medina-Diaz IM. Induction of CYP3A4 by 1alpha,25-dyhydroxyvitamin D3 in HepG2 cells. Life Sci. 2003; 73(2):141–149. [PubMed: 12738030]
13. Drocourt L, Ourlin JC, Pascussi JM, Maurel P, Vilarem MJ. Expression of CYP3A4, CYP2B6, and CYP2C9 is regulated by the vitamin D receptor pathway in primary human hepatocytes. J Biol Chem. 2002; 277(28):25125–25132. [PubMed: 11991950]
14. Xu Y, Iwanaga K, Zhou C, Cheesman MJ, Farin F, Thummel KE. Selective induction of intestinal CYP3A23 by 1alpha,25-dihydroxyvitamin D3 in rats. Biochem Pharmacol. 2006; 72(3):385–392. [PubMed: 16769037]
15. Khan AA, Dragt BS, Porte RJ, Groothuis GM. Regulation of VDR expression in rat and human intestine and liver--consequences for CYP3A expression. Toxicol In Vitro. 2012; 24(3):822–829. [PubMed: 20006981]
16. Thummel KE, Brimer C, Yasuda K, Thottassery J, Senn T, Lin Y, Ishizuka H, Kharasch E, Schuetz J, Schuetz E. Transcriptional control of intestinal cytochrome P-4503A by 1alpha,25-dihydroxy vitamin D3. Mol Pharmacol. 2001; 60(6):1399–1406. [PubMed: 11723248]
17. Thompson PD, Jurutka PW, Whitfield GK, Myskowski SM, Eichhorst KR, Dominguez CE, Haussler CA, Haussler MR. Liganded VDR induces CYP3A4 in small intestinal and colon cancer cells via DR3 and ER6 vitamin D responsive elements. Biochem Biophys Res Commun. 2002; 299(5):730–738. [PubMed: 12470639]
18. Pavek P, Pospechova K, Svecova L, Syrova Z, Stejskalova L, Blazkova J, Dvorak Z, Blahos J. Intestinal cell-specific vitamin D receptor (VDR)-mediated transcriptional regulation of CYP3A4 gene. Biochem Pharmacol. 2010; 79(2):277–287. [PubMed: 19712670]
19. Jurutka PW, Thompson PD, Whitfield GK, Eichhorst KR, Hall N, Dominguez CE, Hsieh JC, Haussler CA, Haussler MR. Molecular and functional comparison of 1,25-dihydroxyvitamin D(3) and the novel vitamin D receptor ligand, lithocholic acid, in activating transcription of cytochrome P450 3A4. J Cell Biochem. 2005; 94(5):917–943. [PubMed: 15578590]
20. Makishima M, Lu TT, Xie W, Whitfield GK, Domoto H, Evans RM, Haussler MR, Mangelsdorf DJ. Vitamin D receptor as an intestinal bile acid sensor. Science. 2002; 296(5571):1313–1316. [PubMed: 12016314]
21. Yasunami Y, Hara H, Iwamura T, Kataoka T, Adachi T. C-jun N-terminal kinase modulates 1,25-dihydroxyvitamin D3-induced cytochrome P450 3A4 gene expression. Drug Metab Dispos. 2004; 32(7):685–688. [PubMed: 15205382]
22. Pascussi JM, Gerbal-Chaloin S, Drocourt L, Maurel P, Vilarem MJ. The expression of CYP2B6, CYP2C9 and CYP3A4 genes: a tangle of networks of nuclear and steroid receptors. Biochim Biophys Acta. 2003; 1619(3):243–253. [PubMed: 12573484]
23. Pavek P, Dvorak Z. Xenobiotic-induced transcriptional regulation of xenobiotic metabolizing enzymes of the cytochrome P450 superfamily in human extrahepatic tissues. Curr Drug Metab. 2008; 9(2):129–143. [PubMed: 18288955]
24. Gascon-Barre M, Demers C, Mirshahi A, Neron S, Zalzal S, Nanci A. The normal liver harbors the vitamin D nuclear receptor in nonparenchymal and biliary epithelial cells. Hepatology. 2003; 37(5):1034–1042. [PubMed: 12717384]
25. Thirumaran RK, Lamba JK, Kim RB, Urquhart BL, Gregor JC, Chande N, Fan Y, Qi A, Cheng C, Thummel KE, Hall SD, Schuetz EG. Intestinal CYP3A4 and midazolam disposition in vivo associate with VDR polymorphisms and show seasonal variation. Biochem Pharmacol. 2012; 84(1):104–112. [PubMed: 22484315]
26. Schwartz JB. Effects of vitamin D supplementation in atorvastatin-treated patients: a new drug interaction with an unexpected consequence. Clin Pharmacol Ther. 2009; 85(2):198–203. [PubMed: 18754003]

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27. Lindh JD, Andersson ML, Eliasson E, Bjorkhem-Bergman L. Seasonal variation in blood drug concentrations and a potential relationship to vitamin D. Drug Metab Dispos. 2011; 39(5):933–937. [PubMed: 21349923]
28. Paine MF, Khalighi M, Fisher JM, Shen DD, Kunze KL, Marsh CL, Perkins JD, Thummel KE. Characterization of interintestinal and intraintestinal variations in human CYP3A-dependent metabolism. J Pharmacol Exp Ther. 1997; 283(3):1552–1562. [PubMed: 9400033]
29. Gascon-Barre M, Gamache M. Contribution of the biliary pathway to the homeostasis of vitamin D3 and of 1,25-dihydroxyvitamin D3. Endocrinology. 1991; 129(5):2335–2344. [PubMed: 1657572]
30. Gray RW, Caldas AE, Wilz DR, Lemann J Jr, Smith GA, DeLuca HF. Metabolism and excretion of 3H-1,25-(OH)2-vitamin D3 in healthy adults. J Clin Endocrinol Metab. 1978; 46(5):756–765. [PubMed: 263717]
31. Ledger JE, Watson GJ, Ainley CC, Compston JE. Biliary excretion of radioactivity after intravenous administration of 3H-1,25-dihydroxyvitamin D3 in man. Gut. 1985; 26(11):1240–1245. [PubMed: 3840765]
32. Kumar R, Nagubandi S, Mattox VR, Londowski JM. Enterohepatic physiology of 1,25-dihydroxyvitamin D3. J Clin Invest. 1980; 65(2):277–284. [PubMed: 7356679]
33. Wiesner RH, Kumar R, Seeman E, Go VL. Enterohepatic physiology of 1,25-dihydroxyvitamin D3 metabolites in normal man. J Lab Clin Med. 1980; 96(6):1094–1100. [PubMed: 7430765]
34. Arnaud SB, Goldsmith RS, Lambert PW, Go VL. 25-Hydroxyvitamin D3: evidence of an enterohepatic circulation in man. Proc Soc Exp Biol Med. 1975; 149(2):570–572. [PubMed: 1153436]
35. Gascon-Barre M. Biliary excretion of [3H]-25-hydroxyvitamin D3 in the vitamin D-depleted rat. Am J Physiol. 1982; 242(5):G522–532. [PubMed: 7081444]
36. Gascon-Barre M. Is there any physiological significance to the enterohepatic circulation of vitamin D sterols? J Am Coll Nutr. 1986; 5(3):317–324. [PubMed: 3016064]
37. Shimada K, Mitamura K, Nakatani I. Characterization of monoglucuronides of vitamin D2 and 25-hydroxyvitamin D2 in rat bile using high-performance liquid chromatography-atmospheric pressure chemical ionization mass spectrometry. J Chromatogr B Biomed Sci Appl. 1997; 690(1–2):348–354. [PubMed: 9106064]
38. Shimoyamada A, Tomiyama S, Shimizu M, Yamamoto K, Kunii S, Yamada S. In vivo metabolism of 24R,25-dihydroxyvitamin D3: structure of its major bile metabolite. Biochim Biophys Acta. 1997; 1346(2):147–157. [PubMed: 9219897]
39. Higashi T, Horike M, Kikuchi R, Shimada K. In vitro and in vivo glucuronidation of 24,25-dihydroxyvitamin D3. Steroids. 1999; 64(10):715–725. [PubMed: 10498030]
40. Higashi T, Miura K, Kikuchi R, Shimada K, Hiyamizu H, Ooi H, Iwabuchi Y, Hatakeyama S, Kubodera N. Characterization of new conjugated metabolites in bile of rats administered 24,25-dihydroxyvitamin D(3) and 25-hydroxyvitamin D(3). Steroids. 2000; 65(5):281–294. [PubMed: 10751640]
41. Hashizume T, Xu Y, Mohutsky MA, Alberts J, Hadden C, Kalhorn TF, Isoherranen N, Shuhart MC, Thummel KE. Identification of human UDP-glucuronosyltransferases catalyzing hepatic 1alpha,25-dihydroxyvitamin D3 conjugation. Biochem Pharmacol. 2008; 75(5):1240–1250. [PubMed: 18177842]
42. Goff JP, Koszewski NJ, Haynes JS, Horst RL. Targeted delivery of vitamin D to the colon using beta-glucuronides of vitamin D: therapeutic effects in a murine model of inflammatory bowel disease. Am J Physiol Gastrointest Liver Physiol. 2012; 302(4):G460–469. [PubMed: 22114117]
43. Bikle DD. Vitamin D: an ancient hormone. Exp Dermatol. 2011; 20(1):7–13. [PubMed: 21197695]
44. Perwad F, Portale AA. Vitamin D metabolism in the kidney: regulation by phosphorus and fibroblast growth factor 23. Mol Cell Endocrinol. 2011; 347(1–2):17–24. [PubMed: 21914460]
45. Bikle D. Nonclassic Actions of Vitamin D. J Clin Endocrinol Metab. 2009; 94(1):26–34. [PubMed: 18854395]
46. Adams JS, Hewison M. Extrarenal expression of the 25-hydroxyvitamin D-1-hydroxylase. Arch Biochem Biophys. 2012; 523(1):95–102. [PubMed: 22446158]

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47. Jones G, Prosser DE, Kaufmann M. 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): Its important role in the degradation of vitamin D. Arch Biochem Biophys. 2012
48. Sakaki T, Sawada N, Komai K, Shiozawa S, Yamada S, Yamamoto K, Ohyama Y, Inouye K. Dual metabolic pathway of 25-hydroxyvitamin D_3 catalyzed by human CYP24. Eur J Biochem. 2000; 267(20):6158–6165. [PubMed: 11012668]
49. Prosser DE, Jones G. Enzymes involved in the activation and inactivation of vitamin D. Trends Biochem Sci. 2004; 29(12):664–673. [PubMed: 15544953]
50. Armbrecht HJ, Okuda K, Wongsurawat N, Nemani RK, Chen ML, Boltz MA. Characterization and regulation of the vitamin D hydroxylases. J Steroid Biochem Mol Biol. 1992; 43(8):1073–1081. [PubMed: 22217851]
51. Gupta RP, Hollis BW, Patel SB, Patrick KS, Bell NH. CYP3A4 is a human microsomal vitamin D 25-hydroxylase. J Bone Miner Res. 2004; 19(4):680–688. [PubMed: 15005856]
52. Gupta RP, He YA, Patrick KS, Halpert JR, Bell NH. CYP3A4 is a vitamin D-24- and 25-hydroxylase: analysis of structure function by site-directed mutagenesis. J Clin Endocrinol Metab. 2005; 90(2):1210–1219. [PubMed: 15546903]
53. Xu Y, Hashizume T, Shuhart MC, Davis CL, Nelson WL, Sakaki T, Kalhorn TF, Watkins PB, Schuetz EG, Thummel KE. Intestinal and hepatic CYP3A4 catalyze hydroxylation of 1alpha,25-dihydroxyvitamin D(3): implications for drug-induced osteomalacia. Mol Pharmacol. 2006; 69(1): 56–65. [PubMed: 16207822]
54. Wang Z, Lin YS, Zheng XE, Senn T, Hashizume T, Scian M, Dickmann LJ, Nelson SD, Baillie TA, Hebert MF, Blough D, Davis CL, Thummel KE. An inducible cytochrome P450 3A4-dependent vitamin D catabolic pathway. Mol Pharmacol. 2012; 81(4):498–509. [PubMed: 22205755]
55. Wang Z, Senn T, Kalhorn T, Zheng XE, Zheng S, Davis CL, Hebert MF, Lin YS, Thummel KE. Simultaneous measurement of plasma vitamin D(3) metabolites, including 4beta,25-dihydroxyvitamin D(3), using liquid chromatography-tandem mass spectrometry. Anal Biochem. 2011; 418(1):126–133. [PubMed: 21784054]
56. Pack AM, Gidal B, Vazquez B. Bone disease associated with antiepileptic drugs. Cleve Clin J Med. 2004; 71(Suppl 2):S42–48. [PubMed: 15379299]
57. Pack AM, Morrell MJ. Epilepsy and bone health in adults. Epilepsy Behav. 2004; 5(Suppl 2):S24–29. [PubMed: 15123008]
58. Pack AM. Treatment of epilepsy to optimize bone health. Curr Treat Options Neurol. 2011; 13(4): 346–354. [PubMed: 21557040]
59. Shah SC, Sharma RK, Hemangini, Chitle AR. Rifampicin induced osteomalacia. Tubercle. 1981; 62(3):207–209. [PubMed: 7314253]
60. Brodie MJ, Boobis AR, Hillyard CJ, Abeyasekera G, Stevenson JC, MacIntyre I, Park BK. Effect of rifampicin and isoniazid on vitamin D metabolism. Clin Pharmacol Ther. 1982; 32(4):525–530. [PubMed: 7116768]
61. Pack AM, Gidal B, Vazquez B. Bone disease associated with antiepileptic drugs. Cleve Clin J Med. 2004; 71(Suppl 2):S42–48. [PubMed: 15379299]
62. Peterson P, Gray P, Tolman KG. Calcium balance in drug-induced osteomalacia: response to vitamin D. Clin Pharmacol Ther. 1976; 19(1):63–67. [PubMed: 173491]
63. Bhan A, Rao AD, Rao DS. Osteomalacia as a result of vitamin D deficiency. Endocrinol Metab Clin North Am. 2010; 39(2):321–331. [PubMed: 20511054]
64. Brodie MJ, Boobis AR, Dollery CT, Hillyard CJ, Brown DJ, MacIntyre I, Park BK. Rifampicin and vitamin D metabolism. Clin Pharmacol Ther. 1980; 27(6):810–814. [PubMed: 7379450]
65. Lee RH, Lyles KW, Colon-Emeric C. A review of the effect of anticonvulsant medications on bone mineral density and fracture risk. Am J Geriatr Pharmacother. 2010; 8(1):34–46. [PubMed: 20226391]
66. Hahn TJ, Birge SJ, Scharp CR, Avioli LV. Phenobarbital-induced alterations in vitamin D metabolism. J Clin Invest. 1972; 51(4):741–748. [PubMed: 4335442]
67. Gascon-Barre M, Vallieres S, Huet PM. Influence of phenobarbital on the hepatic handling of [3H]vitamin D3 in the dog. Am J Physiol. 1986; 251(5 Pt 1):G627–635. [PubMed: 3022599]

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68. Pascussi JM, Robert A, Nguyen M, Walrant-Debray O, Garabedian M, Martin P, Pineau T, Saric J, Navarro F, Maurel P, Vilarem MJ. Possible involvement of pregnane X receptor-enhanced CYP24 expression in drug-induced osteomalacia. J Clin Invest. 2005; 115(1):177–186. [PubMed: 15630458]

69. Zhou C, Assem M, Tay JC, Watkins PB, Blumberg B, Schuetz EG, Thummel KE. Steroid and xenobiotic receptor and vitamin D receptor crosstalk mediates CYP24 expression and drug-induced osteomalacia. J Clin Invest. 2006; 116(6):1703–1712. [PubMed: 16691293]

70. von Borstel Smith M, Crofoot K, Rodriguez-Proteau R, Filtz TM. Effects of phenytoin and carbamazepine on calcium transport in Caco-2 cells. Toxicol In Vitro. 2007; 21(5):855–862. [PubMed: 17412555]

71. Lim LY, Chalasani N. Vitamin d deficiency in patients with chronic liver disease and cirrhosis. Curr Gastroenterol Rep. 2012; 14(1):67–73. [PubMed: 22113744]

72. McConn DJ 2nd, Lin YS, Mathisen TL, Blough DK, Xu Y, Hashizume T, Taylor SL, Thummel KE, Shuhart MC. Reduced duodenal cytochrome P450 3A protein expression and catalytic activity in patients with cirrhosis. Clin Pharmacol Ther. 2009; 85(4):387–393. [PubMed: 19212316]

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Highlights

1. Regulation of *CYP3A4* gene expression by vitamin D
2. Enterohepatic circulation of vitamin D metabolites
3. Metabolism of vitamin D by CYP3A4
4. Vitamin D deficiency and clinical implications

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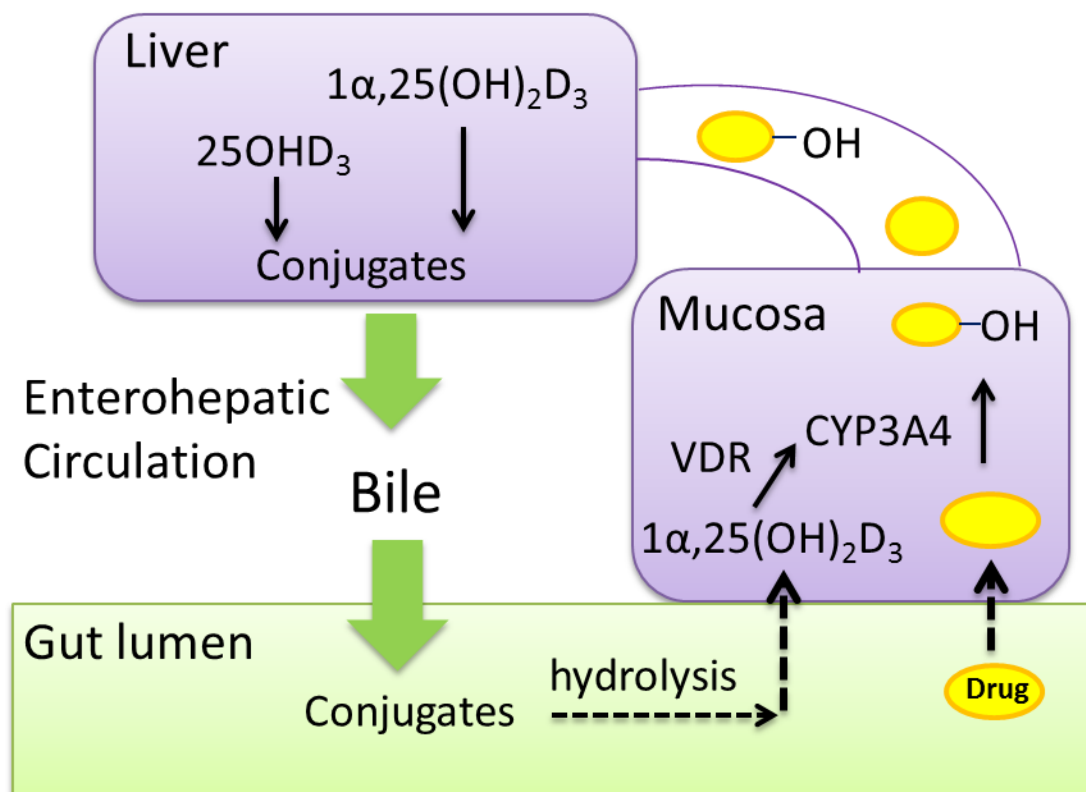

Figure 1.
Proposed mechanism that enterohepatic circulation delivers vitamin D derivatives to the intestine and 1α,25$(OH)_2D_3$ induces intestinal *CYP3A4* expression via VDR-mediated pathway.

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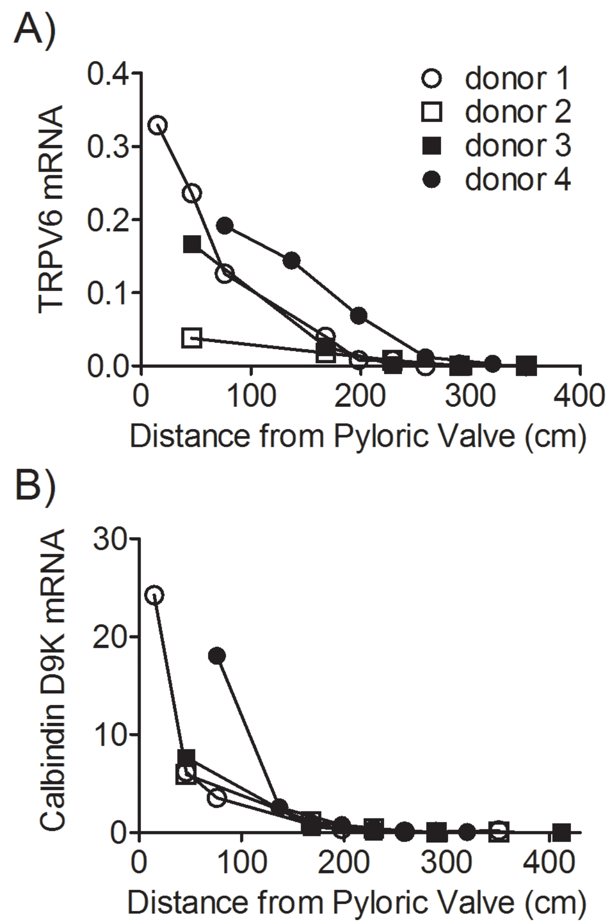

Figure 2. Longitudinal distribution of TRPV6 and calbindin D9k mRNA in the human small intestine

Tissue samples from four different donors were presented. Isolation of total RNA and real-time quantitative PCR were performed as previously described [53]. A) the levels of TRPV6 mRNA were normalized to the corresponding GAPDH mRNA; B) the levels of Calbindin D9K mRNA were normalized to villin mRNA.

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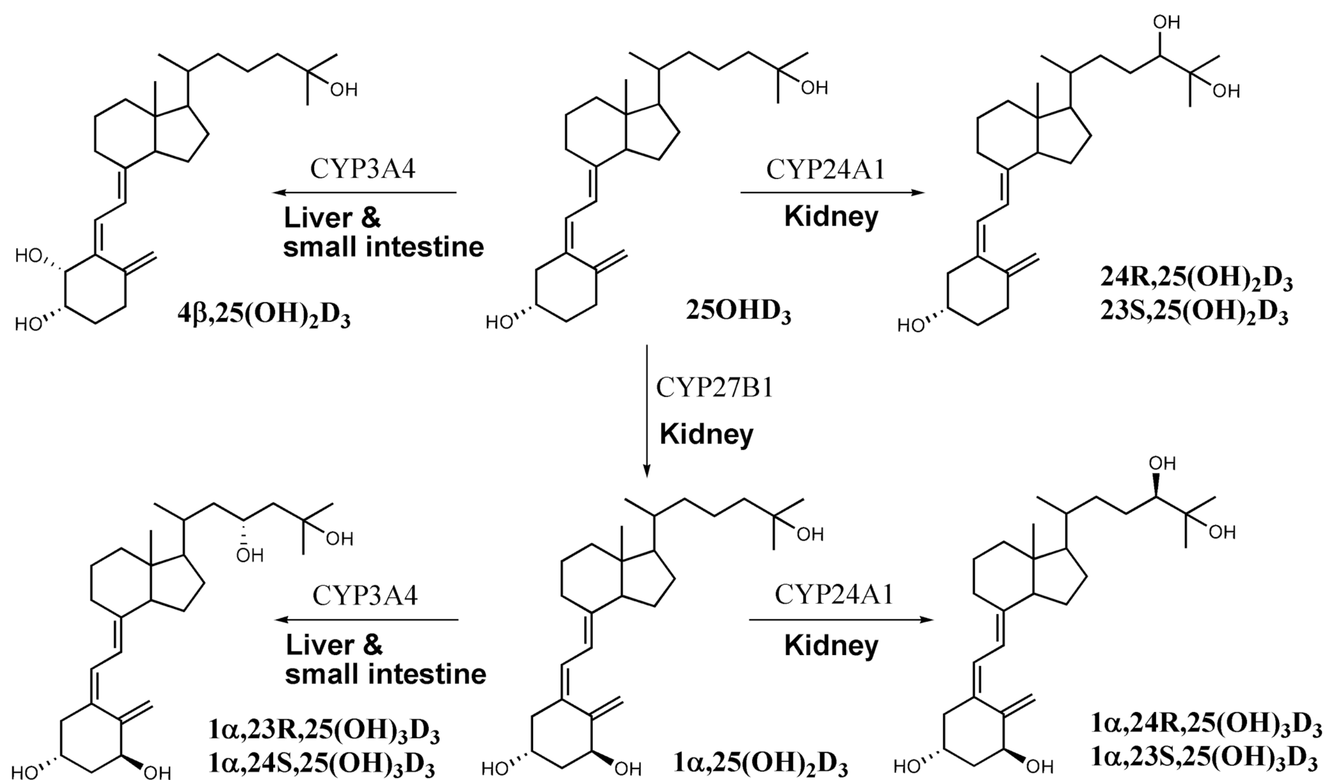

Figure 3. Tissue-specific metabolism of vitamin D metabolites

Under the constitutive condition in the kidney, CYP27B1 catalyzes 1α hydroxylation of $25OHD_3$ for vitamin D activation. While CYP24A1 catalyzes 24R- and 23S-hydroxylation of $25OHD_3$ and $1\alpha,25(OH)_2D_3$ for vitamin D deactivation. In the liver, CYP3A4 is the most abundant enzyme that catalyzes 4β-hydroxylation of $25OHD_3$, and 23R- and 24S-hydroxylation of $1\alpha,25(OH)_2D_3$ for vitamin D deactivation.