Recent Advances in Vitamin D Biology: Something New under the Sun

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INTRODUCTION

Enormous progress has been made over the last two decades in defining the biological roles of vitamin D. This progress is best illustrated in the newest edition of the comprehensive book on vitamin D to be available on October 1, 2023 (Hewison et al., 2023). Although most chapters report linear progress in different fields of vitamin D biology, two chapters on "Photobiology of Vitamin D" and on "Alternative Pathways for Vitamin D Metabolism" review recent data that provide mechanistic explanations for the diverse and sometimes contradictory actions of vitamin D. They also emphasize that UVB-induced vitamin D signaling can be different from that observed after oral vitamin D delivery. These considerations are briefly discussed below.

PHOTOSYNTHESIS OF VITAMIN D

Vitamin D (vitamin D3 [D3] and vitamin D2) is a secosteroid present in living organisms on earth for at least 500 million years. D3 is a product of the photochemical transformation of 7-dehydrocholesterol (7DHC) after it absorbs UVB energy (optimal peak at 295 nm), resulting in the opening of its B ring to generate pre-D3. Pre-D3 is thermodynamically unstable and subsequently undergoes a thermal isomerization to D3 (reviewed in Hewison et al. [2023]and Wacker and Holick [2013]). Exposure of pre-D3 to higher doses of UVB leads to the formation of lumisterol and tachysterol (Hewison et al., 2023; Wacker and Holick, 2013). The presence of singlet oxygen, photosensitizers, and longer UVR wavelength can lead to their further isomerization and degradation with production of 5,6-trans-vitamin D_3, suprasterols, isotachysterols, and cholesta-5,7,9(11)-triene (reviewed in Hewison et al. [2023] and Wacker and Holick [2013]). For decades, only D3 was considered a prohormone, with lumisterol, tachysterol, and other derivatives considered as only biologically inert compounds or products of degradation (Hewison et al., 2023; Wacker and Holick, 2013).

ACTIVATION OF D3

To be biologically active, D3 must be activated by sequential hydroxylations mediated by cytochrome P450 (CYP) enzymes (Hewison et al., 2023; Slominski et al., 2021; Wacker and Holick, 2013). It is well-known that this involves hydroxylation at C25 by CYP2R1 or CYP27A1 producing 25-hydroxyvitamin D3 (25(OH)D3), followed by hydroxylation at C1α by CYP27B1 to produce biologically active 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D3$). This route of activation is defined as the canonical pathway. The $1,25(OH)_2D3$ is inactivated by CYP24A1 (Bouillon et al., 2019; Hewison et al., 2023).

The alternative (noncanonical) pathways of vitamin D activation are initiated by the rate-limiting enzyme of steroidogenesis, CYP11A1. Its products can be modified by CYP27A1, CYP27B1, CYP24A1, CYP2R1, and/or CYP3A4, as described recently (Slominski et al., 2015; Tuckey et al., 2019). Importantly, this noncanonical pathway requires unmodified D3 because CYP11A1 does not exert any catalytic activity on 25(OH)D3 (Slominski et al., 2015). Furthermore, it was found that lumisterol and tachysterol and their precursors were activated by CYP11A1 and CYP27A1 (Slominski et al., 2022b, 2021; Tuckey et al., 2019). These pathways operate in vivo with observable accumulation of the metabolites in the human body (Jenkinson et al., 2021; Slominski et al., 2022b, 2021; Tuckey et al., 2019).

In the skin, these pathways and the generation of different secosteroidal products are dependent on the action of UVB (Figure 1). Besides 7DHC, there are other

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Clinical Implications

- Alternative pathways of vitamin D, lumisterol, and tachysterol activation were discovered.
- Discovered secosteroidal hydroxyderivatives are biologically active in vitro and in vivo.
- They can act on six nuclear receptors, alternatives to the vitamin D receptor.

5,7-dienes that UVB could potentially act on, producing metabolites on which CYP11A1 could hydroxylate, as discussed previously (Slominski et al., 2015). The resulting large number of products with further modifications by cutaneous enzymes (Slominski et al., 2022b, 2020) may explain a variety of local and systemic homeostatic effects of UVB, which are not assigned to $1,25(OH)_2D3$.

The route of vitamin D delivery is important (Slominski et al., 2021) because orally delivered D3 will be predominantly metabolized to 25(OH)D3 in the liver. Therefore, to initiate the noncanonical pathway of vitamin D activation, it must bypass the liver and be transported to organs expressing CYP11A1, including adrenals and other extra-adrenal tissues (Slominski et al., 2021). This challenges the strict reliance on 25(OH)D3 as the sole reflection of D3 load.

BIOLOGICAL ACTIVITY AND MECHANISMS OF ACTION

The metabolites mentioned earlier produced by noncanonical vitamin D activation and activation of lumisterol and tachysterol are biologically active in ex vivo and in vivo experimental models and are nontoxic and noncalcemic at suprapharmacological doses (reviewed in Hewison et al., 2023).

These metabolites can act on the vitamin D receptor (VDR) and on alternative receptors, including the retinoid-related orphan receptors α and γ, aryl hydrocarbon receptor, liver X receptor, and peroxisome proliferator—activated receptor γ (Slominski et al., 2022b, 2020). They inhibit NF-κβ activity and the hedgehog and WNT/β-catenin pathways (Slominski

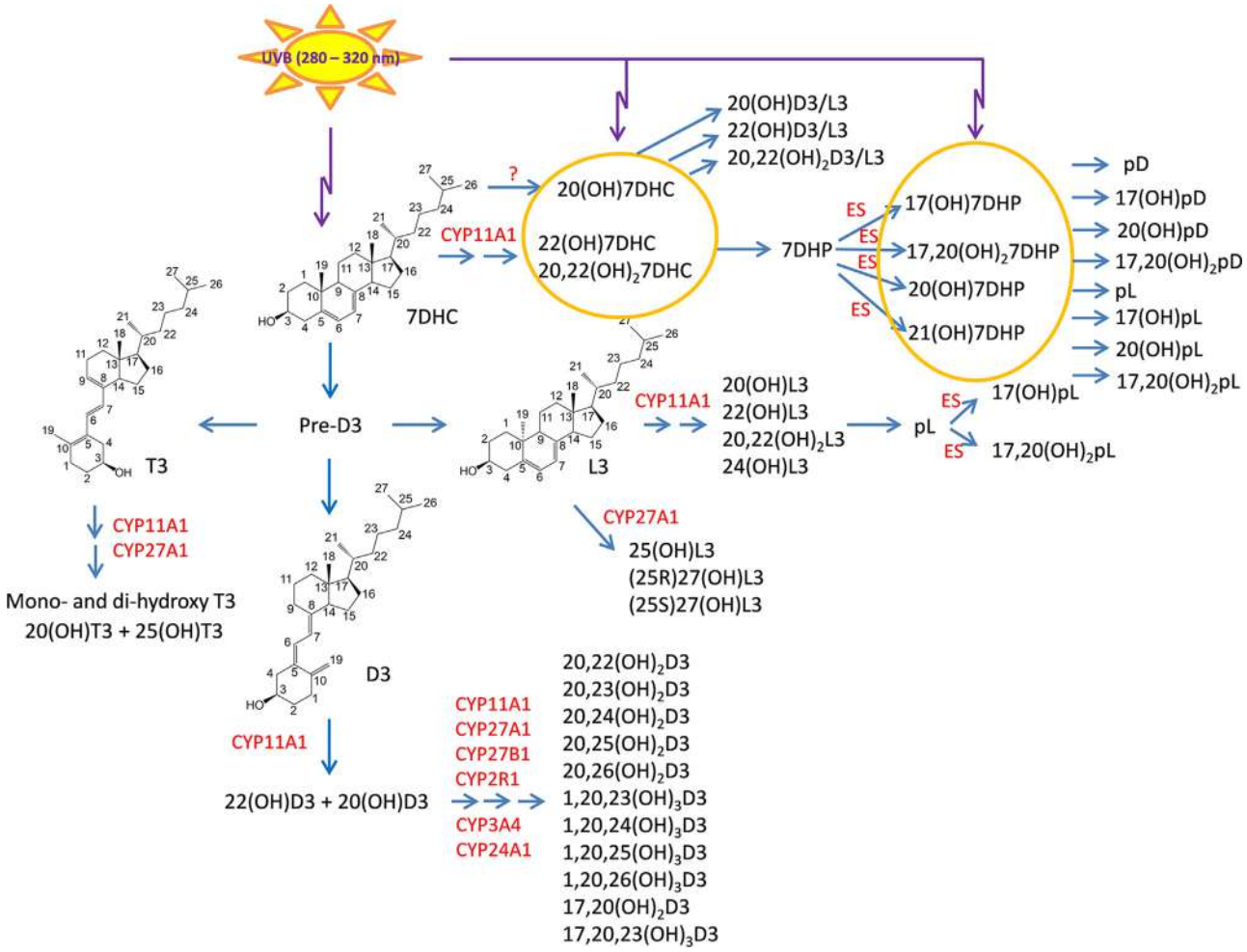

Figure 1. UVB-dependent pathways of secosteroidal activation(s). Vitamin D3, lumisterol, tachysterol, and 7DHC are substrates for CYP11A1 activity that by itself or in cooperation with other CYP enzymes produces the corresponding hydroxyderivatives. In the case of lumisterol and 7HDC, the side chain can be cleaved by CYP11A1 to produce 7DHP or pL, which can be further metabolized by steroidogenic enzymes. Production of tachysterol derivatives is also presented. Image was taken from Slominski et al. (2020) with permission from the publisher. ES denotes steroidogenic enzymes. 7DHC, 7-dehydrocholesterol; 7DHP, 7-dehydropregnenolone; CYP, cytochrome P450; D3, vitamin D3; L3, lumisterol3; pL, pregna-lumisterol; pre-D3, previtamin D3; T3, tachysterol3.

et al., 2022a). They induce the translocation of NRF2 and phosphorylated p53 from the cytoplasm to the nucleus, leading to the activation of downstream regulatory pathways (Slominski et al., 2020), or act in a receptor-independent fashion for antiviral effects (Qayyum et al., 2022). This challenges the narrow view that the biological effects of D3 are strictly dependent on activation of the VDR. Although we accept that $1,25(OH)_2D3$ has the highest affinity to the VDR, it can also act as a lower-affinity ligand on other nuclear receptors. Furthermore, other biologically active hydroxyderivatives of D3 show higher selectivity toward several other nuclear receptors. Thus, the position and number of hydroxyl groups on vitamin D define which nuclear receptor is activated. This opens a Pandora's box of possibilities for medicinal chemistry, health sciences, and dermatology to investigate.

CONCLUSIONS

The recent advances in alternative pathways of vitamin D activation and alternative nuclear receptors for D3 hydroxyderivatives offer an explanation for the observed pleiotropic effects of the D3 prohormone. They also challenge the current consensus conveyed by the majority of the literature that the main biologically relevant, phenotypic effects of D3 can be attributed solely to the activation of the VDR by $1,25(OH)_2D3$. Therefore, defining the biological and physiological effects of secosteroids that are independent of VDR interaction deserves further studies and challenges the conventional concept that the VDR is the sole nuclear receptor activated by the active forms of D3. Furthermore, lumisterol and tachysterol have been defined as prohormones because they can be activated by CYP enzymes to metabolites that exert biological activity through action on nuclear receptors. These possibilities are open for investigation by different laboratories because both biochemical and efficient chemical routes of synthesis of these metabolites have been established, as described in several publications.

In summary, the characterization of alternative signaling pathways by D3 and related molecules offers a new perspective that vitamin D, its photoproducts, and metabolites have a multitude of biologic functions independent of calcium and bone metabolism that requires further investigation. These new findings also show that UVB can generate a myriad of molecules that could eventually regulate local and global homeostasis.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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