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Review

Novel non-calcemic secosteroids that are produced by human epidermal keratinocytes protect against solar radiation

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ABSTRACT

CYP11A1 hydroxylates the side chain of vitamin D3 (D3) in a sequential fashion [D3 → 20*S*(OH)D3 → 20,23(OH)$_2$D3 → 17,20,23(OH)$_3$D3], in an alternative to the classical pathway of activation [D3 → 25(OH)D3 → 1,25(OH)$_2$D3]. The products/intermediates of the pathway can be further modified by the action of CYP27B1. The CYP11A1-derived products are biologically active with functions determined by the lineage of the target cells. This pathway can operate in epidermal keratinocytes. To further define the role of these novel secosteroids we tested them for protective effects against UVB-induced damage in human epidermal keratinocytes, melanocytes and HaCaT keratinocytes, cultured *in vitro*. The secosteroids attenuated ROS, H_2O_2 and NO production by UVB-irradiated keratinocytes and melanocytes, with an efficacy similar to 1,25(OH)$_2$D3, while 25(OH)D3 had lower efficacy. These attenuations were also seen to some extent for the 20(OH)D3 precursor, 20*S*-hydroxy-7-dehydrocholesterol. These effects were accompanied by upregulation of genes encoding enzymes responsible for defense against oxidative stress. Using immunofluorescent staining we observed that the secosteroids reduced the generation cyclobutane pyrimidine dimers in response to UVB and enhanced expression of p53 phosphorylated at Ser-15, but not at Ser-46. Additional evidence for protection against DNA damage in cells exposed to UVB and treated with secosteroids was provided by the Comet assay where DNA fragmentation was markedly reduced by 20(OH)D3 and 20,23(OH)$_2$D3. In conclusion, novel secosteroids that can be produced by the action of CYP11A1 in epidermal keratinocytes have protective effects against UVB radiation.

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Contents

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1. Introduction

The ultraviolet radiation (UVR) spectrum of solar light induces significant damage to the epidermis, which is tightly connected to the production of reactive oxygen species (ROS). These ROS, which include hydrogen peroxide (H_2O_2) and nitric oxide (NO), can cause oxidative damage and reduction of the important antioxidant, glutathione (GSH), as well as inhibition of DNA repair and genotoxic and mutagenic effects [1]. The mutagenic and genotoxic effects of UVB are related to its absorption of wave-lengths in the range of 280–320 nm, particularly by the pyrimidine bases [2], resulting in the formation of cyclobutane pyrimidine dimers (CPD) [3]. CPDs are DNA lesions produced in human skin mainly from exposure to UVB [4]. Tumor suppressor protein p53 mediates the cellular response to stress by activating cell-cycle arrest or apoptosis [5]. Thus, gamma and UV irradiation, hypoxia and some chemicals induce DNA damage and the activation of p53 [6]. The extent of DNA damage and the elevation in p53 levels are proportional [6]. Thus, p53 expression increases with UVB exposure and it initiates growth arrest and repair of damaged DNA [5,7]. Phosphorylation plays an important role in determining the activity of p53 including its ability to bind to DNA [8,9]. Phosphorylation of p53 at Ser-15 and Ser-20 promotes accumulation and activation of p53 and DNA repair, while p53 phosphorylation at Ser-46 closely regulates apoptosis following DNA damage [10]. Some endogenous regulators such as melatonin promote phosphorylation of p53 at Ser-15, thus activating p53 and consecutively inhibiting cell growth, preventing accumulation of damaged DNA and promoting antitumor activity [11,12].

The human epidermis is the main site of photo-induced formation of D3 from 7-dehydrocholesterol (7DHC), representing the most fundamental reaction in photobiology [13–15]. D3 is hydroxylated in positions C25 and C1 at both systemic (liver and kidney) and local (epidermis) levels to produce 1,25$(OH)_2$D3 [14,16,17]. 1,25$(OH)_2$D3, in addition to regulating calcium metabolism, has important pleiotropic effects that include stimulation of differentiation and inhibition of proliferation of cells of different lineage, anti-cancer properties, stimulation of innate immunity, and inhibition of adaptive immunity and inflammation [14,16–21]. In the skin it plays a significant role in the formation of the epidermal barrier and the functioning of the adnexal structures including hair follicles, and has a wide variety of ameliorating effects on skin cancer, and proliferative and inflammatory cutaneous diseases [14,16,18,20,22–24]. Most recently, it was reported that active forms of D3 prevent, attenuate, or even reverse UVB-induced cell death and DNA damage in skin cells [25–31]. Unfortunately, due to its calcemic (toxic) effect, chronic therapeutic use of D3 at pharmacological doses is severely limited, which forms a significant barrier to the use of classical forms of D3 including 1,25$(OH)_2$D3. However, the discovery of an alternative pathway of vitamin D activation initiated by CYP11A1 which produces novel secosteroids which are biologically active but non-calcemic [32], offers promise for therapeutic applications.

The novel pathways of vitamin D metabolism initiated by the action of CYP11A1 are: D3 → 20*S*(OH)D3 → 20,23$(OH)_2$D3 → 17,20,23$(OH)_3$D3 and D2 → 20*S*(OH)D2 → 17,20$(OH)_2$D2 → 17,20,24$(OH)_3$D2 [32–40]. Our studies indicate that these pathways operate *in vivo* with CYP 27B1 being capable of hydroxylating some of the products in the 1α-position [41,42]. In tissues with high expression of CYP11A1, 20*S*(OH)D3 is the main metabolite and is more abundant than 25(OH)D3 [41]. Similarly, tissues expressing low levels of CYP11A1 such as skin [43,44] can also produce 20*S*(OH)D and its hydroxyderivatives [41,42]. The initial metabolite, 20*S*(OH)D3, is the major product of the pathway, and recently we detected it in human serum based on its mass spectrum and identical HPLC retention time to authentic standard [41]. 20,23$(OH)_2$D3 is the second major metabolite of the pathway [41]. Both secosteroids demonstrate biological potency, equal or higher than that of 1,25$(OH)_2$D3, with anti-proliferative, pro-differentiation and anti-inflammatory activities on epidermal keratinocytes, melanocytes, melanoma cells and dermal fibroblasts [32,45–49]. Importantly, 20*S*(OH)D3 is noncalcemic and non-toxic at the highest pharmacological doses tested in rats (3 μg/kg), and in mice (30–60 μg/kg)[50,51], which are up to 100-fold higher than doses of 1,25$(OH)_2$D3 or its precursor, 25(OH)D3, that are toxic.

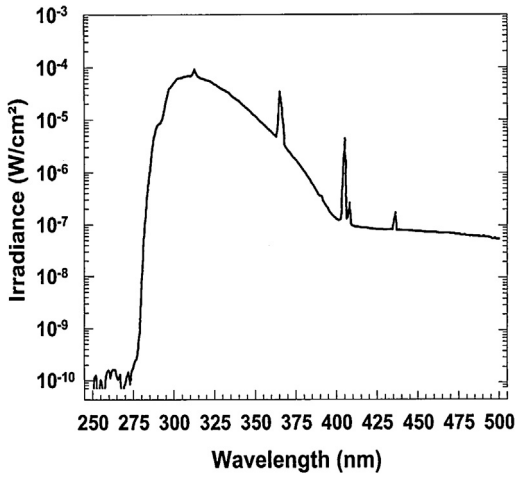

Fig. 1. Spectral irradiance of the Bio-Rad Model 2000 ultraviolet transilluminator passed through the plastic culture petri dish. The UV irradiance spectra were measured using an optronic spectroradiometer, model 754.

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