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Transformation of 6-tetrahydrobiopterin in aqueous solutions under UV-irradiation

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ABSTRACT

Melanogenesis disturbance leads to several pathologies, including vitiligo disease. Ultraviolet (UV) narrowband phototherapy (308 or 311 nm) is used in treating vitiligo; however, the mechanism of phototherapy is not yet understood. Vitiligo is accompanied by three-fivefold increased de-novo synthesis of (6*R*)-L-erythro-5,6,7,8-tetrahydrobiopterin (H_4Bip), its excess and its further oxidation can be considered as significant factors in the pathogenesis of vitiligo. (H_4Bip), as the phenylalanine 4-hydroxylase coenzyme, catalyzes the oxidation of phenylalanine to tyrosine (a melanin precursor). In this context, photo-transformation of H_4Bip in aqueous buffer solutions has been studied. HPLC–MS/MS has demonstrated that pterin products of H_4Bip autoxidation (7,8-dihydropterin (H_2Ptr), dihydroxanthopterin and pterin) predominate over biopterin products (7,8-dihydrobiopterin (H_2Bip) and biopterin). We have shown that UV irradiation accelerates the autoxidation while the products of oxidative degradation of H_4Bip act as photosensitizers. The distinctive feature of photooxidation of H_4Bip from autoxidation is the formation of dihydropterin $(H_2Ptr)_2$ and dihydrobiopterin $(H_2Bip)_2$ dimers. By means of HPLC–MS/MS it was found that formation of dihydropterin dimers is the predominant process. The signal of molecular ion of the dimer $(H_2Ptr)_2$ ($m/z = 331$) was almost a thousand times higher than the signal of $(H_2Bip)_2$ ($m/z = 479$). The key point of the dimerization is photoexcitation (at 310–320 nm) of the intermolecular complex (qH_2Ptr-H_2Ptr) generated in dark. As a result of the photoreaction azacyclobutane dimers have been formed. In the case of alternation of dark and light intervals H_4Bip converted into dimers with 96 % yield. The data obtained are discussed in the context of UV-B narrowband vitiligo phototherapy.

1. Introduction

(6*R*)-L-erythro-5,6,7,8-tetrahydrobiopterin (H_4Bip) is a coenzyme for the series of enzymes: NO synthases, alkylglycerol monooxygenases and aromatic amino acid hydroxylases. H_4Bip is the coenzyme of phenylalanine hydroxylase (EC 1.14.16.1) catalyzing the oxidation of phenylalanine to tyrosine by molecular oxygen in the process of melanogenesis [1]. Melanogenesis disturbance leads is a characteristic feature of certain dermatological pathologies, including vitiligo disease, which results in the emergence of depigmented skin patches. The patients with vitiligo appeared to have three-fivefold increased *de-novo* synthesis of H_4Bip; its excess and its further oxidation can be considered as important factors in the pathogenesis of vitiligo [2–6]. Pterin and its reduced forms absorb light in the ultraviolet spectral region. Recently, tetrahydrocyanopterin has been described as a chromophore within a photoreceptor of several cyanobacteria [7,8]. The role that pterins perform as photoreceptors and as photosensitizers of metabolic reactions is not well understood. It is obvious, however, that these issues are vitally important for photobiology [9] and photomedicine. Apart from our recent work [10], the photochemistry of H_4Bip coenzyme has never been studied. We have demonstrated that biopterin, which has been formed in H_4Bip solution as a result of the dark oxidation, acts as the

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