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Tetrahydrobiopterin Photooxidation: a Key Process in Vitiligo Phototherapy

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Abstract—The processes of the autooxidation and photooxidation of tetrahydrobiopterin (H_4Bip**)** (a coenzyme present in a three- to fivefold excess in vitiligo) were studied in the context of vitiligo pathology and treatment. The study of the kinetics of H_4Bip autooxidation and analysis of the reaction products via high-performance liquid chromatography (HPLC) demonstrated that autooxidation was intensive at a rate constant of 1×10^{-3} s^{-1} with the formation of dihydrobiopterin, dihydropterin, and their oxidized derivatives. Analysis of the autooxidation data led to a new conclusion that the oxidation of the excess of H_4Bip in melanocytes obviously triggers an autocatalytic cycle of the synthesis of the excess of hydrogen peroxide (H_2O_2). This, in turn, activates interferon-inducible GTP cyclohydrolase, which synthesizes an excess of H_4Bip. The autocatalytic cycle of excess H_2O_2 synthesis apparently underlies the pathology of vitiligo. The excess H_2O_2 is also partly spent to activate the immune system. The autocatalytic cycle can be broken via the conversion of H_4Bip into dihydropterin dimers during its UV photooxidation. The kinetics of H_4Bip was studied, the reaction products were identified, and the quantum yields of the formation of dihydropterin dimers were calculated. The action spectrum of UV radiation was constructed based on the quantum yield data. It shows that the range of 300–325 nm is efficient for vitiligo phototherapy.

Keywords: vitiligo, tetrahydrobiopterin, melanogenesis, melanin, oxidative stress, H_2O_2, UVB phototherapy of vitiligo, autocatalytic cycle in vitiligo

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INTRODUCTION

Vitiligo is a dermatological disease characterized by the formation of depigmented spots due to disorders of melanin biosynthesis [1–3]. The incidence of vitiligo by country varies from 0.1 to 4.0% [4–7]. There is an increase in the incidence of this disease, which determines the relevance of this study. Vitiligo is an immune-mediated, multifactorial disease. Genetic predisposition, as well as factors of the internal and external environment, are important in the pathoetiology. An initial look at vitiligo as an autoimmune disease gives way to the understanding that the immune attack on melanocytes is preceded by internal processes in the pigment-synthesizing cells themselves.

The triggering moment of melanogenesis disorders in melanocytes is apparently associated with the functioning of tetrahydrobiopterin (H_4Bip), a coenzyme of phenylalanine hydroxylase (phenylalanine-4-monooxygenase, EC 1.14.16.1). In melanocytes, tyrosine forms during the hydroxylation of phenylalanine with the involvement of the coenzyme H_4Bip; tyrosine is then converted to dioxyphenylalanine (DOPA) by copper-dependent tyrosinase (EC 1.14.18.1), and DOPA-chrome then forms on the way to melanin. With vitiligo, a three- to fivefold excess of H_4Bip, which inhibits tyrosinase (a key enzyme in the synthesis of melanin), is recorded in melanocytes [2, 8–11].

It is important that, as a reduced compound, H_4Bip is easily oxidized by atmospheric oxygen (autooxidation), both in vitro and in vivo [12]. The formation of oxidized derivatives is accompanied by the formation of hydrogen peroxide (H_2O_2). In vitiligo, H_2O_2 in millimolar concentrations was identified in the skin of patients [11], i.e., there is oxidative stress. It was demonstrated [13] that UV radiation of certain wavelength ranges enhances autooxidation due to the excitation of H_4Bip itself ($\lambda_{max\ exc}$ 298 nm), but mainly due to the excitation of oxidized biopterin, which triggers the process of photosensitized H_4Bip oxidation upon irradiation in the area of absorption of oxidized biop-