Vitiligo – A Window in the Darkness

W.

Westerhof

Netherlands Institute for Pigmentary Disorders and Department of Dermatology,
Academic Medical Center, University of Amsterdam, The Netherlands

Dr. Wiete Westerhof, Netherlands institute for Pigmentary Disorders, IWO Building, Academic Medical Center,
Meibergdreef 35, NL-1105AZ Amsterdam (The Netherlands)

In this issue (p. 223), a new treatment protocol for vitiligo applied to 33 patients in a pilot study under the direction of K.U. Schallreuter at the Department of Dermatology, University of Hamburg, is reported. The research development of this new approach in repigmentation is the of continuous basic research on vitiligo by the same group. work by the Hamburg group in collaboration with M. Pittelkow Clinic, Rochester, Minn., USA) showed that vitiliginous keratinocytes established under in vitro conditions had a defect in calcium transport in association with the expression of β_2 -adrenoceptors [1, 2]. The high density of these receptors on keratinocytes led to the discovery that these cells have the full capacity for catecholamine synthesis themselves [3]. Therefore, the release of the hormones from the compartment epidermis seems not to depend on presynaptic nerve endings. In addition, Schallreuter's group found that catecholamine biosynthesis is defective in vitiligo yielding increased norepinephrine levels in both epidermis and plasma of these patients [4]. These results supported earlier findings by Dunerva [5] and, more recently, by Morrone et al. [6], who found elevated levels of catecholamines and metabolites in the urine and plasma of patients with active vitiligo. Our own group in Amsterdam discovered increased catechol-*o*-methyltransferase (COMT) activities in the lesional skin of vitiligo patients [7]. COMT is an enzyme that methylates catecholamines, thereby inactivating these potentially cytotoxic compounds. The rise in COMT is probably a response to the elevated level of catechols in vitiliginous skin. Recently, more detailed examination on regulation of catecholamines led to the fundamental discovery that the

Phenylalanine

lase

Melanin

6-BH4 Catecholamines

6-BH4 7-BH4 – < – 4a-OH-BH4

 λ NAD+ f j H2O $\wedge$ NADH

4a-Hydroxy-BH4 dehydratase

I ^q-BH

GTP cyclohydrolase I

A GTP

Fig. 1. Scheme for the de novo biosynthesis and recycling of 6-tetrahydrobiopterin (6-BH₄) in the regulation of L-tyrosine production by phenylalanine hydroxylase in the human epidermis. L-Tyrosine is the common substrate for melanin biosynthesis by melanocytes and catecholamine biosynthesis by keratinocytes. In vitiligo, it is suggested that the low activity for 4a-hydroxy-BH₄ dehydratase leads to a buildup of 7-BH₄ in the epidermis. As a consequence of this buildup, phenylalanine hydroxylase is inhibited (kindly provided by K.U. Schallreuter).

cofactor (6R)-5,6,7,8-tetrahydrobiopterin is predominantly involved in regulation of melanin biosynthesis. This cofactor is rate-limiting for the production of L-tyrosine from L-phenylalanine by phenylalanine hydroxylase and for the formation of L-dopa from L-tyrosine hydroxylase [8] (fig.1).

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In Science, Schallreuter et al. [8] showed that patients with active vitiligo accumulate biopterins in their entire epidermis (i.e. depigmented and pigmented) originating from an increased de novo synthesis and a defective recycling of this cofactor. One consequence of defective recycling is a buildup of hydrogen peroxide and the non-enzymatic byproduct 7-tetrahydrobiopterin. 7-Tetrahydro-biopterin is a potent inhibitor of phenylalanine hydroxylase in both keratinocytes and melanocytes. The presence of the biopterins in the skin of vitiligo patients yields a characteristic fluorescence which is easily detected with Wood's light. However, the fluorescence is quenched by the presence of melanin in the uninvolved epidermis. Earlier, it has been shown that the epidermis of patients with vitiligo has an extremely low catalase activity [9]. This impaired activity can be the consequence of an excessive hydrogen peroxide burst, leading possibly to the destruction of the catalytic center of the enzyme. One major side effect of the compromised tetrahydrobiopterin recycling is the production of hydrogen peroxide [4J].

In light of this new information, a new topical treatment concept has been developed by Schallreuter and Wood using the replacement of catalase with a pseudocatalase (i.e. a low-molecular-weight inorganic complex with catalase activity), in combination with 10-2 M calcium and short-term UVB exposure. The clinical results reported in this issue are impressive and encouraging compared to the known frustrating treatment modalities of this depigmentation disorder.

A sudden burst of hydrogen peroxide can be very cytotoxic and may explain active depigmentation. Defective catecholamine biosynthesis in patients with vitiligo together with increased activities of monoamine oxidase A in their epidermis can provide a basis for stress-related hydrogen peroxide formation [4 and Schallreuter, pers. commun.]. Since melanocytes have only low catalase activity, the removal of cytotoxic concentrations of hydrogen peroxide is critical for cell survival [10]. However, hydrogen peroxide in very low concentrations (10⁻⁶ M) can serve as a substrate for tyrosinase and consequently act as a scavenger [11].

The claimed cessation of the active depigmentation process in 100% of the patients as reported by Schallreuter is very important as it may also overcome the possible Koebner phenomenon to allow additional successful grafting in this group of patients.

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182

Westerhof

Editorial