Hypothesis: possible role for the melatonin receptor in vitiligo: discussion paper

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Summary
A new unifying hypothesis for the aetiology of vitiligo is proposed, in which we postulate that the final destruction of melanocytes in vitiligo results from a cascade of reactions initiated by a disregulation of melanogenesis, caused by activation of the melatonin receptor. These events result in the high and uncontrolled production of free radicals and toxic products of melanogenesis which sequentially damage or destroy melanocytes and keratinocytes, provoke an autoimmune response against exposed intracellular or altered cell surface antigenes, and increase the propensity of melanocytes to undergo malignant transformation.

Background
To date, there is no really convincing theory for the aetiology of vitiligo, a skin disorder characterized by gradually enlarging areas of depigmentation, and, consequently, no satisfying therapy for this disease. Two current schools of thought can be distinguished: (1) vitiligo results from a pathological autoimmune response against melanocytes; (2) vitiligo results from genetic, environmental, or neural factors which induce autodestruction of melanocytes that subsequently activate an autoimmune response[1].

In this paper, we explore the possible role of the melatonin receptor in the aetiology of vitiligo. In 1959 Lerner hypothesized '. . .that vitiligo results from increased output at peripheral nerve endings in the skin of an agent like melatonin that lightens the color of pigment cells and decreases new melanin formation'[2]. In an extension and modification of this pioneering idea, we present a unifying hypothesis which integrates common knowledge on pigment biology and clinical characteristics of vitiligo into a new aetiological concept.

The main role of the melanocyte is thought to be the transformation of L-tyrosine into melanin in a precise and efficient way without destruction of the melanocyte by the highly toxic reaction sequence[3], whereby melanin acts as a scavenger of free radicals and toxic intermediates of melanogenesis and as an inhibitor of tyrosinase activity[4,5]. Melanogenesis is restricted to the melanosomes[6], controlled by tyrosinase[6], and postdopa-oxidase regulators (e.g. in rodent and human hairbulb melanocytes)[6-9]. Pigment granules are then transported to the keratinocytes via dendritic processes in phagocytic fashion[3].

Any defect connected with (1) increased tyrosinase activity without optimalization of the transformation of intermediates of melanogenesis into melanin; or (2) decrease of melanin production without decrease of tyrosinase activity, may lead to damage or destruction of pigment cells. Subsequently, toxic products may be released into the vicinity of the damaged cell, or metabolically still active melanosomes may be transported into keratinocytes. In both cases, damage or destruction of keratinocytes could result.

In mammals, there is a naturally occurring factor which inhibits melanin synthesis without affecting tyrosinase activity: melatonin[10,11]. Melatonin is synthesized in the pineal gland, retina, in the gastrointestinal tract[12,13], and perhaps other extrapineal sites so far undetected. It excerts its regulatory role by an interaction with a specific receptor[12,13] and is a product of the multistep conversion of L-tryptophan to serotonin and subsequently melatonin[12,13]. The synthesis and secretion of melatonin are stimulated by catecholamines[14]. Melatonin exhibits a host of activities that are only gradually being appreciated[12,13]. Two of the most interesting of them are its immunomodulatory and its antitumour activity[12]. The role of melatonin in human skin, however, is almost completely obscure.

Premises
Hypothesis on aetiology of vitiligo must integrate a number of experimental and clinical findings: (1) Melanocytes in vitiliginous skin are absent or show morphological signs of damage[1]. (2) Vitiligo keratinocytes show signs of damage in lesional and nonlesional skin[15]; keratinocytes are known to support the proliferation and viability of melanocytes by the production bFGF[16]. (3) Intermediates and free radicals produced during melanogenesis can be highly toxic toward melanocytes[4,6,7]. (4) Melatonin can inhibit melanin synthesis without affecting the first steps of melanogenesis[10,11]. (5) Melanosomes are transported directly to keratinocytes[3]. (6) Stress frequently precedes the development of vitiligo, and some association with emotional life crises, psychiatric illness, and neurological diseases has been reported[2,17]. (7) There is an autoimmune response mounted against melanocytes[18] as well as frequent association with other diseases that show autoimmune pathology (eg Graves' disease, Addison's disease)[1]. (8) Vitiligo exhibits the Koebner phenomenon[1]. (9) In about 30% of vitiligo patients there is a history of vitiligo in another family member[1]. (10) People with vitiligo or a family background for it and animals in experimental models of vitiligo show a predisposition of their melanocytes to undergo malignant transformation, as well

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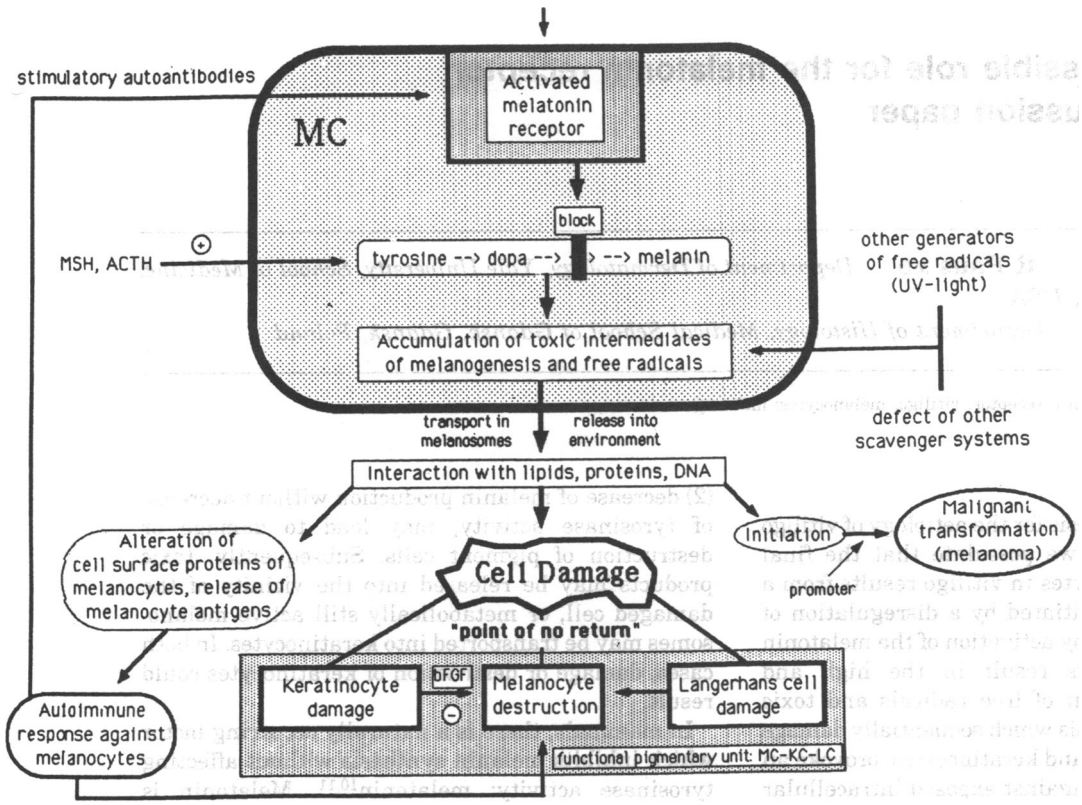

Figure 1. Hypothetical scheme for the development of vitiligo (for details see text). Melanocytes (MC) are depicted to be operative within a functional pigmentary unit (Langerhans cells, melanocytes, keratinocytes) that may be affected as a whole by vitiligo[22]

as a prolonged survival time for the host bearing melanoma[19-21].

Hypothesis

On this basis, we postulate that the final destruction of melanocytes in vitiligo results from a disregulation of melanogenesis induced by activation of the melatonin receptor (Figure 1). This process damages melanocytes by a build-up of toxic products and free radicals generated during melanogenesis without a parallel increase in the production of the scavenger melanin. In addition, keratinocytes are damaged by toxic products released from melanocytes or by transport of metabolically active melanosomes into keratinocytes (cf. autodestruction concept[23]). In addition, other scavenger systems may be defective[24], and render the patient more vulnerable to toxic products generated, eg by u.v. light. In consequence, the melanocyte damage is magnified by a vicious circle - decrease or loss of melanocyte support by keratinocytes within a functional pigmentary unit[22]. A secondary autoimmune response to altered cell surface proteins on the damaged melanocytes, and possibly keratinocytes, as well as to intracellular antigens sharing homology with cell surface antigens (eg melanosomes[25]), finally leads to a massive and irreversible loss of melanocytes ('point of no return').

Figure 1 also depicts how activation of the melatonin receptor and subsequent disregulation of melanogenesis could result in the accumulation of toxic products and free radicals which potentially interact with DNA, thus providing the initiation step of carcinogenesis and predisposing the host to the development of melanoma. At the same time, however, the induction of an autoimmune response against melanocyte antigens could assist in the immunosurveillance of established melanoma cells. An additional direct or indirect antitumour activity of melatonin in general, and in experimental melanoma in particular[12], including human melanoma in vitro[26], may further explain the presumably prolonged survival of vitiligo patients with melanoma.

Basically, the melatonin receptor could be activated via: (1) an increased concentration of melatonin in the skin caused by hyperproduction of melatonin in the pineal gland or in peripheral production sites (perhaps the skin), initiated by an increased release of catecholamines and other neurotransmitters (this would help to explain the association of stress and neural factors with vitiligo[1,2]). (2) A hereditary tendency toward expression of an increased number of melatonin receptors; (3) a dysfunction of the melatonin receptor caused by an intrinsic activation without binding of ligand, activation by binding of another ligand than melatonin or via stimulating autoantibodies against the melatonin receptor. The latter speculation is invited by the association of vitiligo with Graves' disease, which displays stimulatory autoantibodies against TSH receptors. The immunomodulatory properties of melatonin could further contribute to the autoimmune phenomena associated with vitiligo.

Discussion

The melatonin hypothesis of vitiligo allows integration of all the aetiological concepts voiced so far, and does not designate a single primary event leading to the destruction of melanocytes. Instead, it emphasizes the pivotal role of a (hyper-) active melatonin receptor in the initial phase of vitiligo pathogenesis, and stresses the interdependence of the different systems affected. All the experimental and clinical findings mentioned under 'premises', can be explained within the confines of the melatonin hypothesis, including the association with other autoimmune diseases, neurologic/psychiatric disorders

and stress, melanoma, hereditary factors and the Koebner phenomenon (increased vulnerability of damaged melanocytes to further traumatization by mechanical irritation or u.v.-light induced free radicals). Spontaneous or therapeutically induced repigmentation of vitiligo skin lesions would be possible before the 'point of no return' has been reached (cf. Figure 1). The higher incidence of vitiligo in patients with Addison's disease (increased MSH and ACTH) could be explained by the stimulatory effect of these hormones on the generation of further toxic products and free radicals of melanogenesis.

It will, however, be necessary to establish that human melanocytes really do have functional melatonin receptors and that activation of these receptors can lead to a build-up of toxic products of melanogenesis. The recently reported finding that 5-methoxypsolaren (which, together with u.v.-A light, can have a beneficial therapeutical effect in vitiligo[1]) actually increased melatonin serum levels in 11 normal volunteers[27] awaits explanation. In vitiligo, serum melatonin levels may be of minor relevance, as opposed to the melatonin concentration in the skin and the degree of receptor activation of the target cells.

The immunomodulatory and tumouricidal properties of melatonin, particularly with respect to melanoma[12], seem to make a thorough assessment of melatonin's role in vitiligo almost mandatory, since knowledge regarding the mechanisms of melanocyte destruction in vitiligo may be helpful in the development of new therapeutic tools for treating patients with melanoma[28]. The neuroendocrine control of skin and pigment system in humans are exciting and promising areas of future dermatological research: focusing on the putative role of melatonin in vitiligo offers a novel and perhaps clinically useful research approach to the general problem of neuroendocrine control in dermatology.

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