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Melanin, Melatonin, Melanocyte-Stimulating Hormone, and the Susceptibility to Autoimmune Demyelination: A Rationale for Light Therapy in Multiple Sclerosis

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Abstract — Multiple sclerosis is a central nervous system demyelinating disease. Significant evidence, including similarities with its animal model, experimental autoimmmune encephalomyelitis, supports an autoimmune mechanism, activated by putative environmental factors in genetically predisposed individuals. Genetic factors strongly influence the susceptibility to demyelinating diseases in humans and rodents. Understanding the mechanisms governing susceptibility versus resistance may help to identify individuals at risk or design therapeutic strategies. The hypothesis formulated here is based on the observation that resistance to multiple sclerosis and experimental autoimmune encephalomyelitis is associated with dark skin pigmentation. While this may signify a protective role for melanin against environmental factors producing oxidative damage, the mechanism postulated here is that susceptibility to autoimmune demyelination is influenced by hormonal factors, i.e. the neurohormones melatonin and melanocyte stimulating hormone, which have opposing effects on immune functions and, at the same time, are important determinants of the individual's production of melanin.

Introduction

Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). Clinically, it is characterized by neurological deficits of variable degree (frequently exhibiting a relapsing–remitting course), and pathologically by CNS infiltration by lymphocytes and macrophages associated with various degrees of demyelination (1–3). Although its aetiology is still unclear, evidence points to an autoimmune mechanism. The understanding of MS immunopathogenesis has been improved through the study of its animal model, experimental autoimmmune encephalomyelitis (EAE). In EAE and MS the effector cells are T cells of the $CD4^+$ type (4). Recent studies of their cytokine production profile in both MS and EAE indicate that the encephalitogenic T cells belong to the Th1-type subset, characterized by the production of interleukin-2 (IL-2) and interferon-gamma (IFN-γ), and by the facilitation of cell-mediated immunity (5,6).

Active EAE can be induced in susceptible animals

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by immunization with CNS antigens such as myelin basic protein or proteolipid protein, or their encephalitogenic fragments, with appropriate adjuvants. Passive EAE is induced by adoptive transfer of $CD4^+$ T cells reactive to these proteins.

Epidemiological studies of MS have identified populations at risk. A striking latitude gradient has been observed in both hemispheres, the frequency increasing as the distance to either the North or the South Pole decreases. Also, MS is very rare in blacks living in Africa. Although somewhat more frequent in blacks in the USA, it is still less frequent than in US whites of European descent (1), suggesting that the risk at the same latitude is lower in individuals with darker skin pigmentation. Interestingly, the epidemiology of MS, including the geographic distribution and populations at risk parallels the epidemiology of melanoma. Fair-skinned individuals of North European descent appear to be at highest risk for both conditions (7).

Understanding the mechanisms of susceptibility versus resistance to MS is of obvious importance for detecting individuals at risk and for attempts to treat or even prevent this disease. Current knowledge from epidemiological and genetic studies of MS can be summarized as follows: putative environmental factors trigger the autoimmune attack in individuals with genetic predisposition (1,3).

The similarities between EAE and MS have led to investigations of the nature of resistance to autoimmune demyelination in EAE in attempts to find clues to mechanisms of resistance in MS. The nature of EAE resistance has not clearly been elucidated. However, strains of rodents have been identified which, although not immunodeficient, are very resistant to most conventional means of inducing active or passive EAE. Frequently used examples are the Brown Norway rat and the C57B1/6 mouse (8,9).

It was my observation that these strains of animals used as typical examples of EAE resistance also exhibit dark skin and hair pigmentation, that led to the analogy with the low incidence of MS among blacks. A number of possible explanations for this observation can be proposed. Of course, it is possible that the resistance to demyelination and the determination of pigmentation are unrelated. Indeed, just as in humans, resistance to MS is not absolute among blacks, some EAE resistant animal strains, such as BALB/c mice (8), are not black. Alternatively, it is possible that producing more melanin represents an evolutionarily advantageous adaptation for populations exposed to higher levels of environmental factors (for example, UV radiation), and that these factors may be involved in triggering autoimmune demyelination. Finally, the hypothesis I propose is that neurohormonal physiological stimuli that influence melaninogenesis have effects on the individual's immune system which either favour the resistance or the susceptibility to autoimmune demyelination. I will discuss the bases of my hypothesis below, in the context of the pigment melanin and two neurohormones with opposing actions on both skin pigmentation and T-cell activation: melatonin and melanocyte-stimulating hormone (MSH).

Melanin

Melanin is a dark brown or black pigment which functions as a cutaneous sunscreen. Its ability to absorb UV and visible light protects against oxidative damage, as evidenced from the increased susceptibility to such damage in albinism, in which the synthesis of melanin is deficient. Melanin, through its abundance in tyrosine, is an effective scavenger of free radicals (10,11). Free radical damage has been implicated in the pathogenesis of MS and EAE. It is, however, the final, effector mechanism of myelin damage, which takes place locally (in the CNS) (12–14). It is thus unlikely that cutaneous production of melanin could prevent CNS generation of oxygen radicals. Could it be, then, the CNS melanin? Although some CNS neurons contain melanin, which may have a protective effect against oxidative neuronal damage, this neuromelanin is unlikely to play a role in MS. Neuromelanin-containing neurons are not present in areas of the brain usually affected by MS. Also, there is no evidence of a direct correlation between the amount of neuromelanin and that of cutaneous melanin (15). Melanin is also present in variable amounts in leptomeninges, and theoretically could directly inhibit encephalitogenic T cells trafficking into the CNS (15). However, its patchy and highly variable distribution (15) makes it an unlikely candidate as a inhibitory factor of encephalitogenic T cells, and thus, of myelin damage.

In conclusion, it is unlikely that melanin itself plays a direct role in the protection against the demyelinating damage of MS and EAE. The neurohormonal factors that control the production of melanin in skin, however, have significant effects on the immune system, influencing lymphocyte activation, and thus, susceptibility to autoimmunity. The two neurohormones, melatonin and MSH will be discussed below in terms of their effects on the immune system and their potential role in MS and EAE.

Melatonin

N-acetyl-S-methoxytryptamine or melatonin is a hormone produced mainly by the pineal gland. It has

derived its name from its ability to lighten the skin of amphibians. This direct effect has not been demonstrated in mammals. However, there is an inverse correlation between melatonin and skin pigmentation: exposure to light, a potent inducer of melanin in the skin (high in geographic areas with darker-skinned populations), is the most powerful suppressor of melatonin production (16, 17). Conversely, lack of exposure to light (darkness) is a strong stimulus for melatonin production (18), and is geographically associated with areas of high MS prevalence. Moreover, experiments with EAE carried out three decades ago have shown that animals kept in the dark had more severe disease, whereas animals exposed to continuous light (which suppresses melatonin production) were protected (19). Results consistent with those mentioned above were provided by recent experiments with another T cell-mediated autoimmune disease, collagen-induced arthritis, a model for the human autoimmune disease rheumatoid arthritis. In this system, dark exposure or exogenous melatonin administration exaggerated the autoimmune damage (20,21), whereas pinealectomy, a procedure previously known to induce immune suppression (22), prevented it (23).

The main role of melatonin is the regulation of circadian rhythms (16). Thus, melatonin influences the periodicity of immune responses, a function utilized in the design of cancer therapy, in which melatonin also has been beneficial as adjuvant (24). In addition, melatonin has direct, receptor-mediated, effects on cells of the immune system. It enhances antigen presentation and T-cell proliferation (25). Melatonin upregulates IFN-γ production by murine lymphocytes (26), thus exhibiting a stimulatory effect on Th1-cells, which are the important effectors of these autoimmune disorders. Melatonin also counteracts corticosteroid immunosuppression (27), a function relevant to autoimmune demyelination, as endogenous corticosteroid production may be a mechanism of resistance in these diseases. Interestingly, pineal calcification, which has been associated with hypermelatoninaemia (28) is a frequent feature of MS.

Taken together, the above observations justify the hypothesis that melatonin, the secretion of which inversely correlates with skin pigmentation, plays a role in the autoimmune demyelinating processes of MS and EAE.

Melanocyte-stimulating hormone

Melanocyte-stimulating hormone (MSH) is derived from pro-opiomelanocortin (POMC), polypeptide precursor synthesized in the pituitary and subsequently cleaved into α-, β-MSH β-lipotropin, ACTH, enkephalins and endorphins (29). Pigment cells have α-MSH receptors which activate the enzyme adenylate cyclase. Similar receptors exist on the surface of lymphocytes. α-MSH has a number of physiological activities, as a true neurotransmitter and hormone. For example, it triggers ACTH release in the neonate (30), and FSH and LH release in adults (31). MSH has been implicated in the stimulation of melanin production by melanocytes. Thus, MSH production correlates with skin pigmentation in both physiological and pathological states. The amounts of MSH necessary to produce pigmentation are higher than the amounts required for the other direct effects of MSH, including those on the immune system. Of the immunological actions of MSH, an important one is its ability to inactivate lymphocytes (32,33). MSH can counteract the effects of IL-1 (34), an essential macrophage and T-cell activator, which has been implicated in MS and EAE (35–37), and whose inhibition suppressed EAE (37).

In conclusion, MSH, a factor involved in the induction of dark skin pigmentation, is a down-modulator of immune responses, including those involved in the autoimmune processes of EAE and MS.

Conclusion

The evidence presented above supports the hypothesis that neuropeptides involved in the regulation of cutaneous pigmentation, melatonin and MSH, have potentially important, opposing effects on immune functions, and, in particular, on the process of T-cell activation which is a relevant characteristic of autoimmune demyelination. This provides a potential explanation for the higher incidence of MS in populations with lighter skin pigmentation. If future studies of EAE and MS confirm this hypothesis, there are therapeutic implications for MS and, potentially, for other autoimmune diseases. Down-modulation of melatonin or increasing the MSH by pharmacological means or by exposure to light may suppress EAE or MS. Just as melatonin administration represents now a safe measure to provide immune enhancement, light therapy, now a safe and effective therapy in seasonal affective disorders (38), may benefit MS patients in the future.

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