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Do hyporesponsive genetic variants of the melanocortin 1 receptor contribute to the etiology of multiple sclerosis?

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Summary Hyporesponsive genetic variants of the melanocortin 1 receptor result in pigmentary phenotypes exhibiting light skin and light color hair, including red hair. These variants are common in populations with high rates of multiple sclerosis, while rare in populations with low rates. α-Melanocyte stimulating hormone, the major ligand for this receptor, is responsible for phenotype determination, but is also known for its anti-inflammatory and immune modulating effects, including inhibition of factors implicated in multiple sclerosis pathology. As the melanocortin 1 receptor is expressed on various cell types involved in immune response, it is possible that carriers of hyporesponsive variants of this receptor lack the full anti-inflammatory and immune modulating effects of α-melanocyte stimulating hormone. It is proposed that these variants are part of a spectrum of genes involved in the etiology of multiple sclerosis. Related aspects of multiple sclerosis epidemiology are examined.

Introduction

Multiple sclerosis (MS) is a central nervous system (CNS) disease, generally believed to be autoimmune, involving inflammation, demyelination, and axonal loss [1]. Its course is highly variable, but generally leads to accumulation of damage and disability. Studies have found a number of genes associated with the disease, but no one association has been found to explain its incidence or progression. It is generally believed that there is a complex of genes that together establish susceptibility to MS with unknown environmental factors precipitating disease in susceptible individuals [2]. This paper explores the possibility that hyporesponsive variants of the melanocortin 1 receptor (MC1R) contribute to the etiology of MS. The major ligand for this receptor is α-melanocyte stimulating hormone (α-MSH), which has potent immunomodulating and anti-inflammatory effects [3,4]. Lack of full receptor functioning may lead to increased inflammation and activation of cytokines involved in MS pathology.

α-MSH, MC1R, and MS

α-MSH functions as an antagonist of interleukin-1 (IL-1), a proinflammatory cytokine implicated in MS pathology [5], while inducing interleukin-10, an immune modulating cytokine associated with MS suppression [1,3]. It has also been found to modulate nuclear transcription factor κB (NFκB) activation, a crucial step in inflammatory processes [3]. α-MSH down-regulates IL-6, IL-8, monocyte chemoattractant protein-1, nitric oxide, tumor necrosis factor-α, adhesion molecules, and the

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expression of major histocompatibility complex class 1 molecules [3,6]. It suppresses the production of interferon-γ by antigen-stimulated T cells [7], down-regulates expression of costimulatory molecules on dendritic cells [8], and modulates mast cell-dependent inflammation [9]. These are factors generally found to be implicated in autoimmunity and MS pathology [1,3]. Studies on experimental autoimmune uveoretinitis (EAU), which has an immune profile similar to that of MS [10], found that α-MSH induces production of regulatory T cells and transforming growth factor-β (TGF-β), suppressing other effector T cells, and suppressing autoimmunity [7].

Some connections between α-MSH and MS can be found in the literature. A 1992 research study of 25 MS patients experiencing exacerbation found low nocturnal plasma levels of α-MSH in over 70% of patients [11]. In 1995, a hypothesis was proposed that MS etiology is linked to the opposing effects of α-MSH and melatonin [12]. Recent research has shown therapeutic effects in the treatment of experimental autoimmune encephalomyelitis (EAE), the mouse model of MS, for expression constructs that secrete α-MSH [13]. Further research is beginning on use of α-MSH in MS and other autoimmune diseases [7,14], and it is likely that more connections will be forthcoming.

α-MSH, acting on MC1R on melanocytes, is responsible for melanin production [15]. Light skin pigmentation is produced by hyporesponsive (also called loss-of-function) genetic variations of MC1R [16]. These variants also result in poor tanning ability, sun-sensitivity, and increased susceptibility to skin cancer [16], and are centrally involved in hair color determination [16—18]. A small number of hyporesponsive variants, particularly Arg151Cys, Arg160Trp, and Asp294His, are associated with red hair [19]. A study of hyporesponsive variants, including those associated with red hair, found significantly decreased signaling and reduced cyclic adenosine 5′-monophosphate (cAMP) production in response to α-MSH, leading to pheomelanin (red/yellow) over eumelanin (brown/black) production [19].

Although pheomelanin is more vulnerable to oxidative damage than eumelanin [16] and a higher production of pheomelanin may have unknown consequences in MS, a more likely effect of these variants in MS would involve inflammation and immune function. In addition to expression on melanocytes, MC1R is found on a range of cells unrelated to pigmentation, including a subset of cytotoxic T-cells, monocytes/macrophages, B-lymphocytes, natural killer cells [20], mast cells [9], and dendritic cells [8]. It is possible that persons carrying hyporesponsive MC1R variants are more susceptible to MS due to a lack of the normal immunosuppressive and anti-inflammatory effects of α-MSH, many of which, including NFκB inhibition, are believed to be cAMP dependent [3]. As the variants are common and found in people who do not have MS, it is clear that there is a complex of other factors involved.

MS epidemiology and MC1R

Two well-known features of MS are its increased incidence with increasing latitude and its variation among ethnic populations [2]. A small number of hyporesponsive MC1R variants are thought to be primarily responsible for red hair and fair skin, common in Northern Europeans [18,21,22]. These variants are particularly common in populations where MS incidence is high, such as Scottish, English, Irish, and Swedish populations [2,17]. These variants also have heterozygote effects, including effects in persons without red hair [16]. A study found MC1R variants in 82% of red haired subjects, 30% of blonde subjects, 22% of auburn subjects, and less than 20% of brown or black haired subjects [23]. The same study found these variants in over 76% of persons with the lightest skin type, and found that the number of variants decreased with increasing skin pigmentation. Subjects with red hair and light skin had the highest number of genetic MC1R variation.

Some notable exceptions to the latitude gradient of MS are Eskimo, Amerindian, and Maori populations which, even when located in high-risk areas at high latitudes, have a low incidence of MS [2]. These populations have darker skin pigmentation than Northern European populations in which MS is frequently found and are, therefore, less likely to carry hyporesponsive MC1R variants. There is also a very low incidence of MS among Black Africans [2], a population which shows very little polymorphism of MC1R [16,17]. The incidence of MS among African-Americans is much lower than that among Caucasians, but higher than the incidence in Black Africans, a difference possibly explained by admixture [2,17]. The incidence of MS among Asian populations is also low [2]. A study has found that Asians generally do not carry the hyporesponsive MC1R variants responsible for light skin and hair in Caucasians [15].

While the distribution of genetically susceptible populations of Northern European origin may be sufficient explanation for the latitude gradient of MS, various studies support an interaction between

genetics and some environmental factor(s) [2]. One factor varying with latitude, due to ultraviolet (UV) light exposure, is vitamin D [24], an immunomodulatory hormone with therapeutic effects on EAE [25]. There is evidence that, like vitamin D, α-MSH levels may vary with latitude and UV exposure [24,26]. The skin can be seen as a neuroendocrine system secreting in response to UV various neuromediators which have both local and systemic effects [24]. UV induces α-MSH in the skin, and several studies have shown that UV exposure raises systemic blood levels of α-MSH [24,26]. A recent study has shown that UV irradiation of the eye also increases α-MSH in plasma via the hypothalamopituitary system [27]. It is possible that low levels of α-MSH may increase vulnerability to inflammation and/or autoimmunity, particularly among those with hyporesponsive MC1R variants.

Another feature of MS is that pregnancy has a beneficial effect while relapses are frequent postpartum [28]. Immunomodulatory factors, such as TGF-β, are elevated during pregnancy [10], while proinflammatory IL-1 has been found to be elevated postpartum [29]. Females are more susceptible to MS and other autoimmune diseases than males [28,30] and are known to have a stronger immune response to infections and antigens [30]. Females have been shown to have significantly reduced levels, compared to males, of a receptor which binds IL-1 and prevents its activation [30]. A lowered response to α-MSH, an IL-1 antagonist [3,8], may be involved in both postpartum relapse and female susceptibility.

An interesting connection between gender, MC1R, and κ-opioids may have relevance for MS. One study found that women who carried two of the hyporesponsive MC1R variants responsible for red hair and fair skin were significantly more sensitive to κ-opioid agonists than other females [31]. This study also tested mice and found that, in females only, MC1R mediates κ-opioid analgesia. More research is needed on the significance of these connections for MS.

Conclusion

Genetic assessment of MC1R variants in MS patients would be an important first step in understanding their possible influence. However, though such studies could rule out involvement, they could not conclusively indicate a direct connection to disease etiology. These variants are generally known to exist in populations at high risk for MS, but other associated genes in these same populations may be exclusively involved. It could, however, be determined if these variants exist in higher frequency among MS patients than in disease-free individuals in the same high-risk group. Also of interest would be the relative level of the variants among MS patients from populations known to have a low incidence of such variants, such as African-Americans or Asians. As hyporesponsive variants are most common in persons with red hair, the frequency of MS among red-haired persons would be of great interest.

Further studies of α-MSH, or its analogs, on EAE would be of benefit, with subsequent human studies if therapeutic effect is shown. MS is considered by many to be a heterogeneous disease with a number of separate etiologies. It may be that α-MSH could have the greatest effect on those persons who carry the hyporesponsive MC1R variants, or conversely, persons with these variants may not respond to α-MSH. It may also be that MC1R variants affect MS in unexpected ways, possibly due to feedback mechanisms, that could lead to negative responses to α-MSH. Studies of α-MSH and MS could be structured to isolate these effects.

The possible significance of hyporesponsive MC1R variants to MS pathology is yet unknown. They may have no influence on the disease, they may play a minor role, or, in combination with a complex of other factors, they may play a major role in the autoreactive, dysfunctional immune response of MS. Current research hints at MC1R involvement, but this sketchy picture needs further elaboration before hints can become clear directions.

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