UV Irradiation of Skin Regulates a Murine Model of Multiple Sclerosis

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Abstract

Objective: The prevalence of multiple sclerosis follows a latitude gradient, with increased disease at higher latitudes. Previous studies have focused on a vitamin D hypothesis; although recent evidence suggests that exposure to ultraviolet radiation (UVR) itself may be important. In this study, the effects of UVR on the development of experimental autoimmune encephalomyelitis (EAE) were examined.

Methods: C57BL/6 mice were irradiated with a single erythemal dose of UVR (8 kJ/m²), or 4 daily sub-erythemal doses (1 kJ/m²), before sensitisation to myelin oligodendrocyte glycoprotein peptide. The UVR irradiation protocols used do not increase 25-hydroxyvitamin D concentrations in serum of vitamin D-sufficient mice. The onset of EAE was recorded and mice were clinically monitored for 40 days.

Results: A single dose of erythemal UVR (8 kJ/m²) significantly suppressed EAE onset and severity. Four daily exposures of sub-erythemal UVR (1 kJ/m²) also significantly delayed disease onset but was less effective than the erythemal dose.

Conclusion: UV irradiation delayed the onset and reduced the severity of EAE. Continued administration of lower dose UVR following disease onset may be necessary to achieve similar results to a single higher dose delivered pre-sensitisation. Our results give further weight to suggestions that UVR exposure may delay MS onset and progression and UVB phototherapy may provide an option for treatment of MS.

Keywords: Multiple sclerosis; Experimental autoimmune encephalomyelitis; Ultraviolet radiation; Murine model

Introduction

Multiple Sclerosis (MS) is the most common neuroinflammatory condition diagnosed among young adults aged 20-40 years [1]. Characterised by the formation of plaques in the brain and the spinal cord, MS is an autoimmune disease that is mediated by inflammation and demyelination, resulting in the destruction of the protective myelin sheath surrounding axons of the central nervous system (CNS) [2]. As a result, axons have reduced conducting speeds, causing an interrupted function of the brain and spinal cord [3]. There is considerable evidence of environmental risk factors for the development of MS. The prevalence of MS follows a latitude gradient, increasing with greater distance from the equator [4]. In 1960, Acheson and colleagues [5] showed that the strongest correlation was with levels of solar ultraviolet radiation (UVR). Observational epidemiological studies support a protective effect for MS onset of higher levels of sun exposure [6-8]. Exposure of the skin to UVR is the primary source of vitamin D in most locations, and research over the last 10-15 years has highlighted the immunomodulatory roles of vitamin D [9]. Subsequent observational studies have confirmed that higher serum 25-hydroxyvitamin D (25(OH)D) levels are associated with reduced MS risk [10], relapse rate [11] and clinical progression [12]. It is difficult to exclude other contributing factors (such as sun exposure) from these observational studies that are often underpowered and inconsistent. Potential benefits of vitamin D supplementation have been demonstrated for some people with MS [13,14]. However, results of intervention studies have varied and the significance for clinical outcomes is unclear [15-18]. It is possible that low 25(OH)D is acting as proxy for sun exposure and that there are other mechanisms that may be more important [19].

Differentiating between the effects of UVR that are vitamin D-dependent and those that are vitamin D-independent is difficult. Sun exposure and 25(OH)D were independent risk factors for the onset of CNS demyelination [20] and MRI measures of MS [21]. In addition to initiating synthesis of vitamin D in the skin, UV irradiation causes DNA damage in skin cells that stimulates immune suppression through pathways involving both regulatory cells and immunoregulatory soluble mediators [19]. The onset of experimental autoimmune encephalomyelitis (EAE), a robust model for MS, in mice pre-treated with UVR, not vitamin D, has been previously investigated. However, the results have varied despite the use of similar broadband UV lamps. In one study, pre-treatment with UVR was not sufficient to suppress EAE and was only effective when UVR treatment was continued following immunisation with a sensitising peptide [22]. In another, protective effects of pre-treatment with UVR against EAE were detected but continuing UVR exposures were ineffective [23]. In a third study, there was significant suppression of EAE following pre-treatment with four daily doses of sub-erythemal UVR prior to peptide sensitisation [24], and this suppression was boosted by continuing UVR treatment.

In view of this variation, and the possibility of human trials utilising UVB phototherapy, both erythemal and multiple sub-erythemal doses of UVR were investigated in regulation of EAE in a further laboratory. Both doses reduced the time of onset and the intensity of EAE symptoms. These support the potential adaption of UVB phototherapy for patients with MS.

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Received May 13, 2015; Accepted June 13, 2015, Published June 21, 2015

Citation: Geldenhuys S, Mohammad MG, Li H, Hassanpour M, Ng RL, et al. (2015) UV Irradiation of Skin Regulates a Murine Model of Multiple Sclerosis. J Mult Scler (Foster City) 2:144. doi: 10.4172/2376-0389.1000144

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Materials and Methods

Mice

Female C57BL/6 mice were obtained from the Animal Resources Centre (Murdoch, Western Australia). The mice were fed a standard mouse chow (Specialty Feeds, Perth, Western Australia). All experiments were performed with the approval of the Telethon Kids Institute Animal Ethics Committee according to the guidelines of the National Health and Medical Research Council of Australia.

UV-irradiation

A bank of TL40W/12RS lamps (Philips, Amsterdam, The Netherlands) emitting broadband UVR with 65% UVB (280-320 nm) and peak emission at 313 nm was used. The UVB output by the lamps was measured before each treatment using a UVX radiometer (Ultraviolet Products Inc., Upland, CA). Twenty-four hours prior to irradiation, a uniform area of the dorsal skin of both control and irradiated mice (8 mice per group) was shaved (8 cm²). To administer UVR, mice were held in perspex compartments which were covered with 0.2 mm polyvinyl chloride plastic to eliminate wavelengths <290 nm. The compartments were placed 20 cm beneath the UV lamps. Mice were 8-10 weeks old (16-18 g) at the time of irradiation. The maximum dose delivered was 8 kJ/m², equivalent to 3-4 minimal erythemal doses [25]. The single dose of 8 kJ/m² was delivered 3 days before sensitisation to the myelin oligodendrocyte glycoprotein (MOG) peptide. Lower sub-erythemal doses of UVR (1 kJ/m²) were given on days -5, -4, -3 and -2 before sensitisation to MOG peptide. There was an additional group of control mice that received no UV-irradiation.

Induction of experimental autoimmune encephalomyelitis (EAE)

Control and UV-irradiated mice were vaccinated with MOG peptide and the disease progression was clinically monitored as previously described [26,27]. Briefly, the vaccine was composed of 100 µg of MOG₃₅-₅₅ peptide (Sigma, St Louis, MO) in complete Freund’s adjuvant supplemented with 1 mg Mycobacterium tuberculosis HRA37 (Difco, Detroit, MI) in a 100 µl total volume. Mice were vaccinated subcutaneously in both flanks with 50 µl into each side. All animals received an i.p. dose of 200 ng of pertussis toxin (List Biologicals, Campbell, CA) in a total volume of 100 µl on the day of immunization and 2 days later.

Scoring of EAE

Mice were clinically monitored by 2-blinded investigators over a period of 40 days. Mice were scaled on a 0-5 scale: 0, no clinical symptoms; 1, flaccid/limp tail; 2, partially paralysed hind limbs; 3, completely paralysed hind limbs; 4, quadriplegia; 5, moribund or dead. Intermediate clinical phenotypes were assigned intermediate relevant scores.

Statistical analyses

The time to disease onset and disease severity were examined by Kaplan-Meier analysis reporting the log-rank test and two-way ANOVA respectively. A p value of less than 0.05 was considered significant.

Results

Exposure of skin to UVR delays disease onset

In two separate cohorts of mice, the shaved dorsal skin of mice was exposed to either a single acute erythemal dose of UVR (8 kJ/m²) 3 days before the first exposure to MOG peptide, or 4 sub-erythemal doses of 1 kJ/m² on days -5, -4, -3 and -2 before MOG peptide injection. The onset of EAE symptoms (classified as a score of 1) was significantly delayed in both groups of UV-irradiated mice when compared to control mice that received no UVR (Figure 1).

In the first cohort, all mice developed disease. As shown in Table 1, the mean (first, last) day of disease onset was: Control [11.3 (9, 15)], 4 x 1 kJ/m² [14.5 (10, 18)] and 1 x 8 kJ/m² [16.1 (13, 22)]. The difference

![Figure 1: Pre-treatment with UVB delayed the onset of EAE.](image-url)

Table 1. First day of detection of EAE symptoms in mice sensitised to MOG at day 0.
between groups of mice was significant by Kaplan Meier analysis (p=0.0026, Wilcoxon test for equality of survivor) (Figure 1A).

In the second cohort, most mice developed disease with 1 from each group of 8 being disease free. Of the animals with disease, the mean (first, last) day of disease onset was: Control [9.4 (7, 12)], 4 x 1 kJ/m² [13.1 (12, 16)] and 1 x 8 kJ/m² [17.1 (9, 24)]. The difference between groups of mice was significant by Kaplan Meier analysis (p=0.0147, Wilcoxon test for equality of survivor) (Figure 1B).

**Exposure of skin to UVR suppresses disease expression**

Disease expression was followed until all mice (with the exception of 1 animal per group in the second cohort) recorded EAE symptoms. The single acute dose of UVR (8 kJ/m²) was more potent than chronic low-dose UVR (4 x 1 kJ/m²) for reducing EAE symptom intensity in both experimental cohorts. Additionally, EAE clinical scores for both groups of irradiated mice remained lower than scores of control mice for a longer period of time. In both experiments, the effect of UVR (8 kJ/m²) was no longer significant after 21 days (Figure 2).

The effect of 4 consecutive daily doses of 1 kJ/m² before sensitisation to MOG peptide was significant in the days following first expression of EAE symptoms (Figure 2). However, the protective effects were not sustained as long as those measured in response to the single higher dose of UVR (8 kJ/m²). In the first cohort of mice, significant protection by multiple low doses of UVR, was measured until day 18 (Figure 2A) and in the second cohort until day 11 after MOG peptide sensitisation (Figure 2B).

**Discussion**

In this study, a single dose of erythemal UVR before sensitisation to the MOG peptide was sufficient to delay EAE onset, and to reduce maximal disease intensity. Similarly, pre-treatment with four daily doses of sub-erythemal UVR prior to sensitisation with MOG peptide significantly delayed the onset of EAE. However, the result of multiple sub-erythemal doses suggests further repeated exposure may be necessary for sustained reduction in disease symptoms. This result confirms those previously published [22-24] and adds weight to suggestions that if vitamin D supplementation does not deliver the hoped for benefits, UVB phototherapy should be considered for treatment of patients with early stages of MS.

We have previously shown that similar doses of UVR have not significantly altered 25(OH)D levels in vitamin D-replete mice [28]. In our previous studies, neither acute erythemal (8 kJ/m²) or chronic sub-erythemal (8 exposures of 2 kJ/m²) UVR significantly altered 25(OH)D levels. Furthermore, Becklund et al. [22] reported an insignificant elevation in 25(OH)D levels for groups of mice that received pre-treatment with daily doses of 2.5 kJ/m² or 5 kJ/m² UVR for 7 days prior to sensitisation. Continuing administration of 2.5 kJ/m² of UVR every second or third day following disease onset, also did not significantly affect 25(OH)D levels in the mice [22]. To support the argument that vitamin D was not responsible, high dose 1.25(OH)D delayed the onset and severity of EAE, but only at levels that also caused vitamin D toxicity and hypercalcaemia [22,29]. Furthermore, vitamin D-deficient mice develop less EAE, not more as would be expected [30].

In consideration of how UVB may suppress EAE development, several chromophores in skin for UVB photons have been implicated, including trans-urocanic acid (UCA) in the stratum corneum, DNA, RNA, lipids and tryptophan of keratinocytes and antigen-presenting cells, and 7-dehydrocholesterol, the precursor of vitamin D, in keratinocytes [19]. All may initiate pathways involved in signalling from skin to immune cells in draining lymph nodes, and tissues beyond. Importantly, sub-erythemal amounts of UVR in humans can suppress both local and systemic immunity, measured functionally in terms of reduced cell-mediated immune responses. UVB exposure can also alter the migratory behaviour of Tregs [24]. Systemic changes in Tregs were observed in the spleen before symptoms, and in the central nervous system after the onset of EAE symptoms [24].

UVR exposure converts trans-UCA into cis-UCA, which can initiate both local and systemic immunosuppression [31]. Relapsing remitting MS patients have reduced serum levels of cis-UCA (but not trans-UCA) compared to healthy controls [32]. Correale et al. observed several immunomodulatory effects of cis-UCA such as increased IL-10, Treg production and reduced dendritic cell (DC) antigen presenting capabilities that may link with the ability of UVR to cause systemic immunosuppression in MS patients [32].

Our group has shown that UV exposure may also alter immune progenitors in bone marrow [33]. Immune cells in peripheral organs, including DCs that are the most important cells in initiating immunity, are constantly being replaced by bone marrow-derived haematopoietic cells [34]. UVR-induced immunosuppression can be long-lasting; in mice a single irradiation of skin with erythemal UVR suppresses contact hypersensitivity responses at distant skin sites for between 1...
and 3 months, and suggests bone marrow involvement per se [35,36]. Recent studies using chimeric mice engrafted with bone marrow from UV-irradiated mice, demonstrated that UV irradiation of skin alters the differentiation program of DC progenitors in bone marrow so that terminally differentiated daughter DCs are less immunogenic and more regulatory [36]. The reduced immunogenicity (confirmed in skin and airways) causes an attenuated ability of bone marrow-derived DCs to respond to inflammatory signals and associated antigens, and to prime new immune responses. Adoptive transfer of DCs differentiated from the bone marrow of UV-irradiated mice and loaded in vitro with antigen can reduce inflammatory challenge responses in mice already sensitized to that antigen [33,35-37]; a scenario that can be likened to injected DCs suppressing ongoing autoimmune disease such as MS. Importantly, the effect of sub-erythemal and erythemal UVR to skin on bone marrow DC progenitors is by a vitamin D-independent, prostaglandin E, (PGE) dependent process [33,38]. An epigenetic modification of an early myeloid progenitor in the bone marrow may be involved [36].

Systemic immune suppression following UV irradiation has been extensively demonstrated in humans and we propose may contribute to the latitude gradient in MS prevalence. In experimental studies, a single sub-erythemal exposure of either 0.25 or 0.5 Minimal Erythema Dose (MED) UVR suppressed contact hypersensitivity responses by 50 and 80%, respectively, of volunteers with human skin types I/II [39]. Furthermore, in a recent trial, whole-body UVB treatment during allogeneic hematopoietic cell transplantation increased circulating CD4+FoxP3+ Tregs and improved graft-versus-host disease outcomes [40]. Human and murine studies suggest a prominent role in UV-induced immune suppression for DCs and induced Tregs [19,41,42] as well as IL-10-producing B regulatory cells [43], and reduced memory T cell responses [44]. When 24 patients from Scotland with inflammatory skin disease were treated during winter for 4 weeks with narrowband UVB phototherapy, circulating Tregs increased [45].

The present study demonstrates the suppressive effects of UVR exposures on EAE development in a further laboratory and supports the use of UVB phototherapy, as frequently used to treat psoriasis [46], for patients with MS. In a recent pilot study, relapsing-remitting MS patients were given narrowband UVB phototherapy [24]. There were no definitive clinical benefits although the participants subjectively reported feeling better during and after phototherapy (visual analog scale scoring). However, the participants had had their disease for a mean of 14 years, and were on multiple disease modifying drugs [24] and thus may have been refractory to further disease modification. The earliest indication of MS is commonly a first demyelinating event, frequently associated with optic neuritis. We believe that it is now appropriate to test the effectiveness of UVB phototherapy in delaying the progression of disease to clinically definite MS in those people at high risk due to their first demyelinating event.

Acknowledgement

This work was supported by the Australian National Health and Medical Research Council (grant #1067209)

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Citation: Geldenhuys S, Mohammad MG, Li H, Hassanpour M, Ng RL, et al. (2015) UV Irradiation of Skin Regulates a Murine Model of Multiple Sclerosis. J Mult Scler (Foster City) 2:144. doi:10.4172/2376-0389.1000144
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