A.3 The effects of UV radiation on the immune system and resistance to infections

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A.3.1 Introduction

It is well known that exposure to ultraviolet radiation (UVR), especially the B-waveband (UV-B, 280-315nm) may cause skin cancer [1]. Studies on the mechanisms underlying the UVR induced carcinogenesis indicate that immunomodulating effects are initiated in addition to genotoxic (mutagenic) effects [2]. UVR has been shown to suppress both systemic and local immune responses to a variety of antigens, including several micro-organisms. The biological function of this change might be to prevent unnecessary inflammation in the skin in response to UVR-induced neo-antigens or common environmental antigens. If exposure to UVR occurs at the same time or just prior to infection or oncogenesis, then this immunosuppression may be harmful to the host [3].

A multistep process is induced by UVR, starting with the absorption of photons by chromophores (DNA, cis-UCA) in the skin. The following steps involve the production of several mediators by keratinocytes and other cutaneous cells, and phenotypic and functional cellular changes such as in Langerhans cells (LC), the major antigen presenting cells of the epidermis. As a consequence, the activity of T cells is modulated. There is evidence that UVR promotes production of the T helper-2 (Th-2) associated cytokines and reduces the production of T helper-1 (Th-1) associated cytokines [4]. The susceptibility to infections may be changed due to this differential effect on cytokine levels.

Influences of UVR on the resistance to viral, bacterial, and parasitic infections and resulting pathology have been noted [3 5 6 7 8]. In several animal models of infection UVR causes an increase in the microbial load and the severity of symptoms [3]. Although these models are helpful for elucidating how UVR may alter immune functions and hence impair the resistance to infections, the relevance in quantitative terms for humans remains unclear.

A.3.2 Mechanism of immunomodulation by UV radiation

A.3.2.1 Absorbing chromophores

As UVR wavelengths, particularly the B-waveband (UV-B), do not penetrate far into the skin, it is thought that cutaneous photoreceptors are needed to absorb the radiation, change as a result and initiate a complex cascade of responses ending in immunosuppression. Different photoreceptors have been suggested, including DNA and urocanic acid (UCA).

A.3.2.1.1 DNA

It is well known that UVR-induced DNA damage plays a pivotal role in UVR-induced carcinogenesis. In various studies Kripke and co-workers demonstrated that DNA damage is at least partially involved in local as well as systemic UVR-induced immunomodulation [9 10]. In transgenic mice that were deficient in genome repair systems it was shown that NER is crucial in the repair process of distant UVR-induced immunosuppression of CHS [11 12]. From these studies it was concluded that UVR-induced immune suppression involves both TCR and GGR. This implies that the mechanisms of UVR-induced erythema and immunosuppression are different, and that the sensitivity to acute sunburn effects of UVR
may not fully correlate to the sensitivity to the immunosuppressive effects of UVR, at least in mice [13]. On the other hand, Kelly and Young have shown in a study in human volunteers that the sensitivity to UVR-induced distant suppression of CHS and erythema are highly correlated [14].

A.3.2.1.2 Urocanic Acid (UCA)
A second photoreceptor involved in initiating UVR-induced immunosuppression, including reduced resistance to infections, is UCA [15]. The naturally occurring trans-UCA in the stratum corneum isomerises to cis-UCA after UVR exposure and cis-UCA has been shown to act as a down-regulator of immune responses in a variety of systems. For example, in a rat model of oral infection with the worm *Trichinella spiralis* it has been found that exposure to either UVR or cis-UCA led to lowered immune responses to infection and to a higher parasitic load [6]. Furthermore, if rats were injected with a monoclonal antibody with specificity for cis-UCA 2 hr prior to UVR exposure, the UVR-induced suppression of DTH to *T. spiralis* and the increase in larvae counts were significantly inhibited compared with rats that were similarly injected with a control antibody [6]. This result is of particular interest as there is no skin involvement at any stage during the infection and therefore the cis-UCA must be acting systemically. From these data it can be concluded that UCA is an important photoreceptor and that it plays a role in the mediation of the UVR-induced suppression of resistance to infections.

However, it was also demonstrated in rodent models that the DTH might be suppressed at UVR wavelengths that are very inefficient in the trans-to-cis isomerisation of UCA [16] and that the action spectrum for the cis-UCA production in human volunteers appeared to be red-shifted from the action spectrum for suppression of CHS. These results indicate that other mechanisms, like DNA damage, also play a role in mediation of UVR-induced immunomodulation.

A.3.2.2 Microbial antigens in animal models
As indicated earlier, a wide array of infections in laboratory animals has been shown to be affected by UVR [3]. This effect may be mediated by the influence on different cytokines; a shift from a Th-1 to Th-2 cytokine profile has been reported [3 4]. Studies using the parasite infection model *Trichinella Spiralis*, however, indicated that the production of IgE, a Th-2 associated cytokine, is significantly suppressed by UVR [7].

A.3.2.3 Microbial antigens in humans
For extrapolation of laboratory animal data to the human situation, it is of importance to study whether effects as they have been observed in animals in fact occur in humans. It is obvious that experimental infections cannot be studied in humans. Although there are several published papers showing that UVR may cause recrudescences of Herpes Simplex Virus infection (HSV) in some people, the importance of exposure to solar UVR for viral and other infections has still to be substantiated [3]. Effects of controlled UVR exposure on a variety of immune responses that reflect the capacity of the host to react to infectious agents can readily be studied in humans and may shed light on this issue.

A.3.2.4 Immune response after hepatitis B vaccination
Measurement of vaccine responses has been recommended as an opportunity for monitoring immune function in humans [17]. Antibody levels evoked during vaccination indicate the
functioning of the integral immune system and may be subject to different modulating factors. Studying of antibody responses after vaccination is relevant from a public health point of view \[^{18}\]. Furthermore, we may evaluate the effect of UVR on the protection to an infection without the need to induce the infection experimentally or to wait for natural infections to develop \[^{18}^{19}\]. As there is a strong association between exposure to UVR and the season for people living in non-tropical countries, it has been examined whether there was a seasonal difference in antibody titers after hepatitis B virus (HBV) vaccination. Anti-HBs levels were monitored during a standard immunisation protocol (0, 1, 6 months, 20 g Engerix-B, SB) given to health care students (n=522) in Utrecht in the course of the years 1994-2000. During the immunisation procedure a tendency to a lower mean antibody titer was observed in those who received their first vaccine in summer in comparison with students who had their first immunisation in winter. However, at the end of the immunisation procedure (a few weeks after the administration of the third vaccine) no statistically significant differences between summer- and winter-groups could be established. These results may indicate that exposure to ambient UVR influences the antibody responses after vaccination immediately, but the level of clinical protection eventually achieved appears to be unaffected.

A.3.2.5 HSV T cell immunity

There is a lot of evidence that exposure to UVR is a common triggering factor for recrudescence of HSV ("cold soars") \[^{20}^{21}\]. The mechanism underlying this phenomenon is still unknown. UVR may suppress the local immune response to HSV to allow the cytopathic effects of the virus \[^{3}\]. The role of UVR-induced down-regulation of systemic HSV T cell immunity is controversial. UVR exposure given to HSV positive subjects undergoing phototherapy as used in the treatment of psoriasis did not cause an alteration neither in the in vitro lymphoproliferation in response to HSV nor in the HSV-specific cytotoxic T cell activity \[^{3}^{22}^{23}\]. In contrast, the NK-cell activity was significantly reduced shortly after the initiation of the phototherapy \[^{23}\].

A.3.2.6 Granulocyte activity

The systemic effects of whole body UVR irradiation on human peripheral blood phagocytes was studied at different time points, up to 24 hr after a single erythemal dose of UVR radiation. Two phagocyte functions were tested, i.e. adhesion and phagocytosis, and both were found to be reduced by 50%. This functional suppression was accompanied by a decrease in the expression of complement- (CR1 and CR3) and IgG Fc- (FcRII and FcRIII) receptors. These data suggest that UVR irradiation may suppress some important functions of circulating phagocytic cells that may have consequences for resistance to infections \[^{24}\].

A.3.2.7 Conclusions on immunomodulation

In conclusion, some host defence mechanisms in human subjects can be affected by UVR exposure. We found clear effects of UVR on T-cell dependent immune responses in humans such as CHS and on non-specific immune responses. On the other hand, we did not observe effects on specific HSV T cell immune responses and only very marginal, and most likely clinically irrelevant effects on HBV vaccination. Therefore, it remains unsettled whether host resistance to infections in humans is affected by UVR.
A.3.3 Risk assessment in humans

For quantitative risk assessment, information on the dose response relationships between of the infectious disease parameters (microbial load, clinical symptoms) with exposure to UVR in humans is required. As such information is not available in humans, but is available from laboratory animal studies, we have attempted to extrapolate from the models to the human situation. This assumes that the difference in sensitivity for UV-induced modulation of \( \text{in vitro} \) or \( \text{ex vivo situ} \) immunological parameters between rodents and humans reflects the difference in sensitivity for UV-induced impairment of the resistance to infections between rodents and humans. For example, dose response studies in rats infected intravenously with \( \text{Listeria monocytogenes} \) indicated that 6.8 kJ/m² UVR (FS40 lamps) inhibited the specific cellular immune response by 50%. The suppression corresponded with the delay in clearance of the bacteria from the spleen. In order to extrapolate from the rat to the human situation, this dose was multiplied by a factor representing the interspecies difference in sensitivity for the effect of UVR as assessed in the MLRS, which is an \( \text{in situ} \) test.

Humans are less sensitive to UVR-induced induced suppression of the MLRS by a factor 3.85 than rats \([25]\). This means that humans have to be exposed to 3.85 times more UVR in order to induce suppression of the MLRS by the same order as rats (i.e. 50%). For natural killer (NK) cell function the difference was 3.24, which is approximately the same as for MLRS species differences \([26]\). Furthermore, a factor for individual differences in sensitivity to UVR, as was assessed in our study group of 17 human volunteers all with skin type II (intraspecies factor=0.5), was applied. For extrapolation from artificial to solar UVR we used four different action spectra, as it is still unknown what action spectrum is the most relevant for the immunosuppression. Starting from these data and the biologically effective doses of sunlight as calculated by De Fabo et al.\([27]\), i.e. the CHS action spectrum was applied, it could be estimated that exposure for 92 minutes (cumulative dose received during 7 consecutive days) at \( 40^\circ \text{N} \) in July at local noon could lead to 50% suppression of specific T-cell-mediated responses to \( \text{L. monocytogenes} \) in humans \([25, 27]\). By applying the alternative action spectra, the numbers of minutes exposed to cause the same effect could be calculated. The effect of ozone decreases on the level of ambient UVR and hence on the possible immunosuppression during outdoor exposure could be estimated \([26]\).

In the exercise so far we predicted the UVR dose that might lead to a suppression of antigen specific immune responses in humans. A next step is to predict the clinical outcome of such effects. For this reason a model for systemic HSV infection in the rat was recently developed. HSV is neurotropic and intranasal infection may cause neurological symptoms (paralysis, nervousness), that are aggravated by exposure to UVR. In this infection model both the viral load, the clinical outcome and the exposure to UVR prior to infection and their interrelationships could be properly quantified. Applying the action spectrum for suppression of CHS it was estimated that exposure to ambient UVR at \( 40^\circ \text{N} \) in July at clear sky and at local noon during 302 minutes (cumulative dose received during 7 consecutive days) leads to a 10% increase of neurological symptoms due to systemic infection with HSV in humans. Applying other action spectra in the extrapolation yielded alternative estimated number of minutes. The effect of ozone depletion on the ambient UVR levels and as a consequence the percentage of infections leading to clinical symptoms was also estimated.

In conclusion we may say that extrapolation of animal data enabled us to provide an estimate of the immunosuppressive effects of UVR in human populations. UVR at doses relevant for
outdoor exposure impairs the human immune system. As the extrapolation described relies on many assumptions, and data on real day-to-day exposure to ambient UVR have not been incorporated yet, experimental studies with human volunteers and observational epidemiology are needed to verify these results.

A.3.4 Observational studies

A series of epidemiological studies have been performed. The first study concerned a cohort of post-renal transplantation patients, who were monitored for the incidence of skin cancer. The association between the occurrence of skin infections and exposure to sunlight among other immune modulating factors like diabetes and dose of immune suppressive medication (azathioprine, prednison) were examined[28]. No consistent correlation was found between the incidences of infection and the estimate of lifetime cumulative exposure to sunlight. On the other hand, associations with the short-term estimate of exposure (‘season’) were found. Spring and summer were associated with the highest rates of respectively herpes simplex and herpes zoster (‘shingles’). This finding is in accordance with the hypothesis of seasonal differences in ambient UVR that trigger a circannual rhythm in immune responses and hence in the resistance to certain infections in human populations [29]. Sunny season was also associated with the highest incidence of fungal skin infections, in contrast to the lowest incidence of bacterial skin infections found in such periods [28].

Another study was conducted among healthy 1-year-old children who had been recruited from the general Dutch population for a cohort study regarding the determinants of asthma and allergy. It was examined whether short-term exposure to sunlight in the spring and summer of 1998 was associated with a higher incidence of upper respiratory tract infections. In the children’s study it was found that children with low exposure to sunlight showed a statistically significantly higher incidence of symptoms that indicate upper respiratory tract infections in the 4 weeks preceding the filling out of the questionnaire than children with high exposure to sunlight. This correlation was not confounded by other possible determinants of respiratory tract infections as seasonal differences, gender, smoking, atopy of the one of the parents, visits to day care centres etc. Furthermore, this correlation was still found when restricting the analyses to mild respiratory complaints only. This was done in view of the possibility that more severe respiratory complaints may imply that the child stayed indoor and as a consequence received a lower dose of solar UVR. The results of the children’s study suggest a protective effect of sunlight on the occurrence of upper respiratory tract symptoms, a result that was not anticipated. However, children that suffered sunburn in the study period showed increased incidences of upper respiratory tract symptoms, supporting the notion of decreased resistance after higher doses of sunlight.
A.3.5 Concluding remarks

Immunomodulating effects of UVR on the immune system were observed in both animals and humans. In different infection models in the rodent a clear suppressive effect of UVR exposure on the host resistance could be established, leading to both impairment of specific immune response and an increase of microbial load and clinical symptoms. It is hypothesised that this effect is also relevant for human populations, leading to higher incidences of infection and/or a more severe clinical course after infection.

In an extrapolation model (the ‘parallellogram-approach’) data from animal experiments were extrapolated to humans. This exercise shows that at relevant UV exposures decreased resistance to infections may be encountered. The dose needed to give an increase of clinical symptoms due to HSV was 2 - 3 times higher than the dose needed to give an effect on immune responses to Listeria model. This may reflect differences between these types of infections.

The experimental studies carried out in humans, and the epidemiological studies provide evidence to support adverse effects of UV exposure on resistance to infections, yet these indications are not unequivocal and in any case do not reveal dramatic effects.
References