Ultraviolet A Augments Solar-Simulated Ultraviolet Radiation-Induced Local Suppression of Recall Responses in Humans

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Many studies support the role of ultraviolet B in sunlight-induced alteration of the cutaneous immune system. The role of ultraviolet A is less clear, particularly in humans. The aim of this study was to determine the effect of additional ultraviolet A on solar-simulated ultraviolet-induced suppression of recall responses to nickel in humans. Immunosuppression dose–response were induced in volunteers by exposure to solar-simulated ultraviolet radiation for four consecutive days. The ultraviolet A radiation dose was increased daily by providing additional high-dose ultraviolet A either before, or after the solar-simulated ultraviolet radiation. These ultraviolet A doses can be readily achieved through a sunscreen. Two different ultraviolet A spectra were used; 320–400 nm and 330–400 nm. Ultraviolet A alone did not cause significant immunosuppression, but augmented solar-simulated ultraviolet radiation-induced immunosuppression. Additional ultraviolet A reduced the minimum dose of solar-simulated ultraviolet radiation that was immunosuppressive. Both ultraviolet A spectra had this effect, although photoaugmentation was less pronounced with the 330–400 nm spectrum. Ultraviolet A-induced immediate pigment darkening did not protect from solar-simulated ultraviolet radiation-induced immunosuppression. Key words: sunlight/nickel/erythema index/immediate pigment darkening. J Invest Dermatol 118:1032–1037, 2002

Ultraviolet (UV) radiation has been identified as a cause of both immune suppression and skin cancer (Everett et al, 1966; Yoshikawa et al, 1990; Giles et al, 1996). Kinlen et al (1979) noted that patients receiving long-term immunosuppressive therapy had a high incidence of cutaneous malignancy. A better understanding of the complex biologic interactions of UV wavelength, dose, and timing of exposure is required, so that more effective interventions and therapies may be developed for the prevention of skin cancer.

Of the UV wavelengths emitted by the sun, both UVB and UVA reach the earth’s surface. These wavelengths are defined as: UVB (290–320 nm), UVAII (320–340 nm), and UVAI (340–400 nm). The cutaneous effects of UV radiation result from the penetration and absorption of particular wavelengths. UVB is known to cause two biologic events that culminate in skin cancer: (i) direct genetic damage, including the formation of pyrimidine dimers and 6–4 photoproducts (Mitchell, 1988; Kraemer, 1997), and (ii) immunosuppression (Kripke et al, 1992). In addition, UVB induces delayed erythema, melanin pigmentation, and solar elastosis (Gilchrest et al, 1996). Although the photobiologic effectiveness of wavelengths longer than 320 nm is decreased, the sun emits higher intensities of radiation in this range and this varies with the time of day and the region (Peak et al, 1987; de Gruijl et al, 1993). Humans receive a relatively high dose of UVA at dawn, dusk, during winter, and through the use of sunscreens, tanning beds, and phototherapy. UVA causes genetic damage and can contribute to skin cancer (Runger, 1999). UVA has been estimated to contribute 10–20% to the carcinogenic dose of sunlight (de Laat et al, 1997).

It is well recognized that UVB interferes with cell-mediated immunity to contact allergens applied to the site of irradiation (Yoshikawa et al, 1990), but the effect of UVA is less well defined. Whether UVA augments, inhibits, or does not alter immunosuppression is a controversial issue, with conflicting data existing in the literature. These diverse results may be due to different irradiation protocols, differences between animals and humans, or to the different types of immune end-points studied. LeVee et al (1997), found that after a single, local exposure of four minimal erythema doses (MED) of UVAII, using a xenon-arc lamp filtered with a narrow band-pass filter (335 ± 5 nm), significantly fewer volunteers were contact sensitized to dinitrochlorobenzene than in the control group. Using a similar primary contact hypersensitivity (CHS) model in humans, UVA (340–400 nm) offered partial protection from UVB-induced immune suppression to diphenylcyclopropenone (Skov et al, 2000). Other groups have been unable to demonstrate any detectable suppression or protection of the immune system after UVA radiation in humans (Sjovall and Christensen, 1986; Skov et al, 1997). In mice, UVA has been shown to be immunosuppressive (Bestak and Halliday, 1996) and...
to augment the incidence of UVB-induced tumors (Staberg et al., 1983; Strickland, 1986). In contrast to these findings, Reeve et al. (1998) demonstrated that high doses of UVA from a fluorescent lamp source, filtered through window glass to remove the shorter UVA wavelengths, protected hairless mice from UVB-induced immunosuppression. This protection was shown to involve the induction of interferon-γ and heme oxygenase (Reeve and Tyrrell, 1999). Thus, the part UVA plays in immune modulation requires clarification.

The biologic role for immediate pigment darkening (IPD) remains poorly understood. IPD is a transitory darkening of the skin observed within seconds after UVA exposure, which subsequently decreases rapidly (Szabo et al., 1969). It involves structural changes in melanocytes and keratinocytes and a chemical modification of pre-existing melanin (Lavker and Kaidbey, 1982). On the other hand, delayed tanning is caused by an increased melanin density localized to the basal layer or increased synthesis and transfer of pre-existing melanin (Lavker and Kaidbey, 1982). On the other hand, delayed tanning is caused by an increased melanin density localized to the basal layer or increased synthesis and transfer of pre-existing melanin (Lavker and Kaidbey, 1982). On the other hand, delayed tanning is caused by an increased melanin density localized to the basal layer or increased synthesis and transfer of pre-existing melanin (Lavker and Kaidbey, 1982). On the other hand, delayed tanning is caused by an increased melanin density localized to the basal layer or increased synthesis and transfer of pre-existing melanin (Lavker and Kaidbey, 1982).

To study the effects of increased UVA exposure, and IPD, on modulation of the skin immune system caused by sunlight, a model previously developed by our group for studying solar-simulated UV radiation (ssUVR) suppression of the challenge phase to a recall antigen was utilized (Damian et al., 1997, 1999).

MATERIALS AND METHODS

Subjects Volunteers were recruited from the University of Sydney (students and staff), general population, and staff from the Royal Prince Alfred Hospital (Sydney, NSW, Australia). Exclusion criteria included any sun exposure to the lower back 6 wk prior to entry into the study, less than 18 y of age, photosensitivity or relative immunosuppression through medications or illness, history of chronic disease, lactation or pregnancy, and abnormal skin at the test site. All volunteers provided written informed consent prior to entry into the study. Subjects were recruited with approval from both the Central Sydney Area Health Services and the University of Sydney Ethics Committees.

Eighty-seven (six males, 81 females) healthy, nickel-allergic volunteers, of Fitzpatrick skin types I–IV (Fitzpatrick, 1988) were recruited. In addition, 30 age-matched and skin-type-matched volunteers were used for determination of minimum erythematous doses (five males, 25 females). The average age of the volunteers was 38.0 ± 1.4 y and the average MED was 4.1 ± 0.2 J per cm² of ssUVR. All nickel-allergic subjects commencing the study, completed it. Nine subjects were excluded from the results due to insufficient CHS reactions (lack of confluent induration) at both the UV-irradiated and non-UV-irradiated sites, despite adequate reactions at the initial test sites.

Nickel patch testing To determine the degree of nickel sensitivity in each volunteer, the left side of the lower back was initially patch tested with nickel sulfate (NiSO₄·6H₂O) in a petrolatum base. Three concentrations of nickel sulfate (Trolab, Germany), from 0.0125 to 5%,

UV source A 1000 W ozone-free xenon arc lamp with a collimated 7.5 cm square beam (Oriel, Stratford, CT) was used as the ssUVR source. The lamp emission was filtered by two 280–400 nm dichroic blocking filters (Oriel catalog number 81050) in addition to the two dichroic mirrors. Additional filtering through window glass was used, as described by Reeve et al. (1998), to attenuate the shorter UVA wavelengths and produce a 330–400 nm ssUVR spectrum. The solar-simulated and UVA spectra were monitored at 2 nm intervals using a calibrated OL-65 A spectroradiometer (Optronic Laboratories, Orlando, FL) (Fig 1). The proportions of UV radiation that were contained in the simulated UV sources are shown in Table I.

Spectral irradiance was determined at least daily with an IL1350 broadband radiometer using SED 038 (UVA) and SED 240 (UVB) detectors (International Light, Newburyport, MA) calibrated against the xenon-arc solar simulator (Commonwealth Scientific and Industrial Research Organization, Sydney, Australia). The integrated irradiance of the solar-simulated UV at the skin surface measured at 7.5 cm was 5.1 mW per cm² UVB (290–320 nm), 11.8 mW per cm² UVAII (320–340 nm), and 39.2 mW per cm² UVAI (340–400 nm). The 320–400 nm ssUVR had an irradiance of 5.1 μW per cm² UVB, 4.1 mW per cm²,

with an additional petrolatum-only control, were applied to the left lateral back in 9 mm Finn chambers (Epitest, Tuusula, Finland) (Fischer and Rystedt, 1985; Fisher et al., 1989). The patches remained in situ for 48 h, with the reactions assessed 24 h after patch removal, using both a clinical scoring system and a reflectance spectrometer (Duxtron, Hampshire, U.K.). The erythema index (EI) was calculated as the difference between the average of four erythema readings at each of the test sites and adjacent skin using the reflectance spectrometer. Clinically, each reaction was graded from 1 to 10 depending on the degree of vesiculation and induration. The lowest nickel concentration resulting in a uniform, erythematous reaction with papules was determined for each subject. This concentration was then used for the main study.

Table I. Relative proportions of UV wavebands in each studied spectrum

<table>
<thead>
<tr>
<th>Spectrum</th>
<th>% of UVR in each spectral region</th>
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<tbody>
<tr>
<td>1000 W Oriel Solar simulator spectrum</td>
<td>UVB (290–320 nm)</td>
</tr>
<tr>
<td>ssUVR (290–320 nm)</td>
<td>9.1</td>
</tr>
<tr>
<td>UV (320–400 nm)</td>
<td>0.03</td>
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<tr>
<td>UVA (330–400 nm)</td>
<td>0.0002&lt;sup&gt;a&lt;/sup&gt;</td>
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<sup>a</sup>76.1% of the UVB found in this spectrum was > 315 nm.
<sup>b</sup>93.9% of the UVAII in this spectrum was found between 330 and 340 nm.

Figure 1. Comparison of the ssUVR and UVA radiation spectra with sunlight. The solar UV spectral irradiance is the noon solar spectrum on a cloudless October day, in Sydney, Australia, 2001. The spectra used in this study, ssUVR, 320–400 nm UVA and 330–400 nm UVA were measured in 2 nm intervals using a calibrated spectroradiometer (Optronic Laboratories Inc., Orlando, FL). All spectra are normalized to 1.0 at 360 nm.
UVAlI, and 39.1 mW per cm² UVAI. The longer wavelength 330–400 nm UVA had an irradiance of 0.06 μW per cm² UVB, 0.6 mW per cm² UVAlII, and 21.4 mW per cm² UVAI.

**Determination of UVA and ssUVR-induced immunosuppression**

**Protocol for UV irradiation** For the immunosuppression studies, volunteers were irradiated within two separate 6 × 6 cm areas, on each side of the lower back. Each area was subdivided into six, 2 × 3 cm regions. One side of the back was randomly allocated to ssUVR with additional UVA and the other to ssUVR only.

Each volunteer received four fixed doses of ssUVR on separate regions. Some regions received additional UVA, with control patches receiving either no radiation, or UVA only (Fig 2). The suberythemal doses of ssUVR given to each volunteer were; 0.6, 1, 1.5, and 2 J per cm² ssUVR, equivalent to 0.14, 0.24, 0.37, and 0.49 of an average MED. The same protocol was administered daily, for four consecutive days. This protocol has been previously demonstrated by our group to induce immunosuppression in human volunteers (Damian et al., 1997).

There were three study groups. Sixteen volunteers received 17.8 J per cm² 320–400 nm UVA after the ssUVR daily doses, and 30 volunteers received this UVA prior to the ssUVR. A further group of 16 subjects received 17.8 J per cm² ssUVR alone, without additional UVA. UVA radiation given to subjects was equivalent to the amount found in 3 h of midday summer sun in Australia, and therefore is a biologically achievable dose.

**Determination of immunosuppression** On the fourth and final day of irradiation, a nickel patch was applied to each of the eight test sites and to the two sites receiving no ssUVR, or UVA, and two sites receiving UVA alone. The patches were left in situ for 48 h. Nickel-induced erythema and induration was assessed 21–28 h after patch removal, both clinically and with the reflectance spectrometer described above. The reflectance spectrometer measures reflected light at different wavelengths, enabling the determination of both an IE and MI. The EI quantitates the nickel-induced erythema, whereas the MI quantitates pigmentation.

**Effect of UVA on the MED**

MED The MED was determined on the lower back, for each volunteer. A series of ten 6 × 6 mm squares were irradiated with increasing, equal increments of ssUVR. The MED was defined as the lowest dose of ssUVR at which clearly demarcated erythema was visualized at 24 h postirradiation. To determine if UVA (320–400 nm) had any effect on ssUVR-induced erythema, an additional 17.8 J per cm² UVA was delivered either before or after the ssUVR in two groups of 15 volunteers.

**Measurement of IPD** Immediately prior to, then after irradiation of subjects with UVA alone, four background readings of MI and EI were taken with the reflectance spectrometer and averaged. These readings were obtained to determine both the increase in pigmentation (MI) as a measure of IPD and any immediate and delayed erythematous effect (EI).

Analysis of data The IE was calculated as the difference between the average of four nickel-induced erythema readings at the test site compared with adjacent skin. Immunosuppression was calculated as: immunosuppression (ΔEI) = EI (unirradiated control) – EI (test site).

Statistical comparisons were made by comparing CHS responses at the unirradiated (control) sites, with the test sites via paired two-tailed Student’s t tests. Results are presented as the mean ± SEM and are considered significant if p < 0.05.

**RESULTS**

Suberythemal ssUVR irradiation did not impair the nickel CHS response at distant sites Initial trial patches were applied on to non–UV-irradiated sites on subject’s lateral mid-backs, prior to UV irradiation of adjacent sites. Clinical scoring of these reactions demonstrated that they were, on average, the same or smaller than the responses that subsequently occurred at the non-UV-irradiated control sites. Hence our UV irradiation protocol did not suppress the CHS reaction at adjacent nonirradiated sites.

**ssUVR-induced immunosuppression is augmented by additional 320–400 nm UVA** Augmentation of ssUVR-induced immunosuppression occurred in response to all doses of ssUVR that received additional 320–400 nm UVA. Additional 17.8 J per cm² of 320–400 nm UVA given after ssUVR, augmented the level of immunosuppression at each ssUVR dose (Fig 3a). With the addition of UVA, a statistically significant level of immunosuppression occurred at a dose of 1.5 J per cm² ssUVR. The test sites that received ssUVR alone, without additional UVA, also demonstrated immunosuppression in a dose-related manner; however, only the highest dose of ssUVR tested (2 J per cm²) caused a level of immunosuppression that reached statistical significance. The small degree of immunosuppression resulting from the 320–400 nm UVA alone was not statistically significant.

A similar result occurred when the 320–400 nm UVA was given before the ssUVR (Fig 3b). ssUVR alone resulted in a dose-related immunosuppression; however, as in the previous experiment, only the highest dose of ssUVR (2 J per cm²) caused a significant level of immunosuppression. Irradiation with an additional fixed dose of 17.8 J per cm² of 320–400 nm UVA prior to ssUVR, approximately doubled the level of immunosuppression resulting from ssUVR given in the absence of UVA. Again, with the additional UVA, statistically significant immunosuppression occurred at a lower ssUVR dose (1.5 J per cm²). The UVA alone did not cause any detectable immunosuppression in this experiment.

Thus, supplementation of ssUVR with additional 320–400 nm UVA applied either before, or after the ssUVR increased the level
of immunosuppression, decreasing the minimum dose of ssUVR required to cause significant levels of immunosuppression.

The 17.8 J per cm² 320–400 nm UVA dose that augments immunosuppression also caused IPD. The 17.8 J per cm² of 320–400 nm UVA used in the above experiments resulted in a clinically observable increase in pigmentation, occurring within seconds after UV exposure. This is termed IPD. The ssUVR (which was at much lower doses) did not have this effect. To quantitate this pigmentation, the MI was measured by a reflectance spectrometer. A single dose of 17.8 J per cm² of 320–400 nm UVA caused a significant increase in the MI by a mean of 11.7 ± 4.4 (16%) from the background reading (paired Student’s t test; p < 0.02). This increase in MI was equivalent to the difference in MI readings between Fitzpatrick I and II skin types at unexposed sites. A nonsignificant, transient increase in erythema of 13% was observed immediately post-UVA irradiation, which faded within minutes. As it faded too rapidly to be sunburn, it was probably increased blood flow caused by heat generated during the irradiation. As this UVA regimen augmented immunosuppression (Fig 3) whether it was applied before or after ssUVR (i.e., ssUVR irradiation in the presence or absence of IPD), IPD did not protect from immunosuppression.

The 17.8 J per cm² 320–400 nm UVA augments erythema. To determine whether the additional 17.8 J per cm² 320–400 nm UVA affected ssUVR–induced erythema, two groups of 15 non–nickel-allergic volunteers were recruited. Subjects were irradiated with incremental doses of ssUVR, with or without additional UVA (Table II). Additional UVA given either before or after ssUVR augmented ssUVR–induced erythema by causing a similar, significant decrease in the MED. Thus, the ability of the skin to burn was not protected by IPD, as similar results were observed whether the ssUVR was given to skin in which IPD had or had not been induced.

SsUVR–induced immunosuppression is augmented by additional 330–400 nm UVA. In a separate experiment, the 320–400 nm UVA spectrum was additionally filtered with window glass to remove the majority of the wavelengths between 320 and 330 nm (Fig 1). These subjects received the same 17.8 J per cm² of additional UVA given after the ssUVR, but with a different spectrum (Fig 4). In this experiment the 330–400 nm UVA alone did not cause immunosuppression. In the absence of additional UVA, ssUVR caused immunosuppression in a dose-related manner and, like the previous experiments, only the highest dose of ssUVR alone (2 J per cm²) resulted in a level of immunosuppression that reached statistical significance. Supplementation of each ssUVR dose with 17.8 J per cm² of 330–400 nm UVA increased the level of immunosuppression by 27% (average increase in immunosuppression over the four ssUVR doses tested). This is much less than the doubling of immunosuppression that resulted from the additional 320–400 nm UVA (Fig 3). Supplementation of ssUVR with the 330–400 nm UVA reduced the minimum dose of ssUVR, that caused significant immunosuppression from 2 to 1.5 J per cm². Thus, 330–400 nm UVA augments ssUVR–induced immunosuppression, but not to the same extent as 320–400 nm UVA.

DISCUSSION

Studies have previously developed a nickel model in humans to investigate UV-radiation–induced suppression of CHS (Damian et al, 1997, 1999). In these experiments, there is UV-induced suppression of the effector, CHS response to a recall antigen. This protocol enables the determination of UV-immunosuppressive dose–responses in a single group of volunteers. In these experiments it was demonstrated that two different UVA spectra (320–400 nm and 330–400 nm) augmented the immune suppression induced by ssUVR; 320–400 nm had a greater effect than 330–400 nm, indicating that wavelengths in the 320–330 nm band were important for mediating the suppressive effect of UVA radiation. It is well recognized that UVAII has similar properties to UVB,
whereas the biologic effects of UVA1 appear to be distinct from those of UVB (Mutzhas et al., 1991). We also show for the first time that IPD induced by high-dose UVA does not protect from ssUVA-induced immunosuppression.

In previous studies by our group, nickel-induced erythema measured by reflectance spectroscopy was demonstrated to parallel the clinical intensity of the nickel patch test reactions. The erythema indices and clinical scores increased linearly against the log of the nickel concentrations. In addition, UV did not significantly suppress the erythema resulting from application of sodium lauryl sulfate, a nonspecific irritant (Damian et al., 1997). Hence, it was confirmed that this model measures immunosuppression, rather than nonspecific reduction in inflammation.

In mice, the UVA component of both 5 and 10 MED of ssUVR has been demonstrated to protect against UVB-induced suppression (Reeve et al., 1998). We sought to determine whether a similar dose and spectrum of UVA as used by Reeve et al. (1998) modulated UV suppression of recall responses in humans. A relatively high dose of UVA was used in these studies, equivalent to about 3 h in the midday summer sun. Relatively high doses of UVA may commonly be received by sunlight filtered through window glass, or sunscreens. Tanning lamps also deliver high UVA irradiances. Therefore, humans can be readily exposed to the UVA doses used in this study.

UVA-induced immunoprotection was not observed in this study. These experiments differed from those of Reeve et al. (1998), who studied suppression of the induction of systemic immunosuppression in mice, in comparison with the challenge phase of the CHS response in humans used in these studies. Our contrasting results may reflect differences between humans and mice, or the different types of immune responses studied. We went to great lengths to mimic the dose and UVA spectra of UVA used by Reeve et al. (1998) so this is unlikely to account for the different results observed. In our study, the minimum dose of ssUVR that induced immunosuppression was four daily doses of 2 J per cm2. In contrast, significant immunosuppression occurred at 1.5 J per cm2 ssUVR when additional UVA was given either before or after ssUVR. Both UVA spectra lowered the minimum dose of ssUVR that caused significant immunosuppression, but the 320–400 nm UVA spectrum had a larger effect than the 330–400 nm spectrum. This suggests that 320–330 nm UVA, as well as wavelengths above 330 nm can at least contribute to immunosuppression.

The time course, UV spectrum, and dose are each important factors for immunomodulation. Using the same model as in this study, our group has previously demonstrated that a 3 d irradiation protocol of 2 J per cm2 320–400 nm UV on consecutive days caused immunosuppression. This immunosuppression was not evident with longer irradiation protocols (Damian et al., 1999). No immunosuppression occurred in our current study using a considerably higher dose of 320–400 nm UVA (17.8 J per cm2) given alone, over four consecutive days. Thus these studies show that 4 of 4 UVA alone does not cause immunosuppression. These results are also consistent with those of Sjovall and Christensen (1986) and Skov et al. (1997), who did not observe immunosuppression in response to UVA radiation alone, in humans. Skov et al. (1997) assessed the induction of CHS to diphenylcyclopropene, following exposure to a single dose of 3 MED UVA.

Several previous human studies support our observations that UVA contributes to immunosuppression. Using the same nickel recall model, immunosuppression has been demonstrated to be greater after UV irradiation of human skin protected with a narrow spectrum sunscreen compared with a broad-spectrum sunscreen. Addition of sunscreen agents that attenuate UVA such as zinc oxide, were required to prevent significant immunosuppression (Damian et al., 1999). Other studies have confirmed that sunscreens with UVA protection provide better inhibition of immunosuppression than UVB-only protective sunscreens (Fourtanier et al., 2000). High-dose, chronic ssUVR and UVA delivered to large surface areas of the body have also been shown to cause local and systemic suppression of delayed-type hypersensitivity responses to recall antigens in humans (Moyal et al., 1997).
The biologic role of UVA-induced IPD remains poorly understood. Very little work has been performed on IPD in the past decade and no previous studies have examined its effect on the human cutaneous immune system. UVA (320–400 nm) given prior to ssUVR-induced IPD prior to subjects receiving ssUVR. In contrast, as IPD fades rapidly in Fitzpatrick skin types I and II, subjects given UVA after ssUVR received the ssUVR in the absence of IPD. There was no difference between the above groups, demonstrating that IPD did not inhibit immunosuppression (Fig 3). Thus, the chemical and structural changes that occur with IPD do not protect the human skin immune system from ssUVR. Similarly, consistent with previous studies (Paul and Parrish, 1982; Black et al., 1985), IPD did not affect the MED, showing that it also did not protect from sunburn.

To determine any effect of additional UVA on the MED, we gave the fixed dose of UVA either before or after incremental doses of ssUVR. Additional UVA significantly reduced the amount of ssUVR required to induce an MED. This photoaddition, or augmentation of UVB-induced erythema by UVA, has been demonstrated in previous studies (Paul and Parrish, 1982; Willis et al, 1973; Ying et al, 1974; Spiegel et al, 1978). Thus, the results of this study were not unexpected, as we show that UVA contributes to erythema in addition to photoaugmentation of immunosuppression.

Thus we have demonstrated that high-dose UVA exacerbates ssUVR-induced suppression of the elicitation of contact sensitivity in humans. The additional UVA lowered the minimum dose of ssUVR required to cause significant immunosuppression. Both 320–400 nm and 330–400 nm UVA were effective, although the spectrum that included the 320–330 nm waveband had a larger effect. UVA-induced IPD did not provide any protection to the immune system. UVA is undoubtedly immunomodulatory, but its effects are likely to be dependent on the dose, wavelength, timing, and immune parameter being assessed. Complex interactions between different wavelengths are likely to occur. We cannot exclude the probability that UVA could have the opposite effect to the one we have observed under different circumstances.

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