Diurnal Preference Contributes to Maximal UVB Sensitivity by the Hour of the Day in Human Skin In Vivo

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TO THE EDITOR

There is a functional circadian clock in most of the skin's cell types (Plikus et al., 2015). In hairless mouse skin studies, it has been shown that the time of day of UVR exposure influences erythemal response, sunburn-induced apoptosis, p53 formation, and repair of DNA photoproducts, suggesting that the circadian clock plays a role in these UVR-induced responses (Gaddameedhi et al., 2015). In humans, we showed earlier that after exposure to narrow-band UVB, the summarized evening erythema index (EI) scores were higher than the morning scores, thus suggesting that human skin is more vulnerable to UVR in the evening in vivo (Nikkola et al., 2018). Diurnal preference (DP), the behavioral trait for timing daily activities, correlates with the intrinsic period of the human circadian clock (Duffy et al., 2001), and it might thereby influence the timing of being exposed to UVR.

Our current study reports the outcome of narrow-band UVB minimal erythema dose (MED) phototesting in the morning versus evening, being performed 12 hours apart, and defines erythema response of the skin in 36 volunteers (aged 22–65 years) with Fitzpatrick's skin phototype II to III (Fitzpatrick, 1988). The Regional Ethics Committee of Tampere University Hospital District (Tampere, Finland) approved the study protocol. All volunteers gave their written informed consent. We assessed their DP and analyzed whether the DP was associated with narrow-band UVB erythema 24 hours after irradiations.

By applying a single (sixth) item of the modified Morningness-Eveningness Questionnaire for the assessment of DP (Hätönen et al., 2008; Merikanto et al., 2021), 25 participants were of definitely or rather a morning type and 11 participants were of definitely or rather an evening type. Further details of the assessment are available in Supplementary Materials and Methods.

MED testing to define erythema sensitivity was performed twice, 12 hours apart, that is, between 7 and 9 AM and between 7 and 9 PM. The standard MED testing included five UVB doses, ranging from 1 standard erythemal dose increased stepwise by a factor $\sqrt{}$ to 4 standard erythemal dose. Twenty-four hours after exposure, a faint and just perceptible reddening without sharp borders or corners was defined as MED (Dornelles et al., 2004; Heckman et al., 2013; Taylor et al., 2002). MED was quantified by the naked eye (HJ and VN) using a five-point scale as −, (+), +, ++, or +++, where (+) was the MED. EI of the test squares, which represents the intensity of the reflected wavelengths of red and green (Ly et al., 2020), was measured using reflectance spectrometry (DermaSpectrometer; Cortex Technology, Hadsund, Denmark).

The human skin in vivo showed more redness in the evening than in the morning, and the results observed by the naked eye were consistent with the EI readings ($P < 0.001$, Wilcoxon signed-rank test with exact *P*-values; Supplementary Table S1). Furthermore, we found that morning larks appeared to be more prone to evening UVB exposure–induced skin burns than night owls. EI by morning or evening type is shown in Figure 1.

In the evening, the difference in EI between the two types of DPs was significant ($P < 0.001$, generalized estimating equations) (Figure 1). This may indicate that the individual circadian time of the morning types may compromise skin protection against UVR in the evening. In MED testing during morning sessions, no statistical difference between DPs was found in EIs. It is possible that the internal time in the evening type is delayed but not to an extent that could still affect the sensitivity of the skin to narrow-band UVB exposure at 7 to 9 AM. The results from the two alternative assignments to chronotype (morning vs. intermediate vs. evening and morning vs. intermediate + evening) were similar but not significant (Supplementary Figure S1).

It was shown earlier that human proliferating epidermal cells from healthy skin biopsies exhibited circadian rhythms peaking at approximately 1 hour before midnight (the M-phase of the cell cycle) and troughs at noon (Mehling and Fluhr, 2006). In the keratinocyte cell line HaCaT, proliferation was influenced by melatonin, and interestingly, expression in circadian clock genes was modulated by low-dose UVB irradiation (Kawara et al., 2002). Accordingly, many skin functions exhibit circadian rhythms, and the skin seems to be more reactive toward the late afternoon and evening than in the morning and early afternoon (Le Fur et al., 2001).

To conclude, the mechanisms protecting human skin against UVR are proposed to be active in the morning and daytime. However, our current results show that night owls appear to have more active protective mechanisms in the evening hours than morning larks. This may be linked to differences in their circadian clock functions. UVR-induced erythema is an inflammatory response, and therefore, our findings may also reflect time-of-day influence on inflammation.

In addition, independent of DP, evening UVB exposures seem to be more dangerous considering the risk of skin burns. Our results suggest that it might

Abbreviations: DP, diurnal preference; EI, erythema index; MED, minimal erythemal dose

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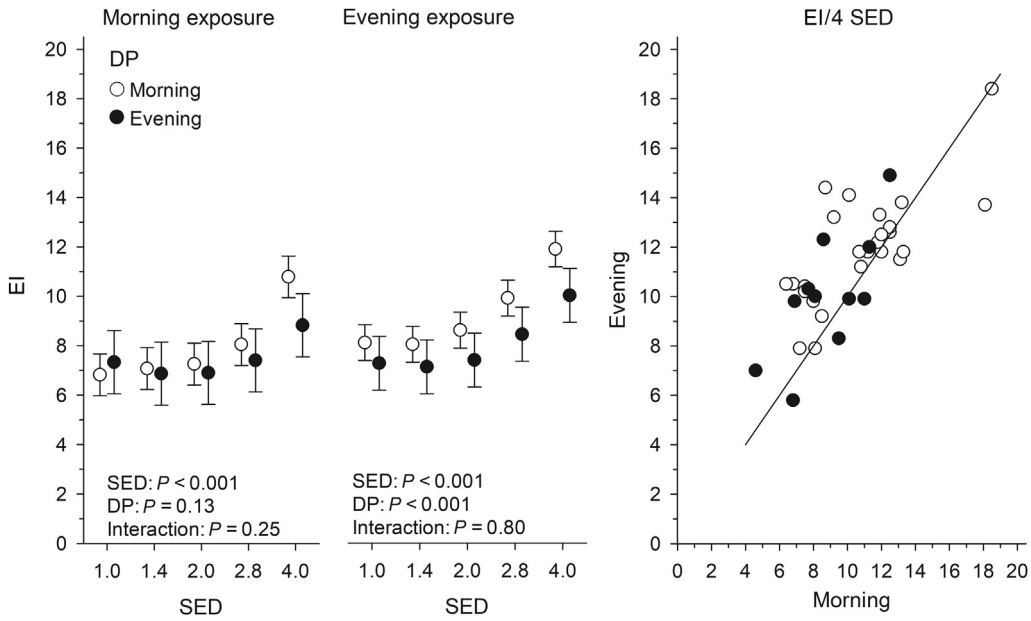

Figure 1. EI by morning and evening type. On the left, the graph shows EI as a function of SED of NB UVB after exposure in the morning and in the evening (n = 36). In the evening, the difference in EI between the morning and evening types as assessed by DP was significant ($P < 0.001$, generalized estimating equations), whereas no significant difference was found in the morning ($P = 0.13$, generalized estimating equations). On the right, the graph shows that 4 SED EIs are higher in the evening for both morning and evening types. DP, diurnal preference; EI, erythema index; NB, narrow band; SED, standard erythemal dose.

be beneficial to assess DP of each patient before testing the photosensitivity defining the MED. In this way, skin burns related to diurnal variation in photosensitivity could be avoided, especially if phototherapy were to be administered in the evening. Being aware of the impact of DP on sunburn sensitivity might be important in protecting the skin from sunlight when traveling across time zones to sunny destinations. Links between the circadian clock of skin cells and the time of UVR exposure may give a new insight into this puzzle.

Data availability statement

All data generated or analyzed during this study are included in this published article and its Supplementary Materials and Methods.

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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Conceptualization: HJ, VN, RHO, LY, ES, RP, TP; Data Curation: AR, IMH, HJ, HK, ES, RP, TP; Formal Analysis: HK; Funding Acquisition: RHO, LY, ES, TP; Investigation: HJ, VN, RHO, ES, RP, TP; Methodology: VN, RHO, LY, HK, ES, TP; Project Administration: AR, IMH, HJ, VN, RHO, LY, ES, RP, TP; Resources: HJ, LY, HK, ES, TP; Supervision: VN, RHO, LY, ES, RP, TP; Validation: AR, IMH, HJ, RHO, LY, ES, RP, TP; Visualization: LY, HK; Writing - Original Draft Preparation: AR, IMH, RHO, LY, HK, ES, TP; Writing - Review and Editing: AR, IMH, HK, ES, TP.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at https://doi.org/10.1016/j.jid.2022.01.021.

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