Interactions Between Ultraviolet B (UVB) Radiation and Circadian Clock in the Skin

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Veera Nikkola, MD, PhD, conducted her PhD studies at the Department of Dermatology and Venereology, Tampere University Hospital, Finland during the period 2016–2021. Professor Emerita Erna Snellman was her main supervisor and the co-supervisor was Professor Timo Partonen. The opponent was Professor Kaisa Tasanen-Määttä from the University of Oulu, Finland. The thesis was defended on March 19, 2021 and can be found at http://urn.fi/URN:ISBN:978-952-03-1874-1

n everyday life, ultraviolet (UV) radiation from the sun is a significant carcinogen. It induces deoxyribonucleic acid (DNA) mutations and, at the same time, is immunosuppressive. From the whole solar UV radiation spectrum, the wavelengths of UVB are the most biologically active part.

There are indications that the timing of UVB exposure may affect sensitivity to sunburn, but these findings have not been confirmed in human studies. However, almost all functions of the human skin are rhythmic in a circadian (approximately a day of 24 h) manner, and most skin cell types have their own intrinsic circadian clock. Similar to the central circadian clock in the brain, the human skin expresses clock proteins, e.g., cryptochromes which are essential to circadian function, and melatonin, which is well known for its ability to influence human chronobiology. So far, little is known about the link between skin clock proteins, melatonin, and erythema.

In the skin, UVB-induced erythema is a consequence of vasodilatation after DNA damage. In this thesis, we aimed to investigate if there were connections between skin erythema and the circadian clock.

In order to investigate the impact of the hour of the day on UVB-induced erythema, we performed photosensitivity testing of the skin of 19 healthy volunteers twice, first in the morning and second in the evening. Using immunohistochemistry we also analysed skin biopsies taken at a different hour of the day, the expression of the core clock proteins. Erythema was found to be more pronounced after evening irradiations than after morning irradiations. Cryptochrome-2 (CRY2) was identified as a possible protecting factor.

The effect of UVB irradiation on circadian time in the skin was studied by performing mRNA expression analyses on skin samples obtained from 12 healthy volunteers. We compared

From left to right: Professor Kaisa Tasanen-Määttä (opponent), MD Veera Nikkola, Professor Teea Salmi and professor emerita Erna Snellman (main supervisor).

expression of clock proteins in non-irradiated and UVB-irradiated skin samples and in corresponding samples of subcutaneous adipose tissue. UVB exposures seemed to modify the expression of *CRY2* in epidermal and dermal skin, and that of Cryptochrome-1 (*CRY1*) and Circadian-associated transcriptional repressor (*CIART*) in subcutaneous adipose tissue. Irradiation also altered the *CRY1/CRY2* ratio.

In a further study, 39 healthy volunteers were analyzed using immunohistochemistry for the presence of melatonin in the non-UVB-exposed buttocks skin at different times of the day. The photosensitivity testing was performed on the skin of all our volunteers. We discovered melatonin content of the non-irradiated skin to vary diurnally. However, melatonin expression in the skin detected by immunohistochemistry did not correlate with the circadian change in erythema sensitivity.

In conclusion, the hour of the day of UVB irradiation seems to influence the erythema formation in healthy human skin. The

connection is also reverse, because UVB irradiation changes the mRNA expression of clock driving proteins. It is possible that UVB serves as a cue for circadian time entrainment through the skin. Even though the melatonin content of the skin varies diurnally, this does not appear to be the reason why UVB induces more erythema in the evening than in the morning. Understanding factors influencing erythema sensitivity of the skin and its interactions with the circadian clock could promote the development of skin cancer prevention strategies as well as dermatological treatments. An extensive understanding of circadian clock entrainment is an important part of overall human health.

List of original publications

I. Nikkola V, Grönroos M, Huotari-Orava R, Kautiainen H, Ylianttila L, Karppinen T, Partonen T, Snellman E. Circadian time effects on NB-UVB-induced erythema in human skin in vivo. J Invest Dermatol 2018; 138: 464–467.

II. Nikkola V, Miettinen ME, Karisola P, Grönroos M, Ylianttila L, Alenius H, Snellman E, Partonen T. Ultraviolet B radiation modifies circadian time in epidermal skin and in subcutaneous adipose tissue. Photodermatology, Photoimmunol Photomed 2019; 35: 157–163.

III. Nikkola V, Huotari-Orava R, Joronen H, Grönroos M, Kautiainen H, Ylianttila L, Snellman E, Partonen T. Epidermal melatonin levels are higher in the evening than morning but do not account for erythema sensitivity. Submitted 2021.