Phototherapy for Dermatological Diseases

20

Matthias Born and Jörg Liebmann

20.1 Introduction

The fact that light has a positive influence on our health has been known for many centuries. Already Hippocrates documented the healing effect of the sun. At the beginning of the twentieth century, the so-called heliotherapy for the prevention, treatment, and rehabilitation of various diseases (e.g., tuberculosis, rickets). The development of special lamp systems with specific wavelengths has enabled the targeted treatment of certain diseases with selective wavelengths for several decades. Since the 1950s, for example, warming **infrared lamps** for pain therapy. In psychiatry, depressive moods— in particular seasonal depression (SAD)—are treated with particularly bright white light, thereby regulating the patient's biorhythm. UVB light is known to produce a precursor of vitamin D3 in the skin, a vitamin that is essential for bone formation. In the field of dermatology, shortwave and high-energy UV light (UVB and UVA) is used today for the therapy of inflammatory skin diseases. In psoriasis, phototherapy with narrowband UVB-311 nm light is successfully used in moderate to severe cases. The advantage over broadband UVB therapy is the lower erythema formation with the same and in many cases higher effectiveness. The effect of UVB light is mainly due to immunosuppressive properties. UVA light is used as monotherapy for eczema diseases as well as in combination with special photosensitive substances such as psoralen. UVA light causes the formation of oxygen radicals in the skin through the stimulation of endogenous photoacceptors. Due to the properties of **psoralen,** the concentration of these photoacceptors in the skin is greatly increased as it itself forms additional oxygen radicals under irradiation and thus intensifies the effect of UV light. UV-based phototherapy is generally very effective and in many cases even leads to a temporary healing of the symptoms. However, inflammatory skin diseases such as psoriasis or certain eczema diseases are chronic and not completely curable. They can recur and therefore require lifelong treatment.

However, since UV light is classified as carcinogenic, treatment with this form of therapy cannot be carried out over a longer period of time.

20.2 Visible Light

Visible light beyond the UV spectrum was long considered inert and photochemically inactive. Nevertheless, the first papers on the effect of visible light (400–750 nm) on human tissue and in particular skin cells were published in the 1980s. Here, mainly the first commercially available

M. Born (✉) · J. Liebmann
Philips Innovation and Strategy - Research, Eindhoven, The Netherlands
e-mail: matthias.born@philips.com

G. Kautz (ed.), *Energy for the Skin*, https://doi.org/10.1007/978-3-030-90680-1_20

He-Ne lasers were used to treat patients with various skin diseases or cell cultures of human skin cells. The mitochondrial **cytochrome C oxidase** is a light acceptor for red laser light (~632 nm), which plays a central role in the oxidative phosphorylation of the respiratory chain. Until the late 1990s, lasers dominated research in this field, because light-emitting diodes (LEDs), although cheap, were available at that time only with very low intensities and comparatively broad spectra. They were used, among other things, for signal and status lighting in electronic devices. Only the development of stable and almost monochromatic LEDs with comparatively high intensities and luminous efficacy in the late 1990s resulted in their increased application in medical research. A special feature here is the development of blue LEDs, the technological breakthrough of which was achieved by Japanese physicists Isamu Akasaki, Hiroshi Amano, and Shuji Nakamura in 1992 and which was awarded the Nobel Prize in Physics in 2014. This groundbreaking invention enabled the use of highly efficient blue and white LEDs in particular. The latter are now widely used in the lighting industry.

In the following years, various works were published describing the influence of visible, mostly red light on different model systems. Effects on wound healing, hair growth, cell proliferation, oxygen radical and nitric oxide production, as well as inflammatory parameters were investigated. Here, however, it became apparent that the heterogeneity of the lighting systems and experimental models in particular produced a large number of sometimes contradictory results. Therefore, phototherapy with visible light is still, with a few exceptions, not a standard therapy.

20.3 Blue Light

An exception, however, is the phototherapy of neonatal jaundice. Blue, UV-free, visible light has long been used here to promote the degradation of bilirubin, a degradation product of hemoglobin. Ideally, a wavelength of 457 nm destroys unconjugated double bonds in the bilirubin and converts the bilirubin to water-soluble lumirubin, which can then be excreted in the urine. Another application is in Crigler-Najjar syndrome, a rare hereditary disease that affects bilirubin metabolism and triggers nonhemolytic jaundice, which can lead to severe neuronal defects if left untreated. Patients with severe forms of this disease often need to be treated with blue light throughout the night and are thus exposed to high cumulative doses of more than 2,600,000 J/cm^2 over a period of 10 years. No side effects have been described so far. In the field of neonatal phototherapy, several articles and studies have been published investigating the development of nevi, which is considered a risk factor for the development of cutaneous melanomas, in children aged 8–9 years. The results are partly contradictory, and a connection of the increased number of nevi with an actual increased skin cancer type has not been proven so far.

Blue Light Therapy for Inflammatory Skin Diseases

Recent studies show that especially blue, UV-free visible light (400–480 nm) has interesting properties that can be used in the treatment of inflammatory skin diseases. Blue light with a wavelength of 453 nm is not toxic for skin cells up to very high doses of more than 500 J/cm^2. In comparison, UVA light already shows toxic effects in these cells from a dose of 30 J/cm^2. UV-free blue light leads to a dose-dependent release of nitrogen monoxide (NO). Light with a wavelength of 453 nm can reduce the proliferation of human keratinocytes dose-dependently and promote their differentiation (Fig. 20.1).

Light intensities of this wavelength, which do not damage keratinocytes and other skin cells, lead to apoptosis in T cells and thus remove them from the inflammatory process. **Psoriasis vulgaris** is an inflammatory chronic skin disease, characterized by hyperproliferation of keratinocytes and an unregulated inflammatory response. These characteristics can be positively influenced by blue light (Fig. 20.2)

This is supported by further research, which also describes the influence of blue light on cer-

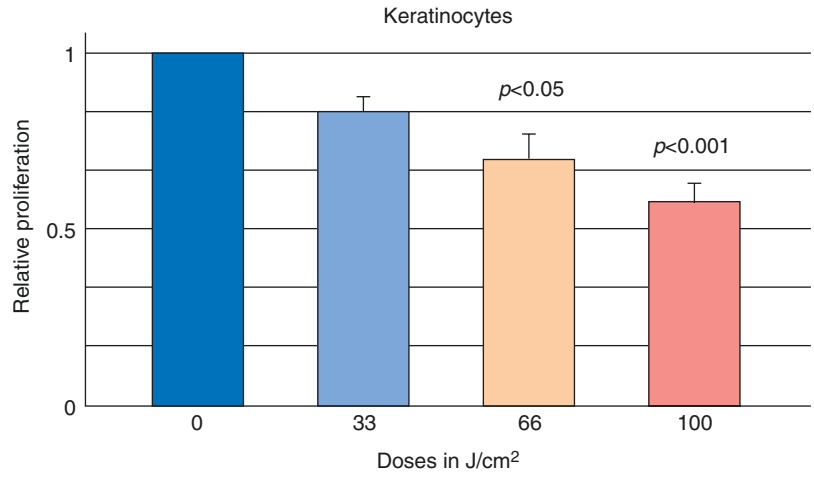

Fig. 20.1 Blue LED light of the wavelength 453 nm inhibits the proliferation of human keratinocytes dose-dependently

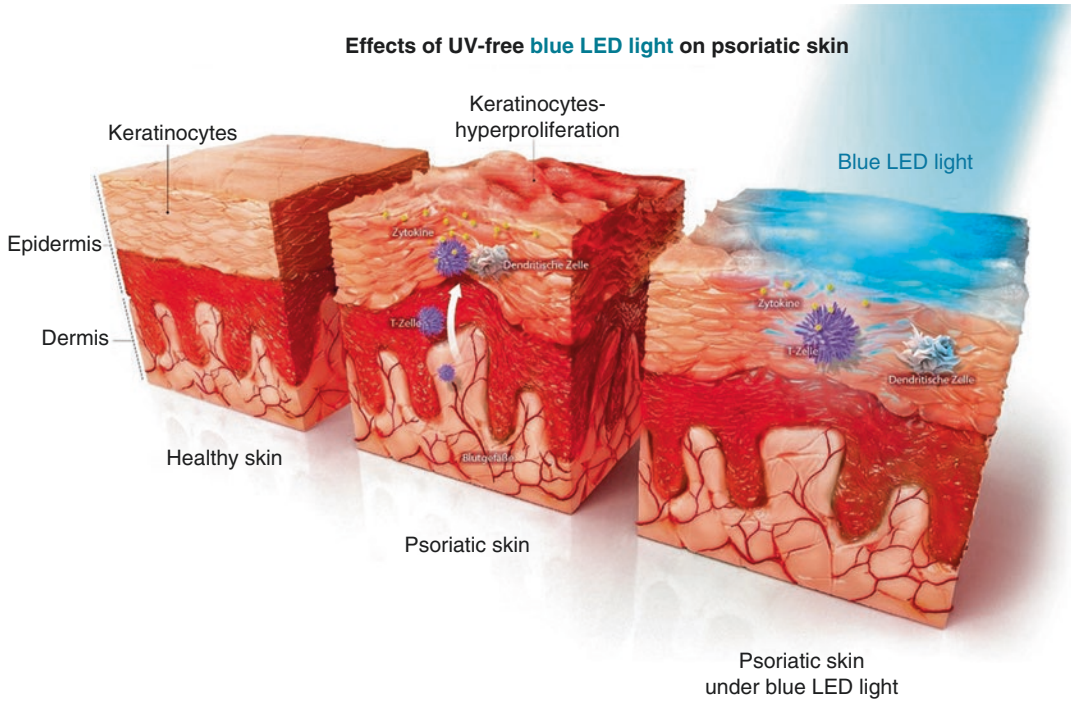

Fig. 20.2 Blue LED light with a wavelength of 453 nm inhibits keratinocyte hyperproliferation in the epidermis and the activation of dendritic cells. This phototherapeutic approach has been shown to significantly reduce plaque symptoms in patients with mild to moderate psoriasis vulgaris

tain inflammation parameters (Fig. 20.3). Fischer et al. found that blue light of this wavelength suppresses the activation of dendritic cells and thus the release of pro-inflammatory cytokines.

Similar results were published in 2016 by Kim et al. In their experiments, they were able to show that blue light can cause processes of the innate immune response through the redistribution of nitric oxide compounds. Based on these

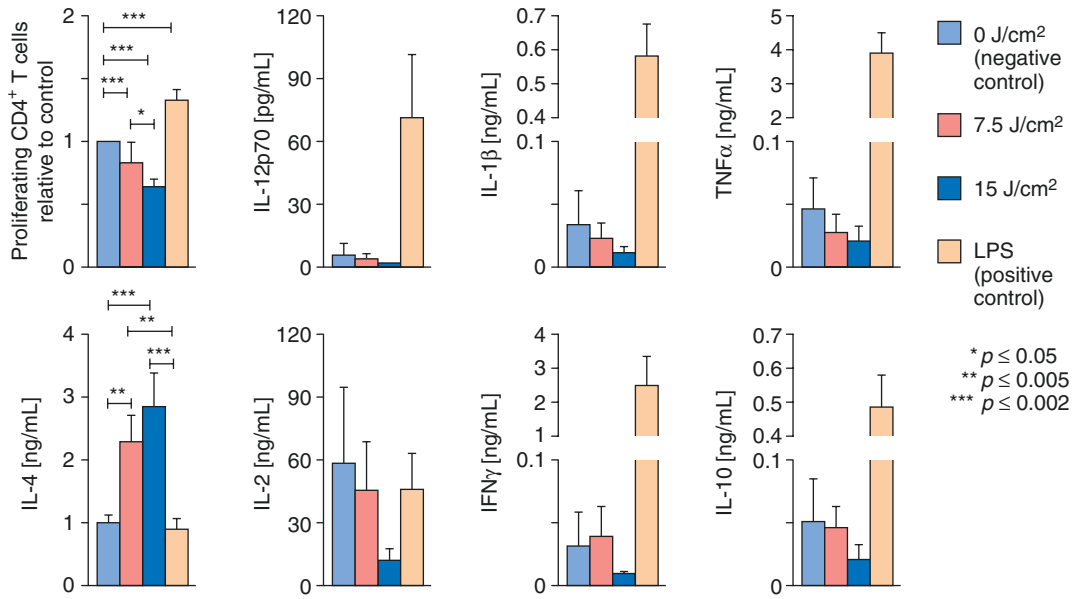

Fig. 20.3 Blue LED light is able to deactivate certain immune cells and thus reduce the release of cytokines

results, four clinical studies on the therapy of psoriasis vulgaris with blue, UV-free light have been published to date. In a first study, Maari et al. investigated the effect of very low doses (10 J/cm^2) on psoriasis and found no improvement in symptoms. Further studies by Kleinpenning et al. used a 420 nm LED light source and treated patients over 4 weeks, three times a week with significantly higher doses of approx. 90 J/cm^2. Here an improvement of the skin redness could be observed. Weinstabl et al. compared two different wavelengths of blue LED light (420 nm vs. 450 nm, 90 J/cm^2) and found a significant improvement of the local psoriasis severity index (LPSI) after 4 weeks of daily treatment. Pfaff et al. also showed a significant improvement in LPSI in another long-term study with 45 patients over 3 months. A portable irradiation device with a wavelength of 453 nm at a daily dose of 90 J/cm^2 was used for the first time. In addition to an average treatment effectiveness of approx. 50% compared to the base value, a very high treatment compliance over this long period was also observed. In all four studies, no serious adverse events associated with the treatment were found. The only known side effect of the blue light is a slight temporary hyperpigmentation, which can be observed in some patients and which disappears spontaneously after the end of the therapy.

20.4 Conclusion

Based on these results, in particular phototherapy with UV-free blue light will be further researched in the future. Studies are currently being carried out on the treatment of the entire body surface and other areas of application, such as atopic dermatitis.

Suggested Reading

Awakowicz P, Bibinov N, Born M, Busse B, Gesche R, Helmke A, Kaemling A, Kolb-Bachofen V, Kovacs R, Kuehn S, Liebmann J, Mertens N, Niemann U, Oplaender C, Porteanu HE, Scherer J, Suschek C, Vioel W, Wandke D. Biological stimulation of the human skin applying health-promoting light and plasma sources. Contrib Plasma Phys. 2009;49:641–7.

Csoma Z, Toth-Molnar E, Balogh K, Polyanka H, Orvos H, Ocsai H, Kemeny L, Szell M, Olah J. Neonatal blue

light phototherapy and melanocytic nevi: a twin study. Pediatrics. 2011;128:e856–64.

Fischer MR, Abel M, Lopez Kostka S, Rudolph B, Becker D, von Stebut E. Blue light irradiation suppresses dendritic cells activation in vitro. Exp Dermatol. 2013;22:558–60.

Kim HJ, Choi MS, Bae IH, Jung JY, Son ED, Lee TR, Shin DW. Short wavelength visible light suppresses innate immunity-related responses by modulating protein S-nitrosylation in keratinocytes. J Invest Dermatol. 2016;136:727–31.

Kleinpenning MM, Otero ME, van Erp PE, Gerritsen MJ, van de Kerkhof PC. Efficacy of blue light vs. red light in the treatment of psoriasis: a double-blind, randomized comparative study. J Eur Acad Dermatol Venereol. 2012;26:219–25.

Liebmann J, Born M, Kolb-Bachofen V. Blue-light irradiation regulates proliferation and differentiation in human skin cells. J Invest Dermatol. 2010; 130:259–69.

Mahe E, Beauchet A, Aegerter P, Saiag P. Neonatal blue-light phototherapy does not increase nevus count in 9-year-old children. Pediatrics. 2009;123:e896–900.

Matichard E, Le Henanff A, Sanders A, Leguyadec J, Crickx B, Descamps V. Effect of neonatal phototherapy on melanocytic nevus count in children. Arch Dermatol. 2006;142:1599–604.

Pfaff S, Liebmann J, Born M, Merk HF, von Felbert V. Prospective randomized long-term study on the efficacy and safety of UV-free blue light for treating mild psoriasis vulgaris. Dermatology. 2015;231:24–34.

Strauss KA, Robinson DL, Vreman HJ, Puffenberger EG, Hart G, Morton DH. Management of hyperbilirubinemia and prevention of kernicterus in 20 patients with Crigler-Najjar disease. Eur J Pediatr. 2006;165:306–19.

Weinstabl A, Hoff-Lesch S, Merk HF, von Felbert V. Prospective randomized study on the efficacy of blue light in the treatment of psoriasis vulgaris. Dermatology. 2011;223:251–9.