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Various biological effects of solar radiation on skin and their mechanisms: implications for phototherapy

Dong Wook Shin

College of Biomedical and Health Science, Konkuk University, Chungju, Republic of Korea

ABSTRACT

The skin protects our body from various external factors, such as chemical and physical stimuli, microorganisms, and sunlight. Sunlight is a representative environmental factor that considerably influences the physiological activity of our bodies. The molecular mechanisms and detrimental effects of ultraviolet rays (UVR) on skin have been thoroughly investigated. Chronic exposure to UVR generally causes skin damage and eventually induces wrinkle formation and reduced elasticity of the skin. Several studies have shown that infrared rays (IR) also lead to the breakdown of collagen fibers in the skin. However, several reports have demonstrated that the appropriate use of UVR or IR can have beneficial effects on skin-related diseases. Additionally, it has been revealed that visible light of different wavelengths has various biological effects on the skin. Interestingly, several recent studies have reported that photoreceptors are also expressed in the skin, similar to those in the eyes.

Based on these data, I discuss the various physiological effects of sunlight on the skin and provide insights on the use of phototherapy, which uses a specific wavelength of sunlight as a non-invasive method, to improve skin-related disorders.

Introduction

Solar radiation is classified based on wavelength. The wavelength of ultraviolet rays (UVR) is less than 400 nm. The wavelength of visible light ranges from 400 nm to 700 nm, and the wavelength of infrared rays (IR) is greater than 700 nm. Solar radiation that reaches the Earth consists of 6.8% UVR, 38.9% visible light, and 54.3% IR (Barolet et al. 2016). There are three major types of UVR: UVC (200 ∼ 290 nm), UVB (290 ∼ 320 nm), and UVA (320 ∼ 400 nm). UVR with shorter wavelengths has a weaker permeability. UVC is shorter in wavelength and is absorbed by the ozone layer and cannot pass through the atmosphere. In contrast, the amount of UVA reaching the surface is approximately 100 times greater than that of UVB. UVB reaches the epidermis of our skin, while UVA reaches the dermis. Most studies on UVR have indicated that it causes skin aging. Therefore, sunscreen should be applied to protect against both UVA and UVB. However, UVR can also be used to sterilize or improve specific skin diseases under controlled conditions (Rodenbeck et al. 2016; Teske and Jacobe 2016; Esmat et al. 2017; Morita 2018; Noh et al. 2018). Unlike UVR, IR radiation can penetrate the epidermis, dermis, and subcutaneous tissue. The effects of IR radiation on the skin have received less attention than UVR. Currently, studies of the effects of IR on the skin have revealed both positive and negative effects (Barolet et al. 2016).

Visible light, which is recognized by the human eye, is a spectrum of electromagnetic radiation with wavelengths between 400 and 700 nm. The main natural source of visible light is sunlight, and artificial sources include laser, LED (Light Emitting Diode), mobile phones, and television and computer monitors (Cohen et al. 2020). Although individuals are exposed to visible light during daytime, little is known regarding the effects of visible light on our skin, except for the eye. Interestingly, photoreceptors that respond to various wavelengths of sunlight have been identified in the skin and their signaling mechanisms have been elucidated (Wicks et al. 2011; Kim et al. 2013; de Assis et al. 2018; Regazzetti et al. 2018; Kusumoto et al. 2020).

In this review, I discuss the various effects of sunlight on our skin and provide insights into phototherapy to improve skin diseases through the use of specific wavelengths of sunlight.

The phototransduction of photoreceptors and their identification in skin

The photoreceptor opsin is part of a G protein-coupled receptor family expressed in the rod cells of the retina,

which is the light-sensitive layer of the eye (Ramirez and Leidy 2018; Gao et al. 2019). Rhodopsin is structurally classified as a chromoprotein. It is composed of opsin (a colorless protein) and 11-cis-retinal (11-cis-retinaldehyde), a derivative of vitamin A. Retinal undergoes photo-isomerization from 11-*cis* to all-*trans*-retinal upon interaction with a light photon. Then, metarhodopsin-II, the activated form of rhodopsin, activates transducin (Gt) and leads to the downstream photo-transduction cascade.

Long-wavelength- and short wavelength-opsin have been reported to be expressed in the melanocytes of mouse skin (Miyashita et al. 2001; Tsutsumi et al. 2009). Rod and cone photoreceptor-like proteins are also present in human skin. Rhodopsin is observed in human melanocytes and is related to UVA, which induces the movement of Ca^{2+} and leads to the synthesis of melanin (Wicks et al. 2011). A recent study has also demonstrated that UVA (4.4 kJ/m^2) activates rhodopsin (known as OPN2) and melanopsin (known as OPN4), and eventually induces pigment darkening, which is mediated by the CAMK II/NOS/sGC/cGMP pathway, in murine melanocytes (de Assis et al. 2018). Rhodopsin, which reacts to violet light, is also observed in the cell membrane of human keratinocytes (Kim et al. 2013). Over-expression of rhodopsin downregulates the mRNA expression levels of keratin-1 and keratin-10, which are well-known markers of keratinocyte differentiation, through the Ga_i signaling pathway. Recently, several photoreceptors that respond to blue light have been identified. OPN3 is a key sensor in melanocytes. It functions in a calcium-dependent manner and activates cAMP-responsive element-binding protein (CREB) to eventually activate melanogenesis enzymes, tyrosinase, and dopachrome tautomerase through phosphorylation of MITF (Regazzetti et al. 2018). Thus, OPN3 may be a novel potential target for modulating melanogenesis and may also protect dark skin from blue light in a pigmentary disorder, such as hypermelanosis or hyperpigmentation. OPN4 is observed in human keratinocytes, melanocytes, and fibroblasts. Blue light stimulates Ca^{2+} influx and the phosphorylation of extracellular signal-regulated kinases 1/2 in an intensity-dependent manner (Kusumoto et al. 2020) (Figure 1).

Ultraviolet (< 400 nm)

UV irradiation has primarily been reported to cause harmful effects on the skin, including sunburn, inflammation, skin cancer, and photoaging (Krutmann et al. 2012; Amaro-Ortiz et al. 2014). Chronic UVA irradiation induces epidermal hyperplasia and alters the thickness of the stratum corneum (Reichrath and Rass 2014). UVB exposure causes detrimental effects, such as DNA damage and the production of reactive oxygen species (ROS) (Widel et al. 2014; Chung et al. 2018). Many studies have demonstrated that UVR generally activates several kinases, such as p38 MAP kinase and c-Jun N-terminal kinase (JNK), and stimulates activator protein-1 (AP-1)-mediated transcription in the skin (Zhang and Bowden 2012; Xu et al. 2014). Thus, protection of the skin from UVR can help to inhibit skin aging.

However, UVR does not only have harmful effects on the skin. UVR interacts with 7-dehydrocholesterol, a cholesterol precursor in the skin that is eventually converted into vitamin D (Piotrowska et al. 2016; Neale et al. 2019). Vitamin D aids the absorption of calcium to form bones. Only 50% of the required amount of vitamin D is obtained from food, therefore sufficient UVR exposure is essential for our health. Additionally, a low dose of UVR (1.5 kJ/m^2) has potential clinical applications for patients requiring local immune-suppression therapy, such as in contact hypersensitivity (Schwarz et al. 2012). Narrowband UVB (311~312 nm) can ameliorate vitiligo and psoriasis (Esmat et al. 2017; Morita 2018). A medium dose of UVA1 (340~400 nm, 50 J/cm^2) can be effective in improving atopic dermatitis and scleroderma, which includes the hardening and tightening of the skin (Rodenbeck et al. 2016; Teske and Jacobe 2016; Noh et al. 2018). These data suggest that appropriate UVR exposure can be used therapeutically to treat skin-related diseases.

Violet light (400 nm ~ 450 nm)

Violet light (410 nm, 10–50 J/cm^2) significantly downregulates the expression of cell differentiation factors and the phosphorylation levels of CREB (Kim et al. 2013). Violet light (410 nm, 30 J/cm^2) has also been reported to reduce the mRNA expression levels of anti-microbial peptides (AMPs), which are responsible for epithelial defense. Violet light significantly inhibits both NF-kB phosphorylation and IkB degradation by stimulating the toll-like receptor (TLR) 3 or TLR5. Interestingly, violet light irradiation is related to the transfer of nitric oxide (NO) between S-nitrosylated proteins that function as NO acceptors or donors, thereby implying that violet light inhibits the innate immune response by regulating protein S-nitrosylation in keratinocytes (Kim, Choi, et al. 2016). A recent study suggested that violet light (410 nm) significantly reduces the transcription level of the clock gene per1 in keratinocytes, thereby indicating that epidermal skin cells can respond to light directly and control the expression level of per1. Furthermore, they revealed that violet light causes ROS production, inflammatory cytokine release, and DNA damage.
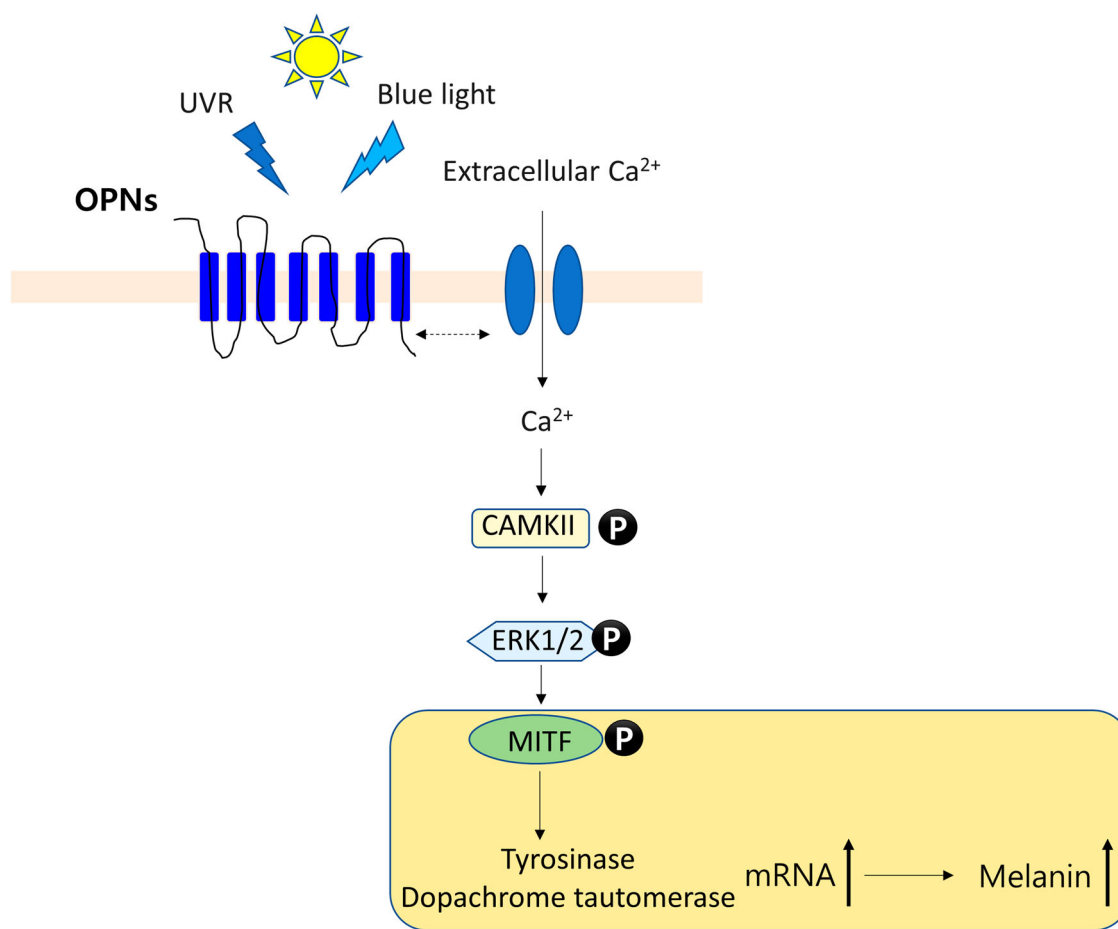
Figure 1. Overview of photoreceptor, OPNs and their underlying signaling in melanocyte. UVR or blue light induces melanin synthesis through the following mechanism in melanocytes. UVR or blue light activates photoreceptors, OPNs, and triggers the influx of extracellular Ca^{2+}, indicating that it shows a calcium-dependent manner. The Ca^{2+} influx is followed by activation of the CAMK II/ERK1/2 pathway and eventually leads to the phosphorylation of MITF, which enhances the melanogenesis enzymes such as tyrosinase, and dopachrome tautomerase.

These deleterious effects can potentially increase overall skin damage over time (Dong et al. 2019).

Keloid is a disease that causes abnormally dense fibrous tissue growth in the wound healing process after skin damage (Ogawa 2017). It grows beyond the size of the wound or inflammation area, with excessive collagen in the dermis, and is involved in the expression of the transforming growth factor β (TGF-β)/Smad signaling system (Mokoena et al. 2018). Violet light (410 nm, twice in 24 h intervals at a UV dose of 10 J/cm^2) significantly reduces the expression of collagen type 1 compared to a negative control, thereby indicating that violet light may inhibit the formation of early keloids (Lee et al. 2017).

Blue light (450 nm ∼ 490 nm)

Blue light has both positive and negative effects on the skin. Human dermal fibroblasts exposed to 450 nm light below mild intensity (< 30 J/cm^2) exhibit inhibitory effects in metabolic activity, such as TGF-β signaling and procollagen I production, and exhibit cytotoxicity at higher intensity (> 30 J/cm^2) (Mignon et al. 2018). Blue light induces oxidative stress in the mitochondria of cultured human keratinocytes by producing superoxide as free radicals and by destroying the autofluorescence of flavin, which is the photosensitizer of blue light (Vandersee et al. 2015; Nakashima et al. 2017; Yang et al. 2017). Blue light (430 ∼ 510 nm) also delays barrier recovery after injury by tape stripping (Denda and Fuziwara 2008).

The positive effects of blue light have been reported in treating acne (*Acne vulgaris*) (Alexiades 2017; Scott et al. 2019). Acne is a skin disease that primarily occurs during puberty and is observed in 85% of the adolescents. Scars (hypertrophic scars) and concave scars (pitted scars) remain on the skin. Although the exact cause is not known, typical causes include increased sebum secretion, colony formation of acne bacteria (*Propionibacterium acnes*, *P. acnes*), inflammatory reactions, and genetic and environmental factors. In particular,

excessive sebum secretion blocks air circulation in the hairs to create an environment that is conducive to the growth of *P. acnes*, an anaerobic bacterium. Porphyrin is produced in acne, and when it is irradiated with blue light as a light-sensitive substance, it produces singlet oxygen, which interferes with the chemical metabolic reaction of acne and eventually kills *P. acnes* (Gold et al. 2011; Wheeland and Dhawan 2011; Dai et al. 2012; Kwon et al. 2013; Amin et al. 2016). Blue light irradiation is also effective for treating severe atopic dermatitis (Becker et al. 2011; Kromer et al. 2019).

Green light (490 nm ∼ 560 nm)

The study of green light is rarely reported compared to other wavelengths of visible light. Green light (490 ∼ 560 nm) has no effect on the barrier recovery rate after damage by tape stripping (Denda and Fuziwara 2008). A recent study reported that green light (520 ± 30 nm, 240 J/cm^2) helps stimulate angiogenesis and myofibroblast differentiation, which is important for the recovery phase of third-degree burns (Simoes et al. 2020). Therefore, further research on the biological effects of green light is needed.

Yellow-orange light (560 nm ∼ 630 nm)

590 nm light irradiation significantly reduces the level of UVA-induced ROS, the phosphorylation level of Jun N-terminal kinases, and the expression level of MMP-1 in human fibroblasts. This phenomenon is due to mitochondrial retrograde signaling that induces expression of the antioxidant enzyme catalase in a peroxisome proliferator-activated receptor γ coactivator-1α-dependent manner (Lan et al. 2015). Another study has reported that LED irradiation (595 ± 2 nm) increases the expression level of collagen type 1 and MMP-1 in human dermal fibroblasts. In an *in vivo* model, 595 nm LED irradiation enhanced the synthesis of collagen type 1 in a dose-dependent manner (Kim, Choi, et al. 2016).

Interestingly, yellow light (590 nm), among other visible light, specifically reduced the size of lipid droplets, which are an organelle of differentiated adipocytes filled with triglycerides. Mechanistically, yellow light (590 nm) significantly reduces triglyceride levels by autophagy-related lysosomal degradation (Choi et al. 2016). Thus, yellow light can be therapeutically useful for reducing unnecessary fat in our body.

Red light (630 nm ∼ 700 nm)

Many studies have shown that red light protects against or mitigates damage caused by exogenous stress, such as UVR and harmful chemicals. Irradiation of red light (660 nm) has been shown to reduce the expression of MMP-1 and increase the expression of collagen I (Gupta et al. 2014). In *in vivo* and *in vitro* models, red light (630 ± 8 nm) upregulates the expression level of collagen I and downregulates the expression level of MMP-1 (Kim, You, et al. 2016). Red light also accelerates the recovery of the epidermal permeability barrier after disruption by tape stripping (Denda and Fuziwara 2008). In a study in which the skin was irradiated with red light every day for approximately 10 days, increased expression of TGF-β and a significant increase in the density of collagen fibers is observed, along with improved dermo-epidermal junction via changes in protein expression related to tissue regeneration (Martignago et al. 2020).

Red light has also been shown to effectively improve wound healing of fibroblasts by stimulating cell proliferation and growth (Barolet et al. 2009; Gupta et al. 2014). SKH-1 hairless mice irradiated with red light (670 nm) were able to mitigate incisional injury in the skin (Erdle et al. 2008). Red light (635 nm) irradiation significantly improves the symptoms of partial-thickness dermal abrasions (Gupta et al. 2014). Red light (630 ± 10 nm, 36 J/cm^2) accelerates re-epithelialization and wound retraction index (WRI) compared to a control during the repair process in third-degree skin burns (Simoes et al. 2020).

Although the beneficial effects of red light on the skin continue to be uncovered, the mechanism by which red light benefits the skin has recently been elucidated. It has been shown that red light protects against UV-induced DNA damage, which enhances the physical interaction of apyrimidinic endonuclease 1 (APE1) with GADD45A, a protein that plays an important role in base excision repair (Kim et al. 2017). Furthermore, red light contributes to protecting human dermal fibroblasts against UVB by regulating the expression level of specific genes related to redox balancing and DNA base excision repair (Kim et al. 2019). These data indicate that red light may be beneficial for the skin and potentially useful in photo-medical applications, such as accelerating wound repair.

Near-infrared (NIR) light (700 nm ∼ 3000 nm)

NIR is known to increase the generation of ROS and damage skin collagen, in a way that is similar to that observed with UVR, indicating that NIR is harmful to human skin (Kim et al. 2005; Akhalaya et al. 2014; Piazena et al. 2014). However, Barolet D et al. have insisted that the intensity of the NIR source used in these studies may be too strong to properly implement NIR radiation (Barolet et al. 2016).

Contrary to previous data, a clinical study revealed that the majority of people (about 51–75 percent) who received

Table 1. The harmful effects and beneficial effects by each wavelength of sunlight.

Each Wavelength	Beneficial Effects	Harmful Effects	References
Ultraviolet (<400 nm)	Vitamin D synthesis Sterilization Vitiligo Psoriasis Atopic dermatitis Scleroderma	Photoaging Skin cancer Inflammation Sunburn	Esmat et al. 2017; Morita 2018 Rodenbeck et al. 2016; Teske and Jacobe 2016 Amaro-Ortiz et al. 2014; Piotrowska et al. 2016; Neale et al. 2019
Violet light (400 ~ 450 nm)	Early keloid	Down-regulation of keratinocyte differentiation Inhibition of innate immunity-related response	Lee et al. 2017 Kim et al. 2013 Kim, Choi, et al. 2016
Blue light (450 ~ 490 nm)	Removal of P. acne Atopic dermatitis	Inhibition of metabolic activity Generation of ROS Delay the barrier recovery	Amin et al. 2016 Kromer et al. 2019 Mignon et al. 2018 Nakashima et al. 2017 Denda and Fuziwara 2008
Green light (490 ~ 560 nm)	Recovery for third-degree burns	Not determined	Simoes et al. 2020
Orange light (560 ~ 630 nm)	Reduction of UVA-induced ROS Up-regulation of collagen Reduction of Triglyceride	Not determined	Lan et al. 2015 Kim, Choi, et al. 2016 Choi et al. 2016
Red light (630 ~ 700 nm)	Up-regulation of collagen Barrier Recovery Wound healing DNA excision Repair	Not determined	Gupta et al. 2014 Kim, Choi, et al. 2016 Simoes et al. 2020 Kim et al. 2017
Near Infrared	Skin tone Up-regulation of collagen Wound healing	Generation of ROS Down-regulation of collagen	Akhalaya et al. 2014 Lee et al. 2006 Barolet et al. 2016 Gupta et al. 2014 Keshri et al. 2016

NIR (830 nm) for approximately six months had improved skin tone and skin roughness (Lee et al. 2006). Other studies have reported that NIR (830 nm) significantly increases the amounts of collagen and elastin fibers in all experimental groups (Rezende et al. 2007) and enhances the protein expression levels of ICAM-1, TNF-α, and connexin 43 (Lee et al. 2007). A recent study has also demonstrated that 850 nm NIR (20 J/cm^2) irradiation stimulates TGF-β signaling and procollagen I production in human dermal fibroblasts without generating intracellular ROS (Mignon et al. 2018). NIR (805 nm) significantly reduces the expression of MMP-1 (Barolet et al. 2016). Low-intensity NIR (810 nm) irradiation enhances collagen accumulation and promotes cellular proliferation and complete re-epithelialization (Gupta et al. 2014). Similarly, NIR (810 nm) irradiation improves wound healing in the dermis of immunosuppressed rats by decreasing the levels of pro-inflammatory factors, such as NF-kB, while increasing levels of re-epithelialization-related proteins, such as fibronectin, HSP-90, and TGF-β2. This NIR irradiation also enhances cellular ATP contents (Keshri et al. 2016). Thus, NIR can be used clinically to improve wound healing through photomodulation.

Conclusion

Given their benefits and drawbacks, light of various wavelengths affects our daily lives both positively and negatively (Table 1). Some studies suggest that high doses of NIR can have a pathological effect on human skin, while low doses of NIR are widely used in medicine to promote wound healing (Barolet et al. 2016). UVR is also a major cause of aging in the skin (Amaro-Ortiz et al. 2014; Chung et al. 2018), but it is effective in promoting vitamin D synthesis and improving skin-related diseases, such as psoriasis (Morita 2018; Neale et al. 2019). Blue light also causes oxidative stress, thereby slowing the recovery of skin barriers, and ultimately adversely affecting the skin (Vandersee et al. 2015; Nakashima et al. 2017), but also contributing positively to the removal of P. acne (Scott et al. 2019). Therefore, it is valuable to utilize the beneficial effects of each wavelength of light under the appropriate conditions.

Many individuals continue to seek non-invasive procedures to improve medical and aesthetic skin diseases. Phototherapy refers to the use of non-thermal or non-invasive light to obtain therapeutic effects. For safety, light of a specific wavelength should be used based on the corresponding chromophore. Therefore, it is essential to identify photoreceptors and elucidate their underlying mechanisms in the skin. Additionally, when combined with systems biology, we can gain insight into which wavelengths are most effective for certain skincare or treatment of skin-related diseases. Strategies to discover each wavelength of light with a specific intensity can help improve the skin.

The light spectrum has different penetration depths of the skin and can be applied to target skin cells or skin tissues for specific therapeutic effects. Recently, there has been growing interest in LEDs, and clinical applications for various medical and cosmetic products have emerged. LEDs have the advantage of delivering sufficient radiation to a target in a short amount of time, which may also be one of the therapeutic mechanisms. The efficient effects of LEDs depend on a sensitive balance between the beneficial and harmful effects of a particular wavelength. Therefore, an appropriate combination of certain LEDs acting on various targets as a phototherapy may be a breakthrough to improve skin-related disorders in the future.

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ORCID

Dong Wook Shin   http://orcid.org/0000-0002-1262-2566

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