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Potential Blue Light Effects on Aging Mechanisms Within Adult Human Skin, a Literature Review

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Synopsis

Blue light is high energy visible light in the region of 400–500 nm in wavelength. There have been questions raised in recent years as to whether this can influence skin in manners like UV light, often centered on the heavy widespread use of mobile devices. Blue light impacts skin through mechanisms such as inflammatory cytokines, cellular viability, and melanogenesis. According to current research conducted on *in vitro* cells as well as *in vivo* skin, it seems that blue light can have an effect on skin that can manifest as extrinsic aging, but this may only occur at the shorter end of the blue light spectrum and at levels of exposure that are sourced from the sun.

INTRODUCTION

BLUE LIGHT

Types of light are categorized by wavelength. Ultraviolet C (UVC) is between 200–280 nm, ultraviolet B (UVB) is 280–320 nm, and ultraviolet A (UVA) between 320–400 nm. Visible light is within the 400–700 nm range (1). Blue light wavelengths have been reported as anywhere from 400–500 nm. Blue light can penetrate even further into the dermis than UVA and UVB light. In the dermis, blue light can potentially be absorbed by hemoglobin, riboflavin and flavoproteins, and other porphyrin-containing enzymes as found in their absorption peaks, which are in the blue light region (2). In the epidermis, melanin can absorb blue light (3). Fluence is defined as the wattage delivered per unit area with which an object is irradiated. Sunlight delivers a fluence of total radiation of 136 mW/cm^2 (1). However, about 40% of sunlight is reflected toward its source. Artificial sources of light provide only a fraction of the exposure levels as compared to the sun as a source. Exposure to a computer screen 18 in away for 10 min can deliver irradiance of 0.6 mW/cm^2 to skin surface (4).

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Table I
A Summary of Aging Events for Extrinsic Versus Intrinsic Aging Types

Skin layer	Extrinsic aging	Intrinsic aging
Dermis	Flattening of the papillary dermis; Abnormal, amorphous, thickened elastic structures; Does not show thinning	Flattening of papillary dermis; Decrease of elastin in papillary dermis; Increase of irregular and fragmented elastin in reticular dermis; Decreased collagen; Thinning
Epidermis	Thickening (5,6), increases in melanocytes (7); Disorderly maturation of keratinocytes (6)	No thickening (6), decrease in melanocytes (7); Reduction in proliferating keratinocytes (7)
Stratum corneum (SC)	Thickening of the SC (5)	Thickening of the SC (5)
Skin mechanics	Reduced ability to resist and recover from applied stress (8)	Reduced ability to resist and recover from applied stress (8)
Appearance	Deep wrinkles (9,6), age spots (8,9)	Fine wrinkles (9,6), age spots (8,9)

SKIN AGING

There are two types of aging affecting the skin: (1) Intrinsic aging occurs mostly regardless of the levels of exposure of the skin to damaging elements at genetically determined rates and (2) extrinsic aging occurs because of external stressors (e.g., prolonged exposure to sunlight). Table I summarizes the main differences in how extrinsic and intrinsic aging manifest in the skin.

BLUE LIGHTS IMPACT ON SKIN

IN VITRO STUDIES

Cell viability. Opländer studied different wavelengths' effects on human dermal fibroblasts obtained from mammoplasty or abdominoplasty. Dermal fibroblast cell viability decreased at 410 and 420 nm at 60 and 90 J/cm^2 (10,11). At 15 and 30 J/cm^2, the reduction in viability was not statistically significant, and at 453 nm and higher, no significant reduction in viability was shown. Cells treated with hydrogen peroxide and blue light reduced cell numbers more than hydrogen peroxide alone, showing that blue light further reduces antioxidant activity of fibroblasts, since the reduction of cell numbers was increased when exposed to blue light. Wavelengths of 453 and 480 nm showed no change.

Blue light at wavelengths 412–426 nm was toxic to endothelial cells and keratinocytes in a dose-dependent manner (as noted by Liebmann). Cells were irradiated at 0, 33, 66, and 100 J/cm^2 every 24 h for 3 d, then 24 h after the last radiation, and the number of viable cells was measured using staining methods. The number of viable keratinocytes and endothelial cells varied inversely with the level of fluence delivered. Cytotoxicity was shown in both types of cells, although keratinocytes were more resistant. At 453 nm, there is no toxicity present at fluences up to 500 J/cm^2, much higher than levels delivered by the sun (12).

Melanogenesis. Regazzetti also studied blue light impact melanogenesis. Human foreskin obtained from children with skin types III and IV was used to culture melanocytes. Cells were irradiated with 415 nm blue light at 50 J/cm^2. Using Western blot to test for proteins, there has been an increased calcium flux with blue light irradiated NHMs, and upregulation of pCAMKII. CAMKII activates CREB, then ERK, and p38 (13). This then phosphorylates melanogenesis-associated transcription factor (MITF), which then

activates melanogenesis enzymes, tyrosinase, and dopachrome tautomerase (DCT) (13). Levels of MITF, actin (which aids in melanin transport), DCT, and tyrosinase were tested in irradiated cells against controls immediately as well as 3 d following irradiation, which indicate melanogenesis activity. Actin and MITF were shown immediately after irradiation; tyrosinase, DCT, actin, and MITF were present 3 days after irradiation.

Reactive oxygen species. NRF2 is a transcription factor that responds to cellular stress such as reactive oxygen species (ROS) and UV light. Its accumulation indicates stressful conditions. It can signal antioxidant response systems to neutralize ROS and other harmful elements. It signals the upregulation of phase 2 antioxidant responders (e.g., glutathione, heme oxygenase, and peroxiredoxins) and UVA light is known to activate NRF2. In a study using human epidermal carcinoma cells injected into mouse skin irradiated with blue light from 400–500 nm, NRF2 was shown to be activated post-irradiation with blue light. Mitochondrial activity decreased beginning at a fluence of 15 J/cm^2 and had an 80% reduction at 45 J/cm^2 after 72 h of exposure (14). This indicates that there is an increase in ROS activity, and therefore a response in antioxidant systems in the skin. Oxidation events in the skin can contribute to damage in lipid and protein structure, leading to decreased tissue integrity.

Inflammatory cytokines. Liebel studied normal human neonatal keratinocytes to analyze free radical production induced by visible light 400–700 nm at 65–180 J/cm^2. Liebel exposed these keratinocytes to TNF_a, UV (290–400 nm), and either 65, 130, or 180 J/cm^2 of visible light, and tested the cells for markers of MAPK/ERK using Western blot. Increased phosphorylation of the epidermal growth factor, detected as phosphor-tyrosine, and the downstream marker of proliferation p42/44 MAPK was detected in the cells treated with TNF_a, UV light, and visible light. This suggests activation of the MAPK/ERK pathway (2). Pretreatment of the cells with Tyrphostin, an EGFR inhibitor, blocked the downstream effects on ERK. This suggests that MAPK/ERK resulted from the activation of EGFR. The author concludes that visible light can induce MAPK/ERK in keratinocytes similarly to UV light.

There was an increase in ROS formation, IL-1a, MMP1, and MMP9 levels, and in the presence of TNFa, an increase of markers of MAPK/ERK pathway activation. However, these levels only reached the levels of UVA/UVB when exposed directly to levels that exceed those delivered by normal sunlight (2).

Liebel's study on free radical production induced by visible light 400–700 nm at 65–180 J/cm^2 was continued using human epidermal equivalents. Cytokine levels were calculated from testing the maintenance medium of the human epidermal equivalents 24 h post-irradiation by immunoassay multiplex kits. The level of MMPs and ROS became significantly increased beginning at 65 J/cm^2, while the level of IL-1a became significantly increased beginning at 130 J/cm^2 (2).

IN VIVO STUDIES

Nitric oxide. NO is a signaling molecule in human skin that can also lead to vasodilation. In addition, NO combines with ROS to form peroxynitrite, which is capable of producing lipid peroxidation and damage (15). This can deplete endogenous antioxidant systems in the skin and lead to damage of moisture-enhancing skin lipids, leading to decreased moisture content. In humans, enzymatic NO is produced by dermal cells. Mitochondrial respiration

can be downregulated by NO (13). Some of the NO molecules formed remain close to their origin as nitroso compounds (e.g., S-nitrosothiols), mercuric chloride nonsensitive nitroso compounds, or the oxidation products nitrite and nitrate. It is known that these derivatives can begin decomposing when exposed to UVA to form bioactive NO. Several studies looked at whether blue light could affect NO release.

Liebmann used keratinocytes and epithelial cell cultures *in vivo*, and irradiated them at 412, 419, and 426 nm at 66–100 J/cm^2, and at 453 nm at 500 J/cm^2. (12) As shown in Liebmann's study, adenosine triphosphate levels also increased in keratinocytes and epithelial cells at 453 nm 500 J/cm^2 (12). At longer wavelengths of blue light, such as 470 nm, mitochondrial respiration is reactivated. Liebmann estimates that this increase in adenosine triphosphate level is due to the release of NO from NO-sensitive complexes of the respiratory chain, such as bovine serum albumin, which act as photo acceptors, as a result of longer wavelengths of blue light.

Liebmann used neonatal keratinocytes as well as reconstituted human epidermal tissue to study the effects of blue light on ROS and cytokines. These cells were exposed to differing doses of blue light ranging from 412–453 nm, UVA at 30 J/cm^2, 412 nm at 33 J/cm^2, 426 nm at 66 J/cm^2, and 453 nm at 100 J/cm^2. Blue light was found to have no effect on IL-8 release of human keratinocytes and endothelial cells (12). However, this study also showed that keratinocytes exposed to UVA also did not show an upregulation of IL-8 levels; only in endothelial cells did this increase for UVA. IL-8 release can lead to a positive feedback loop and upregulation of elastase, leading to dermal matrix breakdown (15). This study suggests that neither blue light nor UVA light contributes to extrinsic aging from the single cytokine IL-8.

For Opländer's *in vivo* studies, volunteers were irradiated with a blue light dose of 30 J/cm^2 for 15 min. Opländer also used a closed chamber to collect NO gas from the forearm of human volunteers. An irradiation of 453 nm produced a small increase in gaseous NO emanating from the skin. Wavelengths in the green and red region did not produce a difference in NO levels. 420 nm, 52 J/cm^2 produced a slight increase in S-nitroso-protein in homogenates of human skin. Cutaneous blood flow was analyzed with a micro-lightguide spectrophotometer. This resulted in greater NO formation than *in vitro* studies of human keratinocytes and resulted in NO-induced changes such as dilation of arteries and decrease in blood flow (10,11). There is a copper-dependence to the NO formation. A solution of nitrite-containing 10 mM $NaNO_2$, as well as bivalent copper ions 2 mM $CuCl_2$, were irradiated with blue light emitting LEDs (420 nm, 453 nm, 50 mW/cm^2). Only the copper solution produced NO and did not produce NO with addition of a copper chelator. NO production was linear as a function of irradiance at 453 nm, and NO production peaked at 420 nm (10,11).

Inflammatory cytokines. Kleinpenning studied the buttocks skin of eight females of Fitzpatrick skin types I–III with an average age of 20.9, via biopsies following exposure to 20 J/cm^2 blue light at 420 nm. The skin was tested for p53, deformed elastin, MMP1, hyperpigmentation, inflammatory cells, keratinocytes, and sunburn cells. MMP1 was found to be present in five volunteer slides but was not significantly different than nonirradiated slides. The level of inflammatory cytokines also did not show a significant increase in irradiated slides from the controls. The author specified that, although blue light does not appear to contribute to extrinsic aging from acute exposure, no conclusions could be drawn from this study about the long-term effects of blue light exposure by the results of this study (19).

Liebel's study on the effect of visible light on ROS continued with human subjects. The foreheads of volunteers were exposed to visible light 400–700 nm at 50 J/cm^2, and ROS was measured by a hydrogen peroxide-sensitive fluorescent probe. Free radical production was shown to increase over the baseline by 85.5% (2).

Falcone performed a study to measure effects of 453 nm blue light on healthy skin perturbed using tape stripping. Included were 22 healthy volunteers with a mean age of 21.9 and Fitzpatrick skin types I, II, or III. No toiletries were used 24 h prior, and no sunbathing was permitted 2 weeks prior to experiment. Histamine iontophoresis and tape stripping was performed on two separate spots 4 cm apart on the volar forearm. Irradiance was delivered in pulsed (PW) or continuous (CW) mode. 15 cm of perturbed area of volar forearm was then irradiated with blue light at 453 nm with a fluence of 18 J/cm^2 at 10 mW/cm^2 for 30 min. The pulsed mode delivered the same fluence but included a peak irradiance of 200 mW/cm^2. Skin surface temperature was also taken from thermocouples of either side of the irradiance area. Six tests were performed over the course of 2 weeks (16).

Skin reaction measured by transepidermal water loss (TEWL), skin surface biomarkers interleukin (IL)-1α, IL-1RA, human beta-defensin (hBD)-1, and hBD-2 were measured by means of transdermal analyses patch, and reflectance confocal microscopy was used to measure SC and epidermal thickness.

All biomarkers IL-1α IL-1RA, ratio IL-1RA/IL-1α, hBD-1, and hBD-2 increased 24 h after tape stripping during control week. All biomarkers, except IL-1a, increased during irradiation week in the group that was perturbed and irradiated compared to nonperturbed and nonirradiated group. The authors conclude that blue light 453 nm light at 18 J/cm^2 results in an inhibitory effect on IL-1a, which will lead to a reduction in release of lamellar bodies, as IL-1a promotes lipid and lamellar body synthesis. This difference was not statistically significant when perturbed and the irradiated group was compared to perturbed nonirradiated group.

At 24 h, TEWL was increased, which the authors suggest is due to the reduced IL-1a levels after irradiation and is the first step in the inflammatory cascade, typically increased following barrier disruption (16). At 72 h, no difference in TEWL and epidermal thickness was noted in comparison of irradiated group and control group, suggesting no antiproliferative effect of single treatment.

Reactive oxygen species. ROS can cause damage to lipids and proteins and can signal release of inflammatory cytokines. Nakashima performed an *in vivo* study looking at red, blue, and UV light using reduction-oxidation sensitive green fluorescent protein (roGFP), a fluorescent protein which can be oxidized by glutathione disulfide (GSSG), which is the oxidized form of cellular glutathione, a major redox protection system in human cells (3). If roGFP is present in the cells, it indicates that glutathione is responding to oxidative stress in the cells. Generation of oxidative species results in damage to skin lipids (17) and signal release of inflammatory cytokines by keratinocytes. roGFP was used due to its change in absorption upon oxidation, so quantification was simplified. Two species of mice were used—one expressed the roGFP in mitochondria, and the other expressed the roGFP in the cytosol and nucleus. Human subjects were also used and experiments performed were conducted within the parameters of the Declaration of Helsinki. The hand of participants was irradiated for 10 min at wavelengths of 400–480 nm at fluences of 11 mW/cm^2. Blue light caused oxidative response via glutathione cascade in mitochondrial roGFP1 cells, as found by autofluorescence measurements, but not cytosol-based roGFP1 cells as shown in the mouse study.

Since the oxidation rate tapers off at higher fluences, the authors conclude that endogenous flavin chromophores are destroyed by blue light. This flavin resulted in autofluorescence and was subtracted from mouse studies to isolate roGFP measurements. Human mitochondrial versus cytosolic oxidative cell responses mirrored mouse experimental results. Wavelengths in the green light region had no effect on oxidative events in the cytosol or the mitochondria. It was found that blue light cannot produce singlet oxygen as found by analysis of NADH and NADPH fluorescence measurements. Human skin exposed to blue light showed a decrease in autofluorescence measurements.

Oxidation and conversion of cellular glutathione to GSSG does not occur very often in healthy cells; usually roGFP will remain in a reduced state. This means that if skin cells are under stress conditions, there may be more GSSG existence in the cells. This chain reaction will occur as a result of superoxide and singlet oxygen. The author concludes that blue light was confirmed to contribute to skin aging by a slow and steady exposure to ROS, not by overwhelming cellular antioxidant levels by acute exposure. Melanin and carotenoids both absorb blue light as well as UVA light, but not green light, suggesting that evolutionarily, they are needed to protect the skin from blue light damage as well as UVA. Human skin exposed to normal sunlight levels of blue light showed a disintegration of endogenous flavoproteins (3). As discussed in earlier sections, this can lead to ROS which can signal activation of the MAPK/ERK pathway.

Although the glutathione redox state was activated, no long-term blue light oxidative stress is indicated by this specific study as this is a short-term event. Per photon efficacy to activate

Table II
Blue Light-Induced Events in Comparison with Known UVA and UVB Events

	Blue light	UVA	UVB
Penetration level	Epidermis, dermis	Epidermis, dermis	Epidermis
Main chromophores	Flavins, heme, more data needed	Flavins, heme, porphyrins, cytochromes	Aromatic amino acids, nucleic acids
Inflammatory cytokines & inflammatory cytokine-induced MMP	IL-1a, MMP1, MMP9, reduction in TNF-alpha, no effect on IL-8	IL-1a, IL-6, IL-8, TNF-alpha	TNF-alpha, MMP1, MMP9, MMP3
ROS species known	No O_2, NO, H_2O_2, more data needed	O_2, OH, NO, H_2O_2	O_2, OH, NO, H_2O_2
DNA impact	8-oxoguanine, T4 endonuclease V (hamster cells *in vitro* only), more data needed	8-hydroxyguanine and formamidopyrimidines, T4 endonuclease V	Pyrimidine dimers
Keratinocytes	Decrease in viability due to differentiation	Decrease in viability	Decrease in viability
Fibroblasts	Reduction in viability for wavelengths below 453 nm	Reduction in viability	Reduction in viability
Wrinkles	May lead to wrinkles by loss in dermal integrity	Known to lead to wrinkles	Known to lead to wrinkles
Melanogenesis	Through OPN3, may lead to age spots via combination of loss of dermal integrity and melanogenesis in skin types III and above	Through p53, known to lead to age spots	Through p53, known to lead to age spots

the glutathione redox state is about 25% of that of UVA light. It would have been beneficial to repeat this study using times of exposure that were more long term (3). This study indicates that there is short-term oxidative events that occur as a result of blue light exposure.

COMPARISON OF BLUE LIGHT SKIN INTERACTIONS WITH UVA AND UVB LIGHT SKIN INTERACTIONS

Table II summarizes the differences between the interactions of skin with the different levels of light, as well as the tissue-level effects of the light-activated mechanisms that have been examined.

Table III
Summary of Previously Examined Data of the Mechanisms Activated by Blue Light

Wavelength	Fluence	Result
410, 412, 415, 419, 420, 426, 453, 460, 470 nm	11 J/cm2 [Nakashima]	Reduction in endogenous flavoproteins in vivo
410, 412, 415, 419, 420, 426, 453, 460, 470 nm	50 J/cm2 [Liebel]	Hydrogen peroxide generated from human foreheads in vivo
410, 412, 415, 419, 420, 426, 453, 460, 470 nm	65 J/cm2 [Liebel]	Increased ROS, no increase in IL-1a, increase in MMP1 and MMP9, Activation of MAPK pathway when in the presence of TNFa
410, 412, 415, 419, 420, 426, 453, 460, 470 nm	130 J/cm2-180 J/cm2 [Liebel]	Increased ROS, increase in IL-1a, increase in MMP1 and MMP9, Activation of MAPK pathway when in the presence of TNFa
410 nm	60 J/cm2 [Oplander]	Significant reduction in fibroblast viability
412 nm	33 J/cm2 [Liebmann]	No effect on IL-8, reduction in keratinocytes and endothelial cells due to differentiation
415 nm	50 J/cm2 [Regazzetti]	OPN3 dependent calcium flux causes upregulation of melanogenesis in FSTs III and above
419 nm	33 J/cm2 [Liebmann]	Reduction in endothelial cells and keratinocytes due to differentiation
420 nm	60 J/cm2 [Oplander]	Significant reduction in fibroblast viability
420 nm	20 J/cm2 [Kleinpenning]	No impact on MMP, No impact on inflammatory cytokines, No increase on p53 levels, which increase melanogenesis
426 nm	66 J/cm2 [Liebmann]	No effect on IL-8, no reduction in keratinocytes, reduction in endothelial viability
453 nm	18 J/cm2 [Falcone]	Decreased IL-1a levels in epidermis following perturbation, increase in TEWL following perturbation, short-lived increase in blood flow following irradiation and perturbation, increase in melanin 72 h after irradiation and perturbation
453 nm	30 J/cm2 [Oplander]	NO release *in vivo*
453 nm	90 J/cm2 [Oplander]	No reduction in fibroblast viability
453 nm	100 J/cm2 [Liebmann]	No effect on IL-8
460 nm	44 J/cm2 [Nakashima]	Increases mitochondrial ROS in keratinocytes
470 nm	3 J/cm2 [Masson-Meyers]	No reduction in fibroblast viability
470 nm	55 J/cm2 [Masson-Meyers]	No reduction in fibroblast viability
470 nm	110 J/cm2 [Masson-Meyers]	Reduction in fibroblast viability
470 nm	220 J/cm2 [Masson-Meyers]	Reduction in fibroblast viability

CONCLUSION

Blue light has been shown to negatively impact the viability of fibroblasts (10,11,18). Acute exposure to blue light does not have any impact on elastin levels (19). However, by way of MMP1 and MMP9, this leads to the breakdown of both collagen and normally oriented elastin in the dermal layer, resulting in long-term contribution to extrinsic aging, with a loss in ability to resist deformation as well as the ability to recover from applied stress. At the epidermal layer, blue light caused melanogenesis in Fitzpatrick skin types III and higher (13). For individuals with this skin type, this can mirror age-spotting extrinsic aging events if the increase in melanogenesis is combined with a loss in dermal integrity (8,9). Blue light can also increase keratinocyte differentiation activity, which leads to a reduction in proliferation. This causes the epidermal turnover rate to decrease, and the stratum corneum will thicken.

Kleinpenning reported a reduction in inflammatory cells; however, this study did not give any specifics regarding the types of inflammatory cells that were examined (19). To contradict Kleinpenning, Liebel's study did report an increase in ROS and IL-1_a levels (2). This research should be expanded to find specifics on how different inflammatory markers can be affected by certain wavelengths of blue light. Table III shows a summary of the previously examined experiments at differing wavelengths and fluences. Wavelengths below 420 nm are likely to contribute to extrinsic aging based on the elicited cellular mechanisms at these wavelengths, while wavelengths 453 and higher are relatively safe at sunlight-level fluences.

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