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# Beneficial effects of UV radiation other than via vitamin D production

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Most of the positive effects of solar radiation are mediated via ultraviolet-B (UVB) induced production of vitamin D in skin. However, several other pathways may exist for the action of ultraviolet (UV) radiation on humans as focused on in this review. One is induction of cosmetic tanning (immediate pigment darkening, persistent pigment darkening and delayed tanning). UVB-induced, delayed tanning (increases melanin in skin after several days), acts as a sunscreen. Several human skin diseases, like psoriasis, vitiligo, atopic dermatitis and localized scleroderma, can be treated with solar radiation (heliotherapy) or artificial UV radiation (phototherapy). UV exposure can suppress the clinical symptoms of multiple sclerosis independently of vitamin D synthesis. Furthermore, UV generates nitric oxide (NO), which may reduce blood pressure and generally improve cardiovascular health. UVA-induced NO may also have antimicrobial effects and furthermore, act as a neurotransmitter. Finally, UV exposure may improve mood through the release of endorphins.

## Introduction

Solar ultraviolet (UV) radiation has been used since ancient times to treat various diseases. This has a scientific background in the fact that a large number of molecules (chromophores) in different layers of the skin interact with and absorb UV. These interactions may have both positive and negative biological implications. In this review we only concentrate on the positive effects other than those directly related to vitamin D production.

## Cosmetic Tanning

Some Africans and Asians avoid sun and use bleaching products to lighten skin, while many Caucasians seek the sun for tanning to achieve a bronze skin to “look good.”<sup>1–3</sup> UV radiation from the sun or from artificial sources increases skin pigmentation.<sup>4,5</sup> There are three phases of tanning: immediate pigment darkening (IPD), persistent pigment darkening (PPD) and delayed tanning (DT).<sup>6,7</sup> IPD occurs during the first minutes of exposure to UVA, and then fades within few hours.<sup>6,8</sup> PPD appears within hours of

higher doses of UVA exposure and persist up to several days or weeks.<sup>7,9</sup> DT develops over 3–7 days after UVB exposure, and then remains for weeks.<sup>10</sup> The mechanisms of UVA- and UVB-induced pigmentation are different.<sup>11</sup> UVA induces IPD and PPD through oxidation of pre-existing melanin or melanogenic precursors.<sup>6</sup> IPD is oxygen dependent, and reactive oxygen radicals are considered to be responsible for this process.<sup>7,12,13</sup> PPD is also due to the upward movement of melanosomes toward the surface of the skin.<sup>10</sup> Persons with lightest skin (skin type I) do almost not tan, while IPD and PPD are strongest in moderately and darkly pigmented skin.<sup>14,15</sup> DT results from synthesis of melanin in the melanocytes, followed by melanin distribution to neighboring keratinocytes.<sup>6,7,10</sup>

The levels of UV radiation from the sun vary with latitude, altitude, weather, time of day and season of year. Facultative pigmentation (i.e., that induced by UV) decays during winter months at higher latitudes due to low temperatures and low UV levels. Some people want to maintain facultative tanning throughout the year for cosmetic purposes. They often use sunbeds or travel south for sunny vacations. Indoor tanning is popular, not only among Caucasians in countries with low annual UV levels (Northern countries),<sup>16,17</sup> but also in countries with high annual UV levels (Australia).<sup>18,19</sup> Sunbeds have several times higher UVA fluence rates than found in solar radiation under relevant conditions,<sup>19,20</sup> and, due to this, IPD and PPD are pronounced after sunbathing. Additionally, under certain conditions UVA-induced pigmentation lasts longer than UVB-induced DP.<sup>9</sup> This can be partly explained by the facts that UVB-induced tanning is located in the upper layers of the epidermis, while UVA-induced tanning is primary localized in the basal cell layer.<sup>11</sup> However, high doses of UV radiation from sun or indoor tanning devices lead not only to tanning, but also to erythema, local and systemic immunosuppression, DNA damage, photoaging and photocarcinogenesis.<sup>17,21,22</sup>

## Photoprotection

UV radiation from sun and sunbeds is the main risk factor for skin cancer.<sup>23–27</sup> Human skin adapts to chronic UV exposure by increasing melanogenesis, thickening of the horny layer, activating of antioxidant molecules, the DNA repair systems, and secretion of cytokines.<sup>28–31</sup>

Melanin provides protection of structures in and below the skin against free, UV-induced radicals. Thus, it acts as a direct shield

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from UV and visible light radiation. UV radiation causes DNA damage in the nuclei of keratinocytes, resulting in activation of p53, which transcriptionally upregulates the expression of the gene encoding proopiomelanocortin (POMC).<sup>32</sup> The POMC precursor polypeptide is processed into several bioactive products, including  $\alpha$ -melanocyte-stimulating hormone ( $\alpha$ -MSH), adrenocorticotrophic hormone (ACTH) and  $\beta$ -endorphin.<sup>32,33</sup> After secretion,  $\alpha$ -MSH binds to the melanocortin 1 receptor (MC1R) located on melanocytes and activates melanin production.<sup>32,33</sup> The anti-inflammatory effects of  $\alpha$ -MSH and ACTH may help relieve irritation and local inflammation in UV-exposed skin.<sup>33,34</sup>

Although UVA- and UVB-induced pigmentations are visually identical, only UVB-pigmentation results in a protection which is as large as corresponding to a factor of about 2 to 3 against DNA photodamage and erythema.<sup>11,35,36</sup> This protection is equivalent to using a sunscreen with a sun protection factor (SPF) of 2 to 3.<sup>4</sup>

UVA tanning is not involved in melanin production, nor in photoprotection.<sup>7,11,36</sup> The evolutionary role of IPD still remains unknown. Recently we have proposed that the biological role of IPD is protection of folates against photodegradation, which would be of large evolutionary importance for early hominids.<sup>37</sup> We found that IPD had an absorption spectrum covering a number of endogenous photosensitizers in skin, such as porphyrins and riboflavin.<sup>38</sup>

UVB induces hyperkeratosis and thickening of the stratum corneum, thus reducing UV transmission.<sup>30,31,39</sup> However, the relative importance of stratum corneum thickening and pigmentation in photoprotection is debated.<sup>30,31,39</sup>

UVA photons excite endogenous chromophores (photosensitizers) in human skin which lead to generation of reactive oxygen and nitrogen species that can cause damage by themselves or enhance the damaging effect of UVB. UVA can cause immunosuppression in human skin. A number of recent studies demonstrate that UVA radiation can provide immunoprotection and also inhibit UVB-induced immunosuppression through modulation of various cytokines and enzymes, such as expression of heme oxygenase-1 (HO-1).<sup>40</sup> UVA exposure increases expression of HO-1 that mediates antioxidant, anti-inflammatory, anti-apoptotic and anti-proliferative effects, and protects cells and tissues against oxidative stress and tissue injury.<sup>40,41</sup>

Actinic or solar elastosis is an accumulation of abnormal elastic tissue in the upper and middle dermis, which may be related to activation of the human elastin promoter by UV radiation or elastin degradation due to an influx of neutrophils that diffuse to the dermis in response to cytokine production after UVB exposure.<sup>42</sup> Solar elastosis is generally considered to be a biomarker for cumulative sun exposure.<sup>42</sup> However, solar elastosis is a protective factor for sporadic basal cell carcinoma.<sup>43</sup> Furthermore, it has been positively associated with melanoma survival.<sup>44</sup> Prognosis for melanoma of the back (low solar elastosis) is worse than that for the face (high solar elastosis).<sup>45–47</sup> Melanomas with elastosis occur at later ages than melanomas without elastosis.<sup>48</sup> Consequently, sun exposure is associated with increased survival from melanoma.<sup>44</sup> Melanoma is more frequent among people with indoor occupations than among people getting large accumulated UV exposures (farmers, fishermen, etc.).<sup>49</sup> Chronic UV exposure

reduces and/or delays the development of melanoma.<sup>47</sup> Holiday sun exposure is not always associated with an increased melanoma risk, and even a protective effect of regular weekend sun exposure has been observed, particularly for limb tumors.<sup>50</sup> Outdoor activities (without sunburn, associated with increased risk of melanoma) in childhood are associated with a lower risk of melanoma.<sup>51</sup> The observed effects could be mediated independently by photoadaptation (development of solar elastosis) and by higher vitamin D levels.<sup>47,50,52</sup>

## Mood Enhancing Effects

Most people judge sun exposure in non-erythemal doses as pleasant. Exposure to sunlight has been linked to improved energy and elevated mood.<sup>53</sup> Tanners feel more relaxed and less tense than non-tanners.<sup>54</sup> The belief that people look better with a tan may partly explain this phenomenon.<sup>53</sup> Additionally, exposure of keratinocytes to UV radiation leads to production of an opioid  $\beta$ -endorphin via stimulation of the POMC promoter.<sup>55–57</sup> This  $\beta$ -endorphin released into the blood during UV exposure may reach the brain in sufficient concentrations to induce mood enhancement and relaxation.<sup>58</sup> However, only one study has demonstrated increased  $\beta$ -endorphin levels in blood after UV exposure of healthy volunteers<sup>59</sup> while three other studies have not found increased levels of  $\beta$ -endorphin.<sup>60–62</sup> At the same time even anxiety associated with the needles used for blood sampling could affect endorphin levels.<sup>62</sup> Other indirect evidences also suggest that endorphins are released to blood. It has been demonstrated that frequent tanners almost always choose sunbed emitting UV radiation.<sup>54</sup> In another study was shown that the use of the opioid antagonist naltrexone, used for treatment of opioid dependence, reduced UV preference and even induced withdrawal symptoms in frequent tanners.<sup>63</sup> Chronical and frequent exposure to UV radiation may result in a tanning addiction and in a pattern of behavior similar to other types of substance-related disorder.<sup>3,64–66</sup>

## Phototherapy

Already several thousands of years ago sunlight (heliotherapy) was used to treat a variety of skin conditions in Egypt, Greece and Rome.<sup>67</sup> At that time, the importance of UV radiation was not recognized, because UV rays were not discovered before 1801.<sup>67</sup> In 1903, Niels Ryberg Finsen was awarded the Nobel Prize “in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science.” Finsen discovered that UV radiation was beneficial in treating lupus vulgaris, a skin condition caused by *Mycobacterium tuberculosis*. UV radiation was the only effective treatment against tubercle bacilli in the skin before the introduction of antituberculous chemotherapy in the 1950s.<sup>68,69</sup> Finsen believed that UV radiation killed *Mycobacterium tuberculosis*, but the detailed mechanism of action is not known.<sup>68</sup> In 1958 it was demonstrated that the UV radiation in Finsen’s lamps can lead to vitamin D production.<sup>70,71</sup> It has been suggested that increased levels of vitamin D could be involved in bacterial killing, and it was

considered as the mechanism of effect of UV therapy on lupus.<sup>70,71</sup> However, a few years ago Wulf's group in Denmark tried to find which wavelengths could be emitted by Finsen's equipment and which mechanisms could lead to the photo-inactivation of *Mycobacterium tuberculosis*.<sup>68</sup> Their experiments have suggested that only glass quartz was used in the treatment. This means that only wavelengths longer than 340 nm (UVA) could be emitted through Finsen's lenses.<sup>68</sup> They have also detected that *Mycobacterium tuberculosis* contains the water soluble porphyrin coproporphyrin III which has its highest absorption peak at 398 nm (the Soret band).<sup>68</sup> Exposure of coproporphyrin III to UVA and blue light leads to the production of singlet oxygen and the photoinactivation of bacteria in the process known as photodynamic therapy (PDT). A mechanism like that operating in PDT seems to be a most plausible explanation why Finsen's therapy worked.<sup>68</sup>

**Modern phototherapy.** In our days phototherapy is a valuable option in the treatment of many psoriatic and nonpsoriatic conditions, including atopic dermatitis, sclerosing skin conditions such as morphea, scleroderma, vitiligo, and mycosis fungoides.<sup>72</sup> Phototherapy is the treatment of certain skin disorders with UV radiation which can be produced by the sun, fluorescent lamps, short arc lamps with UV filters and lasers. Depending on the shape of the spectrum of radiation emitted by the source, phototherapy can be divided into broadband UVB (290–320 nm), narrow band UVB (310–315 nm), monochromatic UVB (308 nm from an excimer laser), broadband UVA (320–400 nm) and UVA-1 (340–400 nm).<sup>73,74</sup> For a detailed review see references 72–79.

**Mechanism of action.** UVB radiation reaches the epidermis and the upper dermis where it is absorbed by DNA, trans-urocanic acid (trans-UCA), and cell membranes.<sup>73</sup> Absorption of UVB by nucleotides leads to the formation of DNA photoproducts, primarily pyrimidine dimers. UVB exposure reduces the rate of DNA synthesis. In addition, UVB radiation causes photoisomerization of trans-UCA to cis-UCA which has immunosuppressive effects. Furthermore, UV radiation can affect extranuclear molecular targets (cell surface receptors, kinases, phosphatases, and transcription factors) located in the cytoplasm and in the cell membranes.<sup>73</sup>

Keratinocytes, circulating and cutaneous T lymphocytes, monocytes, Langerhans cell, mast cells and fibroblasts are all targeted by narrowband UVB.<sup>73</sup> Narrowband UVB induces also local and systemic immunosuppressive effects which may particularly contribute to the beneficial effects of this light source.

UVA radiation penetrates more deeply into the skin than UVB, and reaches not only epidermis, but also dermis with blood vessels affecting dermal dendritic cells, dermal fibroblasts, endothelial cells, mast cells, and granulocytes.<sup>80</sup> UVA radiation is absorbed by pyridine nucleotides (NAD and NADP), riboflavins, porphyrins, pteridines, cobalamins and bilirubin.<sup>80</sup> Porphyrins and riboflavins are photosensitizers. UVA effects are dominated by indirect DNA damage caused by reactive oxygen species such as singlet oxygen. The ability of UVA radiation to cause skin erythema is approximately  $10^3$  to  $10^4$  times lower than that of UVB. As UVA-1 is even less erythematogenic than broadband UVA,

much higher doses of UVA-1 can be tolerated by the patients. UVA-1 phototherapy works mainly through induction of apoptosis of skin infiltrating T cells, T-cell depletion and induction of collagenase-1 expression in human dermal fibroblast.<sup>40,81</sup>

**Psoriasis.** Traditionally, broadband UVB phototherapy has been used to treat psoriasis, which is an inflammatory skin disease, characterized by keratinocyte hyperproliferation with 1–2% prevalence in the general population. However, now more often narrowband UVB or monochromatic UVB are used for the clearance of psoriasis. Narrow-band UVB clears psoriasis faster and produces longer remissions than broadband UVB.<sup>74,77</sup> Action spectra for UV-induced erythema, DNA damage, photoimmunosuppression, squamous cell carcinoma and vitamin D synthesis are very similar, all in the UVB spectral region of 280–310 nm.<sup>38</sup> Narrowband UVB do not contain the most erythemogenic and carcinogenic wavelengths. Even though UVB phototherapy is a standard treatment for psoriasis, the mechanisms underlying its efficacy are incompletely understood. UVB exposure, via induction of DNA photoproducts, is thought to inhibit cell proliferation transiently. It has therefore been speculated that the therapeutic effectiveness of phototherapy mainly relates to its antiproliferative properties.<sup>73,82</sup> Additionally, UVB phototherapy is effective for psoriasis by inhibiting cutaneous immune functions.<sup>74</sup> Recently, vitamin D has been brought in focus.<sup>76,83–85</sup> The beneficial effect of UVB exposure in patients with psoriasis may be explained, at least in part, by the induction of vitamin D, as topical vitamin D derivatives are also effective.<sup>76,83–85</sup> Heliotherapy, broadband and narrowband UVB phototherapy all increase serum 25-hydroxyvitamin D (25(OH)D) levels.<sup>83–85</sup>

**Vitiligo.** Vitiligo is a depigmentation skin disorder with an incidence rate of between 0.1% and 2% in the general population.<sup>86,87</sup> The cause of vitiligo appears to be a combination of genetic effects in both the immune system and in the melanocytes, both resulting in melanocyte destruction.<sup>88</sup> Due to the complexity of the disorder a lot of different treatments are recommended, including phototherapy with narrowband UVB radiation and excimer laser (308 nm) with or without topical application of calcineurin antagonists (tacrolimus and pimecrolimus).<sup>86,87</sup> Phototherapy for vitiligo was initiated by the observation that sun-exposed lesions tend to show follicular repigmentation during the summer months in many patients.<sup>89</sup> This effect is transient but repeatable.<sup>89</sup> The mechanism of action of phototherapy on patients with vitiligo has not been completely elucidated. The melanocytes are destroyed in the epidermis of patients with vitiligo, while the melanocytes in the outer root sheaths of hair follicles are not affected. Repigmentation after phototherapy may be initiated by activation, proliferation, and migration of these melanocytes to the epidermis, where they form perifollicular pigmentation islands.<sup>86</sup> Furthermore, the immunosuppressive action of UVB phototherapy may also contribute to the mechanisms of action.

**Atopic dermatitis.** Atopic dermatitis is a chronic inflammatory skin disease. The estimated prevalence in the United States is around 17%.<sup>90</sup> Narrowband UVB and UVA-1 are the most frequently applied treatment regimens in atopic dermatitis and in other T cell mediated inflammatory skin diseases. UV radiation



induces direct phototoxic effects on T-lymphocytes. Thereby, it causes a gradual reduction of the inflammatory infiltrate and a concomitant improvement of patients' skin.<sup>73,91</sup>

**Localized scleroderma.** UVA-1 phototherapy is used to treat localized scleroderma, also known as morphea.<sup>92</sup> The precise action of UVA-1 phototherapy remains obscure. UVA-1 phototherapy may reduce the number of Langerhans cells and mast cells.<sup>92</sup>

### Pain Relief

Sunbathing or tanning beds seem to have a potential to reduce pain in patients with fibromyalgia.<sup>54</sup> Patients with the chronic pain condition fibromyalgia have reported a greater short-term decrease in pain after exposure to UV compared with non-UV radiation exposure.<sup>54</sup>

### UV Effects on Skin Barrier Functions

Skin exposed to UVB and UVA is more resistant to primary irritants, which may indicate the improvement of skin barrier functions.<sup>30,93,94</sup> Such an improvement is not due to epidermal hyperplasia, which does not appear after UVA exposure, and neither is it due to increase in lipids in the stratum corneum as has been believed earlier.<sup>30,93,94</sup>

### UV Effects on Other Diseases

The risk and/or mortality of autoimmune diseases (multiple sclerosis, asthma and type 1 diabetes mellitus), cardiovascular diseases (hypertension and myocardial infarction), several cancers (bladder, breast, cervical, colon, endometrial, esophageal, gastric, lung, ovarian, pancreatic, rectal, renal and vulvar cancer) and other conditions increases with latitude (decreasing UV dose) of residence.<sup>95,96</sup> Generally, it is believed that the increased risk of these diseases is due to lack of UVB radiation which leads to vitamin D deficiency. No mechanism other than vitamin D production has been proposed to explain the effects of UVB exposure on reducing these disease risk.<sup>96</sup> A growing amount of molecular data demonstrates the involvement of vitamin D in cell proliferation, differentiation, apoptosis, angiogenesis, immune and inflammatory responses.<sup>97,98</sup> These findings provide a strong basis for epidemiological evidences documenting that vitamin D deficiency may be a risk factor for development and progression of some types of cancer. Other molecular mechanisms may explain the role of vitamin D in cardiovascular diseases, diabetes mellitus, cancer, multiple sclerosis, allergy, asthma, infection, muscle weakness, depression, etc.<sup>99,100</sup> Several studies found association between low vitamin D levels and hypertension, coronary artery calcification, heart disease and several cancers.<sup>101–106</sup> Recent meta-analyses have demonstrated reduction in mortality and cardiovascular risk associated with vitamin D.<sup>101–107</sup> Zitterman et al. have performed the meta meta-analysis of prospective cohort studies and found a nonlinear decrease in mortality risk as circulating 25(OH)D increases, with optimal concentrations 75–87.5 nmol/.<sup>106</sup> Some studies do not support any association

between 25(OH)D and cancer risk nor total cancer mortality, except colorectal cancer, breast cancer risk or mortality.<sup>108–111</sup> The evidences of whether vitamin D supplementation may prevent cancer, cardiovascular diseases, and mortality are contradictory.<sup>112–114</sup> Vitamin D has been associated with increased survival rates for several types of cancer.<sup>115,116</sup> Additionally, there is no trend in serum 25-hydroxyvitamin D (25(OH)D) level with latitude.<sup>117</sup> This may be due to imprecise and unreliable vitamin D measurements.<sup>118</sup> It is possible that the reported protective effect of sunlight on the mentioned types of cancer and other diseases are not mediated only through vitamin D but also through other and as yet unknown mechanisms.<sup>110,119,120</sup> A few years ago Becklund et al.<sup>120</sup> demonstrated that vitamin D supplementation is less efficient than UV radiation in suppressing multiple sclerosis in animals. Lukas et al.<sup>121</sup> found in a multi-center case-control study that multiple sclerosis risk decreased with increasing serum 25(OH)D levels, measured at the time of the first demyelinating events, and with increasing UV exposure, estimated by questionnaires or by the degree of actinic damage. Lukas et al.<sup>121</sup> suggested that sun exposure and vitamin D status may play independent roles for development of central nervous system demyelination. A recent population-based case-control from Sweden<sup>122</sup> suggested that UVR exposure may also exert a protective effect against developing multiple sclerosis via other pathways than those involving vitamin D. The role of UV and vitamin D should be evaluated in clinical trials for multiple sclerosis prevention.

African Americans at higher latitudes have a higher rate of vitamin D deficiency than Caucasians have.<sup>119,123,124</sup> However, Caucasians have about two times higher rates of multiple sclerosis than African Americans have.<sup>119</sup> (At the same time, the course of disease is more aggressive among African Americans.)<sup>125</sup> Therefore, the involvement of additional mechanisms, rather than only vitamin D synthesis, has been proposed.<sup>119,120</sup> Other mediators than vitamin D that are induced by UV radiation may be more important for UV-mediated immunomodulation and may be involved in the prevention and progression of immunopathological diseases (psoriasis, multiple sclerosis and asthma), non-immunopathological diseases (cancer) and during infection.<sup>119,126,127</sup> It is clear that exposure to UV radiation is an important environmental interference with immune functions<sup>126,127</sup> which may play important roles in prevention, initiation or progression of several diseases.

### Beneficial Roles of UVA-Induced Nitric Oxide (NO<sup>•</sup>) on Human Health

A few years ago it was demonstrated that nitric oxide (NO<sup>•</sup>), a gaseous free radical, is non-enzymatically induced in skin by UVA.<sup>128–130</sup> However, UVA-induced NO<sup>•</sup> and its influence on human physiology and pathophysiology are not so well studied as the influence of NO<sup>•</sup> produced enzymatically by NO synthases.<sup>131</sup> NO<sup>•</sup> is able to diffuse rapidly across cell membranes, and, depending on the conditions, is able to diffuse more than several hundred microns. The biological half-life of NO<sup>•</sup> is in the range from 1 ms to 2 sec, depending on superoxide (O<sub>2</sub><sup>•-</sup>), antioxidants

and oxygen concentrations.<sup>2</sup> The biological effects of NO<sup>•</sup> are mediated through the reaction of NO<sup>•</sup> with a number of targets, such as haem groups, cysteine residues and iron and zinc clusters. This wide range of targets for NO<sup>•</sup> helps to explain the multiple roles it plays, including vasodilatation, immune defense, neurotransmission, regulation of cell death (apoptosis) and cell motility. Due to the importance of NO<sup>•</sup>, abnormal regulation of the concentration of UV-induced NO<sup>•</sup> may affect a number of important biological processes.

The rapid release of NO<sup>•</sup> following UVA exposure suggests the existence of latent stores. It is well known that part of the endogenously produced NO<sup>•</sup> is converted into nitrite (NO<sub>2</sub><sup>-</sup>), nitrate or nitrosothiols. Earlier it was thought that these compounds are inert end products of endogenous NO<sup>•</sup> metabolism. In 2003 Rodriguez et al.<sup>132</sup> demonstrated that in rat vascular tissue NO<sub>2</sub><sup>-</sup> and nitrosothiols, but not nitrate, are converted back to NO<sup>•</sup> under UVA exposure: NO<sub>2</sub><sup>-</sup> + hν → NO<sup>•</sup> + O<sup>-</sup>.

The action spectra for NO<sup>•</sup> release from nitrite and from nitrosothiols have a peak at around 335 nm and lie in the range from 310 to 400 nm.<sup>132</sup> Human skin and dermal vasculature contains high quantities of NO<sub>2</sub><sup>-</sup> (8.4 μM) and nitrosothiols (2.9 μM), which can be recycled by environmental stimuli, such as UVA radiation, to form NO<sup>•</sup>.<sup>128–130,133</sup> The skin of a human weighs approximately 4 kg and can be considered the largest human storage organ for NO derivatives such as nitrite and nitrosothiols.<sup>133</sup> Thus, they represent an important alternative non-enzymatic physiological source of biologically active NO<sup>•</sup>. Healthy human skin contains 25-fold higher concentrations of NO<sub>2</sub><sup>-</sup> than plasma of healthy volunteers.<sup>130</sup> It has been demonstrated in human keratinocytes *in vitro* and in healthy volunteers that UVA exposure induces NO<sup>•</sup> in concentrations comparable to, or even higher than, those produced enzymatically by NO synthases.<sup>129</sup>

**Protective effects of UV-induced NO<sup>•</sup>.** Low concentrations of NO<sup>•</sup> protect cultured keratinocytes and skin from oxidative stress and UVA-induced apoptosis.<sup>130,131,134</sup> The mechanism and the required concentrations for this protective action in skin are still unknown. Induction of Bcl-2 expression and inhibition of caspase activation have been suggested in some studies,<sup>130</sup> but this fails to explain the rapid timescale of the response. It is possible that UVA-induced NO<sup>•</sup> may protect skin against solar radiation induced damages within 20–30 min, depending on UVA dose. Two independent studies have demonstrated that UVA exposure of human skin specimens leads to non-enzymatic NO<sup>•</sup> formation which reaches a maximum after 20 min (320–400 nm, 40 J/cm<sup>2</sup>) or after 30 min (350–400 nm, 30 J/cm<sup>2</sup>).<sup>128,133</sup>

In 2009 Oplander et al. demonstrated that irradiation of healthy individuals with biologically relevant doses of UVA lead to a sustained reduction in blood pressure.<sup>129</sup> In 2010 it was proposed that many of the beneficial effects of sunlight related to cardiovascular health may be mediated by mechanisms that are independent of vitamin D and exposure to UV alone, but through UVA-induced NO<sup>•</sup> and nitrite.<sup>135</sup> NO<sub>2</sub><sup>-</sup>, for a long time considered biologically inert at low concentrations, is now known, not only to dilate blood vessels in its own right, but also to protect organs against ischemia/reperfusion damage.<sup>136</sup> Hemoglobin, myoglobin, xanthine oxidoreductase, cytochrome P-450, and

mitochondrial enzymes can all generate NO<sup>•</sup> from NO<sub>2</sub><sup>-</sup> under hypoxic conditions.<sup>135,137</sup> In adults, skin and blood are of comparable weight and volume. The total amount of NO<sub>2</sub><sup>-</sup> in the epidermis is around 135 μM, while the total amount of NO<sub>2</sub><sup>-</sup> in blood rarely exceeds 13–15 μM.<sup>133,135</sup> Thus, mobilization of only a fraction of the relatively large epidermal pool of NO<sub>2</sub><sup>-</sup> by sunlight is likely to be sufficient to increase plasma NO<sub>2</sub><sup>-</sup> concentrations transiently. Thus, Feelisch et al. suggested that NO<sub>2</sub><sup>-</sup> can be delivered to the systemic circulation and exert coronary vasodilator and cardioprotective as well as antihypertensive effects.<sup>135</sup> NO-containing gas is effective in tissue disinfection and regulating inflammatory processes associated with acute and chronic wounds.<sup>138–140</sup> It has been proposed that UVA-induced NO<sup>•</sup> may also have antimicrobial effects, be involved in cutaneous wound healing as well as have antitumor activity.<sup>130,141</sup>

UVA-exposure of human skin releases NO<sup>•</sup> into the circulation. In the bloodstream, NO<sup>•</sup> can reach the nervous system.<sup>129</sup> In this way, UVA can influence transmission of nerve signals indirectly.<sup>38</sup>

However, NO<sup>•</sup> can represent, not only beneficial effects, but also toxicity, and, due to this, it is known as a Janus molecule.<sup>130</sup> Many of the local and systemic UV-induced responses, including erythema and edema formation, inflammation, premature aging and immune suppression, can be influenced by UVA-produced NO<sup>•</sup>. Its role in the induction and in the progression of skin cancer remains uncertain. The direct toxicity of NO<sup>•</sup> is modest, but is greatly enhanced by reactions with superoxide (O<sub>2</sub><sup>-</sup>) to form the powerful oxidant peroxynitrite (ONOO<sup>-</sup>), which can promote oxidative damage to blood vessels and skin. Under normal conditions O<sub>2</sub><sup>-</sup> is rapidly removed by superoxide dismutases (SOD). NO<sup>•</sup> is quickly removed by its rapid diffusion through tissues into red blood cells where it is converted to nitrate and nitrite by a reaction with oxyhemoglobin. This limits the biological half-life of NO<sup>•</sup> *in vivo* to less than a second.

## Conclusions

UV radiation may affect many processes in the human body independent of vitamin D production. However, it is very difficult or even impossible, to understand which of the processes are mediated by UV alone and which via vitamin D. Even in situations where it has been doubtlessly assumed that only UV radiation is responsible for the effect (i.e., skin tanning and photoprotection), vitamin D may play an important role.<sup>142–144</sup> More studies similar to those of Becklund et al.<sup>120</sup> must be performed with the laboratory animals and all precautions must be taken to distinguish the influence of vitamin D and UV radiation in the development and progression of different disorders. Another approach might be to identify the responses that are due to vitamin D, and those independent of vitamin D, would be to study the effects of UV radiation in laboratory animals which are unable to make calcitriol or which have a mutated vitamin D receptor (VDR).

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