REVIEW

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The ultraviolet influence upon soft eye tissues

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Abstract

The climate changes, which occurred during the last decades, put all living species in front of new challenges. Human biology is no exception to it, all tissues have to face new effects, with unpredictable consequences. Many cancers, mainly affecting the skin, but also many of the eye various structures diseases, have ultraviolet radiation as recognized causative agent. The aim of our work is to highlight the changes that can occur after exposure to ultraviolet radiations of soft tissues, including eye structures, by reviewing data from the scientific literature regarding the matter. Responsible for severe diseases, including cancer, ultraviolet negative effects on various soft tissues can be limited by better comprehension. Their knowledge can contribute to improving public health, by finding new preventive methods, which might represent the foundation of effective public health programs.

Keywords: ultraviolet radiation, soft tissues, eye.

Introduction

Ultraviolet (UV) radiation is part of the electromagnetic spectrum emitted by the sun. UV spectrum is located between the X-ray and visible area, including electromagnetic radiation with wavelengths in the range 100–400 nm. This spectrum is subdivided in three groups: UV-A, containing wavelength 400–320 nm, UV-B with wavelength between 320–280 nm, and UV-C with wavelength ranging between 280–100 nm. Whereas UV-C rays (wavelengths of 100–280 nm) are absorbed by the atmospheric ozone, most radiation in the UV-A range and about 10% of the UV-B rays reach the Earth's surface. The destruction of the ozone layer in the upper atmosphere has led to an increase in UV radiation reaching the Earth's surface [1–4]. Exposure to solar radiation in the UV-B range can cause a wide range of negative consequences on living tissues of various species, such as sublethal effects on amphibians eggs and tadpoles, including reduced growth rates [5, 6], increased occurrence of developmental mortalities [7], decreased locomotor performance [8] and altered behaviors [9, 10]. Exposure to UV-B radiation also synergistically enhances the negative effects of other stressors [11–16]. Sensitivity to UV-B radiation varies between species [14] and between populations, with populations at higher elevations considered to be at greater risk of UV-B associated damage than populations at lower elevations, because they receive higher levels of solar UV-B radiation [17].

The effects of UV radiation on human and animal body

Both UV-A and UV-B are of major importance to human health. Sunlight exposure presents some particulars depending on altitude, particulars which become more effective especially in aeronautical activities. The sun generates a multivalent radiation, which is transformed while crossing the atmosphere. The existence of the ozone, water steam and carbonic gas layers determines the different absorption of rays, depending upon the wavelength [18, 19].

Beside natural UV, humans are exposed to some artificial sources produced by fluorescent lamps in the voltaic arc welders, incandescent mercury vapor, UV lamps used for sterilization in surgery rooms or areas for small children and infants.

Small amounts of UV are essential for the production of vitamin D in people, yet overexposure may result in acute and chronic health effects on the skin, eye and immune system becoming responsible for diseases like erythema, immunodeficiency and skin aging.

Human exposure to solar UV radiation has important public health implications. Evidence of harm associated with overexposure to UV has been demonstrated in many studies. Skin cancer and malignant melanoma are among the most severe health effects, but a series of other health effects have been identified. The *World Health Organization* (WHO) reports provide a quantification of the global disease burden associated with UV. The information presented forms a knowledge base for the prevention of adverse effects of UV exposure that is achievable with known and accessible interventions. UV prevention focuses on protecting the skin and other organs from UV radiation.

Under such circumstances, pointing out on the most recent and most important knowledge regarding the UV effects on soft tissues remains an interest topic.

The acute effects of UV-A and UV-B exposure are both short-lived and reversible. These effects include mainly sunburn (or erythema) and tanning (or pigment darkening). The chronic effects of UV exposure can be much more serious, even life threatening, and include premature aging of the skin, suppression of the immune system, damage to the eyes, and skin cancer.

Sunburn (or erythema) is redness of the skin, which is due to increased blood flow in the skin caused by dilatation of the superficial blood vessels in the dermis

because of exposure to UV radiation. High UV doses may also results in edema, pain, blistering, and peeling of the skin a few days following exposure. UV-B radiation is believed to be mainly responsible for sunburn as it is more erythmogenic by a factor of 1000, however since there is more UV-A radiation reaching the Earth's surface, UV-A contributes 15–20% to the sunburn reaction in the summer months. Tanning results from an increase in the number of functions melanocytes (pigment cells) resulting in increased activity of the tyrosinase enzyme. Premature aging of the skin encompasses a number of clinical signs that reflect structural changes in the dermis, including dryness, wrinkles, accentuated skin furrows, sagging, loss of elasticity, and mottled pigmentation, and is the result of degenerative changes in elastin and collagen [20, 21]. The degenerative changes accumulate over time and are largely irreversible [21]. It is believed that as much as 80% of premature aging of the skin may occur within the first 20 years of life. UV-A radiation has been found to be an important contributor to premature aging of the skin. Whereas UV-B is 1000 to 10 000 times more efficient than UV-A in terms of induction of sunburn and non-melanoma skin cancer, respectively, with premature aging of the skin, UV-B radiation is only 20–50 times more efficient than UV-A [20].

UV-B exposure suppresses immune function in many vertebrate species, including fishes [22], mice [23], rats [24] and humans [25]. The mechanisms for this immunosuppressive effect vary from local damage or killing of important antigen-presenting cells in the skin [26] to stimulation of keratinocytes to release cytokines that induce systemic immune suppression [27] or, indirectly, through an increase in concentrations of corticosteroids (cortisol or corticosterone), important stress hormones that also have an immunosuppressive function [28].

Cellular and molecular changes induced by UV radiation

Early exposure to UV-B radiation decreases immune function later in life [29]. UV radiation induces a state of relative immunosuppression that prevents tumor rejection. This is mainly accomplished by interfering with the normal surveillance function of antigen-presenting Langerhans cells in the epidermis, which are responsible for T-lymphocyte activation in response to foreign antigens [21]. The number of Langerhans cells and their characteristics are altered from exposure to UV radiation while similar cells that are responsible for the selective induction of suppressor lymphocyte pathways are resistant to UV damage. This creates an imbalance in the local T-cell function and a shift from helper to suppressor pathways, which ultimately favors tumorigenesis and progression. Skin cancers are the most commonly occurring cancers in terms of incidence in the world. There are different types of skin cancer including the non-melanoma skin cancers, basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), and melanoma. Exposure to UV radiation is thought to be an important factor in each of these cancers as it induces DNA damage, however the types of exposure necessary to cause the different types of skin cancer may vary. Solar UV-B is carcinogenic. Nucleotide excision repair (NER) counteracts the carcinogenicity of UV-B by excising potentially mutagenic UV-B-induced DNA lesions. UV can induce DNA damage through direct as well as mediated mechanisms. Mutagenic cyclobutane pyrimidine dimers (CPDs), 6–4 photoproducts, DNA strand breaks, and DNA cross-links are the direct consequences of UV-B action. If not repaired properly, this DNA damage can result in mutations in the genome, ultimately contributing to skin carcinogenesis [30]. On the contrary, UV-A rays are mostly responsible for DNA damage mediated by oxidative stress. However, both UV-A and UV-B have been shown to be responsible for photocarcinogenesis and photoimmunosuppression [31].

UV radiation induces less DNA damage and higher rate of apoptosis of damaged cells in darker skin than in lighter skin, a combination that results in a greatly reduced risk of carcinogenesis [32].

Another key mechanism, through which UV induce melanomagenesis, is the production of reactive oxygen species (ROS). UV induce a dose-dependent response by human melanocytes leading to production of H_2O_2 [33, 34] decrease in catalase activity, and reduced heme oxygenase-1 (HO-1) expression [35–40]. Similarly, it has been established that there is a role of ROS in the cell damage caused by UV radiation [41, 42]. The vulnerability of melanocytes to oxidative stress can be explained by their greater ability to produce ROS compared with keratinocytes and fibroblasts due to melanin production [43]. In fact, the melanosome is thought to be the main source of the high levels of ROS observed either in melanocytes or in melanoma cells [44–49]. However, there are conflicting data in the literature on the pro-oxidant and antioxidant effects exerted by melanin. Some studies showed that the levels of H_2O_2 after exposure to UV are inversely related to the amount of melanin, which would thus possess an antioxidant effect [38].

Despite this capacity for DNA repair, non-melanoma skin cancers and apparently normal sun-exposed skin contain huge numbers of mutations that are mostly attributable to unrepaired UV-B-induced DNA lesions. UV-A is about 20-times more abundant than UV-B in incident sunlight. It does cause some DNA damage but this does not fully account for its biological impact. The effects of solar UV-A are mediated by its interactions with cellular photosensitizers that generate ROS and induce oxidative stress. The proteome is a significant target for damage by UV-A-induced ROS. In cultured human cells, UV-A-induced oxidation of DNA repair proteins inhibits DNA repair [38]. For the non-melanoma skin cancers, cumulative sun exposure is believed to be important, whereas for melanoma the intermittent exposure hypothesis has been postulated. This hypothesis proposes that infrequent intense exposure of unacclimatized skin to sunlight is related to the increasing incidence of melanoma and is more important than chronic sun exposure [50]. The incidence of all types of skin cancer is increasing. The risks of skin carcinogenesis and melanomagenesis may be lowered through the modulation of UV-activated cell signaling pathways and/or generation of oxidative stress [51, 52].

The effects of UV radiation on the eye

UV rays can also damage the eyes as more than 99% of UV radiation is absorbed by the front of the eyes,

causing to the anterior pole of the eye damages ranging from minor (pterygium) to serious photokeratitis.

Corneal damage, cataracts, and macular degeneration are all possible chronic effects from UV exposure and can ultimately lead to blindness.

Melanoma, a type of skin cancer, can also develop within the eye. Intraocular melanomas are the most common ocular malignancy in whites. These melanomas originate in the uveal melanocytes, which are found the iris, ciliary body, and choroids of the eye. Uveal melanoma is the most common primary tumor of the eye with an annual incidence of approximately two cases per million in southern European countries to eight cases in northern European countries [53].

Incidence increases with latitude in a highly significant manner [53]. Whether this association can be attributed to the exposure to sunlight of variable intensity or not, remains a matter of discussion [54–57].

Uveal melanoma shows a mutation pattern that is clearly distinct from cutaneous [58–62], mucosal [63] and conjunctival melanomas [64].

The mutations typically encountered in cutaneous and conjunctival melanomas, BRAF and NRAS, are rare in uveal melanomas that are characterized by mutations of the G-proteins GNAQ and GNA11 occurring in mutual exclusive manner in 85% of the cases [65, 66]. The mutation pattern observed by exome sequencing in cutaneous melanoma is clearly consistent with an etiological role of sunlight exposure [67].

The cornea is the transparent and avascular structure, which allows the transmission of incident light to posterior ocular structures. It is a structure constantly exposed to a wide spectrum of radiation including UV light [68]. According to some studies, the adverse effects of UV radiation include corneal stromal thinning, keratoconus, corneal vascularization, fibrosis and keratosis [69, 70].

The best-known effect of acute exposure to UV radiation is photokeratitis, characterized by enhanced apoptosis and exfoliation of the corneal epithelium, the appearance of ulceration, inflammation and edema of the corneal stromal structure, giving a sensation of ocular discomfort. The irradiation of the anterior pole of the eye with UV caused significantly microscopic changes in all histological structures of the eye [71].

The first aspect observed by authors of the study was the irregular thickening and the distortion of irradiated corneas, mainly in center, where the spotlight was higher. Growth in the cornea thickness was determined mainly by the fluid swelling in stroma, which led further to fibrillar collagen disorganization at this level. Thus, collagen fibers appeared disrupted, occasionally broken and weakly stained. An accumulation of inflammatory cells and angiogenesis blood vessels at the stroma level also contributed to the thickness of the cornea. In some places, the anterior epithelium of the cornea appeared detached by Bowman membrane, due to edema liquid storage between epithelium and its basement membrane. Superficial cells of the epithelium exhibited pseudo-keratinization, while intermediate cells appeared polyhedral, with enlargement of intercellular spaces and desmosomes exhibition, extensive and deep necrotic areas, with lymphatic cells infiltration and overall denudation of Bowman membrane. In the same study, corneal stroma appeared strongly infiltrated with lymphatic and macrophages mononuclear cells, associated with a number of angiogenic vessels with a structured wall of CD34-positive cells placed on a basal membrane made of collagen IV. The authors also noted a close relationship between the intensity of inflammatory angiogenesis and vessel density [71].

Another study demonstrated that UV-C irradiation-induced decreases in cell volume lead to Src/FAK (focal adhesion kinase) activation due to a rapid loss of K^+ ions through membrane Kv channels. UV-C irradiation induced both size and volume shifts in human and rabbit corneal epithelial cells. UV-C irradiation-induced decrease of cell volume elicited activation of Src and FAK, characterized by increased phosphorylations of SrcY416, FAKY397, and FAKY925 [72–74].

The effects of UV corneal irradiation on the cornea also provided the start point for a therapy procedure: corneal cross-linking. Corneal cross-linking (CXL) with UV-A irradiation and riboflavin, introduced by Wollensak *et al.* (2003) has become an established treatment for arresting keratoconus progression. UV-A irradiation activates riboflavin, a photosensitizer, leading to an increase in the linkage between corneal collagen fibrils, resulting in significantly increased stiffness of the treated cornea [75].

Recently, it was speculated that CXL reduces the conductance and increases average tortuosity, which might result in decreased corneal permeability. Stewart *et al.* (2009) simulated physiological corneal ageing in a porcine eye model using methylglyoxal to induce non-enzymatic cross-linking. The authors found a significant reduction in the corneal permeability after non-enzymatic CXL [76, 77].

The effect of CXL on corneal permeability when using riboflavin and UV-A is still under debate. Two previous studies, one from Stewart *et al.* [76] and one from our group [77], demonstrated significant decreases in corneal permeability in different animal models, *ex vivo* and *in vivo*. Until now, no human data about the impact of CXL on corneal permeability have been available. However, our present *in vivo* data in human subjects, together with the findings reported by Litvin *et al.* for living rabbits, do not support any clinically relevant negative effect of CXL on corneal permeability [78].

Sunlight exposure and UV-B exposure have been found to be associated with cortical cataract [79–81].

Regarding the UV radiation on the crystallin lens, UV light is believed to exert an impact on proteins and to induce damage on cells [82, 83]. Moreover, UV light exposure is considered to be one of the environmental factors involved in lens cataractogenesis during aging [84]. UV-C is a shortwave UV irradiation (λ_{max} 254 nm) and belongs to the major wavelengths in the UV spectrum. UV-C irradiation is the most biologically damaging range of solar radiation [85]. Several researchers have reported that UV irradiation has an adverse impact on proteins, and several hypotheses accounting for the interaction(s) have put forth: involvement in the generation of free radicals or ROS, or modification of protein structures [86–88]. Certain studies undoubtedly highlighted the close association among disulfide bond cleavage/formation, intermolecular interactions, and the resultant formation

of aggregates of human γD-crystallin (HGDC) induced by UV-C irradiation [89].

The detailed interacting mechanisms, however, remain largely unknown. The conformational and functional consequences of UV-C irradiation have already been demonstrated for a variety of proteins, but not for HGDC [90, 91]. Human γD-crystallin is a principal protein component of the human eye lens and associated with the development of juvenile and mature-onset cataracts. Exposure to UV light is thought to perturb protein structure and eventually lead to aggregation.

Several previous studies have provided evidence that the structural and biochemical features of proteins can be affected by UV light. Exposure to UV irradiation could be correlated with the structural perturbation of proteins which might eventually lead to protein aggregation [92–94]. Moreover, the photo-oxidation of proteins induced by light exposure can result in various kinds of modifications, such as cross-linkages [32], fragmentation of covalent bonds, and changes in different amino acids [95, 96].

The eye is a highly metabolically active structure, continually bathed in light. Thus, oxidative and particularly photo-oxidative processes are critical factors in ocular pathological conditions, especially those associated with aging [97, 98].

In the eye, the vitreous gel is a compact, homogeneous, and clear body at birth. With aging, the vitreous gel can undergo progressive degeneration characterized by vitreous liquefaction and weakening of the vitreoretinal adhesion between the posterior vitreous hyaloid and the inner limiting membrane (ILM). In about 25–30% of the population, this degeneration may result in posterior vitreous detachment (PVD) [99, 100], increasing the risks of major diseases such as macular holes, epimacular membranes, vitreoretinal traction syndrome, and retinal detachment [101]. Since they may be sight-threatening conditions, there is growing interest in unveiling their pathogenic mechanisms [102]. In the literature, these processes have been speculated to be promoted by the same molecular mechanisms [103–105], but their underlying pathogenesis is still poorly understood: different factors are presumed to play a role and, among them, an increase in the production of free radicals [106, 107]. An imbalance between free radicals production and antioxidant defenses may produce oxidative stress. Since the eye is continuously exposed to light, incident light may be a major factor that promotes the production of free radicals [108].

In addition to the photoprotection offered by some oxidative scavenger molecules of the eye, in physiologic conditions, ocular tissues such as the cornea and the lens filter harmful radiations of the visible spectrum, ensuring additional protection for the retina [109]. However, in pathological conditions where an aged lens is replaced with an implant, one of the main photoprotective tissues of the eye is lost. For this reason, intraocular lenses (IOLs) with transmittance properties similar to the human lens have been developed. Today, two main types of IOLs, differing in terms of light transmittance, are available: colorless UV-blocking IOLs and yellow-tinted IOLs. The first type effectively blocks UV light, but the transmission properties differ from those of the aged lens, which is more comparable to tinted lenses that block blue light [110, 111]. Surprisingly, little is known about the influence these different types of lenses may have on the oxidative status of the vitreous. Current IOLs, even with UV absorber, do not ensure the same photoprotection offered by natural lenses affected by corticonuclear cataracts. Furthermore, a relevant correlation between the increased presence of peroxidation products in the vitreous and an evident PVD has been observed, but the nature of this relationship requires further study [112].

Since we found lipid peroxidation was higher in the vitreous of patients with lens implants, proving whether adequate photoprotection could effectively reduce the peroxidation products in the vitreous and the retina, thus avoiding sight-threatening complications, is an important question to be addressed in future studies. These will allow us to understand whether improving light filtering could be a possible method for effectively reducing oxidative stress in the eye.

The severity of the damage depends upon the radiation intensity, duration of exposure, pigmentation degree of the retina. It also depends, upon the refraction state of the exposure eye-emmetropia or uncorrected ametropia; and upon the crystallin lens state. This kind of injury occurs seldom, after prolonged sunlight exposure, but more frequently after having watched a sun eclipse without adequate protection. Radiation burns most frequently are caused by UV rays exposure, in case of extended sunlight exposure. This radiation is almost entirely absorbed by the cornea, but a small amount is absorbed by the crystallin lens and some of it may also cross it, toward the retina.

Same as the majority of the retina, the macular cells are particularly exposed to the release of "free radicals", due to exposure to light and to the abundant presence of oxygen [113–116]. The latter are eliminated under normal circumstances but their accumulation may lead to toxic reactions [117, 118].

The lipid membranes of visual cells (cones and rods) are the main target of the newly created free radicals [119–123]. However, numerous defense mechanisms exist normally in the retina [124]. Firstly, there is extremely rapid renewal of photoreceptive visual cells, particularly of their external segment and of the molecules of the discs of which they are comprised [125]. Combined with this is enzymatic restoration of the injured molecules [126]. Finally, the retina has its own defense mechanisms, based on the presence of the melanin. Melanin is a photon trap, capable of eliminating free radicals.

However, it is gradually reduced with age, by 50% between the ages of 24 and 72 years [127]. The damage of macular cells leads to age-related maculopathy, also known as age-related macular degeneration (AMD), and other macular diseases [128, 129]. AMD is the leading cause of irreversible vision loss in people aged 65 and older in the western world. This increasing prevalence worldwide is largely attributable to increasing longevity and lifestyle changes associated with Western society.

Although the pathogenesis of AMD remains poorly understood, there is now generally agreed that oxidative stress and cumulative blue light damage are of major importance in AMD development [117, 130].

The macular cells, as an important provider of vision,

are widely exposed to non-ionizing radiation generated by the sun, as a major factor in our environment. The specific sensitivity of the eye explains the fragility of the ocular tissue with regard to the thermo-luminous aggression that is responsible for the occurrence of various ophthalmologic injuries, specifically chorioretinal, and macular area is the most sensitive to photonic aggression. Amongst these pathologies, AMD is first and foremost and it is currently considered that this process can be accelerated or aggravated by prolonged exposure of the eye to the sun's UV rays.

Under the circumstances of a sunny environment, rich in UV radiation, correlated with the ozone layer destruction, the research regarding UV effects on living tissues becomes a necessity of public health. Understanding the deep mechanisms of negative effects generated by UV radiation on soft tissues in general, including eye tissues effects, may provide the key for prevention and for a better maintenance of a good, lifetime, ocular state of health.

Conclusions

The exposure of various soft tissues to UV radiations generates many changes, mostly with damaging results. The eye structures are no exception to this phenomenon. Wide researches in the entire scientific world revealed the negative effects of UV exposure. Reviewing such knowledge is an opportunity to highlight the importance of UV radiations as causative agents in many cancers, most often affecting the skin but also the eye, and their contribution to various ocular diseases, which may involve all the components of the visual organ. Considering all data on the matter might lead in the future to public health prevention programs, effective enough to help living species face the new challenge of changing climate radiations.

Conflict of interests

The authors declare that they have no conflict of interests.

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