REVIEW ARTICLE

Annals of Agricultural and Environmental Medicine 2012, Vol 19, No 4, 805-809
www.aaem.pl

The sun – our friend or foe?

Agnieszka Osmola-Mańkowska[1], Wojciech Silny[1], Aleksandra Dańczak-Pazdrowska[1], Karolina Olek-Hrab[1], Bartosz Mańkowski[2], Krzysztof Osmola[2], Dorota Hojan-Jezierska[3], Leszek Kubisz[3]

[1] *Department of Dermatology, University of Medical Sciences, Poznan, Poland*
[2] *Department of Maxillofacial Surgery, University of Medical Sciences, Poznan, Poland*
[3] *Department of Biophysics, University of Medical Sciences, Poznan, Poland*

Osmola-Mańkowska A, Silny W, Dańczak-Pazdrowska A, Olek-Hrab K, Mańkowski B, Osmola K, Hojan-Jezierska D, Kubisz L. The sun – our friend or foe? Ann Agric Environ Med. 2012; 19(4): 805-809.

Abstract

Introduction and objective: Sunlight is the major source of the energy on Earth. Visible light, ultraviolet and infrared radiation are necessary to sustain life on our planet. However, besides the range of positive effects, such as photosynthesis in plants, warmth, vision, and synthesis of vitamin D, sunlight may also be responsible for negative biologic effects – sunburn, induction of photodermatoses or carcinogenesis. Ultraviolet is regarded as the major environmental, physical hazard to the human skin.

Abbreviated description of the state of knowledge: The acute clinical effect of ultraviolet involves melanogenesis, i.e. tanning, which protects from sunburn if exposure is overdosed. A single exposure, as well as acute suberythemal irradiation, suppresses sensitization of the contact hypersensitivity. The chronic biological effects are photoageing and skin cancer, especially squamous cell carcinoma (SCC). Vitamin D synthesis is regarded as a benefit of natural acute and chronic exposure to ultraviolet. Ultraviolet also plays an important role in aetiology of the group of disorders characterized by photosensitivity. On the other hand ultraviolet is a known inducer of immunosuppression in the skin; therefore, phototherapy is a therapeutic option for patients with activation of dermal immunity.

Summary: Without sunlight, the existence of life on Earth is not possible. On the other hand, UVR radiation is regarded as representing one of the most important environmental hazards for human skin. For a better understanding of the mechanisms related to the influence of UVR on human skin, and the most dangerous chronic effects of carcinogenesis, it is necessary to undertake some protective activities. Moreover, UVR may become our ally in the treatment of selected skin disorders.

Key words

ultraviolet radiation, photodermatoses, skin cancer, photoaging, phototherapy, photoprotection

INTRODUCTION

Sunlight is the major source of the energy on the Earth. Visible light, ultraviolet and infrared radiation are necessary to sustain life on our planet. However, besides the range of positive effects, such as photosynthesis in plants, warmth, vision, and synthesis of vitamin D, sunlight may also be responsible for negative biologic effects – sunburn, induction of photodermatoses or carcinogenesis. Ultraviolet is the major environmental, physical hazard to human skin. There are many variables, including geographical region – latitude, altitude, year season, time of day, pollutions, cloud cover, natural reflectants, such as snow, water and sand, which influence the intensity of UVR at ground level. Personal exposure to UVR is modified by behaviour, clothes, time spent outdoors, and profession. Approximately 60% of UVR exposure at our latitude is acquired during 4 hours around midday on summer days, while up to 30% of the annual dose of UVR is experienced during a 2-week vacation. According to Canadian studies the largest occupational groups exposed to high amounts of UVR are farmers, construction labourers and landscapers. Individual susceptibility to UVR can be predicted by measuring the Mminimal Erythema D ose (MED), or indirectly, by determination of the skin type according to Fitzpatrick, from I – which never tans, always burns, to VI – concerning people with a darker pigmentation of skin [1, 2, 3, 4, 5, 6].

Ultraviolet radiation (UVR) constitutes only approximately 5% of the whole electromagnetic spectrum emitted by the sun and which reaches the Earth's surface. According to the wavelength and its biological effect, UVR is divided into 3 ranges: UVA (320-400nm), UVB (290-320nm) and UVC (200-290nm). Terrestrial UVR, which reaches our skin, consists mostly of UVA (95%) and only 5% of UVB. UVC is filtered-off normally by the stratospheric ozone layer. However, the observation in the 1980s of ozone layer depletion may indicate that this function of the atmosphere is impaired, which allows the short waves of UVB to reach our skin [5,6]. Initiation of the Montreal Protocol implementation and elimination of the production of chlorofluorocarbons (CFCs) and other gases responsible for ozone layer depletion, resulted in a 14% decrease in worldwide skin cancer risk estimated for the year of 2030 [7, 8].

Biological effect of UVR on human skin. The depth of penetration of the UVR into the human skin depends on its wavelength: the longer the wave, the deeper its penetration. UVC of the shortest wavelength, but the highest energy, irritates the skin and cornea and has a very strong mutagenic

Address for correspondence: Agnieszka Osmola-Mańkowska, Department of Dermatology, University of Medical Sciences, 49 Przybyszewskiego, 60-355 Poznan, Poland.
E-mail: agnieszka.osmola@wp.pl

Received: 12 September 2012; accepted: 15 November 2012

potential. The UVB band, which is responsible for tanning and sunburn reaction, reaches only the epidermis, being absorbed mainly by the horny layer, and affects keratinocytes, Langerhans cells and melanocytes. Long-wave but low energy UVA with a range of 320-400nm is less erythemogenic. UVA is not filtered-off by window glass, it penetrates deeper, and in approximately 50% reaches the papillary dermis. It is therefore able to affect different targets, such as dendritic cells, fibroblasts, matrix metalloproteinases, T-lymphocytes, mast cells, and endothelial cells. In this way, UVA is regarded as being responsible for the photoaging of the skin and induction of phototoxic and photoallegic reactions [1, 2, 3].

According to the duality of the nature of light, a particle of light energy – the photon – is absorbed by different molecules of human skin, called chromophores – endogenous (DNA, urocanic acid, porphyrins) or exogenous – such as psoralens. Absorption of UVB by DNA results in the formation of the characteristic 'UVB signature' – cyclobutane pirymidine dimers (CPDs). This mutations may initiate cancerogenesis if the natural protecting mechanisms, such as nuclear excision repair (NER), are impared. This defect in repairing enzymes provides the basis for the inherited condition called xeroderma pigmentosum, characterized by early onset of premalignant conditions and skin cancers. Another important mechanism of UVB action is isomerisation of urocaic acid (UCA), which induces the release of immunosupressive cytokines. At the cellular level, it results in the formation of an inflammatory infiltrate, the formation of apoptotic 'sunburn cells' and the modification of antigen presenting cells (APCs).

The key molecule which absorbs UVA is not known. The mechanism of action is thought to be indirect and related to the formation of Reactive Oxygen Species (ROS), such as the 'UVA signature' – 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxo-dG), but recent studies show that UVA may also generate CPDs [9, 10, 11]. Other studies have shown that 85% of CPDs caused by UVA, compared to 40% induced by UVB, are thymidine T-T dimers. This special type of mutation is less mutagenic than thymidine-cytosine T-C or C-T dimmers, but it may play a role in the development of melanoma.

UVA constitutes up to 95% of the terrestrial UVR, penetrates deeper and UVA-induced repair mechanisms are less effective. On the other hand, the cutaneous DNA damage activation spectrum was defined to be in the UVB band, with the peek at 300nm [12]. Moreover, recent studies suggest a protective role of long-wave UVA for the skin immune responses due to induction of haemeoxygenase-1 [13].

The acute clinical effect of UVR involves melanogenesis, i.e. tanning, which protects from sunburn if UVR exposure is overdosed. A single exposure to UVR, as well as acute suberythemal irradiation, suppresses sensitization of the contact hypersensitivity (CHS). The chronic biological effects of UVR are photoageing and skin cancer, especially squamous cell carcinoma (SCC). Vitamin D synthesis is regarded as a benefit of natural acute and chronic exposure to ultraviolet.

Vitamin D synthesis. Vitamin D is known to take part in calcium and phosphates homeostasis, but it may also play a role in other metabolic processes, and is one of the most important regulators of cell life [15]. Multiple studies show that vitamin D deficiency may be related to higher risk of development of cancers in different organs, such as breast, bowel, prostate or leukaemia, especially in countries with less sunlight [16]. Over 90% of the total amount of vitamin D is gained due to UVB-induced cutaneous photosynthesis, while the rest is assimilated from the diet. The UVR is known to be the most important environmental factor in the development of skin cancer [17]. The strict no-sun policy and skin cancer prevention campaigns may lead to sun avoidance behaviour and lead to vitamin D deficiency. However, it is not known how extensive an exposure is necessary for adequate vitamin D levels, without an increased risk of the development of skin cancer. During the summer, it is recommended that exposure to direct sunlight should be avoided between 10:00-16:00: on the other hand, in winter, exposure of the face and hands associated with daily physical activity is sufficient for appropriate vitamin D synthesis. In patients with photodermatoses (e.g. lupus patients), or in case of patients with an intake of photosensitizing drugs who completely avoid the sun, the use of very strict sun protection plus oral supplementation should be advised [18].

Photoaging. UVR is the major factor responsible for the exogenous process of skin aging, which is avoidable. The Clinical pattern of photoaging is characterized by the presence of deep wrinkles, dryness of the skin, atrophy, hyperkeratotic lesions, hyperpigmentations, and decreased skin elasticity. UVB is responsible for hyperkeratotic skin lesions, features of atypia, and impared function of Langerhans cells. UVA acts as a cofactor of this processes and enhances the effect of UVB, but it mainly affects connective tissue. UVA, which penetrates deeper into the dermis, impairs microcirculation, angiogenesis and destroys the fibres of connective tissue, resulting in the accumulation of elastosis. The mechanism of an indirect action of UVA is connected with the formation of Reactive Oxygen Species (ROS), due to the process of oxidation of cell components, such as lipids, proteins and DNA. Studies have revealed that chronic exposure to UVR may also result in mutations of mitochondrial DNA [19]. UVR activates kinases responsible for the expression of nuclear transcription factor AP-1, which leads to stimulation of gene transcription involving the matrix metalloproteinases: MMP1, MMP3 and MMP9. The family of metalloproteinases exhibits proteolytic activity, targeting matrix proteins. MMP1 destroys types I and III collagen fibres. Moreover, UV also affects the synthesis of collagen fibres by decreasing the expression of procollagen I and III [20]. The rapidly proliferating studies regarding the cellular and molecular basis of the process of photoaging, include the search for protective measures, such as sunscreens, and natural anti-oxidants, such as tocopherol, ascorbic acid or retinoids [21].

Induction of photodermatoses. UVR also plays an important role in the aetiology of a group of disorders characterized by photosensitivity. Idiopathic photodermatoses can be immunologically-induced, such as polymorphic light eruption (PLE), chronic actinic dermatitis, actinic prurigo, hydroa vacciniforme or solar urticaria; they can be connected with chemical phototoxicity, exogenous in drug-induced photosensitivity, or endogenous, for example, in porphyria. Finally, they can result from DNA repair disorder, e.g. xeroderma pigmentosum [1, 22]. One of the most common acquired idiopathic photodermatoses is PLE, the mean incidence of which in the European Union is approximately 18%. It is usually precipitated by UVB, UVA, or both bands. The aetiology of PLE remains unclear. Recent

studies suggest T-cell mediated autoimmune reaction against the unidentified photo-induced antigen resulting from a defective UV-induced immunosuppression. Moreover, the incidence of skin cancer in patients with this condition is reduced [23, 24].

An increasing number of drug-induced photosensitivity cases following administration of systemic, as well as topical drugs, usually related to long-wave UVA exposure, is also a very important phenomenon. The majority of these reactions reflect simple phototoxic mechanisms, but others can also include photoallergic reactions. The most common groups of drugs known to be phototoxic are: thiazides, amiodaron, several non-steroidal anti-inflammatory drugs (NSAIDs), e.g. ketoprofen, fluoroquinolones and tetracyclines. Some of them manifest a potential for induction of photosensitivity for a long time after cessation of drug administration, such as amiodaron or thiazides, for even up to 6 months [1, 22]. The classic phototoxic reaction also includes phytophotodermatitis due to the contact of the skin with plant furocoumarins, followed by UVR exposure. Such a reaction might be seen in everybody, but usually appears in workers who have contact with a variety of plants, mostly Compositae spp. or Umbiliferae spp., fruit and vegetables – celery pickers, carrot processors, parsnips, bartenders of outside bars using limes, giant hogweed or cow parsley. The disease in this case is called strimmer's dermatitis [25, 26, 27].

Occupational photodermatoses of farmers are usually induced by sunlight, but might also be promoted by germicidal lamps, while the substances responsible might be of plant origin, other sources could be pesticides, food additives, or veterinary drugs, as in the typical photoallergic reaction described in a farmer following contact with chloropromazine-contaminated pig fodder [28]. Another group constitutes the so-called photoaggravated dermatoses, which can develop in the absence of light, but the course of which is aggravated by UVR. Common UV-aggravated dermatoses are lupus erythematosus, dermatomyositis, actinic lichen planus, herpes simplex infection, rosacea, and seborrhoic dermatitis. Less commonly, UVR may aggravate pemphigus and pemphigoid, acne aestivalis, Darier's disease, erythema multiforme, psoriasis, atopic dermatitis, and pellagra [1, 22].

UV-induced carcinogenesis. Epidemiologic, experimental and clinical studies support the relationship between skin cancer and UVR exposure. UVR is one of the most important carcinogenic factors, beside the smoking. It is responsible for the occurrence of the most common cancer of the skin wordwide, including non-melanoma skin cancers (basal and squamous cell carcinomas), as well as malignant melanoma. An increased incidence of skin cancer may result from ozone layer depletion, as well as from the wide-spread use of tanning beds [29]. Carcinogenesis results from the interplay of genetic and environmental factors. The genetic factors include skin type, capacity of DNA repair and immune status. Apoptosis is the crucial mechanism responsible for suppression of cancer transition and the key molecule is the tumour suppressor protein p53 [30]. The most important function of this molecule is activation of cell cycle arrest at the G1/S phase. This action provides time for the repair of DNA damage. When the amount of DNA mutations is higher than the cell can repair, or they result from higher UVR doses, the p-53 independent apoptosis mechanisms are initiated. Death receptors Fas or TNF-RI are aggregated due to UV-induced membrane alterations or in a ROS-dependent manner [31]. The mechanism of UVR carcinogenic action reflects not only a direct mutagenic effect on DNA, as mentioned earlier, but also from immunosuppression generated by UVR. This was first shown more than 30 years ago in experiments on animal models in which this immunosuppression is mediated, and might be transmitted by regulatory T lymphocytes [32, 33, 34, 35]. This immunosuppression inhibiting reactions to skin-associated antigens probably evolved to protect against autoimmunisation. The cellular decision to induce repair mechanisms or undergo apoptosis is responsible for skin barrier homeostasis. Animal studies strongly support the conclusion concerning which UVR range induces SCC development. SCC probably results from an accumulation of UVR exposure effects, while melanoma and basal cell carcinoma seem to be the consequence of an intermittent high dose exposure, especially during childhood [36].

Sun beds. Since the 1980s, the indoor tanning industry has been one of the most rapidly growing industries. Sunbeds generate both bands of ultraviolet radiation – UVA and UVB. UVB is responsible for sunburn and tanning, but the most potent component of the radiation emitted by indoor tanning beds is UVA, which causes immediate pigmentation. The process of melanogenesis is always preceded by DNA damage. The doses of UVR emitted by tanning beds are higher than those experienced on a sunny day at midday. The World Health Organisation (WHO) considers tanning devices to be carcinogenic. Induction of beta-endorphins as an adverse event is probably responsible for feeling in a good mood and leads to sun-seeking behaviour [37]. Recent cohort studies provide evidence for a dose-dependent relationship between tanning bed use and the risk of skin cancers, especially basal cell carcinoma (BCC), SCC and invasive melanoma, and a stronger association for patients at a younger age to exposure (less than 35-years-old). Current health policy should be directed to restricting indoor tanning in young people, under the age of 18 [38].

Photoprotection. Novel and complex photoprotection includes proper behaviour: avoidance of direct exposure to sunlight for 2 hours before and after midday, and appropriate clothing: wide-brimmed hat, long sleeves, fabrics with ultraviolet protective factor (UPF), and finally, use of high protection sunscreens [1, 2, 39]. Sunscreens were originally invented to protect from sunburn and primarily protected against erythemogenic UVB. Studies supported the potential role of UVA in photoaging and carcinogenesis; this resulted in the development of products protecting against these two bands. Novel topical sunscreens consist of a mixture of chemical absorbers and mineral reflectants. Several studies have shown that the use of sunscreens does prevent the development of premalignant conditions, e.g. actinic keratosis, nor do they decrease the risk of SCC. However, the introduction of sunscreens in adults probably did not interfere with the occurrence of BCC and melanoma. The efficacy of each sunscreen is expressed in so-called Sun Protection Factors (SPF), defined by the energy of UV involving MED of protected skin as related to that involving MED for unprotected skin. The SPF on sunscreen labels is usually higher than that obtained on patients' skin because of inadequate application, usually less than 2mg/cm^2 [40].

Per analogiam to SPF-UVA protection factor is determined by Immediate Pigment Darkening (IPD), or more often by Persistent Pigment Darkening (PPD) of sunscreen protected to unprotected skin. Some systemic substances are also known which exhibit UV-protective properties, such as plant Polypodium leucotomos extracts, or green tea polyphenols [41, 42]. A wide administration of topical sunscreens may result in the induction of contact or allergic contact sensitization, related mainly to chemicals, e.g. benzophenones. Novel forms of photoprotection are topically-administered liposomes containing DNA repairing enzymes, such as T4 endonuclease V. *In vitro* studies have shown that they may protect from UV-induced DNA damage. Clinical studies with T4N5 on patients suffering from xeroderma pigmentosum revealed reduction in the incidence of actinic keratosis and SCC [43, 44].

Dermatological phototherapy. UVR is a known inducer of immunosuppression in the skin; it is therefore used to treat patients with activation of dermal immunity. Clinical observations in some patients with dermatoses, such as psoriasis or vitiligo, may benefit even from natural heliotherapy, leading to the development of artificial sources of UVR. The main, currently used approach to phototherapy employs broad band (BB) UVB, narrow band (NB), UVB 311nm and photochemotherapy (a photosensitizer, psoralen plus UVA (PUVA)). UVB radiation from artificial sources represents, generally, the first line of treatment in patients with vitiligo, psoriasis or atopic dermatitis. Indications for PUVA treatment include the same dermatoses if the UVB is not effective, but also in the early stages of cutaneous lymphoma, mycosis fungoides, pigmentary urticaria, PLE [1, 2, 3, 45, 46]. It is obvious that these methods are not free from acute and chronic hazards, including the most important one: an increased risk of skin cancer. The risk of skin cancer, especially SCC, is lower for UVB than for PUVA. Studies estimating phototherapy-related risk of skin cancer using mathematical models allow the formulation of guidelines to not exceed 300-350 UVB and 150-200 PUVA treatments [47, 48].

The novel form of phototherapy is UVA1. Lamps which emit long-wave UVA-1 radiation of 340-400nm were produced in 1980s, but it was not until after 1992 that Krutmann et al. published very good results in the treatment of atopic dermatitis (AD) using high doses of UVA1 [49, 50]. Since that time, some evidence exists in the literature that also some patients suffering from sclerodermoid graft versus host disease (GvHD), localised scleroderma or mycosis fungoides, may benefit from this form of therapy [51, 52, 53, 54]. The group of sclerotic skin disorders seems to be especially important because in this cases no alternative treatment exists. Advantages of UVA1 phototherapy include the evident avoidance of systemic side-effects typical of psoralens, such as nausea and vomiting, or photokeratitis, as well as lower risk of phototoxic reactions with deeper penetration of radiation. Its disadvantages include high cost of equipment, thus reducing the accessibility of the treatment to specialized centres. The place of phototherapy in the era of biologic drugs is still unaltered and the perspectives are connected with development of new sources or photosensitizers [55].

Without sunlight the existence of life on the Earth is not possible. On the other hand, UVR radiation is regarded to represent one of the most important environmental hazards for human skin. For a better understanding of the mechanisms related to the influence of UVR on human skin, and the most dangerous chronic effect of carcinogenesis, it is necessary to undertake some protective activities. Furthermore, UVR may become our ally in the treatment of selected skin disorders.

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