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Influence of dermal exposure to ultraviolet radiation and coal tar (polycyclic aromatic hydrocarbons) on the skin aging process

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ABSTRACT

Background: Ultraviolet radiation (UVR) and crude coal tar (CCT) containing PAHs can accelerate the skin-aging process (SAP). However, UVR induces the formation of an important protective factor in SAP (vitamin D).
Objective: To determine the relation of SAP to selected risks and benefits of combined dermal exposure to UVR and coal tar (PAHs).
Methods: The study group consisted of patients with chronic stable plaque psoriasis and treated by Goeckerman therapy (GT; daily dermal application of UVR and 5% CCT ointment). The levels of urinary 1-hydroxypyrene (1-OHP), oxidative stress (DNA and RNA damage), genotoxic damage (chromosomal aberration in peripheral lymphocytes; ABC), 25-hydroxy-vitamin D [25(OH)D] and the PASI score were evaluated before and after GT.
Results: Intensive dermal absorption of PAHs was confirmed by increased levels of 1-OHP ($p < 0.01$). After the therapy, we found an increased level of oxidative stress ($p < 0.05$), an increased level of genotoxic damage (ABC; $p < 0.001$), a high efficiency of the treatment ($p < 0.001$) and an elevated production of 25(OH)D ($p < 0.01$). We also found a relationship between the duration of UVR and the genotoxic damage ($p < 0.01$), vitD ($p < 0.05$) and the PASI score ($p < 0.05$). Furthermore, we found a relationship between oxidative stress and 25(OH)D ($p < 0.05$) and between genotoxic damage and the PASI score ($p < 0.05$).
Conclusion: Dermal exposure to UVR and coal tar (PAHs) enhances the level of oxidative stress and genotoxic damage and thus contributes to SAP. However, the exposure is very effective as a treatment and elevates the production of 25(OH)D, the protective factor in SAP. According to our results, UVR is probably a more hazardous factor in SAP.
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1. Introduction

Skin cells are constantly exposed to reactive oxygen species (ROS) from exogenous and endogenous (environmental) sources. ROS induce oxidative stress and contribute to aging [1]. In addition to classical sources of exposure from the environment, some medical therapies may even represent a significant source of adverse health effects including oxidative stress [2].

Psoriasis is a multifactorial relapsing and remitting inflammatory skin disease that affects approximately 2–4% of the population in western countries [3]. The Goeckerman therapy (GT) represents an effective treatment of the plaque form with moderate to severe psoriasis [2,4,5]. GT is based on the daily dermal application of pharmaceutical grade crude coal tar (CCT) ointment with a high portion of polycyclic aromatic hydrocarbons (PAHs) and subsequent whole body exposure to ultraviolet radiation A (UV-A) and ultraviolet radiation B (UV-B). The use of GT has recently decreased for several reasons including suspected mutagenic and carcinogenic effects [6,7].

Ultraviolet radiation (UVR) is one of the most important environmental factors in the skin aging process and the

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development of skin cancer [8]. The primary effects caused by UV are generally direct DNA oxidation or the generation of free radicals, which form and decompose extremely quickly but can produce effects that can last for hours, days, or even years. The UVR induced generation of ROS in the skin leads to the development of oxidative stress (redox-dysregulation) when their formation exceeds the ability of the antioxidant defense [8,9]. The IARC (International Agency for Research on Cancer) classification includes the UV-containing light in group 1 (proven carcinogens for humans) [9].

According to IARC, the PAHs represent ubiquitous mixtures of mutagens/carcinogens (group 1 and group 2A) that are generated from different sources of human activities (industry, traffic, and heating) [10]. The significant mutagenic/carcinogenic hazard of PAHs consists of their metabolic conversion into reactive metabolic intermediates, which are capable of binding to DNA and RNA structures and creating the corresponding adducts with them. The best known carcinogenic benzo[a]pyrene (BaP) is metabolized into a highly reactive benzo[a]pyrene-7,8-diol-9,10-epoxide (BPDE) that is able to create BPDE-DNA adducts [2,11]. An alternative carcinogenic pathway of PAHs includes the induction of oxidative stress caused by redox cycling between PAHs dihydrodiols and PAH-o-chinons with the subsequent formation of various oxidized forms of nucleobases and nucleosides [12,13].

Biological monitoring of the exposure to mixtures of PAHs is complicated due to the large number of substances and their metabolites that are present in biological fluids. Pyrene has been selected as a representative of PAHs due to its sufficient and relatively permanent content in mixtures of PAHs with various origins. The main metabolite of pyrene is considered to be 1-hydroxypyrene (1-OHP), and thus, this metabolite in urine was designed as the biological marker of the exposure to the mixtures of PAHs [14,15].

Although exposure to UV-B (290–320 nm) is primarily responsible for photo-aging and skin cancer, UV-A (320–400 nm) exposure also plays a significant role in a given process [16,17]. An increasing number of studies have demonstrated that UV-A alone, or in combination with other common environmental pollutants, can significantly increase visible photo-damage and the risk of skin cancer [17]. In both the UV-B and the UV-A DNA damage can be enhanced by PAHs pre-exposure, while the effects seen that the UV-A were stronger [18,19].

However, UV-B is essential for vitamin D_3 production [20]. Its precursor (7-dehydrocholesterol) is converted by the action of UV-B into the pre-vitamin D_3, which is isomerized into vitamin D_3 [21]. Vitamin D_2 is derived from a dietary ergocalciferol. Vitamins D_3 and D_2 are subsequently hydroxylated (at position 25) into 25-hydroxy vitamin D [25(OH)D], which is the major circulating metabolite. The 25(OH)D plays a major regulatory role in human biology. It controls bone and calcium homeostasis, regulates cell proliferation and differentiation and modulates the immune system [22]. Thus, perturbations in these areas are linked to a wide range of common diseases including cancer, cardiovascular diseases and metabolic diseases [21,22].

With regard to skin aging, disease, epidemiologic, and laboratory studies suggest that vitamin D (and its metabolites) may have a risk reducing effect [20]. This role of vitamin D is divided into a primary function that prevents oxidative damage to DNA and a secondary function that regulates the growth rate of human cells [23].

UVR has an ambivalent character in the sense that it increases but also reduces the health risks related to oxidative stress. In the present study, the therapeutic combination of pharmaceutical tar (containing PAHs) and UVR was used as an example of exposure, which was able to increase the risks associated with the induction of oxidative stress and simultaneously reduce these risks through increased production of vitamin D.

The main objective of this study included the assessment of the relationship between the degree of oxidative stress, cytogenetic damage and the rate of production of vitamin D during therapy. The secondary objectives were focused on (1) the relationship between the extent of cytogenetic/oxidative damage and the basic characteristics of the therapy (days of GT, total duration of UV exposure and surface of the skin lubricated with tar), (2) relationship between the levels of vitamin D and the basic cited characteristics of the therapy and (3) evaluation of the total effectiveness of the therapy.

2. Material and methods

2.1. Observed group

The cohort created a group of patients with chronic stable plaque psoriasis that were hospitalized at the Clinic of Dermal and Venereal Diseases, University Hospital, Hradec Kralove (Czech Republic) and treated by GT. The data were collected over two years. The group consisted of 13 women and 19 men (14 smokers and 18 nonsmokers, an average age of 57 years, and an age range of 21–75 years). The patients who had significant occupational or non-occupational exposure to PAHs and/or artificial UVR were excluded from the monitored group. The study was approved by the Ethics Committee of the University Hospital in Hradec Kralove, Czech Republic. Informed written consent was obtained from each patient.

2.2. Goeckerman therapy

For this therapy, dermatological ointment containing 5% CCT was administered daily (overnight) on the psoriatic lesions. According to the extent of lesions, 16–58% of the total body surface was covered by CCT ointment. Each morning the residues of the CCT ointment were removed from the body (using an oil bath) and the patients were whole-body irradiated by UVR.

UVR exposure was dosed according to the skin condition and was temporarily suspended in cases of adverse reactions. For this reason, the total duration of GT (in days) may not be equivalent to the frequency of UVR exposure. The irradiation duration was individually adjusted according to the patient's disease status (1–15 min/day). The density of the used UV radiation was 248.55 $\mu W/cm^2$ of UV-B and 130.1 $\mu W/cm^2$ of UV-A (controlled by Sola–Scope 2000 spectrometer; Solatell, UK). The duration of the treatment was modified according to the treatment effectiveness (an average duration of 13 days; an interquartile range of 10–15 days).

2.3. Selected PAHs in CCT

As described previously [2], the pooled sample of CCT (0.1973 g) was sonicated (30 min) with 25 ml of n-hexane and subsequently diluted fifty times. An instrumental analysis of the extract was performed by gas-chromatography-mass detection: GC Agilent HP 6890/MS HP 5975; column HP–5 ms, Agilent, 30 m/0.25 mm/0.25 μm [2].

2.4. The level of urinary 1- OHP (biological monitoring of the exposure to PAHs)

Urine samples were collected immediately after the first and last therapeutic procedure. Quantification of the urinary 1-OHP level was conducted by the gas chromatography/mass spectrometry (GC/MS) method [24]. Because of the reduction of the impact

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