Original Article

Serum Levels of Aryl Hydrocarbon Receptor, Cytochromes P450 1A1 and 1B1 in Patients with Exacerbated Psoriasis Vulgaris

(aryl hydrocarbon receptor / psoriasis / cytochrome P450 / CYP1A1 / CYP1B1 / Goeckerman therapy / crude coal tar)

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Abstract. The aryl hydrocarbon receptor (AhR) is highly expressed in psoriasis skin lesions. The aim of this study was to investigate serum concentrations of AhR, cytochromes P450 (CYP) 1A1 and 1B1 in patients with exacerbated psoriasis vulgaris treated with combined therapy of ultraviolet radiation (UVR) and crude coal tar. The analyses were performed by using enzyme-linked immunosorbent assays. Before the treatment, the patients had significantly higher serum levels of AhR and CYP1A1 than healthy controls. AhR median noticeably decreased after the therapy; nevertheless, it remained significantly higher compared to the controls. CYP1A1 levels measured before and after the therapy did not differ significantly. Serum CYP1A1 positively correlated with AhR values before and after the treatment. The serum values of CYP1B1 were very low and we did not see any differences between the study group and the control group. The study demonstrated that serum levels of AhR and CYP1A1 could indicate their immunopathological and metabolic roles in exacerbated psoriasis.

Introduction

Psoriasis vulgaris is a chronic multifactorial skin disease with worldwide prevalence of 1–3 % (Lebwohl et al., 2014). Its pathogenesis involves enhanced proliferation and shortened maturation of keratinocytes, perivascular infiltration of T cells, dendritic cells, macrophages and neutrophilic granulocytes, and imbalance in apoptotic pathways (Schaerli et al., 2004; Sabat et al., 2007; Avramidis et al., 2010). The aryl hydrocarbon receptor (AhR), highly expressed in skin lesions, controls the inflammatory response and terminal differentiation of keratinocytes and T cells (Kim et al., 2014; Stockinger et al., 2014). The deficiency of this receptor results in excessive reactivity of proinflammatory stimuli and development of exacerbated inflammation (Di Meglio et al., 2014).

AhR is a cytosolic ligand-dependent transcription factor synthesized mainly in the liver, lung, gut and skin (Esser et al., 2013). AhR ligands have a sterically planar structure and a size corresponding to three benzene rings. They involve environmental pollutants (polycyclic aromatic hydrocarbons, PAHs), dietary components (glucosinolates, flavonoids, indocarbinols), indole compounds of microbial origin, and endogenous products of

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Abbreviations: AhR – aryl hydrocarbon receptor, ARNT – AhR nuclear transporter, BPDE – benzo[a]pyrene-7,8-diol-9,10-epoxides, CCT – crude coal tar, CYP1A1 – cytochrome P450 1A1, CYP1B1 – cytochrome P450 1B1, FICZ – 6-formylindolo[3,2-b] carbazole, GT – Goeckerman therapy, PAHs – polycyclic aromatic hydrocarbons, PASI – psoriasis area and severity index score, UVR – ultraviolet radiation.

tryptophan catabolism generated under the exposure to ultraviolet radiation, UVR (Denison and Nagy, 2003). The binding of the ligand promotes AhR activation, heterodimerization with AhR nuclear transporter (ARNT), translocation into the nucleus, and induced transcription of genes possessing conserved AhR response elements. The products of AhR activation facilitate excretion of the ligand through the bile and urine (Colonna, 2014).

The AhR response elements are located in promoters of many genes, including those expressing cytochrome P450 biotransformation enzymes (CYP), specifically *CYP1A1* and *CYP1B1* genes. Increased catalytic activities of CYP found in psoriasis lesions lead to faster metabolism of AhR ligands and attenuation of psoriasiform inflammation (Di Meglio et al., 2014). The level of CYP1A1 in psoriasis lesions and in non-lesional skin was reported to be higher than in healthy individuals both before and after phototherapy (Karadag et al., 2017). In CYP1B1 enzyme, prior studies observed no significant difference between patients and controls (Karadag et al., 2017). However, its activity in skin cells could be induced by UVR and become even more active than CYP1A1 (Katiyar et al., 2000; Baron et al., 2001).

Goeckerman therapy (GT) is used in the treatment of moderate-to-severe forms of psoriasis vulgaris. It consists of crude coal tar (CCT) applied in combination with UVR (Dennis et al., 2013). Hundreds of PAHs predominantly contained in CCT make skin more responsible to UVR, which could contribute to stronger activation of the AhR pathway. PAHs are subsequently metabolized via CYP1A1 and CYP1B1 enzymes to active PAH intermediates, possibly increasing the risk of cutaneous genotoxicity and carcinogenesis (Esser et al., 2013; Siddens et al., 2015). In this study we aimed to investigate the serum concentrations of AhR, CYP1A1 and CYP1B1 in patients with exacerbated psoriasis vulgaris before and after the cycle of GT.

Material and Methods

Subjects

The study group consisted of 22 patients (12 women and 10 men) with exacerbated psoriasis vulgaris with the median age of 52 years, range 19–76 years. Eleven of them were smokers and 11 non-smokers. According to the basic characteristics of the current disease status (erythema, desquamation, and skin infiltration), the activity of the disease was expressed as psoriasis area and severity index score (PASI). Psoriasis with the PASI score < 10 was defined as mild, 10–20 as moderate, and > 20 as severe. The patients were without any treatment for at least two weeks before enrolment. Their exposure history was examined using a questionnaire. The patients who had significant prior exposure to PAHs and/or artificial UVR and patients with acute infections, psoriatic arthritis, or other inflammatory diseases were excluded from the study. The control group consisted of 20 healthy volunteers (9 women and 11 men, median age 51 years, range 50–53 years). Neither the patients nor the controls were treated by any drugs influencing the inflammatory response. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Charles University Hospital in Hradec Kralove, Czech Republic. Informed written consent was obtained from each subject.

Goeckerman therapy

The therapy was based on daily application of dermatological ointment containing 3 % of CCT on psoriatic lesions. Depending on the extent of lesions, 16–58 % of the total body surface was covered by the ointment. Each morning, the CCT ointment residues were removed using an oil bath, and total body UVR was applied. The length of irradiation was tailored individually depending on the disease status (1–15 min). The density of the used irradiation was 249.75 mW/cm^2 of UV-B and 131.8 mW/cm^2 of UV-A under a Sola-Scope 2000 spectrometer (Solatell, Croydon, UK) control. The duration of the treatment was modified according to the treatment effectiveness (average duration of 12 days; range of 3–22 days) calculated from the basic characteristics of the current disease status.

Immunochemical analyses

Samples of peripheral blood were collected before and after GT from the cubital vein using Vacutainer sampling tubes (Becton Dickinson, Franklin Lakes, NJ). The separated serum was stored at –70 °C until analysis. Repeated thawing and freezing were avoided. The serum levels of AhR were determined by using the ELISA Kit for AhR, product number SEB354Hu (version 11) (Cloud-Clone Corp., Katy, TX). The dynamic range was 0.312–20 ng/ml. The samples were diluted 1 : 20 before analysis. The serum concentrations of P450 CYP1A1 and CYP1B1 were assessed by using the ELISA Kit for Cytochrome P450 1A1 (CYP1A1), product number SED295Hu (version 11, dynamic range 0.156-10 ng/ml), and the ELISA Kit for Cytochrome P450 1B1 (CYP1B1), product number SED297Hu (version 11, dynamic range 1.56-100 ng/ml), respectively; both manufactured by Cloud-Clone Corp. The samples were diluted 1 : 5 before CYP1A1 analysis. In the case of CYP1B1, the samples were used without any additional dilution. The kits were used according to the manufacturer's instructions. The absorbance values were read at 450 nm using a Multiskan RC ELISA reader (Thermo Fisher Scientific, Waltham, MA). For evaluation of samples with CYP1B1 concentrations lower than the dynamic range, the extrapolation method was used. All experiments were done in duplicates.

Statistical analysis

The data were statistically processed with R software version 3.3.2 using the "nortest", "compute.es", and "ggplot2" packages. Based on the Anderson-Darling test for the data distribution, a parametric or nonparametric

test was used to ensure proper test sensitivity. Associations between laboratory and clinical parameters were evaluated by Pearson's correlation test; intergroup differences were assessed using Wilcoxon rank-sum test and Fisher's exact test for count data. The differences were considered statistically significant when the probability level (P) was below the α level of 0.05.

Results

The study group did not differ from healthy controls in terms of the median age (52 vs 51 years, P = 0.970) and gender distribution (P = 0.762). The PASI score in the patients ranged from 0.3 to 41.8 (median value 15.9, interquartile range 12.2–22.0). The values of the measured parameters are summarized in Table 1. Before the treatment, the patients had significantly higher serum concentrations of AhR and CYP1A1 than the controls (7.30 vs 4.15 ng/ml and 6.55 vs 2.70 ng/ml, respectively; P < 0.001 for both analytes). In the case of serum CYP1B1, the obtained values were very low and no difference between the study and control groups was observed (median, 0.60 vs 0.60 ng/ml).

Serum CYP1A1 before the treatment positively correlated with AhR values (Pearson r = 0.787; P < 0.001; Fig. 1a). Other significant associations between the investigated parameters, including age, smoking status, PASI score, length of radiation, and duration of treatment, were not found.

The median of the PASI score was reduced from 15.9 to 5.5 (interquartile range 3.8–7.6, P < 0.001) after the treatment and showed a beneficial therapeutic effect of

Table 1. Median values (and interquartile ranges) of the investigated parameters

Parameter [unit]	Controls	Psoriasis patients	
		before GT	after GT
AhR [ng/ml]	4.15 (3.90–5.42)	7.30[&] (5.75–9.50)	6.30[&,§] (5.42–8.35)
CYP1A1 [ng/ml]	2.70 (1.00–4.30)	6.55[&] (4.60–9.50)	6.60[#] (4.45–7.60)
CYP1B1 [ng/ml]	0.60[$] (0.45–0.90)	0.60[$] (0.40–1.10)	0.60[$] (0.33–0.88)

[&] P < 0.001 to controls; [§] P = 0.021 to the value before GT; [#] P = 0.002 to controls; [$] data evaluated using the interpolation method

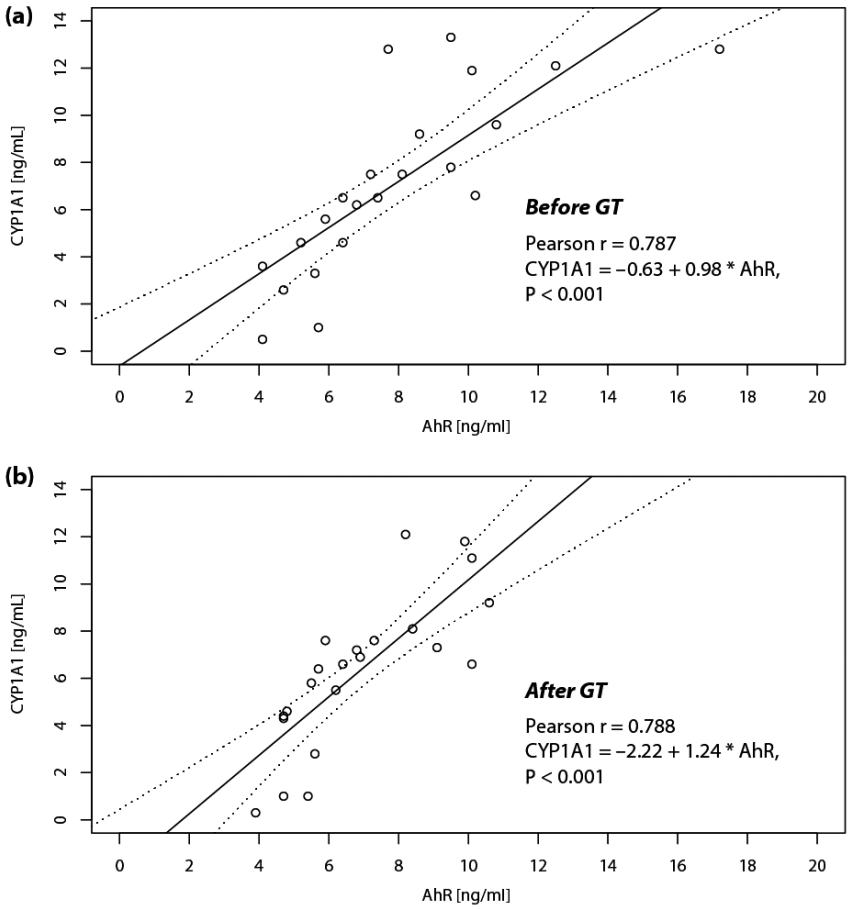

Fig. 1. Relationship between the serum levels of CYP1A1 and AhR (**a**) before Goeckerman therapy (GT) and (**b**) after the therapy. Solid lines depict the linear regression fit with 90% confidence boundaries plotted as dotted curves.

combined CCT and UVR application. As demonstrated in Table 1, the AhR median decreased after the therapy from 7.30 to 6.30 ng/ml ($P = 0.021$); nevertheless, it remained significantly higher compared to the controls ($P < 0.001$). The values of serum CYP1A1 and CYP1B1 measured before and after the therapy did not differ significantly. The level of CYP1A1 determined after the treatment again positively associated with AhR values (Pearson $r = 0.788$; $P < 0.001$; Fig. 1b).

Discussion

Developed psoriasis vulgaris impairs barrier and immune functions of the skin. Our previous studies reported increased levels of C-reactive protein and other markers of inflammation in psoriatic blood, and their decrease after GT (Kondelkova et al., 2015; Beranek et al., 2017). Nevertheless, a suitable laboratory biomarker reflecting the severity of psoriasis, efficacy of the therapeutic approach used, and beginning relapse has not been identified to date.

In this study we investigated serum concentrations of AhR, CYP1A1 and CYP1B1 in patients in exacerbated phase of the disease to assess their values as the markers of psoriasis. AhR and CYP enzymes could be secreted into the serum, plasma and other biological liquids through exosomes, small cell-derived vesicles with a size of 30–100 nm. Present in the circulation, exosomes deliver these and thousands of other specific proteins and RNA molecules from one cell to another via membrane vesicle trafficking to mediate adaptive immune response and metabolism of endogenous or exogenous compounds. Two distinct forms of CYP were recently reported to exist in the blood plasma: CYP packaged in exosomes and free circulating CYP molecules. Both these forms contain substrate-induced and functional enzymes (Kumar et al., 2017).

AhR is considered a pivotal regulator of immune and metabolic responses. Tightly controlled expression of the *AhR* gene is initiated in a wide range of human tissues (Stockinger et al., 2014). The canonical pathway of AhR drives metabolism of naturally occurring substances (kynurenine, 6-formylindolo[3,2-b]carbazole (FICZ), bilirubin, equilenin, arachidonic acid metabolites, etc.) and xenobiotic agents such as PAHs, halogenated dioxins and polychlorinated biphenyls (Nguyen and Bradfield, 2008; Dietrich and Kaina, 2010; Smith et al., 2016). Increased expression of the *AhR* gene was observed in skin cells of coal miners and cigarette smokers, which indicates its importance in the regulation of cell cycle and carcinogenesis (Esser et al., 2013). Later, elevated AhR expression was reported in the psoriasis lesions (Kim et al., 2014). Other investigators showed that AhR activated by FICZ or CCT attenuates psoriasiform inflammation and promotes differentiation of keratinocytes, regulatory T cells, Th17 and other cells (Colonna, 2014; Di Meglio et al., 2014; Stockinger et al., 2014). In untreated patients, we found higher serum levels of AhR than in healthy subjects. Their values decreased after the applied therapy but remained significantly higher than in the controls. No signs of additional AhR activation induced by PAHs or UVR after GT were observed.

The endogenous ligand triggering AhR activation in psoriasis has not yet been determined. There are several candidate molecules able to activate the AhR machinery including kynurenine, lipoxin 4A, prostaglandin G2 and other metabolites of arachidonic acid (Nguyen and Bradfield, 2008). Their presence in the skin initiates antioxidant response and psoriasiform inflammation via induction of cyclooxygenase-2, activator protein-1, CCAAT/enhancer-binding protein β, indoleamine 2,3-dioxygenase, signal transducer and activator of transcription 3, nuclear factor erythroid 2-related factor 2 and other cellular pathways (Nguyen et al., 2013; Stockinger et al., 2014; Koch et al., 2017; Sekhon et al., 2017). During GT, the ligands could be subject to enhanced catabolism.

CYP genes are expressed in cells under AhR control. High expression of *CYP1A1* and *CYP1B1* genes was described to be linked with increased activity of AhR in keratinocytes, endothelial cells of blood vessels, skin epithelial cells, lung and gastrointestinal tract (Nebert et al., 2004; Di Meglio et al., 2014; Stockinger et al., 2014). Both coded biotransformation enzymes rapidly degrade FICZ, PAHs and other polycyclic compounds, which subsequently limits the activated AhR (Esser et al., 2013). In keratinocytes, elevated levels of the enzymes were found after exposure to PAHs or UVR (Katiyar et al., 2000; Denison and Nagy, 2003). Additionally, increased CYP1A1 activity was observed in psoriasis lesions compared to controls (Karadag et al., 2017), although a low number of *CYP1A1* transcripts in lesional skin cells was reported by others (Kim et al., 2014).

In our patients, serum levels of CYP1A1 were notably higher than in the healthy controls. We obtained a strong positive correlation between CYP1A1 and AhR both before and after GT, albeit CYP1A1 values did not change significantly. Similar results from punch biopsies performed before and after UVR exposure have been published recently (Karadag et al., 2017). The findings suggest that the expression of CYP1A1 could be regulated by mechanisms other than AhR and remains induced after GT. In this context, more receptors that interact with the substrates inducing CYP genes have been reported (Denison and Nagy, 2003). Alternatively, although GT could primarily reduce CYP1A1 expression, the compounds contained in coal tar subsequently enhanced additional CYP1A1 synthesis. Several transcriptional and translational regulatory mechanisms are thus probably activated in lesional skin cells, and the definitive explanation why serum CYP1A1 did not decrease after GT remains unclear.

CYP1B1 is the dominating CYP enzyme in Langerhans cells with a lower degree of expression in human skin than CYP1A1 (Katiyar et al., 2000). In comparison with *CYP1A1*, the induction of the *CYP1B1* gene is not strictly dependent on AhR, and CYP1B1 synthesis is primarily influenced by oestrogen receptor

α or effectors of activated protein kinase A (Esser et al., 2013). As the canonical CYP1A1 pathway is predominantly involved in detoxication processes, CYP1B1 activity is required for metabolic activation and PAH-induced immunotoxicity and carcinogenesis (Nebert et al., 2004; Dietrich and Kaina, 2010). Karadag et al. (2017) found no significant difference in CYP1B1 levels in psoriatic skin compared to healthy controls and their slight increase after phototherapy. Our data showed very low concentrations of serum CYP1B1 in the patients and healthy volunteers, and negligible difference in CYP1B1 before and after GT. Thus, no tangible influence of PAHs or UVR on the CYP1B1 enzyme appearing in the serum was discovered.

CYP1A1 and CYP1B1 are important phase I enzymes metabolizing PAHs to reactive species such as benzo[a] pyrene-7,8-diol-9,10-epoxides (BPDE) responsible for their genotoxic effects. Evaluating psoriatic subjects treated with UVR and CCT, several papers described tobacco smoking to be an important factor contributing to the total PAH uptake and genotoxicity (Izzotti et al., 1991). However, other papers did not confirm these findings (Santella et al., 1995; Beranek et al., 2016). No significant differences in the serum CYP1A1 concentrations between smokers and non-smokers were observed in this study as well. Our psoriasis patients were only light smokers (up to five cigarettes per day) and their smoking was irregular even in normal life, and during hospitalization they nearly quit smoking completely. Thus, very low frequency of smoking did not probably induce CYP1A1 expression. To the best of our knowledge, no other study evaluating serum CYP enzymes in smokers and non-smokers has been published yet.

Summarizing the obtained results, our study was the first to demonstrate a significant increase of serum AhR and CYP1A1 in patients with exacerbated psoriasis compared to healthy subjects. Both analytes strongly associated to each other before as well as after GT. Nevertheless, no association of AhR or CYP1A1 with the PASI score, the most widely used scoring tool for evaluation of psoriasis severity, was apparent. The existence of a relationship with PASI score should be considered crucial for each future laboratory marker of psoriasis. In the past, several such analytes significantly correlated with PASI: fibrinogen (Kanelleas et al., 2011), C-reactive protein, interleukin 6 (Coimbra et al., 2010), TNF-α (Serwin et al., 2007), platelet P-selectin (Ludwig et al., 2004), endothelin 1 (Bonifati et al., 1998), osteopontin (El-Eishi et al., 2013), visfatin, fetuin A (Okan et al., 2016), and CD86 (Nguyen et al., 2018). From this point of view, neither AhR nor CYP1A1 sufficiently reflected the psoriasis severity.

Our work with AhR and CYP enzymes has several limitations. The study had a cross-sectional design and contained a limited number of included participants. Broader longitudinal studies should verify our preliminary data in the future. Another limitation of the study was the unknown cellular source from which AhR, CYP1A1 and CYP1B1 were released into the circulation. Currently, there is no simple way to determine their origin since both AhR and CYPs possess identical or almost identical protein sequences in various human tissues. Finally, the performed immunochemical analysis was not able to distinguish whether AhR and CYPs found in the serum are complete and functioning molecules or their degradation end products. Further solution of these issues could help us to better understand the metabolic processes activated in exacerbated psoriasis and to suggest more targeted treatment.

Disclosure of conflicts of interest

Authors' conflict of interest disclosure: none declared.

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