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Influence of UVA and UVB irradiation on hepatic and cutaneous P450 isoenzymes

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Abstract The influence of UVA and UVB irradiation of the skin for 1, 2 and 4 weeks on the activities of the hepatic and cutaneous P450 isoenzymes was investigated in female Wistar rats before and after systemic administration of hexachlorobenzene (HCB), a well-known porphyrogenic agent, which additionally induces P450 1A1 and P450 1A2 isoenzymes. UVA and UVB irradiation of the skin of the controls and HCB-treated animals did not influence porphyrin metabolism. In the nonporphyric rats hepatic EROD (P450 1A1) activity was induced by UVB, but the activity of ADM (P450 2B) and EMDM (P450 3A) was either minimally or not affected. In the HCB-treated (porphyric) rats UVA and UVB irradiation resulted in a significant depression of HCB-induced EROD in the liver and in the skin. In both the nonporphyric and the porphyric rats UVA and UVB irradiation had no effect on hepatic ADM activity. In the liver of the nonporphyric animals EMDM activity remained unchanged after UVA and UVB irradiation, whereas in the HCB-treated animals the activity of this enzyme was increased. Finally, after UVA and UVB irradiation cutaneous EMDM activity was increased in the controls, whereas the HCB-induced increase of this enzyme in porphyric animals was decreased. In addition long-term (28 days) UVB irradiation decreased hepatic GSH content significantly in normal and porphyric rats. These experimental findings cannot be directly extrapolated to humans; however, they suggest that exposure of human skin to UV radiation may result in alterations in the activity of cutaneous, hepatic and other extracutaneous P450 isoenzymes.

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Abbreviations *ADM* aminopyrine-*N*-demethylase, *AHH* arylhydrocarbon hydroxylase, *ALA-S* δ-aminolevulinic acid synthase, *BCG* bacterium Calmette Guérin, *EMDM* erythromycin demethylase, *EOCD* ethoxycumarin-*O*-deethylase, *EROD* ethoxyresorufin-*O*-deethylase, *GSH* glutathione, *HCB* hexachlorobenzene, *IFN* interferon, *IL* interleukin, *3-MC* 3-methylcholanthrene, *TCDD* tetrachlorodibenzodioxin, *TNF* tumour necrosis factor, *UV* ultraviolet

Introduction

In recent years, a large number of investigations have demonstrated that irradiation of the skin and of various cell cultures with UVB and UVA is capable of inducing a great variety of biochemical reactions [21], as well as the production of ILs [17, 24, 33, 48], TNFs [25, 54], hormones and neuropeptides [22, 50], prostaglandins [31], oxygen metabolites [18] and stress or heat-shock proteins [22]. Additionally, systemic photoimmunological, photoneuroimmunological and biochemical processes are known to be triggered by UV irradiation of skin in vivo [22, 43, 47].

Apart from the above cited immunological defence mechanisms, biochemical reactions exist, mainly phase I enzymes such as P450 isoenzymes, are able to prevent disturbances induced by various exogenous influences, primarily naturally occurring toxic compounds or toxic xenobiotics. Infectious diseases [35], bacterial endotoxins [26] or BCG [37] are able to interfere with P450 isoenzymes. Renton et al. [35, 36] initially demonstrated that IFN or IFN inducers such as poly-IC [36] can inhibit P450 isoenzymes. It has been shown subsequently by various groups in vivo and ex vivo, that different cytokines and mediators such as TNF [7], IL-1 [2, 5, 52], IL-2 [19] and IL-6 [3, 6, 48, 52] can modify P450 isoenzyme activity in the liver and also in extrahepatic tissues [9, 38].

The influence of visible light, UVA and/or UVB on hepatic and cutaneous P450 isoenzymes has not been studied in detail. Exposure of plants (*Phaseolus aureus*) to light (60-W tungsten lamps) has been shown to result in a reduction of P450 content, whereas darkness has the opposite effect [13]. In animals, Tredger and Chhabra [46] have demonstrated a light-dependent circadian rhythm of P450 isoenzymes in the liver, lung and other extrahepatic tissues.

In previous investigations we have demonstrated distinct alterations in the activities of P450 isoenzymes, e.g. 7-ethoxycumarin-*O*-deethylase (EOCD), arylhydrocarbon-hydroxylase (AHH) and aminopyrine-*N*-demethylase (ADM), in the liver and/or the skin of immunologically impaired rodents following long- and short-term irradiation with UVA and/or UVB [8, 39]. The aim of the present study was to investigate the influence of UVA and UVB irradiation (for 1, 2 and 4 weeks) on the activities of hepatic and cutaneous P450 isoenzymes of immunocompetent animals (Wistar rats) before and after systemic administration of hexachlorobenzene (HCB), a well-known porphyrogenic agent which preferentially induces P450 1A1 and P450 1A2 isoenzymes.

Material and methods

Adult female Wistar rats (180–220 g; Zentralinstitut for Laboratory Animal Breeding, Hannover, Germany) were kept at room temperature (25 ± 2° C) with a 12-h light-dark cycle. The rats were fed with a standard diet (Altromin) or Altromin® (Lage, Germany) containing 0.05% HCB with free access to water.

UV administration

UVA radiation was administered using a UVASUN lamp (Mutzhas, Munich, Germany) emitting in the wavelength range 320–460 nm, and UVB radiation was administered using a UV 800 lamp (Waldmann, Villingen, Germany) emitting in the range 285–350 nm. A Centra dosimeter was used for UVA and a UV-21 dosimeter (Waldmann, Villingen, Germany) for UVB.

Analytical methods

Urinary porphyrin and porphyrin metabolites were analysed by the methods of Doss and Schmidt [4] and Seubert and Seubert [42], respectively. Livers were analysed as follows: porphyrins by the method of Vizethum et al. [49], porphyrin metabolites by the method of Seubert and Seubert [42], ALA-S by the method of Marver et al. [23], protein by the method of Lowry et al. [20], GSH by the method of Tietze [45] and P450 by the method of Omura and Sato [30]. ADM, EMDM and EROD in livers and skin were analysed by the methods of Schoene et al. [41], Jugert et al. [14] and Pohl and Fouts [32], respectively.

Experimental procedure

A total of 108 adult female Wistar rats were divided into 18 groups of 6 animals each. Nine groups were fed with a diet containing 0.05% HCB for 78–115 days. These rats developed hepatic porphyria evidenced by a significantly increased urinary excretion of porphyrins (129 ± 45 vs controls 10 ± 8 nmol porphyrin/rat per day). A group of untreated (nonporphyric) rats and of porphyric (HCB-treated) rats were irradiated with UVA 50 J/cm^2 per day for 7, 14 or 28 days and compared with the corresponding unirradiated controls. Except for a defined shaved area (25 cm^2) on the upper back, the animals were covered with a black drape. The temperature was controlled continuously by two ventilators. Another group of the rats was irradiated with UVB 0.1 J/cm^2 per day for the same period. The rats were sacrificed 24 h after the final irradiation, and the skin and livers were removed and examined immediately. Microsomes of each liver were prepared according to the method of Kamath and Rubin [15]. The prepared skins of each group were pooled and microsomes were isolated as described by Jugert et al. [14].

Results

In the controls and the HCB-treated animals the concentrations of total porphyrins, particularly of their higher carboxylated derivatives (uro-, hepta- and hexaporphyrins), in the urine and the liver remained unchanged following UVA and UVB irradiation (data not shown).

The activity of ALA-S was significantly induced in the liver of porphyric (HCB-treated) rats. UVA and UVB irradiation had no effect on the activity of this enzyme in nonporphyric animals. In porphyric rats, UVB irradiation for 7 and 14 days resulted in a further induction of hepatic ALA-S, whereas the activity of this enzyme was unaffected by UVA irradiation (Table 1).

The GSH-content of the livers was significantly reduced by the 28-day UVB irradiation in both control and HCB-treated rats (Table 2).

Table 1 Influence of UVA and UVB on hepatic δ-ALA-S (nmol/l ALA/h per g liver) in normal and HCB-treated (porphyric) Wistar rats

Treatment	Irradiation		
	7 days	14 days	28 days
Controls	116 ± 19	158 ± 78	115 ± 16
UVA	135 ± 15	145 ± 21	133 ± 37
UVB	138 ± 19	170 ± 62	100 ± 21
HCB controls	354 ± 48	510 ± 190	818 ± 287
HBC + UVA	443 ± 124	675 ± 169	902 ± 187
HBC + UVB	555 ± 126*	1003 ± 241*	825 ± 205

* $P < 0.01$

Table 2 Influence of UVA or UVB on the hepatic GSH concentration (μmol/g liver) in normal and HCB-treated (porphyric) Wistar rats

Treatment	Irradiation		
	7 days	14 days	28 days
Controls	5.7 ± 0.6	5.0 ± 0.3	5.2 ± 0.8
UVA	5.7 ± 1.2	3.8 ± 1.9	5.5 ± 0.6
UVB	4.6 ± 0.9	5.5 ± 0.7	2.2 ± 1.4*
HCB controls	6.2 ± 1.1	4.3 ± 0.7	4.6 ± 0.6
HBC + UVA	5.5 ± 1.1	4.4 ± 0.7	3.9 ± 1.1
HBC + UVB	5.9 ± 0.8	4.4 ± 1.1	2.4 ± 1.2*

* $P < 0.01$

Table 3 Influence of UVA and UVB on hepatic EROD activities (pmol resorufin/min/mg protein) in normal and HCB-treated (porphyric) Wistar rats

Treatment	Irradiation		
	7 days	14 days	28 days
Controls	25 ± 11	21 ± 8	12 ± 3
UVA	27 ± 7	25 ± 14	14 ± 4
UVB	105 ± 33**	38 ± 10*	30 ± 10*
HCB controls	823 ± 124	433 ± 63	360 ± 69
HBC + UVA	221 ± 41***	249 ± 55**	182 ± 51**
HBC + UVB	407 ± 67**	222 ± 61**	119 ± 29**

* $P < 0.025$; ** $P < 0.01$; *** $P < 0.001$

Table 4 Influence of UVA and UVB on cutaneous EROD activities (pmol resorufin/min/mg protein, pooled skin) in normal and HCB-treated (porphyric) Wistar rats

Treatment	Irradiation		
	7 days	14 days	28 days
Controls	0.15	0.36	0.16
UVA	0.12	0.02	0.05
UVB	0.11	0.27	0.11
HCB controls	0.35	0.59	0.35
HBC + UVA	0.07	0.37	0.21
HBC + UVB	0.23	0.38	0.12

Table 5 Influence of UVA and UVB on hepatic ADM activities (nmol formaldehyde/min/mg protein) in normal and HCB-treated (porphyric) Wistar rats

Treatment	Irradiation		
	7 days	14 days	28 days
Controls	2.7 ± 0.6	3.1 ± 0.8	4.2 ± 0.4
UVA	3.2 ± 0.5	2.5 ± 0.6	3.6 ± 0.3
UVB	2.9 ± 0.6	3.2 ± 0.4	4.3 ± 0.6
HCB controls	1.0 ± 0.5	1.5 ± 0.3	2.0 ± 0.4
HBC + UVA	1.3 ± 0.2	1.8 ± 0.7	1.8 ± 0.2
HBC + UVB	1.6 ± 0.6	1.2 ± 0.5	2.5 ± 0.4

In nonporphyric rats UVB irradiation for 7, 14 and 28 days caused a significant increase in the activity of EROD (P450 1A1) in the liver, but EROD remained unaffected by UVA (Table 3). In the HCB-treated animals, the EROD activities in the livers and the skin were significantly reduced after both UVA and UVB irradiation (Tables 3 and 4). Interestingly, in nonporphyric animals, the activity of this enzyme in the skin was clearly reduced following UVA irradiation for 14 and 28 days but remained unaffected by UVB (Table 4).

The activity of ADM (P450 2B) significantly decreased in the livers of HCB-treated rats. However, in both the controls and the porphyric rats UVA and UVB irradiation had no effect on hepatic ADM activity (Table 5).

In the livers of nonporphyric animals there was no significant change in EMDM (P450 3A) activity after irradiation with either UVA or UVB (Table 6). In the livers of HCB-treated rats, the activity of this enzyme significantly increased after the 28-day irradiation with either UVA or UVB (Table 6). In the skin of nonporphyric animals the activity of EMDM was clearly increased after the 7- and 28-day irradiations with UVA and after the 7-, 14- and 28-day irradiations with UVB (Table 7). Treatment of the animals with HCB resulted in a significant increase in EMDM activity which was reduced following the 14- and 28-day irradiations with UVB and following the 28-day irradiation with either UVA or UVB (Table 7).

Table 6 Influence of UVA and UVB on hepatic EMDM activities (nmol formaldehyde/min/mg protein) in normal and HCB-treated (porphyric) Wistar rats

Treatment	Irradiation		
	7 days	14 days	28 days
Controls	0.7 ± 0.2	0.5 ± 0.3	1.2 ± 0.3
UVA	0.9 ± 0.2	0.2 ± 0.1	0.8 ± 0.2
UVB	0.9 ± 0.1	0.1 ± 0.0	1.6 ± 0.3
HCB controls	0.9 ± 0.4	0.3 ± 0.1	0.6 ± 0.1
HBC + UVA	0.9 ± 0.1	0.7 ± 0.3	1.0 ± 0.1*
HBC + UVB	0.5 ± 0.1	0.4 ± 0.2	1.3 ± 0.1**

* $P < 0.025$; ** $P < 0.001$

Table 7 Influence of UVA and UVB on cutaneous EMDM activities (nmol formaldehyde/min/mg protein, pooled skin) in normal and HCB-treated (porphyric) Wistar rats

Treatment	Irradiation		
	7 days	14 days	28 days
Controls	0.04	0.04	0.12
UVA	0.10	0.04	0.18
UVB	0.15	0.08	0.36
HCB controls	0.13	0.11	0.27
HBC + UVA	0.11	0.10	0.07
HBC + UVB	0.11	0.06	0.15

Discussion

Accumulating evidence indicates that UV irradiation is capable of inducing diverse biochemical and biological processes in various in vitro cellular systems, in animals, and in humans. In particular, delayed cutaneous hypersensitivity is inhibited following UV irradiation of the skin as a consequence of a decrease in the antigen-presenting capacity of Langerhans cells and/or an induction of antigen tolerance through an increased formation of T-suppressor cells [43]. Furthermore, combined administration of UVB or UVA with photosensitizers (porphyrins or 8-methoxypsoralen) results in an induction of matrix metalloproteinases, e.g. collagenases, which could readily explain the pronounced elastosis and blister formation in exposed skin of patients with porphyria cutanea tarda [16, 40, 51].

In the present study a minimal induction of hepatic ALA-S was found in HCB-treated rats after UVB exposure in comparison with HCB controls, whereas the concentrations of porphyrins and their precursors in the livers and the urine of all irradiated animals remained unaffected by UVA and UVB irradiation. It therefore seems reasonable to suggest that UVA and UVB irradiation exerts no significant effect on porphyrin metabolism either in normal rats or in rats with HCB-induced hepatic porphyria.

A reduction in hepatic GSH concentration was demonstrated in both normal and HCB-treated animals following the 28-day UVB irradiation. In mice, UVB treatment induces a reduction in GSH concentration in the skin (epidermis and dermis) [44]. Furthermore, in the liver of UVB-treated mice an increase in GSH-peroxidase has been found [12], which could result in a decrease in the GSH content in the liver. The decrease in hepatic GSH content in HCB-treated rats did not influence porphyrin metabolism.

Isoenzymes of the cytochrome P450 supergene family are an important biochemical defence, being capable of inactivating by hydroxylation or oxidative dealcylation a wide variety of low molecular compounds (M_r = 250 ± 200), drugs and xenobiotics [10, 11, 29, 53]. Direct effects of visible and ultraviolet light on P450 isoenzymes in microsomes or on reconstituted enzymes have been demonstrated [27]. Such direct effects may explain the alterations in the activities of the cutaneous P450 isoenzymes found in the present study. A direct influence of UV irradiation on the liver of the exposed animals is impossible. Although significant alterations in the hepatic P450 isoenzyme activities were found in the irradiated animals, the liver P450 content in the nonporphyric and HCB-treated rats apparently remained unaffected by UVA and UVB irradiation. These findings might be explained in terms of a differential influence of the irradiation on P450 isoenzymes which might be associated with opposite effects on the P450 content. Nevertheless, the possibility that the latter might have changed after irradiation, but the method used was not sufficiently sensitive to detect the change, cannot be definitely ruled out.

In untreated rats UVB (but not UVA) irradiation of the skin increased the activity of hepatic EROD (P450 1A1), whereas in HCB-treated rats, the HCB-induced increase in the activity of this enzyme was significantly reduced by both UVB and UVA. In cultures of human hepatic cells (HepG2), the induction of P450 1A1 caused by 3-MC is nearly abolished as shown by decreased mRNA and protein levels after the addition of IL-2 [19] or IL-6 [6] to the medium. These Ils and others such as IL-1, IL-8, IL-10 and IL-12 can be induced in epidermal cells not only in vitro but also in vivo. They are then released into the circulation, following UVB irradiation of human and animal skin [21, 22, 48]. It therefore seems reasonable to suggest that the release of cytokines, probably IL-2 and/or IL-6 induced by UVB radiation might have inhibited HCB-dependent P450 1A1 activity in the livers of porphyric rats, but this cannot explain the induction of hepatic EROD in nonporphyric rats which were exposed to UVB.

Tryptophan metabolites are known to be formed and released after irradiation of skin with UVB [1, 34]. They are capable of binding to the Ah-receptor with a higher binding affinity than TCDD or other hydrocarbons. However, the inductive capacity for P450 1A1 and 1A2 is less than that of TCDD [28, 29, 34]. Thus, it is possible that tryptophan metabolites released after skin irradiation bind to hepatic Ah-receptors of nonporphyric rats and induce EROD, whereas in HCB-treated rats they may interfere with the more potent inducer HCB for binding to the hepatic and cutaneous Ah-receptors and cause a decrease in the induction of EROD by chlorinated benzene.

The multiple P450 isoenzymes are regulated by various biochemical mechanisms. In contrast to its pronounced influence on the hepatic and cutaneous P450 1A1 of the UV-exposed rats, UV irradiation had little or no effect on the activities of isoenzymes belonging to the P450 2B (ADM) and P450 (EMDM) families. Thus, hepatic ADM activity remained unchanged following UVA and UVB irradiation of normal and HCB-trated rats. In UV-exposed normal rats hepatic EMDM activity was not altered, as compared with the controls, whereas in porphyric rats 28-day UVA and UVB irradiation resulted in a minor decrease. In the skin of nonporphyric animals UVB induced EMDM throughout the experiment, whereas the 14- and 28-day irradiation of HCB-treated rats led to a decrease in the induction of this enzyme.

The results of the present study clearly show that irradiation of rat skin with UVB and partially also with UVA is capable of modifying the activitiy of P450 isoenzymes (particularly of P450 1A1) not only in the skin but also in the liver. These experimental findings cannot be directly extrapolated to humans, but they suggest that exposure of human skin to UV radiation may result in alterations in the activity of cutaneous, hepatic and other extracutaneous P450 isoenzymes.

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