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Review

PUVA (psoralen + UVA) photochemotherapy: processes triggered in the cells

Z. Zarebska [a,*], E. Waszkowska [a], S. Caffieri [b], F. Dall'Acqua [b]

[a] *Institute of Biochemistry and Biophysics, Polish Academy of Sciences, Ul. Pawinskiego 5, PL-02106 Warszawa, Poland*
[b] *Department of Pharmaceutical Sciences, University of Padova, and Center for Chemical Investigations of Drugs (associated to the National Institute for the Chemistry of Biological Systems), National Research Council, Padua, Italy*

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Dedicated to Professor Pietro Pratesi

Abstract

Photochemotherapy using psoralens and UVA is a treatment used widely in some skin diseases, in cutaneous lymphomas and in autoimmune diseases. This review has selected recent publications dealing with the photochemical processes triggered in the cells by UVA radiation and psoralen treatment. The photochemical changes initiated in the cell membranes were described.

Keywords: Psoralen photoaddition; Phospholipids; Apoptosis; PUVA-photochemotherapy

1. Introduction

In PUVA therapy [1], which includes the joint action of psoralens as drug and of UVA as sensitising radiation, various cellular targets are hit, among which blood peripheral circulating lymphocytes play a particular role [2]. The therapy, by initiating some reactions in lymphocytes, leads to alleviation of many human diseases which are associated with immune imbalance [3]. The role of lymphocytes in restoring the immune balance was brought up by a successful treatment of cutaneous T-cell lymphoma by the photopheresis: extracorporeal irradiation of only 1/8 of the whole peripheral lymphocytes has improved the state of patients significantly [2]. Although numerous studies were devoted to the mechanism of PUVA treatment, no straightforward correlation was found between photochemical damage and immune response reflected in apoptosis [4,5] and in the spectrum of cytokine release from the cells [6,7]. This is in contrast with the cell cytotoxicity exerted through nuclear DNA damage [8] or pigmentation induced by DNA repair in melanocytes [9,10], phenomena rather well understood and connected directly to DNA photoproducts. In this review an attempt was made to collect the data on photochemical reactions in the cell membranes in the context with observed physiological responses of the whole cell.

In the early microscopic studies carried out on guinea pig treated topically with PUVA it was noted that psoralen shows preferential binding to the keratine layer, cell membranes and intercellular matrix [11]. After UVA irradiation, the photoadducts were localized in the same sites, and the photoadducts in nuclear DNA were revealed only after special pretreatments with ethanol, alkali or proteolytic enzymes. Although those studies were fairly qualitative, they have indicated that psoralen photoproducts formation in the membrane input a significant damage to the cell different from that induced in the cell nuclei. It was suggested that phospholipids of the cell membranes [12,13] and their proteins [14–17] in addition to nuclear DNA [8,17] can be a target of action of PUVA therapy.

* Corresponding author. Fax: +48-39-121 623.
E-mail address: zozar@ibbrain.ibb.waw.pl (Z. Zarebska).

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2. Treatment by UVA and PUVA

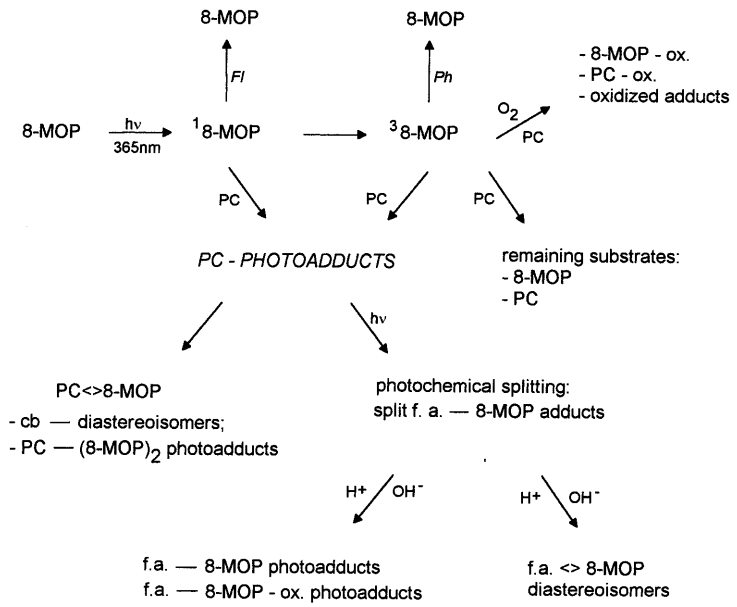
A number of clinical trials in which UVA radiation without sensitizing drugs was applied successfully as a treatment for psoriasis [18] and for atopic dermatitis [18,19] would indicate that under PUVA treatment at least two synergistic mechanisms are operating: one induced by UVA radiation and the second triggered by UVA-excited psoralen. Cell lysis by UVA alone was earlier noted on lymphocytes [20]. Both treatments, UVA alone and (psoralen + UVA) induced cell apoptosis (see below), however PUVA exerted stronger effects. For example, in cultured keratinocytes 8-methoxypsoralen (8-MOP) + UVA induced apoptosis eight times more efficiently than UVA alone [21]. During PUVA therapy in the form of photopheresis the isolated patient's lymphocytes undergo apoptosis at conditions in which nuclear DNA damage is far from being lethal for the cells [22–24]. The above findings were a prerequisite for investigating the role of membrane psoralen-photoadducts in inducing apoptosis.

3. Photoaddition of psoralens to unsaturated fatty acids

Sá e Melo et al. [25–27] have pointed out the influence of solvation medium on the reactivity of psoralens in their excited states. Their findings can explain the apparent low quantum yield of 8-MOP photoadducts in relation to those formed with psoralen or trimethylpsoralen. However, the routes of energy transfer from the excited psoralens towards neighbour biomolecules remains still obscure, especially why 8-MOP with so high triplet yield is so poor donor in the photoaddition reactions. The photooxygenation of olefinic bonds of unsaturated fatty acids can compete with the photoaddition to the same bonds. In the course of UVA-irradiation of keratinocytes in the presence of psoralens, the enhancement of oxidized fatty acid release to the medium was not noticed [26]. Likewise, during extracorporeal photoimmunotherapy with 8-MOP as sensitizing drug, the oxidative damage to proteins and lipids was not detected to increase in plasma and in the cells [28]. The relation of lipid oxidation versus lipid photoaddition seems to be important regarding the constitutive cell repair machinery which is well equipped for the removal of lipid oxygenated products [29].

4. Lecithin–psoralen photoadducts characterized in vitro

The lecithin–psoralen photoadducts formation and their characterization in vitro have been described in several reports [30–32]. The main photoproducts were cyclobutane adducts to unsaturated fatty acids [33] and cyclobutane adducts to lecithins [32] which were accompanied by photoisomerization of fatty acids [33] and photooxygenation of lecithins [34]. In addition to the primary cyclobutane adducts, some other adducts of partially destroyed psoralens were found [35]. Scheme 1 presents the complexity of lecithin photolysis in the presence of psoralens.



Scheme 1. Photolysis of lecithin in the presence of psoralens in vitro [35]. 8-MOP, 8-methoxypsoralen (^{1}8-MOP and ^{3}8-MOP refer to the singlet and triplet excited states of the molecule, respectively); PC, lecithin; f.a., unsaturated fatty acid: PC-ox and 8-MOP-ox, photochemically oxidized molecules.

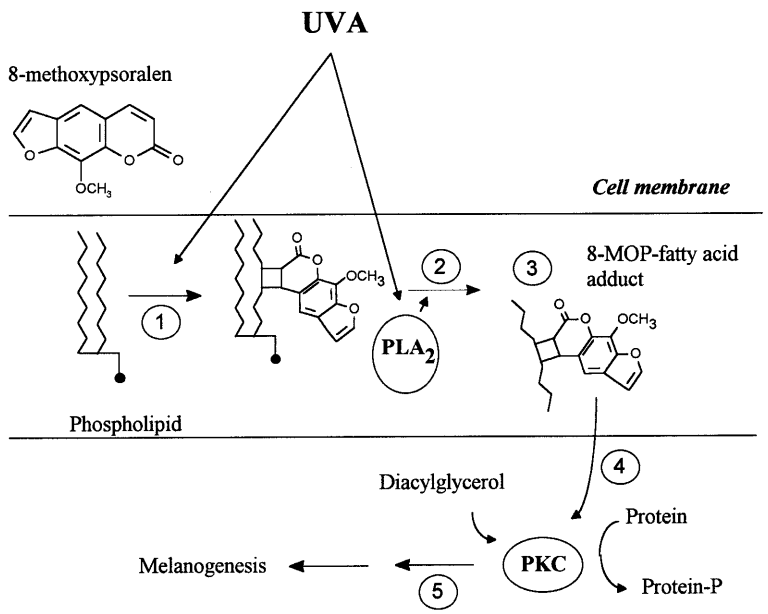
The characterization of lecithin photoproducts shown in Scheme 1 was based on mass spectroscopy and NMR analysis [31,32,35]. Mass spectra of cyclobutane photoadducts had to be determined by soft ionizing technique since under electron impact technique the cyclobutane ring underwent splitting [32]. The best way was to separate irradiated mixture by HPLC connected with simultaneous ion spray mass spectrometric detector [31]. Alternatively, the NMR techniques are at hand to trace the photoadduct formation by means of two-dimensional NMR analysis carried out on lecithin–psoralen irradiated mixture, without any purification step [35]. In fact, the set of four cross-peaks indicating cyclobutane ring protons resonate in a region of the spectrum (between 3 and 2 ppm) in which they are not hidden by other signals of either psoralen or lecithin, thus allowing their easy detection. Moreover, these protons have slightly different chemical shifts depending on the stereochemistry of isomers (table 1 of Ref. [35]).

Characterization of photoadducts in the mixture is complicated by the accompanying oxidation reactions of both lecithin and psoralen molecules. For instance, the photoaddition of a water molecule to psoralen can also occur in oxygenated solutions [36,37]. The adducts are unstable in the various eluents used with TLC separation, and it was noted that the cyclobutane adducts of non esterified fatty acids appeared to be less stable in comparison to their more stable methyl esters or lecithin adducts [32,34]. The latter feature seems to explain the difficulty of their detection in vivo.

In contrast to the great effort devoted to study the photochemical reactions of psoralens with lipids in vitro, scarce evidence is available on their detection in vivo or in cell cultures: photoadducts of trimethylangelicin to oleic and linoleic acids were found in rat skin [30], the 8-methoxypsoralen cyclobutane adduct to linoleic acid was detected in lymphocytes [38], and oxidized unsaturated fatty acids were detected in keratinocyte cell culture [26].

5. Cyclobutane adducts of psoralen in melanogenesis

The cyclobutane adducts in vivo might be stable enough to initiate the cascade of signal transduction. It was shown that enhancement of protein kinase C (PKC) activity in human platelets occurs upon addition of freshly HPLC-isolated psoralen cyclobutane adducts of oleic, linoleic and linolenic acids [39]. The enhancement of kinase activity induced by external addition of cyclobutane adducts seems to be important in melanogenesis as it was found with cultured human melanocytes [40,41]. It was suggested that the cyclobutane adducts of psoralen to unsaturated fatty acids can mimic the action of 1,2-dioctanoylglycerol (DAG) [40], a known agent which stimulate human melanogenesis [42]. In contrast to the fatty acid adducts, analogous lecithin adducts seem to be inactive in platelets, their action probably requiring enzymatic release of photoadducts by phospholipase A_2 (PLA_2). The resulting residue of enzymatic lysis by PLA_2, lysophosphatidylcholine, was shown to enhance synergistically the DAG dependent activation of PKC [43]. Scheme 2 presents the proposed scheme of melanogenesis activation by lecithin photoadducts.



Scheme 2. Melanogenesis activation by PUVA treatment [40]. Circled numbers 1–5 indicate consecutive stages of reaction. Protein-P, phosphorylated protein.

According to Scheme 2, UVA-excited 8-MOP undergoes cyclobutane-type attachment to phospholipids, from which the photoadduct of fatty acid is released by PLA_2. The 8-MOP-fatty acid adduct, transferred from membrane to the cytosol, activates protein kinase C, playing the role of second messenger. The activation of PKC was monitored by measuring the extent of phosphorylation of P47 protein in human platelets, and PKC stimulation has been observed in concentrations similar to DAG [31,39]. These reactions lead then to melanogenesis through unknown pathways.

6. PUVA and immune response

Recently, an increasing number of research works has indicated that photochemically damaged cells participate in regulating the immune response upon treatment with PUVA or UV alone [19]. The enhanced synthesis of MHC I receptors [44] or induction of MHC-I-associated peptides [45,46], overexpression of IL-15 cytokine [47] or transcription factor NF-κB [48] following photochemical treatment could be examples of that line of research. Also photooxidation of lipids [12–14,29] and of psoralens themselves [49] may lead to better understanding an overall picture of transformations induced by UVA/PUVA treatment. The protein photochemistry is lagging behind; the promising study of a psoralen–tyrosine photoconjugate [50] will hopefully initiate a new line of research.

The particular information on PUVA-induced immune response derives from studies on photopheresis [23]. In this treatment, peripheral blood leukocytes are separated and exposed for 1.5 h to 8-MOP and UVA irradiation, followed by reinfusion back to the patient. The withdrawn patient's blood (125 ml per cycle) is centrifuged in extracorporeal photopheresis (ECP) machine, and the buffy coats of six cycles are collected sequentially in the treatment bag. The centrifuged plasma and erythrocytes are directly reinfused into the patient, before starting a new cycle. The stabilized aqueous solution of 8-MOP is added to the treatment bag at the final concentration of 100–150 ng/ml [23]. Alternatively, the patients are given orally the appropriate amount of 8-MOP in capsules [24]. The treatment bag is connected to a disposable system where the leukocytes are exposed to UVA irradiation (2 J/cm^2). The ECP treatment is given every 4 weeks on 2 consecutive days.

It was observed that reinfused lymphocytes are still viable, however gradually undergoing apoptosis within several days [23,22]. It was hypothesized that during the highly regulated process of apoptosis the irradiated lymphocytes have altered membrane receptors and release cytokines which modulate the whole immune system [6,23].

7. Apoptosis

Apoptosis is considered to be the main mechanism of action of ultraviolet light therapy and PUVA chemotherapy which induces reduction of number of activated lymphocytes infiltrating the skin [51]. Apoptosis studies enabled to differentiate a fraction of T-cell of the circulating lymphocytes [21–24], and of T-helper cells infiltrating the skin abundantly in some diseases [18].

It was directly evidenced that narrow band UVB (312 nm) induces apoptosis of T cells residing within psoriatic lesions [52]. Treatment by psoralen + UVA suppress proinflammatory cytokine release from monocytes [6] and induces apoptosis of lymphocytes [22] and apoptosis of epidermal cells in culture [21,53].

Godar has postulated that there are two main routes of apoptosis induction in the lymphocytes: one 'preprogrammed' which can be detected within 20 min up to 4 h after the irradiation, and the other, starting 12–24 h afterwards [54]. It can be hypothesized that early induced apoptosis does not require sensitizing drug but is triggered by UVA radiation alone which affects cell receptors and appropriate transcription factors [48]. The delayed stage of induced apoptosis could be triggered by photoproducts derived from DNA and from plasma membranes. It was noted that UVA-induced delayed apoptosis is accompanied by the decline of expression of proteine kinase C, and of all its six isoenzymes [55].

Recently, it was discovered that apoptosis is connected with overproduction of Bcl-2 and Bax proteins regulating caspase chain reactions [56,57]. Endothelial rat aortic cells irradiated with pharmacological doses of 6 J/cm^2 of UVA were inducing overexpression of Bcl-2 mRNA, persisting 48 h. Alternatively, Bax overexpression was detected in the cells not activated by the proinflammatory cytokines and in the presence of nitric oxide synthase inhibitors [57]. The concept of nitric oxide and Bcl-2 protein acting as antioxidants [56] looks promising since it furnishes the experimental insight into the cell defense mechanism against UVA radiation. The apoptosis of lymphocytes infiltrating the skin induced by UVA/PUVA treatment was suggested to be a way of recovering balance in some skin disorders [51,52,58,59].

8. Conclusions

Characterization of photoproducts of the membrane phospholipids made a progress in understanding of the mechanism of PUVA treatment. Kinase phosphorylation induced by those photoproducts, cytokine synthesis and overexpression of proteins regulating apoptosis were the physiological reactions triggered by PUVA

within the cell studied mostly. Apoptosis studies made possible to quantify the number of lymphocytes affected by the UVA/PUVA treatment, localized in both sites: residing in the skin and circulating in the peripheral blood.

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