Mechanisms of phototherapy and photochemotherapy for photodermatoses

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ABSTRACT: Most photodermatoses represent indications for preventive ultraviolet (UV) phototherapy and/or psoralen plus ultraviolet A (PUVA) photochemotherapy. The aim of treatment is to prevent the outbreak of disease by increasing the patient's tolerance to sunlight. The mechanisms by which ultraviolet B (UVB) and PUVA induce such tolerance are not completely understood. Pigmentation and skin thickening may be important factors in the protective effect, but they cannot sufficiently explain the degree of protection induced. Other mechanisms that may be of critical importance for the therapeutic efficacy encompass a variety of immunomodulatory effects on human skin known to be induced by UVA, UVB, and PUVA. Obviously the mechanisms of prophylactic phototherapy are strongly intertwined with the pathogenesis of the photodermatoses. The possible mechanisms of photoprevention are discussed for polymorphic light eruption (PMLE), actinic prurigo, chronic actinic dermatitis, and solar urticaria.

KEYWORDS: actinic prurigo, chronic actinic dermatitis, mechanisms, photochemotherapy, phototherapy, polymorphic light eruption, solar urticaria

All photodermatoses have two factors in common: first, they are precipitated by electromagnetic radiation in the ultraviolet (UV) or visible range, and second, the exact pathomechanism leading to the clinical manifestation of these diseases remains unclear but presumably is based on immunologic mechanisms. In particular, it is still entirely unknown which chromophores are responsible for the initiation of the photochemical reactions that ultimately lead to the development of skin lesions. Essentially all photodermatoses represent well-established indications for phototherapy and photochemotherapy with psoralen plus ultraviolet A (PUVA). The aim of treatment is to prevent the outbreak of disease by increasing the patient's tolerance to sunlight.

At first glance it appears somewhat bizarre to use light treatment to prevent a condition that is caused by light, and the mechanisms by which ultraviolet B (UVB) and PUVA induce tolerance to sunlight are not completely understood. Pigmentation and thickening of the stratum corneum may be important factors for the protective effect, and UVB, high-dose ultraviolet A (UVA), and PUVA are efficient triggers of both. Although these local effects may provide some barrier against photosensitivity, they probably do not suffice to explain the degree of protection induced in many patients. Thus other mechanisms may be involved, since photodermatoses do occur in dark-skinned subjects. The ability of UV radiation to affect the skin immune system was first recognized in the early 1970s in numerous studies. It is therefore now generally accepted that UVA, UVB, and PUVA therapy exert a variety of immunomodulatory effects on human skin and that this is of critical importance for the therapeutic efficacy of phototherapy.
It is important to know that most of the immunomodulatory effects that have been described thus far are not specific for a single wavelength or treatment modality. Under in vitro conditions, UVA, UVB, and PUVA radiation may have very similar or even identical immunosuppressive effects. The actual therapeutic relevance of these effects is mainly determined by the depth of penetration for the type of UV radiation employed. UVB mainly affects epidermal keratinocytes and Langerhans cells, whereas UVA penetrates more deeply into the dermis, thereby affecting dermal fibroblasts, dermal dendritic cells, endothelial cells, and skin-infiltrating inflammatory cells such as T lymphocytes, mast cells, and granulocytes. Many of these effects have been identified by using animal models or through in vitro studies employing cultured human skin cells.

In lesional psoriatic tissue treated with PUVA, the growth of keratinocytes was found to be suppressed, while skin infiltrating lymphocytes were largely depleted (1). It was hypothesized that the selective toxic effects on lymphocytes may be decisive for the therapeutic effect of PUVA in lymphocyte-driven skin diseases such as psoriasis and cutaneous T-cell lymphoma. It has been shown that peripheral T lymphocytes were significantly more sensitive to the cytotoxic effects of PUVA, while antiproliferative effects were similar in all cell types (2). PUVA also induced apoptosis (programmed cell death) in activated T lymphocytes (2), and these cells were significantly more susceptible to PUVA-induced apoptosis than were the monocytes (3). Such a lymphocyte-selective cytotoxic mechanism is an intriguing explanation for the success of PUVA in preventing polymorphic light eruption (PMLE), actinic prurigo, and chronic actinic dermatitis because all three diseases are characterized by lymphocyte-rich infiltrates. UV radiation can induce a variety of immune effects, many of which have been shown to suppress T-cell-mediated responses. UVB can diminish the number of epidermal Langerhans cells as well as alter the T-cell-activating function of these antigen-presenting cells in favor of preferentially stimulating Th1 cells (4). Both UVB and PUVA can induce keratinocytes to secrete an array of cytokines including interleukin (IL)-10, a potent inhibitor of Th2 cells (5). In any case, the mechanisms of prophylactic phototherapy are strongly intertwined with the pathogenesis of the photodermatoses. In the following paragraphs, possible mechanisms of photoprevention are discussed for four photodermatoses.

**PMLE**

The precise etiology of PMLE is still to be elucidated. Two phenomena may provide some insight into the pathogenesis and a rationale for phototherapy. The first phenomenon is the delayed appearance of symptoms relative to sun exposure, typically requiring several hours to days. This indicates a T-cell-mediated immune response hypothetically directed against a cutaneous neoantigen generated by UV radiation (6). The second phenomenon is that PMLE develops as a consequence of the first high-intensity sun exposure after the winter, decreasing during the summer with increasing sun exposure. This natural “hardening” has inspired the use of UV irradiation as a preventive measure (7).

Immunopathologic observations suggest a contribution of a delayed-type hypersensitivity (DTH) reaction to endogenous antigens induced by UV exposure (8,9). According to this hypothesis, UV irradiation converts some precursors in the skin to those antigens that cause the DTH reaction, resulting in the clinical appearance of the disease. The nature of the precursors or antigens, however, remains obscure. Although the hardening phenomenon is one of the basic features of prophylactic phototherapy (10), its mechanism has not been clarified either. It has been attributed variously to increased melanization, stratum corneum thickening, depletion of hypothetical antigens, and immune mechanisms (11). The down-regulation of cell adhesion molecule expression at the hardening site suggests a decrease in DTH reaction (12). In addition, the decreased number of CD1a+ cells indicated the destruction of Langerhans cells exerting a suppressive influence on the DTH reaction. The hardening phenomenon could be induced at the sites irradiated by sufficient doses of UV for reproduction of lesions. Cooper et al. (13) demonstrated that even suberythemogenic UV exposure had a significant down-regulatory effect on the T-cell-mediated response to antigens introduced through irradiated skin. Thus the immunosuppressive effects of UV radiation and the depletion of the hypothetical antigens may be partially responsible for the hardening phenomenon (14). Several keratinocyte-derived factors such as IL-10 and tumor necrosis factor (TNF)-α or prostaglandins may play a role in UVB-induced immunosuppression (15).

The hardening effect in PMLE may last for several weeks, suggesting that it takes quite some time for recovery from UV-induced immunosuppression or depletion of antigens. Di Nuzzo et al. (16)
showed that alterations in the T-cell population induced by a single exposure to UVB remained for 2–3 weeks. Whether repeated exposures, as is usually used in PMLE prevention, have a longer effect has not been determined yet. Clinical experience teaches us that the hardening lasts during the summer as long as it is maintained by repeated exposure to sunlight. The nature of the hypothetical antigens or precursors remains speculative and direct evidence of the depletion of the antigen at the site of induced hardening is missing. Moreover, the hypothetical mechanism of the hardening phenomenon may not be the same in all patients because the clinical features and action spectra of PMLE vary considerably.

**Actinic prurigo**

Actinic prurigo (AP) is a not infrequent, persistent, pruritic, excoriated, papular or nodular eruption mostly of sun-exposed (to a lesser extent, non-exposed) skin. It is worse in summer and frequently does not clear completely in winter. It usually arises in childhood and sometimes remits at puberty. The condition somewhat mimics a persistent variant of the sometimes coexistent PMLE, but is clinically different. A similar condition is hereditary or familial PMLE, predominantly affecting native North, Central, and South Americans and Inuits, in whom the disease is usually more severe and persists into adulthood.

Sun exposure appears to be the inducing event in AP because the disorder is more severe in spring and summer, and abnormal skin responses after monochromator irradiation are present in up to two-thirds of patients, more commonly with UVA than UVB. In addition, simulated solar radiation may on occasion evoke a response resembling that of PMLE, while a dermal, perivascular mononuclear cell infiltrate similar to that of PMLE may sometimes be seen in early lesions. So far there have been no immunohistochemical investigations.

AP may be a slowly evolving DTH reaction, a suggestion further emphasized by the fact that quite a few AP patients have close relatives with PMLE, and there may be a genetic component responsible for converting PMLE into AP. In addition, some patients with the genetic characteristics of AP demonstrate clinical PMLE but have persistent lesions, suggesting a relationship between the two conditions. The inducing chromophores have not been elucidated, but may arguably be similar to those for PMLE. From all these observations we may speculate that similar mechanisms operate in the preventive use of phototherapy or PUVA in this condition.

**Chronic actinic dermatitis**

Chronic actinic dermatitis (CAD) may also represent a T-cell-mediated disease that begins as a photoallergic dermatitis and persists as a chronic dermatitis. The mechanism underlying the transition from photoallergy to CAD, in cases where this disorder is in fact a precursor, remains unclear, and any explanation needs to account for the increased UVB, rather than just UVA, sensitivity of skin that has had no direct contact with relevant chemicals. However, it seems very possible (17) that during the initial localized photoallergic reaction, a normal skin constituent is altered to become antigenic, the induction of the local response apparently beginning with UVA-dependent covalent photochemical binding of hapten to endogenous protein, followed by an eczematous DTH response. In the localized reaction, hapten must be present, but with the progression to CAD, UVB ± UVA irradiation may trigger the immune response at any site, very possibly by the continuing formation of antigenic photoproduct from the ubiquitous endogenous carrier protein. This outcome now also appears possible, and in fact usual, without any prior photoallergy. The histologic and immunohistochemical features of CAD, including the concomitant adhesion molecule expression, are essentially the same as those of persistent allergic contact dermatitis (18,19), or in more severe cases, of cutaneous T-cell lymphoma (CTCL). In particular, the dermal infiltrate consists predominantly of T lymphocytes, with a significant trend toward lower CD4+/CD8+ ratios in patients with more florid histology (18), features which may also occur in persistent, and pseudolymphomatous forms of allergic contact dermatitis. Thus the occurrence of the actinic reticuloid variant of CAD may reflect prolonged and marked endogenous antigenic stimulation.

Allergic contact dermatitis commonly coexists with CAD, often preceding the onset of any photosensitivity (20), reactivity to one or more allergens occurring in 75% of CAD patients (21,22). Sesquiterpene lactone extracts from Compositae plants are implicated most commonly, but other allergens may include fragrance, colophony, rubber, and sunscreens. Such substances apparently do not cause positive photopatch test reactions, although they may perhaps have phototoxic properties in vitro (23–25), including the ability to
oxidize histidine. Thus such responses following exposure to contact allergens might contribute to altering endogenous protein to antigenic forms, leading to CAD, and as also proposed for persistent light reactivity; the avoidance of such substances may conceivably result in gradual resolution of the condition (26,27). In addition, chronic cutaneous immunostimulation from constant patient exposure to airborne allergens during simultaneous UV exposure, as in gardening, may assist in enabling cutaneous immune recognition of the putative endogenous photoallergen.

Although photoallergy may progress to CAD and then to the actinic reticuloid variant (28) in a portion of patients, there is often no evidence of such preceding photoallergy. CAD is thus likely to represent an end state that may arise from a number of predisposing conditions, namely photoallergic contact dermatitis, allergic contact dermatitis to substances with phototoxic potential, endogenous eczema (29,30), perhaps PMLE (31), and finally human immunodeficiency virus (HIV) infection (32). PUVA and UVB may mediate their therapeutic effects in these diseases by suppressing abnormal immune responses (possibly of the Th1 type) through perturbed antigen presentation and/or secretion of down-regulatory cytokines.

**Solar urticaria**

Solar urticaria is caused by an immediate-type antigen-antibody reaction that develops within minutes to a few hours after sun exposure (33). The cutaneous or circulating antigen is produced in the skin from a precursor after the absorption of light energy. Antibodies induced in the serum or plasma by light exposure become photoallergens. Both a circulating photoallergen and reaginic antibodies have been demonstrated (34). A circulating photoallergen in the serum would explain why some individuals with solar urticaria develop a wheal at the site of injection of their own serum that had been exposed to light in vitro before injection (35).

Two types of solar urticaria have been proposed. Type I is an IgE-mediated hypersensitivity to specific photoallergens generated only in solar urticaria patients. Type II is an IgE-mediated hypersensitivity to a nonspecific photoallergen that is generated in both solar urticaria patients and other people (36). Therefore, in type I solar urticaria, passive transfer tests may be positive or negative, while in type II solar urticaria, passive transfer tests are always positive.

The action spectrum differs from person to person, extending from shortwave UV light to the visible range. This diversity can be attributed to differences in the nature of the photoantigens (37). Evidence has been presented that the photoallergen may be localized in the epidermis (38), and this makes it difficult to define the reaction as an IgE-mediated process (39). It has been suggested that the binding sites of IgE on mast cells in the skin remain occupied by the photoallergen during the state of tolerance and that repeated exposure to UV during desensitization specifically blocks IgE-mediated release of histamine from mast cells (40). The phenomenon of photoinhibition which denotes the suppression of light-induced urticaria by subsequent exposure to radiation of longer (and in rare cases shorter) wavelengths has been documented in a few patients (41). The fact that solar urticaria can be treated by irradiation with longer wavelengths than those inducing the condition suggests that photoallergens can be destroyed or converted back into precursors (42); however, this does not explain why preirradiation with the inhibition spectrum suppresses the urticarial reaction (43).

In many patients, chronically exposed skin, such as the face and the dorsa of the hands, becomes tolerant. Based on this observation, patients with solar urticaria are treated with repeated artificial UV exposures. This can be done with narrowband UVB, broadband UVB, UVA alone, with a combination of UVB and UVA, and even with visible light. The major disadvantage of phototherapy is that the tolerance obtained usually lasts only a few days. PUVA therapy appears to be the most effective preventive treatment available. Tolerance to sunlight can be increased 10-fold or more after a single treatment course; the protection provided usually lasts several weeks. Such regimens do not alter tissue histamine content or mast cell numbers, however, and they may act via nonspecific photoinduced stabilization of the mast cell activation mechanism or possibly through the persistent occupation of IgE binding sites with photoallergen. Also, down-regulation of IgE production has been implicated in the therapeutic effect (44).

**References**