Pathomechanisms in Physical Urticaria

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Various exogenous stimuli, e.g., rubbing, pressure, cold, heat, or electromagnetic waves, have been described to elicit whealing reactions, the so-called physical urticarias. They may occur as isolated diseases or in association with other types of urticaria. In many cases, the respective physical factors can be defined exactly, e.g., the degree of temperature changes or the range of eliciting ultraviolet wavelengths. In contrast, the underlying pathomechanisms are mostly still obscure. In the past, often contradictory results have been reported regarding the role of IgE, complement factors, histamine, or even mast cells. Recently, many investigations have been performed on solar urticaria where subgroups of patients with different clinical and pathophysiological features could be defined and mechanisms of tolerance induction have been studied that also offered an efficient treatment modality. Therefore this review will mainly focus on this type of disease as a paradigm of the pathomechanisms of physical urticaria. Key words: mast cells/photoallergen/solar urticaria/tolerance. Journal of Investigative Dermatology Symposium Proceedings 6:135–136, 2001

The physical urticarias form a heterogeneous group of diseases due to the wide range of eliciting stimuli or clinical pictures as well as their association with other types of urticaria. Dermographic, cold, and pressure urticaria often occur together with chronic idiopathic, cholinergic, or other physical urticarias. In contrast, solar or heat urticaria mostly appear either as isolated diseases or are associated only with other types of physical urticaria (Henz, 1989). This suggests that in the former types nonspecific mechanisms play a role, e.g., a lowered threshold of mast cell activation or higher reactivity of target cells. This has been observed in patients with dermographic urticaria, who may also suffer from bronchial hyperreactivity to histamine or metacholine. In contrast, more specific mechanisms may be important in solar and heat urticaria; however, many questions concerning the pathomechanisms of physical urticarias remain to be clarified: How is a physical stimulus transformed to the level of molecular and cellular activation? Do IgE molecules and mast cells play a decisive role? Which mediators derived from mast cells or other sources are responsible for the activation of endothial cells, dermal nerve endings, and the influx of inflammatory cells? What is the role of this inflammatory infiltrate?

In the past, many functional and biochemical studies led to inconsistent or even contradictory results. All these data on the different types of physical urticaria cannot be discussed in detail here, therefore I will focus on the pathomechanisms of solar urticaria, as many interesting investigations have been performed recently.

PHOTOALLERGENS

In about 75% of patients from a large survey reported by Japanese authors, photosensitive activity could be observed in the serum that produced a wheal and flare reaction upon intradermal injection following in vitro irradiation using individual eliciting wavelengths (Uetsu et al, 2000). The fact that irradiated patient serum injected into the skin of healthy recipients fails to produce such a reaction argues against a phototoxic mechanism in solar urticaria. The origin of the postulated circulating photoallergen is still unclear. Blocking the arterial blood supply prevented an urticarial reaction upon irradiation in some patients, suggesting an extracutaneous production of a photoallergen (Ramsay et al, 1970). Leenutaphong et al (1989), however, reported a patient who failed to respond to injection of his irradiated serum, but reacted to eluates from in vivo irradiated skin or irradiated eluates from the epidermis. In addition, stripping off of the horny layer or removal of the suction blister roof abolished urticarial reactions upon irradiation. From this, it may be concluded that in some patients a photoreactive precursor molecule is produced in the epidermis and forms a photoallergen upon activation by UV or visible light. Few attempts have so far been made to characterize the circulating photoallergen. A 25–45 kDa molecule that displayed wheal and flare activity could be demonstrated in patients with an action spectrum between 400 and 500 nm. In one case, reactivity to UVA and short-wave visible light from 330 to 520 nm was associated with an additional high molecular weight activity of 300–1000 kDa, and in patients showing a broad spectrum of activity from UVB to visible light multiple photoallergens seemed to be present (Kojima et al, 1986). This relationship between the individual action spectrum and the nature of the photoallergen is also interesting with regard to the different action spectra prevailing in different groups of patients: among 24 Belgium patients, most reacted to UVA alone or to UVA together with UVB or visible light (Ryckaert and Roelandts, 1998). In a series of 40 Japanese patients the majority (n = 24) was only responsive to visible light. This indicates that the nature of the responsible photoallergen may be dependent on either racial or environmental factors.

Among patients with solar urticaria, two groups (types I and II) could be classified based on their skin reaction to in vitro irradiated serum (Leenutaphong et al, 1989). Type I patients only responded to their own serum, in the type II group a reaction also developed with irradiated serum from normal subjects. Therefore, in the first group,
an abnormal photoreactive factor seems to be produced that can lead to an allergic reaction, but in the type II patients a physiologic precursor molecule forms an allergen upon activation by irradiation. As a consequence, passive transfer experiments, i.e., injection of patient serum in healthy recipients and subsequent irradiation, will only occasionally give positive results with type I serum if specific IgE as well as the abnormal precursor molecule are transferred. In contrast, type II serum transfer usually gives a positive reaction as the photoreactive precursor is also produced by normal subjects. Type I patients are most responsive to visible light, whereas type II patients show a predominant action spectrum in the visible range (Keahey et al., 1984). Induction of unresponsiveness by repeated injection of histamine liberators like polymyxin B, however, did not prevent a urticarial response to irradiation in all patients (Torinuki et al., 1983). In addition, antihistamines often produce an unsatisfactory clinical effect. Interestingly, in cases of heat, cold, and solar urticaria, terfenadine may suppress whealing and itch, whereas the development of erythema still occurs (Cox et al., 1989). These observations correspond with data from a sequential ultrastructural analysis in solar urticaria: within 3 min of UV irradiation, when only erythema had developed, signs of increased endothelial permeability, platelet activation, and swelling of nerve fibers could be observed. Only 10 min later, mast cell degranulation and accumulation of eosinophils accompanied cutaneous whealing. Thus not all mast cell degranulation may be involved in the early phases of solar urticaria. At the time of 4 h, erythema and whealing had almost disappeared, but signs of mast cell degranulation were still present together with the extravasation of eosinophils (Horio et al., 1988). Production and inhibition of solar urticaria by visible light may be considered as a relevant mechanism. The occupation of allergen binding sites on cutaneous tachyphylaxis to histamine seems unlikely as the response to histamine injection was not altered after tolerance induction. General exhaustion of the photoallergen or the precursor molecule by repeated irradiation can be excluded by the fact that solar urticaria can still be evoked in areas shielded during tolerance induction. The occupation of allergen binding sites on mast cells by repeated irradiation may account for the tolerance phenomenon (Leenutaphong et al., 1990). Additionally, specific inhibition of intracellular IgE-dependent signaling in mast cells is discussed, whereas other mast cell activators such as codein and polymyxin B are still active.

Although different therapeutic approaches are described for physical urticarias, an effective treatment often remains a challenging task for the physician. A better understanding of relevant pathomechanisms should help us to obtain more satisfying therapeutic results.

**REFERENCES**


**IGE, MAST CELLS, AND INFLAMMATION**

A pathophysiologic role of IgE in physical urticaria is mainly inferred from passive transfer experiments, but definite proof is still lacking. Positive results in demographic urticaria have been doubted, whereas cold and solar urticaria reactions could be reproduced. The role of mast cells in the pathogenesis of solar urticaria has also to be clarified: an increase of histamine in the effluent blood after local irradiation has been observed together with histologic signs of mast cell degranulation in lesional skin (Keahey et al., 1984). The role of mast cells in the pathogenesis of solar urticaria has also to be clarified: an increase of histamine in the effluent blood after local irradiation has been observed together with histologic signs of mast cell degranulation in lesional skin (Keahey et al., 1984). The role of mast cells in the pathogenesis of solar urticaria has also to be clarified: an increase of histamine in the effluent blood after local irradiation has been observed together with histologic signs of mast cell degranulation in lesional skin (Keahey et al., 1984). The role of mast cells in the pathogenesis of solar urticaria has also to be clarified: an increase of histamine in the effluent blood after local irradiation has been observed together with histologic signs of mast cell degranulation in lesional skin (Keahey et al., 1984).