

REVIEW

The pathogenesis of chronic idiopathic urticaria: new evidence suggests an auto-immune basis and implications for treatment

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We know that about 40% of patients with chronic urticaria (defined as occurrence of daily or almost daily weals for, at least, 3 months) will still be suffering the same problem 10 years later. These patients suffer serious disability in social and economic terms but the cause in the vast majority of them is unknown [1]. Most of the causes, listed in current textbooks of dermatology, may be pertinent to acute but not chronic urticaria. That the cause is obscure in most cases would matter less if the signs and symptoms in these patients could be readily blocked by antihistamine treatment. Unfortunately, this is generally not the case and although some reduction in itching is experienced by most patients with severe urticaria even the newer 'low sedation' antihistamines have, at best, a modest influence on the appearance of the weals themselves.

Patients with chronic urticaria are generally convinced that they are reacting to a dietary constituent or, that their urticaria is due to 'stress'. That emotional stress aggravates urticaria is self-evident, but the role of food factors is more controversial. Juhlin, in 1981 [2], reported that one-third of his patients with chronic urticaria could be shown to react to various food additives on challenge-testing. However, it is our experience that these reactions are difficult to interpret because, if they are repeated, they are almost always negative. Intracutaneous skin-testing is unhelpful and at least in our population of patients with chronic urticaria we are not convinced that reaction to food additives is other than a rare cause. Between 10 and 20% of patients experience a flare-up following oral aspirin challenge [1,2] but the response is rarely specific and imposition of a low salicylate diet usually leads to little or no improvement. The frequency of an atopic history is no greater than that of the general population and the

serum IgE level is within or only slightly above the upper limit of normal in most patients [3].

There have been reports of an increased frequency of thyroid auto-immunity in patients with chronic urticaria. Lenzhoff and Sussman [4] reported that 90 of 624 patients (14%) with chronic idiopathic urticaria and angio-oedema had evidence of thyroid auto-immunity. However, no control group was studied in this investigation.

A similar criticism applies to a second, apparently separate, Toronto study which reported an incidence of thyroid auto-immunity of 13% [3].

Likewise, little progress has been made in recent years in clarification of the molecular and cellular basis of chronic idiopathic urticaria. Histologically, the main feature is a non-specific perivascular infiltrate without significant vascular damage [5]. Other authors [6] have emphasized the intense neutrophil granulocyte component of the infiltrate in some cases and the increased population density of mast cells [7]. There have been a number of reports of pharmacological anomalies of the skin in chronic idiopathic urticaria. That histamine plays a role as a mediator is supported by the finding of elevated blister fluid histamine levels in affected and clinically normal skin in chronic urticaria [8]. However, a number of factors, including the duration of the weals (at least 12 h in most patients) and the propensity of histamine to show tachyphylaxis in respect of vasopermeability argue against histamine as the sole mediator [9]. That enhanced local wealing reactions occur in response to injection of a wide range of vasoactive agents including histamine, kallikrein and vasoactive intestinal peptide into the skin of patients with chronic urticaria has been suggested by a number of authors [10–12]. These results point to a non-specific increase in sensitivity of the cutaneous vasculature to vasopermeability-enhancing agents in chronic idiopathic urticaria, but tell us little about pathogenic mechanisms.

The possibility of one or more circulating histamine-releasing factors being involved in the pathogenesis of

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chronic urticaria was suggested first by Rorsman [13]. Later, Greaves *et al.* [14] and Kern and Lichtenstein [15] demonstrated that histamine release stimulated by anti-IgE from basophils of urticaria subjects was reduced when compared with controls. In 1986, Grattan [16] demonstrated that autologous serum injected intradermally caused a weal-and-flare reaction, lasting about 8 h, in patients with chronic urticaria. Autologous serum from patients who were in remission was found to be inactive. Histologically, the positive autologous serum reaction showed mixed mono-nuclear, neutrophil and eosinophil granulocyte infiltration, reminiscent of a late phase IgE-mediated reaction [17]. It also closely resembled the histology of chronic urticaria, and ultra-structurally showed mast cell degranulation [17]. In an attempt to characterize serum histamine-releasing activity of the patients, the sera of 25 chronic idiopathic urticaria patients were studied [18]. Twenty of these patients demonstrated a positive autologous serum intradermal response and sera of 14 patients elicited histamine release *in vitro* from the basophils of normal donors. Histamine release could also be demonstrated from human skin slices *in vitro* (Francis *et al.* unpublished results). Sera from 10 healthy individuals and five patients with symptomatic dermatographism were inactive both *in vivo* and *in vitro*. Biological significance of the histamine-releasing factor in the patients was suggested by a reduction in the basophil leucocyte count in patients with chronic urticaria compared with basophil counts in blood of healthy control individuals [18] as previously reported by Rorsman [13]. Ultra-filtration established that this activity was confined to the > 100 kDa fraction and protein G affinity column chromatography indicated that most of the histamine-releasing activity was attributable to the IgG isotype.

Since the high affinity IgE receptors (FcεRI) are activated by crosslinking, we proposed that histamine-releasing auto-antibodies crosslinking IgE/FcεRI complex or possibly reacting with other epitopes associated with FcεRI play a fundamental role in urticaria.

The presence of anti-IgE auto-antibodies has previously been reported in the sera of patients with a range of inflammatory dermatoses, including cold urticaria, atopic eczema and urticarial vasculitis [19–21]. However, their pathological importance remained obscure, because they were usually found as immunological binding activity and five out of six anti-IgE auto-antibodies recovered from sera of patients with atopic eczema were biologically inactive [20]. That, however, at least some of the histamine-releasing activity in the sera of chronic urticaria patients is attributable to anti-IgE auto-antibodies is suggested by a number of experimental findings [18]. Sera from chronic urticaria patients appeared to 'de-

sensitize' basophil leucocytes to other chronic urticaria sera and to authentic anti-IgE. More importantly, removal of basophil leucocyte-bound IgE by lactic acid reduced the capacity of the same basophils to respond to both sera of patients with chronic urticaria and anti-IgE. This reduction of response could be partially reversed by passive sensitization to myeloma IgE.

One, additional, striking fact emerged from the experiments. Some chronic urticaria sera evoked histamine release *in vitro* from basophil leucocytes which are unreactive to authentic anti-IgE antibody because of poor sensitization with endogenous IgE (non-IgE-sensitized basophils). This histamine-releasing activity was competitive with IgE since it was blocked by passive sensitization of basophils by myeloma IgE and removal of cell-bound IgE restored responsiveness of the cells. Moreover, basophils of a relatively high serum IgE donor (IgE sensitized basophils) which were poorly reactive to these sera became reactive after removal of cell surface IgE. These results raised the possibility that the histamine-releasing factor in the sera of some patients with chronic urticaria could be reacting with an epitope associated with the binding site for IgE expressed by the high affinity IgE receptor (FcεRI) itself rather than IgE [22].

In order to further investigate this possibility sera from four patients were studied in detail [22]. The monoclonal antibody, 6F7, which reacts specifically with the alpha-sub-unit of FcεRI (FcεRIα) was used as a positive control reagent. The serum from each patient was subsequently subjected to protein G column chromatography. The purified IgG fractions contained the same histamine-releasing activity as the original sera. To explore the possibility that the IgG histamine-releasing activity was attributable to an auto-antibody against FcεRIα, we tested the ability of the human recombinant extracellular domain of the alpha-sub-unit to elicit concentration-dependent inhibition of the histamine-releasing activity of the four patients' sera and the monoclonal antibody 6F7.

There was complete inhibition in all cases and we therefore concluded that the serum of some patients with chronic urticaria contains auto-antibodies reacting with FcεRIα expressed by basophils and mast cells. Thus, the pathogenesis of chronic urticaria, at least in some cases, may have an auto-immune basis, the auto-antibodies responsible for mast cell degranulation being anti-FcεRI, anti-IgE or both. The distribution of the two types of auto-antibodies in a large population of patients remains to be studied, but the relation between histamine-releasing activity on IgE sensitized basophils (anti-IgE like-activity) and that on non-IgE sensitized basophils (anti-FcεRI-like activity) amongst a group of 35 patients with chronic idiopathic urticaria is illustrated in

Fig. 1. It will be seen that most patients' sera possess activity against both types of donor cells. It may be either due to the presence of non-IgE competitive type anti-FcεRIα auto-antibody, or coexistence of anti-FcεRIα auto-antibody and anti-IgE auto-antibody. In any case, it is likely that auto-antibodies against FcεRIα represent the major mechanism in the pathogenesis of wealing in this disorder. Auto-antibodies against IgE presumably may play a role in some patients, but their precise characteristics ought to be further investigated since apparently identical auto-antibodies are found in some normal individuals by immunoassay [21]. Furthermore, serum IgE, a minimum level of which is necessary for sensitization of mast cells and basophils could neutralize anti-IgE auto-antibodies in the circulation. The view that IgG auto-antibodies are functionally important in chronic urticaria also receives support from our recent finding that plasmapheresis induces temporary remission or improvement in patients with chronic idiopathic urticaria who possess autologous serum intradermal reactivity and whose sera possess *in vitro* histamine-releasing activity [23].

Auto-antibodies against receptors are recognized to be involved in the pathogenesis of a number of diseases

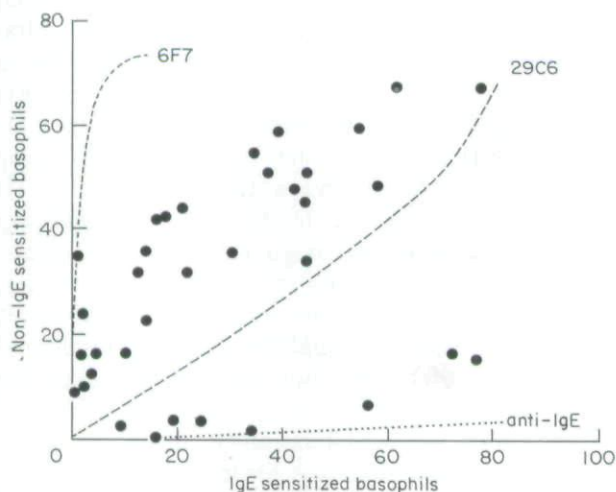


Fig. 1. Correlation of histamine release from endogenously IgE-sensitized and non-IgE-sensitized basophils by sera from chronic urticaria patients with positive autologous serum skin tests. Each point (●) represents data from a patient's serum tested on non-IgE-sensitized basophils from a single healthy donor (serum IgE < 1 IU/ml) and on IgE-sensitized basophils with similar responses from one of two donors (serum IgE > 140 IU/ml). Curves illustrating histamine release by monoclonal anti-FcεRIα antibodies 6F7 (IgE-competitive), 29C6 (IgE non-competitive), and polyclonal goat anti-human IgE, were derived from dose response studies on both non-IgE-sensitized and IgE-sensitized basophils.

including myasthenia gravis, Graves' disease and insulin resistance [24–26]. In most of these cases, unlike our patients with chronic urticaria, the auto-antibodies cause disability by disruption of the normal function of the receptors. However, in chronic urticaria the role of the auto-antibody more closely resembles that of the anti-thyroid stimulating hormone auto-antibody in Graves' disease [26] since in both cases the auto-antibody appears to cause disease by receptor activation.

In addition to the auto-antibodies against IgE and those against FcεRIα, we have identified a distinct type of histamine-releasing activity in sera of other patients with chronic urticaria with a positive autologous serum skin test. It induces histamine release from basophils of only particular types of donors. The activity in one patient, unlike auto-antibodies against FcεRIα from the four patients above, induced secretion from both normal human basophils and rat mast (RBL-2H3) cells. This activity was identified as attributable to IgG auto-antibodies. The study using RBL-2H3 cells suggested an interaction with FcεRI, but not with FcεRIα since the activity is not neutralized by the recombinant extracellular domain of FcεRIα (Hide *et al.*, in preparation).

These patients are of special interest since use of the antibody to map the epitope employing appropriate cDNA probes may well reveal a novel pathway for activation of mast cells and basophils.

Our results raise the possibility that, at least in some patients, chronic 'idiopathic' urticaria may have an auto-immune aetiology. On the same lines as Koch's 'postulates' implicating a particular micro-organism in the pathogenesis of a given disease, similar criteria (Witebsky's postulates) have been proposed to define criteria for auto-immune disease [27]. On this basis we have fulfilled most of the requirements, including passive transfer *in vivo* and *in vitro*. The notion that chronic idiopathic urticaria falls within the group of disorders collectively termed auto-immune diseases is not entirely novel given the reported association with organ specific auto-antibodies [4] and prompts a number of important therapeutic implications. We have already shown that immunotherapy by plasmapheresis leads to effective although short-lived remission [23]. We have also achieved remission by low dose cyclosporin [28], and the use of intravenous gamma globulin therapy [29] is being actively explored. Biotechnology also offers more subtle and specific approaches. These include use of antisense oligo-nucleotides to down-regulate mRNA expression for the relevant sequence of the alpha-sub-unit, and structure-based design by computerized molecular modelling of truncated peptide sequences which block but do not activate the alpha-sub-unit of FcεRI.

The prospects for effective treatment of patients with intractable chronic urticaria at long last show welcome signs of improving.

Acknowledgements

We thank the Eleanor Naylor Dana Charitable Trust, the Kieckhefer Foundation and the Dunhill Trust for financial support. C.E.H.G. was supported by a Fellowship provided by the British Association of Dermatologists. Dr J. Hakimi, J. P. Kochan and R. Chizzonite (Hoffman La Roche, Nutley, NJ) kindly supplied the monoclonal antibodies 6FZ and 29C6, and the human recombinant FC ϵ RI α .

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