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Autoantibodies against the High-Affinity IgE Receptor as a Cause of Histamine Release in Chronic Urticaria

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ABSTRACT

Background Most urticarias are induced by vasoactive mediators such as histamine released from mast cells. Although mast cells are activated by allergens through cross-linking of cell-surface-bound IgE, this mechanism does not appear to explain most cases of chronic urticaria, which, when allergic, infectious, drug-induced, or physical causes cannot be identified, are classified as idiopathic.

Methods We recruited 26 patients with chronic idiopathic urticaria, in whom intradermal injection of autologous serum caused a wheal-and-flare response. Serum from four patients that induced marked histamine release from basophils from a donor with very low serum IgE levels was studied with respect to the IgE dependence of the histamine release, the activity of the IgG fractions, and the neutralizing effect of a recombinant preparation of the soluble extracellular domain of the α subunit of the high-affinity IgE receptor (sFc ϵ RI α).

Results The histamine-releasing activity of the serum was abolished by passive sensitization of basophils with myeloma IgE, enhanced after dissociation of IgE by treatment with lactic acid, and induced by IgG fractions from the serum of all four patients. Preincubation of the serum and isolated IgG with sFc ϵ RI α resulted in almost complete neutralization.

Conclusions Histamine-releasing IgG autoantibodies against the α subunit of the high-affinity IgE receptor are present in the circulation of some patients with chronic urticaria. Autoantibody-induced cross-linking of IgE receptors may be an important mechanism in the pathogenesis of chronic urticaria and other diseases mediated by mast cells.

Chronic urticaria is a common skin disorder characterized by recurrent, transitory, itchy wheals. It is known that the binding of antigen (allergen) to antigen-specific IgE on mast cells and basophils causes the cells to degranulate, resulting in the release of histamine and other vasoactive mediators, which in turn evoke the clinical symptoms^{1,2}. However, no specific allergic trigger for mast-cell or basophil activation has been identified in most patients with chronic urticaria³. It has been shown that in the majority of patients with severe chronic urticaria, intradermal injection of autologous serum elicits an immediate wheal-and-flare response and mast-cell degranulation^{4,5}. In addition, the serum of most such patients induced the release of histamine from basophils of healthy subjects⁶. We recently demonstrated that such histamine-releasing activity in serum from some patients with chronic urticaria was attributable to the presence of autoantibodies with the functional properties of anti-IgE⁶. We also observed, however, that serum samples from some patients induced histamine release from the basophils of a blood donor with a low serum IgE concentration (less than 20 IU per milliliter). The donor's basophils were unresponsive to anti-IgE,⁶ suggesting the presence of non-IgE-dependent histamine-releasing factors. In the current study, we demonstrated the presence of novel autoantibodies against the high-affinity IgE receptor (FcεRI) that induce the release of histamine by acting directly on the αsubunit of FcεRI (FcεRIα) in the absence of IgE.

Methods

Patients and Controls

Patients with chronic idiopathic urticaria, defined as recurrent wheals lasting less than 24 hours and occurring at least twice a week for more than two months, were screened by skin testing with autologous serum. Twenty-six patients with positive skin tests were recruited (6 men and 20 women; mean age, 43 years; range, 19 to 63) ([Table 1](#)). Patients with urticaria resulting predominantly from physical causes were excluded. Antihistamine treatment was stopped at least 48 hours before skin testing was performed or serum samples were collected. None of the patients were taking steroids or immunosuppressive drugs at the time of the investigation.

PATIENT No.	SKIN-TEST RESULT†	NET HISTAMINE RELEASE‡	
		DONOR 1	DONOR 2
	<i>mm</i> ³	<i>percent</i>	
1	81	67±0.3	78±3
2	57	51	45±15
3	18	0	4
4	26	15	77±4
5	15	16	5
6	34	2±0.3	34±5
7	29	46±2	2±1
8	89	3	25±9
9	9	0	2
10	45	0	0
11	73	42	18±4
12	22	17	72±2
13	36	12	4
14	98	23±7	2±1
15	13	0	12
16	14	0	1
17	13	1	0
18	41	16±2	2±1
19	132	2	2
20	35	25±2	15±4
21	19	45	44
22	+	10	2
23	+	4	2
24	+	2	1
25	+	44	21
26	42	-2	0
Controls	0.4±1.4	0.7±0.1	0.1±0.4

*All data for each patient were obtained with serum taken on the same occasion.

†A plus sign indicates a positive skin test (wheal volume, >9 mm³).

‡Plus-minus values are the means ±SE of 3 to 7 independent experiments, except for controls, for which 10 experiments were done.

Table 1. Skin-Test Results for 26 Patients with Chronic Urticaria and 10 Normal Subjects and Differential Release of Histamine from Donor Basophils Induced by Serum Samples.

The control group consisted of 10 healthy members of the laboratory staff without urticaria, 2 of whom had a history of atopy. Informed consent was obtained from all participants, and the investigation was approved by the institution's ethics committee.

Skin Testing with Autologous Serum

Autologous-serum skin tests were performed as previously described⁶. Briefly, 50 microl of autologous serum was injected into the dermis of the volar forearm. The wheal volume (in cubic millimeters) was determined at 60 minutes and corrected for the value obtained after a control injection of phosphate-buffered saline. Wheal volumes exceeding 9 mm³ were considered to indicate a positive response.

Histamine-Release Assay

Histamine-release assays were performed as previously described,⁶ with the use of leukocytes prepared from 60 to 120 ml of peripheral blood from two healthy blood donors. Serum IgE levels were less than 1.0 IU per milliliter in Donor 1 and 190 IU per milliliter in Donor 2, indicating that the basophils of Donor 1 were poorly sensitized with endogenous IgE and those of Donor 2 were essentially fully sensitized.

Leukocytes were incubated for 40 minutes in buffer (usually 200 microl) containing a twofold (or other, as indicated) dilution of serum from the patients or controls; serum IgG fraction; goat antihuman IgE (ϵ -chain specific, Sigma, Poole, United Kingdom) at a dilution that resulted in optimal histamine release (1:1000), unless stated otherwise; IgE-competitive anti-Fc ϵ RI α monoclonal antibody 6F7⁷; 5 microM calcium ionophore A23187 (Sigma) or buffer alone. The calcium ionophore was included in all experiments as a nonimmunologic positive-control histamine-releasing agent. Histamine release was measured by an automated fluorometric assay⁸ and expressed as the percentage of histamine released after subtraction of the amount of spontaneously released histamine and appropriate serum blank values. Spontaneous release accounted for less than 3 percent of the histamine in each of the donor samples.

Passive Sensitization and Dissociation of IgE from Basophils

Mixed leukocytes were suspended in calcium-free buffer and passively sensitized with 10 μ g of myeloma IgE per milliliter (gift of the Binding Site, Birmingham, United Kingdom) or treated with 10 mM lactic acid (pH 3.9) to dissociate IgE, as described elsewhere^{6,9}. An aliquot containing approximately two thirds of the basophils prepared from Donor 1 was passively sensitized with myeloma IgE (sensitized cells), and the remaining cells were kept in buffer alone as control cells. The sensitized cells were thoroughly washed and divided into two aliquots. Then, the IgE was dissociated from one aliquot by treatment with lactic acid (dissociated cells). Cells from each treatment group were washed and then simultaneously challenged as described for the histamine-release assay. Basophils from Donor 2 were prepared similarly, except that an aliquot of cells was treated with lactic acid to remove endogenous IgE (dissociated cells) before being passively sensitized with myeloma IgE (sensitized cells).

Isolation of IgG and Neutralization of Histamine-Releasing Activity

Fractions of IgG were separated from the serum or plasma with a protein G agarose column (Mabtrap, Pharmacia, Milton Keynes, United Kingdom) according to the manufacturer's instructions, except that solutions were prepared without a preservative and 2.5 times the stated

volume of buffer was applied as a washing solution before IgG was eluted. Eluates containing IgG were concentrated with Amicon YM30 membranes or Centricon-30 microconcentrators (Amicon, Stonehouse, United Kingdom). The purity of IgG in the final solutions was confirmed by sodium dodecyl sulfate-polyacrylamide-gel electrophoresis with Coomassie blue staining. No other protein was detected. IgG concentrations in whole serum and IgG fractions were measured by radial immunodiffusion with a kit (the Binding Site).

Serum samples and IgG fractions from the patients were incubated at 37 °C for 30 minutes with various concentrations of the soluble extracellular fragment of Fc ϵ RI α (sFc ϵ RI α) before they were incubated with leukocytes from Donor 1 as described above. The sFc ϵ RI α was obtained from culture medium of stably transfected Chinese hamster-ovary cells⁷.

Results

Histamine Release from Basophils of Two Healthy Donors

The basophils from Donors 1 and 2 were characterized by the release of histamine in response to goat antihuman IgE antibody and calcium ionophore. The basophils from Donor 1 released only a small amount of histamine in response to anti-IgE (mean [$\pm$ SE], 7 $\pm$ 1 percent of total cellular histamine; n = 14 experiments), whereas exposure to A23187 produced a stronger response (52 $\pm$ 3 percent, n = 15). In contrast, the basophils from Donor 2 released a large amount of histamine after stimulation with anti-IgE (68 $\pm$ 1 percent, n = 9) and with A23187 (72 $\pm$ 6 percent, n = 8). These results suggested that the basophils from Donor 1 were poorly sensitized and those from Donor 2 were essentially fully sensitized. This speculation was confirmed by passive sensitization to IgE and dissociation of IgE from the basophils of each donor. None of the serum samples from healthy controls induced substantial release of histamine from the basophils of either donor ([Table 1](#)).

Histamine Release Induced by Patients' Serum

Serum from 17 of the 26 patients with positive skin tests induced histamine release of 10 percent or more in vitro from basophils from one or both of the healthy donors ([Table 1](#)). Serum from five patients (Patients 4, 6, 8, 12, and 15) induced histamine release from Donor 2's basophils (which were responsive to anti-IgE) that was more than four times that induced from Donor 1's basophils (which were unresponsive to anti-IgE); these results suggested the presence of anti-IgE autoantibodies. However, serum from the other 12 patients induced the release of either similarly high levels of histamine from basophils of the two donors (Patients 1, 2, 20, and 21) or levels that were several times higher in the basophils from Donor 1 than in those from Donor 2 (Patients 5, 7, 11, 13, 14, 18, 23, and 26), suggesting the presence of histamine-releasing activity that was not related to anti-IgE. To identify the histamine-releasing factor, we selected four patients (Patients 7, 14, 18, and 20) and studied their histamine-releasing activity in detail. Serum from all four patients induced substantial release of histamine from the basophils from Donor 1 but smaller (Patient 20) or only negligible (Patients 7, 14, and 18) amounts of histamine from the basophils from Donor 2. The histamine-releasing activity from the basophils from Donor 1 induced by the serum from all four patients was heat stable (incubation at 56 °C for 60 minutes, data not shown), negating the possibility of involvement of complement or a major contribution of aggregated IgE. The serum IgE levels of Patients 7, 14, 18, and 20 were 18, 49, 9.6, and less than 1.0 IU per milliliter, respectively.

The Effect of Fc ϵ RI Occupancy by IgE

The effect of Fc ϵ RI occupancy by IgE on serum-induced histamine release was further studied by passive sensitization of basophils with IgE or dissociation of IgE by treatment with lactic acid. The

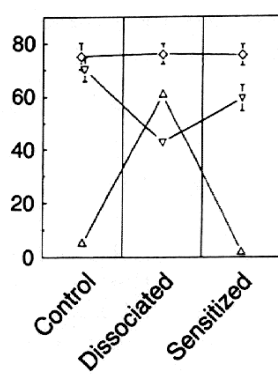
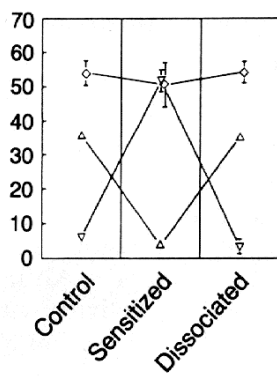
histamine release from Donor 1's basophils induced by the patients' serum was abolished by IgE sensitization ([Figure 1B](#)), as was histamine release induced by monoclonal antibody 6F7 against Fc ϵ RI α ([Figure 1A](#)), whereas anti-IgE-induced histamine release was greatly enhanced ([Figure 1A](#)). Dissociation of IgE from the sensitized basophils by treatment with lactic acid restored the release of histamine evoked by serum from Patients 7, 14, 18, and 20 and by 6F7 to the levels induced by serum of 6F7 from basophils from untreated controls and abolished histamine release evoked by anti-IgE ([Figure 1](#)). The release of histamine from untreated-control basophils of Donor 2 (which were responsive to anti-IgE) induced by serum from Patients 7, 14, and 18 ([Figure 1B](#)) and 6F7 ([Figure 1A](#)) was only marginal, but was greatly enhanced after the removal of IgE by lactic acid ([Figure 1](#)). The release of histamine induced by anti-IgE was substantially reduced by treatment with lactic acid ([Figure 1A](#)). All the above changes were reversed by subsequent resensitization of the cells with IgE ([Figure 1](#)).

Net Histamine Release (%)

A

Donor 1 Basophils

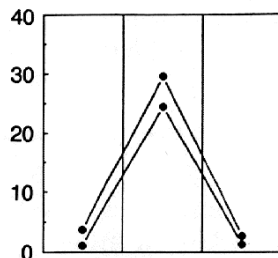
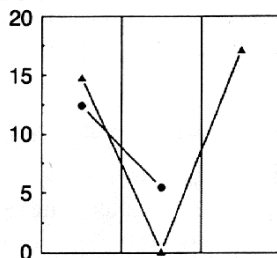
Donor 2 Basophils



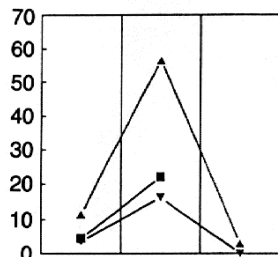
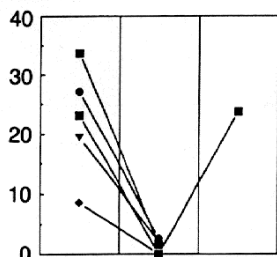
Net Histamine Release (%)

B

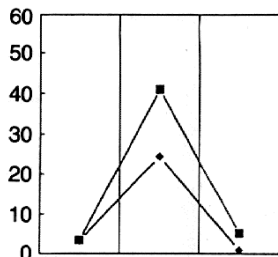
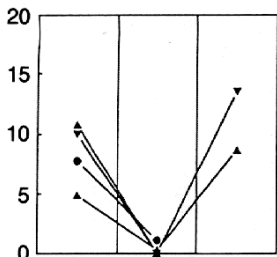
Patient 7



Patient 14



Patient 18



Patient 20

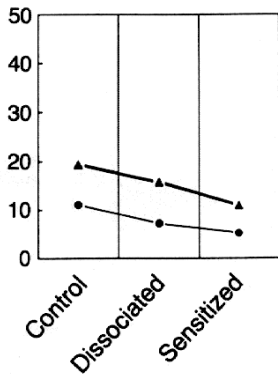
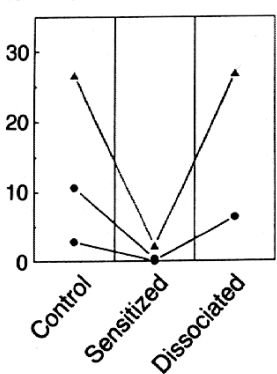


Figure 1. Effect of Passive IgE Sensitization and Lactic Acid-Induced Dissociation of IgE on Histamine Release from Basophils from Donors 1 and 2 in Response to Goat Anti-IgE (inverted open triangles), Anti-FcεRIα Monoclonal Antibody 6F7 (open triangle), and A23187 (open diamond) (Panel A) and to Serum from Four Patients with Chronic Urticaria (Panel B).

Values are the means ($\pm$ SE) of three to six independent experiments with A23187 and anti-IgE and of one experiment with 6F7 (concentration, 50 ng per milliliter) (Panel A). Results obtained with the same batch of serum are shown with the same symbol (Panel B).

Histamine-Releasing Activity of Serum IgG

To determine whether the histamine-releasing activity was detectable in the IgG fraction, serum IgG from each patient was isolated by protein G chromatography and histamine-releasing activity was measured from basophils from Donor 1. All IgG fractions showed histamine-releasing activity with dilution curves similar to those of whole serum and 6F7 ([Figure 2](#)). These data demonstrate that the serum contains IgG with histamine-releasing activity that competes with IgE for the binding region for Fc ϵ RI. A possible candidate for such activity is autoantibody against Fc ϵ RI α . Fc ϵ RI α contains the binding region for IgE^{10,11}.

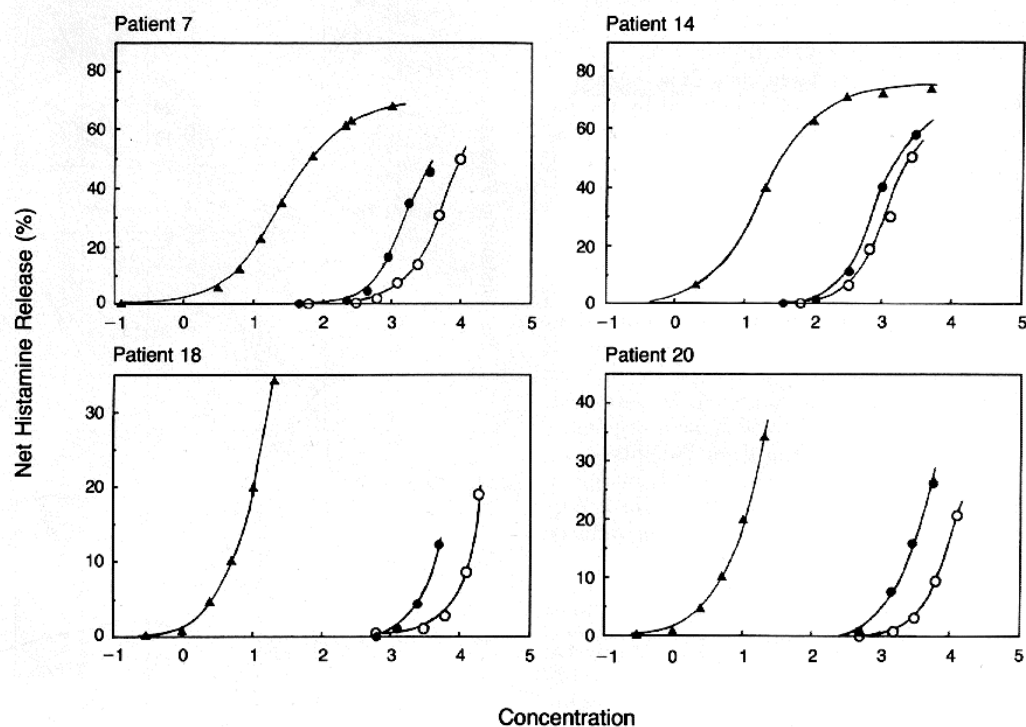


Figure 2. Histamine-Releasing Activity of Whole Serum (solid circle), IgG Fractions from Four Patients with Chronic Urticaria (open circle), and Anti-Fc ϵ RI α Monoclonal Antibody 6F7 (solid triangles).

The concentrations are expressed as log values for IgG in serum and IgG fractions (micrograms per milliliter) and 6F7 (nanograms per milliliter).

Neutralization of Histamine-Releasing Activity by sFc ϵ RI α

Finally, to prove a direct interaction between the autoantibodies and Fc ϵ RI, we studied the effect of sFc ϵ RI α on histamine-releasing activity. As predicted, the histamine-releasing activity of whole serum and 6F7 was neutralized in a concentration-dependent manner by preincubation with sFc ϵ RI α ([Figure 3A](#)). The histamine-releasing activity of the purified IgG was also abolished ([Figure 3B](#)).

The soluble fragment of FcεRIα had no effect on anti-IgE-induced histamine release from either nonsensitized (Figure 3A) or IgE-sensitized (Figure 3C) basophils.

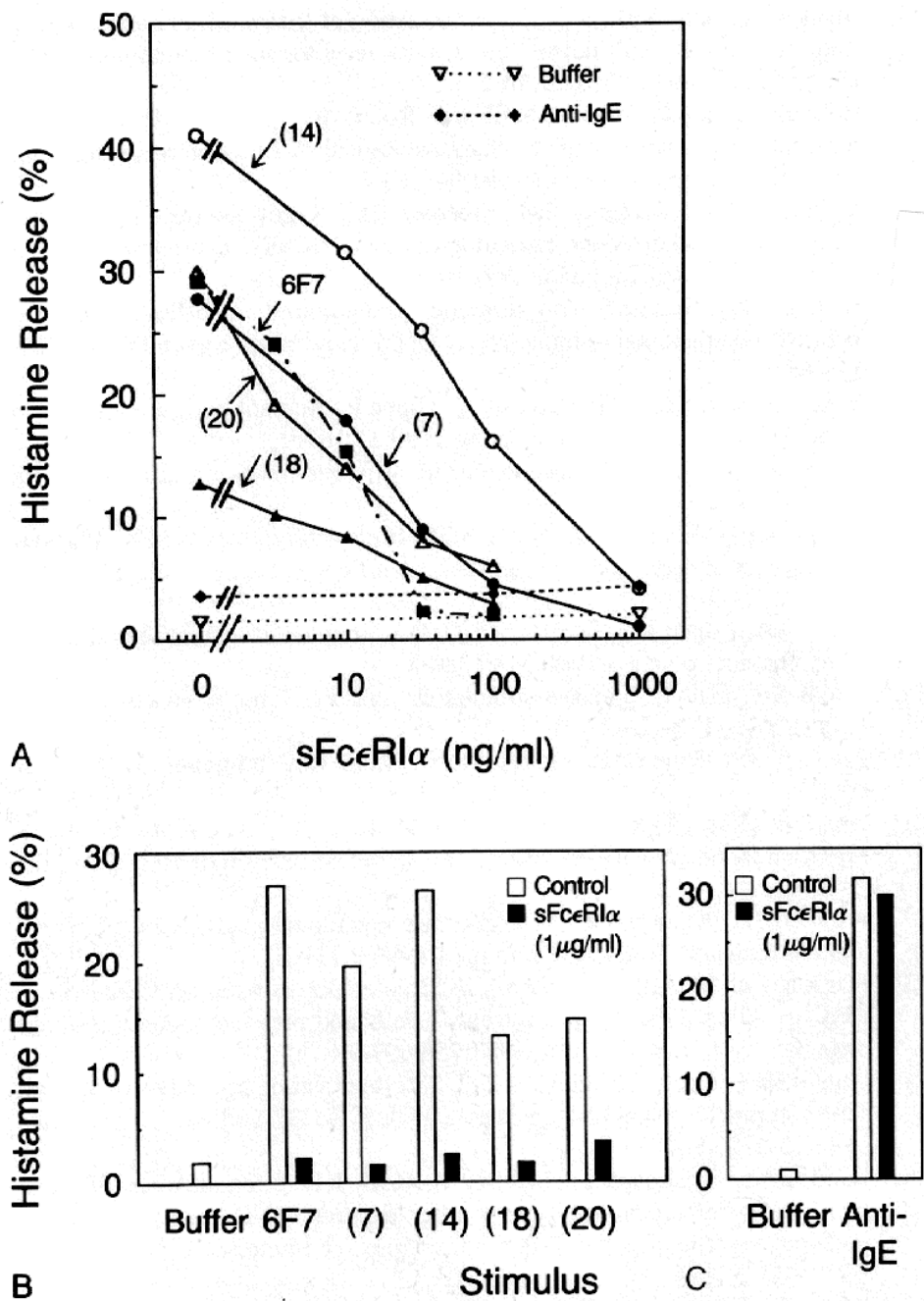


Figure 3. Concentration-Dependent Inhibition by sFcεRIα of Histamine Release from Basophils from Donor 1 Induced by Whole Serum (Panel A) and IgG Fractions (Panel B) from Four Patients with Chronic Urticaria.

The numbers in parentheses are the patients' numbers. The concentration of 6F7 was 30 ng per milliliter. The cells in Panel A and Panel B were not sensitized, and the cells in Panel C were sensitized with myeloma IgE. Anti-IgE antibody was used at a dilution of 1:1000 for nonsensitized cells (Panel A) and 1:50,000 for sensitized cells (Panel C). Histamine release is expressed without correction for spontaneous release.

Discussion

Proinflammatory mediators derived from mast cells and basophils have a pivotal role in the pathogenesis of urticaria and allergic diseases^{2,12}. However, a trigger for the release of mediators can rarely be identified in patients with chronic urticaria³. We recently reported that serum from the majority of patients with severe chronic idiopathic urticaria induced the release of histamine from basophils from healthy subjects⁶. We also identified autoantibodies with the functional properties of anti-IgE in the serum of some patients with chronic idiopathic urticaria⁶. In the present study we identified novel autoantibodies against FcεRIα in the peripheral blood of four patients with chronic urticaria. Purified IgG from the patients' serum induced histamine release with dilution curves similar to those of whole serum and anti-FcεRIα monoclonal antibody 6F7. The recombinant extracellular domain of the FcεRIα caused a dose-related inhibition of histamine release by the serum as well as almost complete inhibition of histamine release by the purified IgG. The mechanism of histamine release induced by the autoantibody against FcεRIα is unusual in that IgE sensitization of basophils is not necessary and can be inhibitory, whereas histamine release induced by allergens, anti-IgE antibodies, and some of the cytokine-like histamine-releasing factors¹³ is dependent on cell-surface IgE. It is noteworthy that all four of our patients who were studied in detail had relatively low levels of serum IgE. Although the histamine-releasing activity of serum from three patients (Patients 7, 14, and 18) competed with IgE for receptors on the basophils from both donors, the histamine release induced by the serum of Patient 20 from the basophils from Donor 2 was apparently unaffected by IgE sensitization (Figure 1B). Since some monoclonal antibodies against human FcεRIα are known not to compete with IgE for binding to FcεRIα and can induce histamine release irrespective of the degree of IgE sensitization of basophils,⁷ it is possible that anti-FcεRIα autoantibodies in some patients may not compete with IgE for receptors. This feature may account for the observation that serum from some patients (Patients 1, 2, 21, and 25) induced substantial histamine release from basophils from both donors (Table 1). Taken together, these results suggest that anti-FcεRI activity is a major cause of histamine release among our patients with chronic idiopathic urticaria (Table 1). Mapping of the precise locations of the epitopes for the autoantibodies is currently under way.

Although a wide range of different autoantibodies have been described, only a limited number are known to be directly involved in the pathogenesis of human diseases^{14,15}. However, the autoantibodies against FcεRIα and IgE in chronic urticaria appear to be closely associated with the pathogenesis of the disease for several reasons. First, they are biologically active in terms of histamine release from basophils from healthy donors in vitro and from skin mast cells in vivo (as suggested by positive autologous-serum skin tests)^{5,6} (Table 1). Second, no such biologically active autoantibody was detected in serum from healthy controls⁶ (Table 1). Third, the number of toluidine blue-stainable basophils in peripheral blood, which would be directly exposed to the autoantibodies, is reduced in patients with chronic urticaria^{6,16}. Finally, patients severely affected by this condition, including three patients studied in this report, had clinical remission (Patients 7 and 14) or improvement (Patient 20) after treatment with plasmapheresis¹⁷ (the three patients were identified as Patients 1, 2, and 4, respectively, in a previous study¹⁷). The histamine-releasing activity of their serum was substantially reduced in vitro in parallel with their clinical response¹⁷. The disease specificity of such autoantibodies remains to be studied, but histologic analysis of the cutaneous reactions to the injection of autologous serum showed mixed leukocyte infiltration resembling the late-phase response of immediate hypersensitivity reactions in patients with atopy⁵. Histamine-releasing autoantibodies may be important in the pathogenesis of other mast cell-mediated diseases as well as chronic idiopathic urticaria. Since the histamine-releasing activity of the anti-FcεRIα autoantibody was effectively neutralized by sFcεRIα (Figure 3), sFcεRIα or its fragments containing the epitope or epitopes for the autoantibodies may have potential as a new therapeutic agent.

The pathologic changes in autoimmune diseases are evoked by the blockage or disruption of the structure or functions of cells or tissues by autoantibodies or autoreactive T cells^{14,18}. Autoantibodies against the thyroid-stimulating hormone receptor in hyperthyroidism (Graves' disease) are an exception: the autoantibodies mimic the action of thyroid-stimulating hormone on target thyroid cells^{14,19}. On the other hand, the anti-FcεRIα autoantibody described in this report is an example in human disease of an autoantibody against a receptor that activates normal cell function by receptor cross-linking. In addition to FcεRI, many other cell-surface molecules, such as IgG Fc receptors (FcγRs),^{20,21} and T-cell surface receptors (antigens)^{20,21,22,23,24,25} are activated by cross-linking^{20,21,22,23,24,25,26,27,28}. Since antibodies against such molecules have been shown to activate them in vitro,^{20,21,22,23,24,25,26,27,28} autoantibody-induced cross-linking of receptors may be an important mechanism in the pathogenesis of many other diseases that result from abnormal cell activation.

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