

Chronic idiopathic urticaria: Profiles of skin mast cell histamine release during active disease and remission

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Chronic idiopathic urticaria (CIU) is characterized by the increased releasability of histamine by mast cells in normal-appearing skin. In active CIU, this abnormality is consistently present. To determine if this finding subsides when the disease goes into remission phase, we analyzed the histamine secretion in patients with CIU in remission (CIUR) compared with that of patients with CIU and in normal control (NC) subjects, with the skin-chamber technique. The profiles of histamine release in sites challenged with compound 48/80 were significantly different in the groups with CIU and CIUR. Furthermore, patients with CIUR did not differ from NC subjects in terms of histamine releasability under compound 48/80 stimulation ($p > 0.1$). These data suggest that the state of excessive skin mast cell sensitivity is a reversible and transient phenomenon in CIU disease. (J ALLERGY CLIN IMMUNOL 1992;89:1139-43.)

Key words: Urticaria, remission, skin, chronic, histamine, compound 48/80, mast cell

During the past two decades, several studies have attempted to determine a better definition for the pathophysiology of CIU.¹ Although no unified theory has yet emerged, some facts are now very well established, namely, the role of histamine,²⁻⁴ the dermal infiltration by activated T cells,^{5,6} and the increased skin mast cell releasability of mediators.¹ Our group has contributed to these efforts by the use of a modified heat-suction blister technique. Indeed, we have demonstrated that the skin-chamber challenge with compound 48/80 (2.4 mg/ml) was characterized by an elevated peak of histamine response in subjects with CIU during the first 2 hours after stimulation.⁷ In a follow-up study, we were among the very few investigators to report on the reproducibility of increased mast cell releasability in subjects with active CIU who had been evaluated prospectively on two separate occasions at 1-month intervals.⁸ Our data documented that the increased histamine secretion by skin mast

Abbreviations used

CIU:	Chronic idiopathic urticaria
CIUR:	Chronic idiopathic urticaria in remission
NC:	Normal control
PBS:	Phosphate-buffered saline
ANOVA:	Analysis of variance
HR:	Histamine release

cells was a persistent finding when CIU remained symptomatic.

Therefore, this observation raised another important question: does this increased skin mast cell HR constitute a transient phenomenon only manifested when CIU is clinically active or is it an intrinsic mast cell abnormality permanently expressed in subjects prone to urticaria? Consequently, we have designed this study to verify whether patients with CIU in complete remission (CIUR) and not receiving treatment, continue to display this state of skin mast cell hyper-reactivity.

MATERIAL AND METHODS

Study group

Thirty-nine skin-chamber studies were performed on 32 subjects after written informed consent was obtained. We studied 14 patients with CIU who had persistent or recurrent idiopathic urticaria lasting for at least 6 weeks and who also had not received corticosteroid drugs for at least 1 month

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TABLE I. Characteristics of the study groups

	N	Age (yr)		Sex
		Mean	Range	F/M
CIU	14	38	25-58	5/5
CIUR	11	39	26-65	6/5
NC subjects	14	20	18-24	6/8

and antihistamine drugs for at least 72 hours before this study. Eleven patients with CIUR were selected on the basis of a clear-cut past history of CIU and an absence of symptoms for at least 6 months, but not more than 24 months, while they were not taking any systemic corticosteroid or classic H_1 and H_2 blockers. Among these 11 volunteers with CIUR, seven volunteers had also been studied in the past while they were symptomatic and are therefore included in the group with CIU. Finally, 14 healthy normal volunteers were selected on the basis of an absence of CIU and of any significant diseases. The three groups were studied between 1987 and 1990, and their demographic characteristics are displayed in Table I. All subjects, excluding the skin lesions of patients with CIU, had a normal physical examination and a normal laboratory workup, including complete blood count, sedimentation rate, SMA-12/60, urinalysis, anti-nuclear antibody, complement profile, and thyroid function.

Skin-chamber technique

Skin-chamber studies were performed as previously reported.^{7,8} In brief, two skin blisters of a 1 cm diameter base were induced simultaneously on nonlesional skin of the volar aspect of one forearm by combination of heat and suction. Each blister was aseptically unroofed, and a collection chamber was appended directly over the denuded blister base. After irrigation of the sites with PBS, each chamber was filled with either PBS alone or with compound 48/80, 2.4 mg/ml, for 30 minutes. The chamber fluids were then replaced by fresh PBS at 30 minutes, 1, 2, 3, and 4 hours after the beginning of the challenge. Samples were recovered at each time and stored at -70°C until histamine determination was performed.

Histamine assay

The levels of histamine in the skin-chamber fluids were assessed by a radioenzymatic assay, as previously reported by our group.⁷ This assay reliably detects histamine concentrations as low as 100 pg/ml in all biologic fluids, and the dosage is not affected by the presence of compound 48/80 in the specimen. All samples of chamber fluids, obtained from 1987 to 1990, were assayed on a single occasion at the end of study.

Analysis of results

The increase in histamine concentration (nanograms per milliliter) in the chamber fluid was calculated in each subject by subtracting the level of histamine at PBS-challenged site from that measured at compound 48/80-stimulated site. Results were expressed in means $\pm$ SEM and were analyzed

TABLE II. Spontaneous HR (nanograms per milliliter $\pm$ SEM) in patients with CIU (14), CIUR (11), and NC subjects (14)

Time (hr)	CIU	CIUR	NC subjects
0.5	0.11 $\pm$ 0.11	0.0 $\pm$ 0.0	0.01 $\pm$ 0.01
1	0.10 $\pm$ 0.10	0.03 $\pm$ 0.03	0.02 $\pm$ 0.01
2	0.36 $\pm$ 0.13	0.16 $\pm$ 0.07	0.08 $\pm$ 0.06
3	0.27 $\pm$ 0.18	0.10 $\pm$ 0.07	0.07 $\pm$ 0.05
4	0.06 $\pm$ 0.06	0.12 $\pm$ 0.08	0.07 $\pm$ 0.07
Cumulative	0.90 $\pm$ 0.47	0.40 $\pm$ 0.15	0.25 $\pm$ 0.19

p. Not significant for patients with CIU versus CIUR or NC subjects, and for patients with CIUR versus NC subjects.

with the one-tail Student's unpaired or paired *t* test. For continuous variable, ANOVA was used for additional statistical tests.

RESULTS

Each set of experiments from these three groups made it possible to achieve the profile of HR from nonlesional skin after challenge with either compound 48/80 or buffer during a 4-hour period.

First, there was no statistical difference in the spontaneous HR (PBS) when either the groups with CIU and CIUR or the groups with CIU and NC subjects were compared (Table II). In addition, in the group with CIU, the histamine levels in skin chamber appended to sites challenged with compound 48/80 were significantly higher (data not presented; *p* < 0.05) than levels of control sites (PBS) and for each time point, as previously reported.⁷

However, after compound 48/80 challenge, unequivocal differences were observed between patients with CIU and CIUR when the HR curves were compared (Fig. 1; ANOVA, *p* > 0.05). In fact, the amounts of histamine recovered were about three to four times higher in patients with active CIU than in subjects with CIUR, particularly at 30 minutes (7.4 ± 2.0 versus 2.0 ± 0.8 ng/ml; *p* = 0.02), 1 hour (9.9 ± 2.3 versus 2.2 ± 0.7 ng/ml; *p* = 0.01), and 2 hours (4.5 ± 0.8 versus 2.9 ± 0.5 ng/ml; *p* = 0.05). More importantly, when our subgroup of seven patients were being analyzed who were evaluated on both occasions, CIU and CIUR, the same difference was observed (Fig. 2) either at 30 minutes (6.3 ± 2.1 versus 2.8 ± 1.2 ng/ml; *p* = 0.09), 1 hour (10.1 ± 2.6 versus 3.3 ± 1.1 ng/ml; *p* = 0.05), or 2 hours (6.8 ± 1.4 versus 3.0 ± 0.7 ng/ml; *p* = 0.05).

Finally, the profiles of skin HR were compared between patients with CIUR and NC subjects. There was no statistical difference in the spontaneous HR (control site) during the 4-hour experiment (Table II).

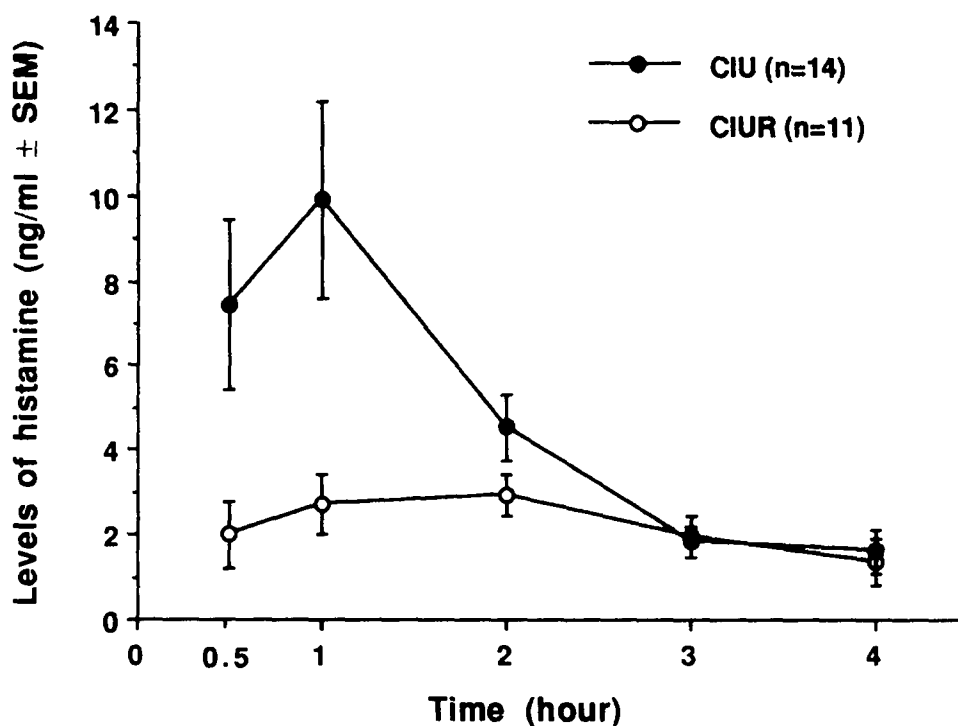


FIG. 1. Profile of HR in skin chamber after stimulation with compound 48/80 in patients with CIU and CIUR.

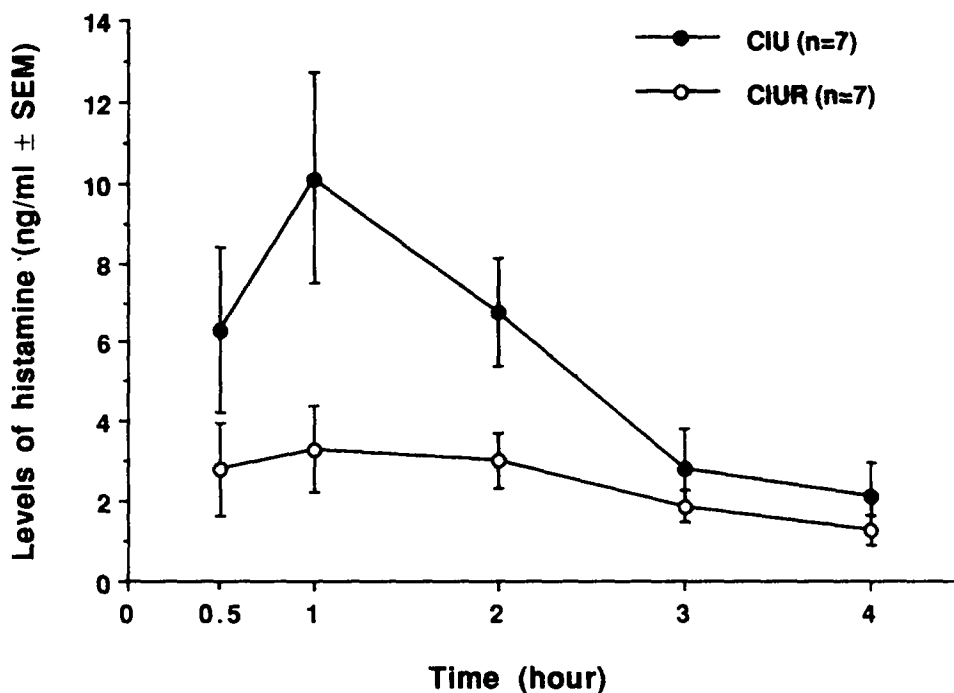


FIG. 2. Comparison of HR after stimulation with compound 48/80 in a subgroup of seven patients studied in active disease, CIU, and in CIUR.

Moreover, the profile of compound 48/80-induced HR was comparable in the two groups (Fig. 3), particularly at 30 minutes (2.0 ± 0.8 versus 3.5 ± 0.6 ng/ml; $p = 0.07$), and 1 hour (2.7 ± 0.7 versus

3.5 ± 0.5 ng/ml; $p = 0.2$). Univariate ANOVA also demonstrated that the means of histamine released during the 4-hour period for the same two groups were not significantly different ($p = 0.2$).

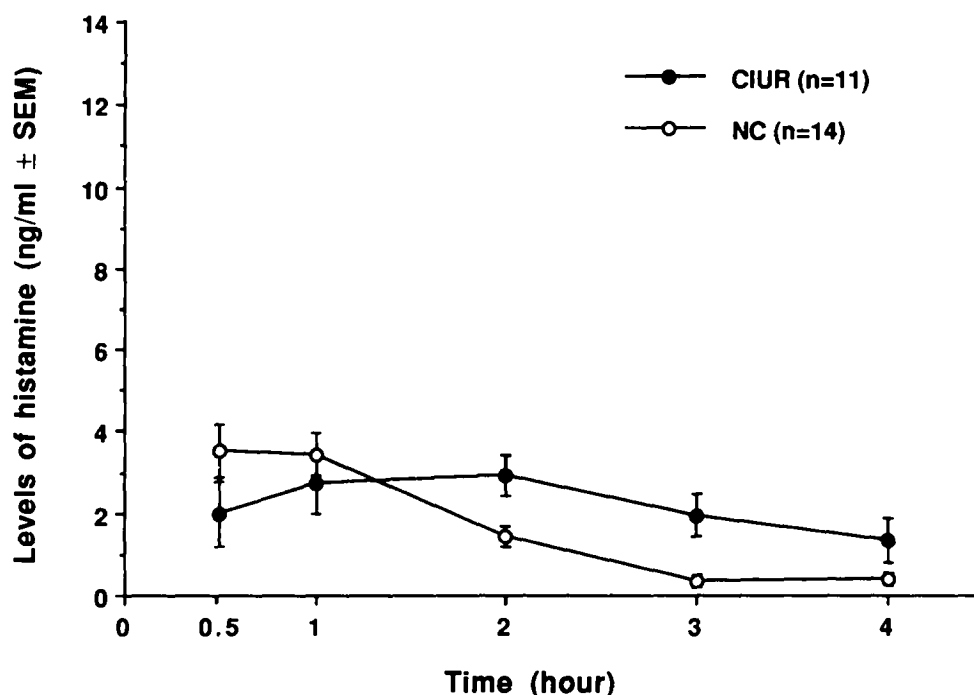


FIG. 3. Profile of HR after stimulation with compound 48/80 in patients with CIUR and NC subjects.

DISCUSSION

Several pathogenic mechanisms have been proposed to understand the origin of CIU, and they have been reviewed elsewhere.¹ Very few of these findings, however, have been reproduced in patients studied at different intervals while they were still symptomatic. In addition, there are rare studies on the outcome of quantitative or qualitative abnormalities of the skin or the blood compartment when urticaria becomes inactive. There is one observation by Grattan et al.⁹ (1985) demonstrating that the serum of some patients with CIU contains a mediator that will produce a wheal reaction on reinjection into their skin, whereas there was no response in NC subjects. When the serum-positive patients were retested after 1 year, only patients whose disease remained active had a positive skin challenge with their freshly drawn serum. Although the number of subjects studied on the two occasions was small, these results suggested to the investigators that a serum mediator could be demonstrated only when the urticaria was active.

In contrast, two groups of researchers demonstrated indirect evidence that patients with urticaria display persistent abnormalities, even though the disease has become inactive. First, there is a study by Cohen and Rosenstreich¹⁰ (1986) who found that urticaria-prone patients exhibit a skin sensitivity to codeine that is 100 times that of allergic individuals or NC subjects. It is important to note that the group studied was very

heterogeneous, poorly defined, and included individuals with varying degrees of urticaria, ranging from asymptomatic to severe cases. These investigators have not, also, prospectively followed this cohort of patients with CIU at different stages of disease activity. More recently, Maxwell et al.¹¹ have demonstrated in patients with CIU, who were asymptomatic for approximately 1 month, a prolonged skin response to intradermal injections of histamine but not to leukotrienes. They suggested that an impaired metabolism of histamine might explain that finding. It would have been interesting to know if these patients would have manifested the same response after a longer period of remission.

Earlier studies conducted by our group⁷ have demonstrated that the skin-chamber challenge with compound 48/80 is a useful model to assess the *in vivo* mast cell response occurring in the skin of patients with CIU. We have found a persistent increased histamine releasability by cutaneous mast cells of patients with active CIU in their normal-appearing skin when they were compared with NC subjects. In the present study, we have observed no difference in the spontaneous HR in either the group with CIU, the group with CIUR, or the group of NC subjects. In our first study (1986),⁷ we found a significant increase in the spontaneous HR in patients with CIU and this finding was only for the 4-hour cumulative challenge. However, in the present study, as well as the study in 1990,⁸

no difference was observed in the HR at PBS sites, either at each interval of time or cumulatively. Overall, these data suggest that the spontaneous HR in nonlesional skin of patients with CIU is not different from that measured in NC subjects. More importantly, in the present study, we have demonstrated that the profiles of skin HR after compound 48/80 stimulation return to a normal level when CIU comes into remission.

In an other study,¹² we have also stressed that higher histamine concentrations were found in the skin of patients with CIU only when the skin mast cells were stimulated with a critical amount of compound 48/80. This finding suggested to us that elevated histamine levels in the skin milieu of patients with CIU were dependent on the degree of cellular activation rather than a defective catabolism of histamine.

Other mechanisms have also been described with respect to the pathogenicity of CIU disease. One of these mechanisms relates to the increased tissue responsiveness to released histamine. In the studies undertaken by Krause and Shuster,¹³ as well as Juhlin and Michaelsson,¹⁴ a larger wheal-and-flare response to intradermal injections of histamine was noted in patients with CIU as opposed to that of NC subjects. It is noteworthy that these authors have not studied their patients while they were in total remission, but only during active disease. Further studies will be necessary to support better this hypothesis.

A second phenomenon implicated in the pathophysiology of CIU includes an increased number of cutaneous mast cells with normal releasability of histamine. A study by Natbony et al.⁵ demonstrated a tenfold increase in mast cell numbers at the lesional sites compared with that of normal individuals. Their evaluation, however, failed to analyze the histology of normal-appearing skin in those patients. Our observations relate to nonaffected skin in which we previously found a normal number of mast cells.⁷ In the present study, no skin biopsies were performed.

In conclusion, a number of epidemiologic studies have suggested that CIU is a self-limited disease lasting between 3 to 5 years.¹⁵ However, the authors could not indicate any useful parameter or clinical characteristics that could help to predict the outcome of the disease. Our data suggest that the increased dermal mast cell histamine releasability is present only when urticaria is active. This observation supports more strongly the possibility of a transient functional im-

balance in sufferers with CIU that could occur after a variety of triggers, rather than an intrinsic skin mast cell abnormality. Further studies are needed to understand better the possible regulatory and modulatory factors involved in this intriguing disease.

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