

Correspondence

Activation of the blood coagulation cascade is involved in patients with chronic urticaria

To the Editor:

Chronic urticaria (CU) is a continuously recurrent whealing of the skin with pruritus and usually defines its course as 6 weeks and more. As reported in the JACI, Asero et al.¹ found that the tissue factor pathway of blood coagulation might be active in patients with CU.

Thirty adult patients (men/women, 11/19; median age, 40.88 years; range, 18-66 years) with CU and 30 normal subjects (men/women, 11/19; median age, 39.93 years; range, 18-58 years) were enrolled in the study. Disease activity was estimated according to the number of wheals presented. Prothrombin time (PT) and partial thromboplastin time (APTT) were measured by the coagulation method (Dade Behring Marburg GmbH, Marburg, Germany). The level of D-dimer was tested with a turbidimetric immunoassay kit (Dade Behring Marburg GmbH). Levels of plasma activated Factor VII (FVIIa) and thrombin-antithrombin complex (TAT) were measured by ELISA kit (FVIIa: American Diagnostic Inc, Stanford, Conn; TAT: AssayPro, St Charles, Mo). Means were compared by *t* test. Differences in the levels of FVIIa, TAT, and D-dimer were assessed by the Wilcoxon-Mann-Whitney nonparametric test. Correlations between the various parameters were assessed by the Spearman test.

Disease activity of patients was graded as slight, 4; moderate, 11; severe, 7; and very severe, 8. The results in Table I show that PT and APTT were in the normal range, and the levels of FVIIa, TAT, and D-dimer were all significantly elevated. Although in the cases studied only the level of FVIIa was significantly correlated with the disease activity ($r_s = 0.5110$; $P < .05$), the positive correlations were shown between levels of FVIIa and TAT ($r_s = 0.6493$; $P < .001$), and TAT and D-dimer ($r_s = 0.6318$; $P < .001$). Because FVIIa, TAT, and D-dimer are the ordinal products of blood coagulation cascade, the correlations indicate that the internal coagulation cascade is clearly activated in CU. However, thrombin generation and secondary fibrinolysis are in a dynamic balance, resulting in the PT and APTT normalization as it may be explained for our current results.

The human skin mast cell is critical in the pathogenesis of CU. Proteinase-activated receptors (PARs), which are all expressed by the human skin primary mast cell, are a novel family of G protein-coupled proteinase-activated receptors including 4 members, PARs 1 to 4. Among them, PAR-2 agonists are able to induce

Ca²⁺ mobilization, which enables histamine release, indicating that PAR-2 regulates inflammatory and immune responses by skin mast cells.² Thrombin, as the agonist for PAR-1, PAR-2, and PAR-3, can cause inflammatory reactions and histamine release of murine mast cells *in vitro*.³ Because FVIIa is the agonist for PAR-2,⁴ in the current CU cases studied, that the FVIIa level, but not level of TAT, was correlated with disease activity, we assumed FVIIa might play a more important role by activating PAR-2 via thrombin-promoted histamine release.

We can add the following findings to those of Asero et al.¹ First, PT and APTT levels were normal, suggesting that minor changes in blood coagulation are not reflected by the coagulation cascade. Second, because our results for FVIIa were closer to the mean levels for normal than those of Asero et al.,¹ the ELISA would be a preferable assay for this sort of study. Third, we agree with the conclusion of Asero et al.¹ and FVIIa may have effects on mast cell degranulation via PARs, very like thrombin. Furthermore, activated factor X (FXa) is also an agonist for PAR-2. Not only thrombin but also other coagulation factors may be involved in the pathogenesis of CU and need to be further studied intensively.

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Fang Wang, MB

Hui Tang, MD

Jin-hua Xu, MD

Ke-fei Kang, MD

From the Department of Dermatology, Huashan Hospital, Fudan University, Shanghai, China. E-mail: huihuicandy@hotmail.com.

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TABLE I. Plasma levels of PT, APTT, FVIIa, D-dimer, and TAT in patients and controls

Identification	Number	PT (s)	APTT (s)	FVIIa (ng/mL)	TAT (pg/mL)	D-dimer (μg/L)
CU	30	10.93 ± 0.54	25.46 ± 2.65	9.59 ± 2.41	420.91 ± 72.66	0.32 ± 0.59
Controls	30	11.15 ± 0.60	26.94 ± 3.37	7.20 ± 1.55	347.36 ± 58.83	0.13 ± 0.05
<i>t</i>		-1.4866	-1.8851	—	—	—
<i>Z</i>		—	—	4.194	-4.377	2.410
<i>P</i> value		>.05	>.05	<.001	<.001	<.05