

Evaluation of serum neuropeptide levels in patients with chronic urticaria

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Sir,

Stress is known to influence the course of a number of skin diseases possibly via neuropeptides, which possess vasoactive properties. Neuropeptides are implicated in non-immunologic mast cell activation and histamine liberation contributing to lesion induction in chronic urticaria. Substance P (SP), stem cell factor (SCF), and nerve growth factor (NGF) were found to be the foremost neuropeptides triggering mast cell activation, as well as calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), and neuropeptide Y (NPY). [1]

The aim of this study was to compare the levels of selected neuropeptides in serum samples of 57 chronic urticaria patients with 46 age and sex-matched healthy controls. Descriptive features of the study group are presented in [Table 1]. In all patients, autologous plasma skin test was performed and severity of urticaria was determined by urticarial activity score (UAS). Levels of neuropeptides in patients and controls is depicted in [Table 2]. The only neuropeptides showing significant elevation in urticaria patients compared to controls were stem cell factor and substance P.

Table 1: Descriptive and clinical characteristics of patients and controls

	Patients (n=57)	Controls (n=46)	P
Sex F/M	43/14	35/11	0.93*
Age (mean±SD)	39.140±17.099	33.347±11.702	0.052**
Urticarial activity score (mean±SD)	1.789±1.633	-	-
Autologous plasma skin test positivity, number of patients (%)	25 (43.9)	-	-

*Chi-square **Independent-samples T test, SD: Standard deviation

Table 2: Serum neuropeptide values in patients and control subjects

	Group	Mean±SD	Median (min-max)	*P
SCF (ng/ml)	Patients	4.76±5.42	2.70 (0.41-21.69)	0.001
	Controls	2.79±3.83	1.25 (0.47-18.80)	
CGRP (ng/ml)	Patients	0.49±0.66	0.36 (0.12-5.22)	0.052
	Controls	0.47±0.15	0.44 (0.26-0.98)	
VIP (ng/ml)	Patients	0.60±0.17	0.58 (0.36-1.30)	0.089
	Controls	0.56±0.11	0.52 (0.42-1.08)	
SP (pg/ml)	Patients	31.47±7.66	33.90 (16.20-46.70)	0.000
	Controls	16.23±3.13	16.60 (10.20-23.10)	
NPY (ng/ml)	Patients	0.67±0.34	0.59 (0.26-1.80)	0.235
	Controls	0.72±0.36	0.62 (0.33-1.96)	
NGF (pg/ml)	Patients	15.33±3.48	15.19 (10.70-30.51)	0.287
	Controls	14.76±3.95	14.84 (7.94-25.92)	

*Mann-Whitney U Test, SCF: Stem cell factor, CGRP: Calcitonin gene-related peptide, VIP: Vasoactive intestinal peptide, SP: Substance P, NPY: Neuropeptide Y, NGF: Nerve growth factor, SD: Standard deviation

In a previous study, no statistically significant difference in serum stem cell factor levels was found in urticaria patients with positive autologous serum skin test compared to controls. [2] In contrast, our study demonstrated significant elevation of this peptide in chronic urticaria patients compared to controls while there was no significant difference in levels between APST-positive and negative patients. Although substance P has mostly been assessed in chronic skin diseases, there is a single recent study performed in chronic urticaria in which no significant difference was found in substance P levels between patients and controls. However, in a few patients higher serum substance P concentrations were suggested as a trigger of urticarial symptoms. [3] In our study, stem cell factor and substance P were determined as the most important neuropeptides in the development of urticaria [Table 3]. Absence of a significant difference in neuropeptide Y levels from controls could be explained by the selective uptake of this peptide by lesional skin. In addition, on logistic regression analysis, neuropeptide Y was found as the selected peptide predictive of APST positivity [Table 4]. Though recent evidence has identified the significance of neuropeptide Y in pathogenesis of autoimmune diseases, [4] its role in the pathogenesis of autoimmune chronic urticaria may be considered a novel observation of the present study. These results require further investigation for validation.

Table 3: The effect of neuropeptides on development of urticaria in 103 individuals

Risk factors	B	SE	Wald	*P	*R	95% CI for exp (B)	
						Lower	Upper
SCF	0.26	0.111	1.308	0.253	1.135	0.914	1.0410
CGRP	1.912	0.398	3.671	0.055	1.148	0.021	1.047
VIP	0.129	4.085	0.001	0.975	1.138	0.000	3440.492
SP	0.784	0.215	13.285	0.000	2.191	1.438	3.342
NPY	2.460	1.216	4.091	0.043	11.708	1.081	127.292
NGF	0.175	0.159	1.199	0.273	1.191	0.871	1.628

*Logistic regression analysis, SCF: Stem cell factor, CGRP: Calcitonin gene-related peptide, VIP: Vasoactive intestinal peptide, SP: Substance P, NPY: Neuropeptide Y, NGF: Nerve growth factor, CI: Confidence interval, SE: Standard error

Table 4: The effect of selected neuropeptides on APST positivity in urticaria patients

Risk factors	B	SE	Wald	*P	*R	95% CI for exp (B)	
						Lower	Upper
SP	-0.083	0.054	2.335	0.126	0.921	0.828	1.024
NPY	4.211	0.829	5.304	0.021	67.455	1.873	2429.982
NGF	0.153	0.130	0.904	0.237	0.858	0.665	1.106

*Logistic regression analysis, SP: Substance P, NPY: Neuropeptide Y, NGF: Nerve growth factor, CI: Confidence interval, SE: Standard error

Bonini et al. have previously reported elevated serum nerve growth factor levels in 14 patients with chronic urticaria. [5] In contrast, our study found elevated nerve growth factor levels only in APST-negative patients. Release of neuropeptides in skin microenvironment could be insufficient to cause increase in blood concentration or rapid inactivation of this peptide might account for our results. When the role of mast cells in the pathogenesis of chronic urticaria was considered, this finding in patients might be attributed to the limited effects of nerve growth factor on mast cell activation, while it is comparable to stem cell factor regarding its effects on mast cell differentiation. [1]

Calcitonin gene-related peptide might possess initial effects in tissue rather than peripheral blood. Being a weak histamine releaser, [1] it seems to have limited effects on mast cells compared to substance P, as confirmed by our results. In addition, the explanation for similar vasoactive intestinal peptide levels in patients and controls could be the raised metabolism and increased sensitivity of microvasculature to this peptide in chronic urticaria patients.

Previous studies have not demonstrated that any serum markers correlated with disease severity in chronic urticaria. This study too did not find any correlation of levels of neuropeptides with disease activity (urticarial activity score). However, since the mean UAS in our patients was classified as mild, it is suggested that UAS correlation needs to be re-evaluated in patient groups with moderate and severe disease activity also.

In conclusion, this study demonstrated the participation of serum stem cell factor, substance P, and neuropeptide Y among the selected neuropeptides in the pathogenesis of chronic urticaria. Moreover, a novel finding of this investigation was revealing of neuropeptide Y as the most important peptide predictive of APST positivity. The role of neuropeptides in this complex system of interactions seems to be an important component of chronic urticaria pathogenesis and is, therefore, worth exploring in further clinical studies.

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