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INVESTIGATIVE REPORT

Plasma Neuropeptides and Perception of Pruritus in Psoriasis

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The aim of this study was to evaluate the influence of selected neuropeptides on itching in psoriatic individuals. Fifty-nine patients (43 pruritic and 16 non-pruritic) with psoriasis were included in the study. The severity of psoriasis, measured using the Psoriasis Area and Severity Index scale, ranged between 2 and 43.7 points. The intensity of pruritus was evaluated using a Visual Analogue Scale. The plasma levels of substance P, vasoactive intestinal peptide, calcitonin gene-related peptide and neuropeptide Y were measured radioimmunologically. The plasma level of neuropeptide Y was significantly decreased in patients with pruritus compared with those without pruritus (21.6 ± 39.6 pg/ml and 144.3 ± 385.7 pg/ml, respectively; p=0.03). Levels of other neuropeptides did not differ significantly between pruritic and non-pruritic patients; however, a tendency to lower plasma levels of substance P and vasoactive intestinal peptide in patients with itching was noted. Moreover, a significant negative correlation was observed between pruritus severity and levels of substance P (r = –0.36; p=0.02), as well as between pruritus severity and plasma levels of vasoactive intestinal peptide (r = –0.34; p=0.03). The imbalance of neuropeptide activity in the sera of pruritic subjects may suggest a role for neuropeptides in perception of itching in psoriatic individuals. ***Key words: psoriasis; neuropeptides; substance P; calcitonin gene-related peptide; vasoactive intestinal peptide; neuropeptide Y.***

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Psoriasis is one of the most common chronic inflammatory skin diseases. Its aetiopathogenesis is complex, multi-factorial and not fully understood. It is estimated that approximately 1–2% of the general population of highly developed countries has psoriasis (1). Several factors are usually thought to play an important role in the development of psoriatic lesions, including genetic predisposition, hyperproliferation of keratinocytes, vascular alterations in the skin, up-regulation of cytokines, and immunological and auto-immunological disturbance (1, 2). In addition, environmental factors, such as stress, infections, some drugs, alcohol intake and smoking, can provoke exacerbation of psoriasis (1, 3). Stress may induce worsening of psoriasis by several possible mechanisms. It may lead to activation of the hypothalamic-pituitary-adrenal axis with hypersecretion of corticotrophin-releasing hormone (CRH), which has pro-inflammatory properties and may activate mast cells, stimulate angiogenesis and modulate immune cells (4, 5). Both CRH and its receptors have been noted to be up-regulated in psoriatic skin (5). Stress may also be responsible for exacerbation of psoriasis, by releasing numerous pro-inflammatory oligopeptides, such as substance P (SP), calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), neuropeptide Y (NPY) or somatostatin from dermal nerve endings (6–8). These substances may degranulate mastocytes, activate dendritic cells, lymphocytes, macrophages and neutrophils, and may produce vascular changes in the skin by inducing angiogenesis, dilatation of vessels and stimulation of nitric oxide synthesis. They also stimulate synthesis and release of many pro-inflammatory cytokines from mast cells, lymphocytes, dendritic cells, fibroblasts and keratinocytes, induce expression of vascular adhesion molecules on endothelium and may exert a hyperproliferative effect on keratinocytes (6, 7, 9). Therefore, the release of neuropeptides from nerve endings during stress may lead to the exacerbation of existing psoriatic lesions or development of new ones. The importance of the nervous system in psoriasis is also supported by the observation that psoriatic lesions resolve in areas of sensory denervation (7).

Approximately 70–80% of psoriatic patients have moderate to severe pruritus (10, 11). Although this unpleasant sensation is common in psoriasis, this symptom was, for a long time, underestimated and until now little has been known about its pathogenesis in psoriasis. This lack of knowledge about the pathogenesis of pruritus in psoriasis corresponds to a lack of effective therapies. Itch in psoriasis is unresponsive to most available anti-pruritics (12). A recent review of available treatment modalities for pruritus in psoriasis mentioned several therapy possibilities, but they were generally oriented towards healing of psoriatic lesions and, as a consequence, concomitant reduction of pruritus (12). However, the improvement in psoriatic lesions may take several weeks.

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The severity of pruritus correlates only poorly, if at all, with disease severity (10, 11). Histamine, one of the major mediators of pruritus, seems not to be involved in pruritus development in psoriasis, as there was no correlation between pruritus intensity and histamine plasma level and no difference in histamine plasma levels between pruritic and non-pruritic patients with psoriasis (13). Moreover, a treatment with anti-histaminics rarely brings relief, and this seems to be connected with its sedative effect rather than with anti-histaminic properties (11). In our previous study we found that the presence and intensity of pruritus in patients with psoriasis may be related to perceived stress (14). Recently, Nakamura et al. (15) demonstrated increased density of nerve fibres within the skin of psoriatic patients with pruritus compared with non-pruritic patients. In addition, significantly higher expression of SP-positive nerve fibres around dermal vessels was found in patients with pruritus compared with subjects without itching (15). It is also known that intradermal injection of SP or VIP provokes itching in healthy subjects (16, 17). In addition, increased expression of several neuropeptides was detected in other pruritic dermatoses, such as atopic eczema and prurigo nodularis (17–19). To prove whether neuropeptides are involved in the pathogenesis of pruritus in psoriasis we correlated the plasma levels of SP, CGRP, VIP and NPY with the presence of pruritus and its intensity in patients with psoriasis.

MATERIALS AND METHODS

The study was approved by the local ethics committee (KB 3/2005). All patients agreed to participate in the study and gave their written consent.

Patients and sample collection

General demographic and clinical data were obtained from all patients using a specially designed anonymous questionnaire. All patients underwent careful dermatological examination: the severity of psoriasis was assessed according to the Psoriasis Area and Severity Index (PASI) (20) and pruritus intensity according to a standard Visual Analogue Scale (VAS) (11). Although the VAS is a highly subjective scale, it has been widely accepted for pruritus intensity assessment (18, 21) and was also used by our group in previous studies on pruritus (11, 13, 14). Both disease severity and pruritus intensity were measured on the same day as blood sampling. The study population comprised 59 patients in the active stage of psoriasis, who were recruited consecutively from inpatients over a 1-year period. There were 33 men (55.9%) and 26 women (44.1%) in the age range 23–89 years (median 47 years; quartiles 31–51 years). The patients had not been under any anti-psoriatic and anti-histaminic treatment (both systemic and topical) for at least 3 weeks before inclusion in the study. Subjects with other concomitant dermatological or systemic disorders that might influence achieved results were excluded from the study. The detailed characteristics of the enrolled patients are shown in Table I. The control group comprised 32 healthy non-stressed volunteers (27 men and 5 women) age range 18–63 years (median 35.5 years).

Blood samples (3 ml) were collected from patients at identical time points (between 07.00 h and 08.00 h) in order to control for the circadian rhythm of studied parameters. Blood samples were collected using a cooled disposable syringe with ethylenediamine tetra-acetic acid (EDTA) (1 mg/ml of blood) (S-Manovette®, Sarstedt, Nürnberg, Germany). Immediately after blood collecting, a protease inhibitor was added, samples were centrifuged (1600 rpm), and the plasma was stored at –70°C for further analysis.

Table I. *Clinical characteristics of patients with psoriasis*

Parameter	*n* (%)
Age (years)	
< 40	22 (37.3)
40–54	27 (45.8)
≥ 55	10 (16.9)
Gender	
Women	26 (44.1)
Men	33 (55.9)
Type of psoriasis	
Psoriasis vulgaris	43 (72.9)
Arthropathic psoriasis	16 (27.1)
Positive family history of psoriasis	
Yes	24 (40.7)
No	35 (59.3)
Positive family history of atopic diseases	
Yes	14 (23.7)
No	45 (76.3)
Psoriasis onset (years of age)	
<35	43 (72.9)
≥35	16 (27.1)
Disease duration (years)	
<5	7 (11.9)
5–19	29 (49.1)
≥20	23 (39)
Duration of the last exacerbation (months)	
<3	7 (11.9)
≥3	52 (88.1)

Evaluation of plasma concentration of neuropeptides

Plasma concentrations of SP, CGRP, VIP, and NPY were measured by radioimmunoassay (RIA) using commercially available kits (SP – RIK7451; CGRP – RIK6009; VIP – RIK7161, NPY – RIK7180; Peninsula Laboratories Inc., San Carlos, CA, USA) according to the manufacturer's instructions. The method of determination of all neuropeptide plasma concentrations was similar. During the first day a specific antibody against the analysed neuropeptide was added to each 100 µl of evaluated plasma sample diluted with 100 µl of RIA buffer (supplied in the kit) and the samples were incubated at 4°C for 20 h. All analyses included negative (200 µl RIA buffer) and positive (100 µl antibody +100 µl RIA buffer) controls. On the second day 100 µl of solution containing a standard neuropeptide labelled with radioactive iodine (^{125}I) isotope (supplied in the kit) was added to each sample and all samples were incubated for further 20 h. Next, 100 µl of goat serum against rabbit immunoglobulin G (IgG) was added and the samples were incubated for a further 90 min. Finally, the samples were centrifuged at 3000 rpm (4°C, 20 min), the supernatant was removed, and the radioactivity of each sample was measured by Gamma-Counter 1275-Minigamma (LKB, Wallac, Turku, Finland). The plasma concentration of neuropeptides was calculated using a standard curve (prepared using solutions with known amount of neuropeptides: 1, 2, 4, 8, 16, 32, 64 and 128 pg). A higher level of radioactivity in the centrifuged sample corresponded to a lower plasma concentration of neuropeptides.

Statistical analysis

Statistical analyses were performed using Statistica 6.0 software (Statsoft, Kraków, Poland). Minimum, maximum, median values and quartiles were calculated. To evaluate significant differences between groups of patients, Mann-Whitney *U* test or Kruskal-Wallis analysis of variance (ANOVA) were used, where appropriate. Spearman's rank correlation test was used to assess possible correlations between studied parameters. *p*-values less than 0.05 were considered significant.

RESULTS

Forty-three (72.9%) of the patients with psoriasis had pruritus, the remaining 16 (27.1%) did not have this symptom. The median pruritus intensity measured according to the VAS was 5.5 points (quartiles 4–7, range 2–10). The median disease severity in pruritic subjects assessed according to PASI was 12.8 points (quartiles 8.3–20.6, range 2.4–42) and was slightly higher than in patients without pruritus (median 9.5 points, quartiles 6.2–15.2, range 2–34.5, p=0.16). We did not observe any significant correlation between pruritus intensity and disease severity (r=0.27; p=0.09). Duration of the current disease exacerbation was the only clinical parameter that influenced itching intensity in psoriatic patients (r=0.35; p=0.02), although the presence of pruritus was not dependent on the duration of the current disease worsening (data not shown). None of the other analysed clinical parameters (age, gender, type of psoriasis, positive family history of psoriasis and/or atopic diseases, time of psoriasis onset or disease duration) significantly influenced the presence or intensity of pruritus (data not shown).

The comparison of plasma concentrations of SP, CGRP, VIP and NPY between pruritic and non-pruritic patients with psoriasis is presented in Table II. Median NPY plasma level in patients with pruritus was significantly decreased compared with patients without pruritus (median 7.1 pg/ml, quartiles 5.7–9.3 pg/ml, range 3.1–232.1 pg/ml vs. median 21.4 pg/ml, quartiles 7.3–51.6 pg/ml, range 4.8–1514.8 pg/ml, respectively; p=0.03) (Fig. 1). The concentrations of other neuropeptides did not differ significantly between psoriatic patients with and without pruritus (Table II). The median plasma levels of neuropeptides in healthy non-stressed volunteers were as follows: SP 57.9 pg/ml (quartiles 44.6–82.6 pg/ml, range 30.8–175.3 pg/ml), CGRP 13.5 pg/ml (quartiles 7.3–24.9 pg/ml, range 3.1–106.1 pg/ml), VIP 60.1 pg/ml (quartiles 45.2–73.9 pg/ml, range 29.4–91.0 pg/ml), NPY 8.2 pg/ml (quartiles 6.4–14.2 pg/ml, range 4.6–548.7 pg/ml). The plasma concentration of CGRP and VIP was significantly elevated in psoriatic patients compared with healthy volunteers (p <0.01 and p=0.04, respectively) (for details, see 22).

When analysing the intensity of pruritus according to plasma concentration of SP, CGRP, VIP and NPY in patients with pruritus we observed weak, but significantly negative, correlations between pruritus intensity and SP plasma level (r=–0.36, p=0.02) (Fig. 2) as well as VIP plasma level (r=–0.34, p=0.03) (Fig. 3). There was no significant correlation between itching intensity and CGRP (r=0.11, p=0.47) and NPY plasma level (r=–0.2, p=0.19). No correlations between psoriasis activity (assessed by PASI) and analysed neuropeptides (SP, CGRP, VIP, NPY) were observed, either in the patients with pruritus, or in the whole group of patients: (SP) r=–0.08 p=0.59 and r=–0.15 p=0.27, (CGRP) r=–0.13 p=0.42 and r=–0.02 p=0.89, (VIP) r=–0.01 p=0.97 and r=–0.02 p=0.89, (NPY) r=–0.05 p=0.76 and r=–0.02 p=0.9.

Table II. *Comparison of plasma concentration of selected neuropeptides between psoriatic patients with and without pruritus (all results in pg/ml)*

	Patients *with* pruritus Median (quartiles) (min–max)	Patients *without* pruritus Median (quartiles) (min–max)	p^*
Substance P	50.5 (34.1–79.3) (10.4–206.0)	69.5 (46.9–106.3) (27.4–184.8)	0.11
Calcitonin gene-related peptide	46.5 (9.7–79.6) (2.7–160.3)	29.1 (6.6–57.3) (4.4–128.2)	0.33
Vasoactive intestinal peptide	63.8 (50.6–74.2) (1.7–141)	75.2 (63.9–85.9) (48.3–118.3)	0.07
Neuropeptide Y	7.1 (5.7–9.3) (3.1–232.1)	21.4 (7.3–51.6) (4.8–1514.8)	0.03

Min: minimum; max: maximum.
*Mann-Whitney *U* test.

DISCUSSION

Pruritus is an unpleasant sensation that provokes a desire to scratching. Many patients with psoriasis suffer from

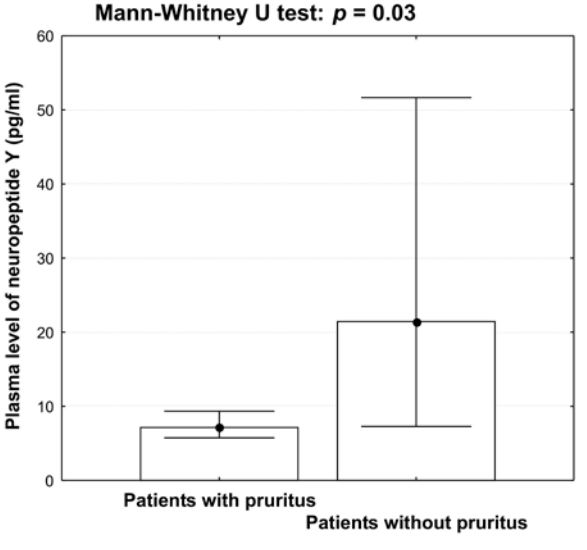

Fig. 1. Comparison of neuropeptide Y plasma level between pruritic and non-pruritic patients with psoriasis. ⌶ 25%–75%. ● Median

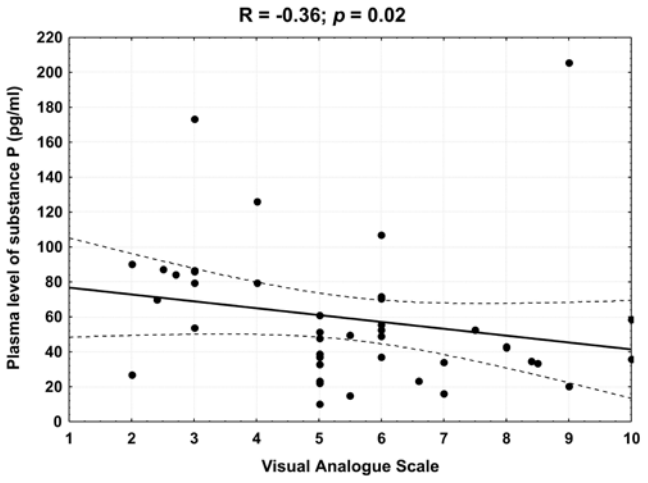

Fig. 2. Correlation between pruritus intensity (VAS 1–10) and plasma level of substance P.

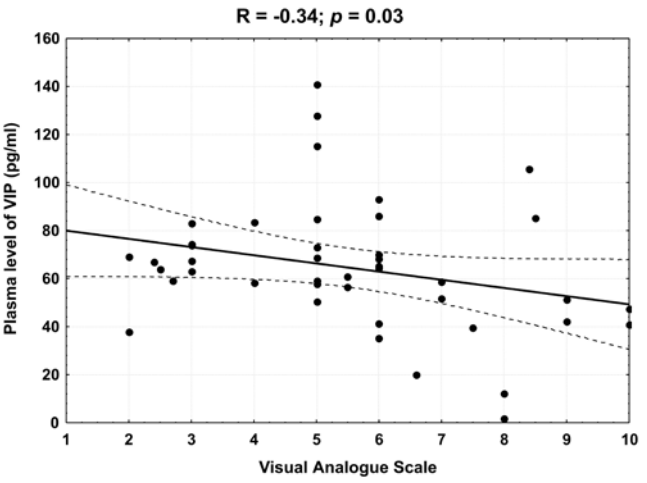

Fig. 3. Correlation between pruritus intensity (VAS 1–10) and plasma level of vasoactive intestinal peptide (VIP).

generalized pruritus (10, 11). Because trauma to apparently healthy skin in psoriasis may lead to the development of new psoriasis lesions, referred to as the Koebner phenomenon (12), it is important to be able to control this symptom effectively. However, before we can help these patients, we have to understand how pruritus develops in psoriasis. Unfortunately, the pathogenesis of itching in psoriasis, as in several other cutaneous or systemic forms of pruritus, remains unclear.

In the current study we evaluated plasma levels of selected neuropeptides in pruritic and non-pruritic individuals with psoriasis in order to prove whether these substances could mediate itching in psoriasis, especially in subjects with generalized pruritus. Interestingly, we found significantly decreased levels of NPY in patients with pruritus as well as higher SP and VIP plasma levels correlated with the lower pruritus intensity. In our opinion there are several explanations for these observations.

It could be speculated that neuropeptides released from dermal nerve endings might directly trigger itching in psoriasis, but that the reduced plasma concentrations may reflect an increased level of consumption or degradation of these substances. According to this hypothesis, overexpressed neuropeptides in psoriatic lesions (23) would be responsible (at least in part) for itching, but would lead to concomitantly higher expression and/or activity of degrading enzymes, which, in turn, would lead to rapid degradation of neuropeptides directly in the skin. Several reports may support this hypothesis. It is known, that neuropeptides are rapidly degraded in the tissue after release from nerve endings (24). The balance between chymase- and tryptase-positive mast cells was shown to be disturbed in lesional psoriatic skin (25), and an increased number of mast cells showing degranulating processes was reported in the papillary dermis of the lesional skin from pruritic psoriatic patients (15). Patients with psoriasis were also characterized by higher serum activity of angiotensin-converting enzyme, which was normalized after effective anti-psoriatic treatment (26). In addition, Nakamura et al. (15) noted increased expression of SP-positive nerve fibres in psoriatic skin from patients with pruritus compared with non-pruritic individuals, although no difference was revealed for other neuropeptides, such as CGRP, VIP, somatostatin or NPY. It was also shown that topically applied capsaicin effectively reduced pruritus in psoriasis (27). The long-term administration of capsaicin depleted neuropeptides (especially SP) in unmyelinated, polymodal C-type and small myelinated A delta-type cutaneous nerves that conduct pruritus and pain (27). In our opinion, neuropeptides released from dermal nerve endings may be responsible for some aspects of pruritus in psoriasis, but the problem of frequently observed generalized pruritus remains unsolved. Moreover, we noted significantly increased plasma levels of VIP and CGRP in psoriatic subjects compared with healthy individuals (22), thus it is difficult to explain the decreased level of neuropeptides in pruritic psoriatic patients solely by the fact of increased degradation.

Another possible explanation for our findings is that neuropeptides are not directly involved in the pathogenesis of pruritus in psoriasis, but play an important role only in the development of psoriatic lesions. However, high concentrations of neuropeptides would lead to higher expression and/or activity of proteases, which might be true pruritogenic mediators in psoriasis acting via proteinase activated receptors (PARs). According to this hypothesis, neuropeptides would participate only indirectly in pruritus stimulation. Recent findings suggest that proteases are not only degrading enzymes, but rather represent a group of mediators communicating with nerves, and thereby modulating inflammation, pain and pruritus (16). A massive itch behaviour was noted in mice overexpressing epidermal kallikrein-7 (16). Tryptase and microbial proteases induced itch by

the PAR-2-mediated neurogenic mechanism (16, 28). Activation of PAR-2 induced itching in both mice and humans (29, 30). Because PAR-2 is irreversibly activated by proteinases, it might also be a good candidate for the explanation of chronic itch (29). Although the hypothesis of the major role of proteases in pathogenesis of pruritus in psoriasis is encouraging, it needs to be proven directly, as our results provide us only with the possibility of speculation.

It could also be argued that plasma levels of neuropeptides may not reflect the neuropeptide concentration in the skin, but rather the global content of these substances in the human body, including the central nervous system (CNS). It has to be remembered that pruritus, like all other perception stimuli, is modulated at the CNS level (17). Unfortunately, published data on neuropeptide release within the CNS during pruritic stimulus are limited. However, some hints about the mechanism of itch can be taken by analogy from pain studies. Regarding these data, it seems that NPY could be of special interest. This neuropeptide has been shown to inhibit painful stimuli acting in different regions of the CNS, including spinal cord and hypothalamus, mainly via Y1 receptor (31–34). As there are some similarities between pruritus and pain, it could be speculated that NPY may also be involved in blocking pruritogenic stimuli. If the level of neuropeptides in the plasma corresponds to their expression in the CNS, it is likely that patients with a lower plasma concentration of NPY have a lower content of NPY in the CNS and, therefore, a lower threshold for itching. This suggestion could explain our observation that pruritic patients with psoriasis have a significantly reduced plasma level of NPY.

Conflict of interest: None to declare.

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