Arch Dermatol Res (1997) 289 : 611–616

ORIGINAL PAPER

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Intraepidermal nerve fiber expression of calcitonin gene-related peptide, vasoactive intestinal peptide and substance P in psoriasis

Received: 3 March 1997

Abstract **In order to evaluate more fully the role of neuropeptides in the pathogenesis of psoriasis, skin biopsies were obtained from 36 patients with psoriasis to identify substance P (SP), vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP). Lesional and nonlesional skin was examined from these biopsies and the results compared with those from biopsies taken from patients with a variety of other inflammatory dermatoses, including lichen planus, lichen simplex chronicus, spongiotic dermatitis, and seborrheic dermatitis. Also studied was a series of nine biopsies taken from patients with no known skin disorders. We found an increase in the number of SP-positive nerve fibers within the epidermis in biopsies from lesional skin of psoriasis patients (8.4 nerves per 3-mm biopsy) compared with nonlesional psoriatic skin (2.6 nerves per 3-mm biopsy) and normal skin (2.0 nerves per 3 mm biopsy). Other inflammatory disorders also demonstrated fewer SP-positive nerves than lesional psoriatic skin; lichen planus (0 nerves per 3 mm biopsy) and lichen simplex chronicus (1.3 nerves per 3 mm biopsy). The difference in SP-positive nerve expression between lesional psoriatic skin and the group comprising nonlesional skin, normal skin, lichen planus, and lichen simplex chronicus attained statistical significance ($P < 0.013$). SP-positive intraepidermal nerve fibers in lesional psoriatic specimens were fewer than in spongiotic dermatitis (17.4 nerves per 3 mm biopsy). There was no significant difference in numbers of VIP- or CGRP-immunopositive intraepidermal nerve fibers between psoriatic skin and the group comprising all other material tested. However, in five patients with psoriasis, there was a marked increase in the expression of intraepidermal CGRP (up to 10.7 nerves per 3-mm biopsy) and VIP (up to 8.3 nerves per 3-mm biopsy) which was not observed in control groups. These findings suggest that neuropeptides SP, CGRP, and VIP play a role in the pathogenesis of psoriasis.**

Key words Neuropeptides · Psoriasis · Substance P · Vasoactive intestinal peptide · Calcitonin-gene-related protein

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Introduction

Psoriasis is a complex, multifactorial disease whose pathogenesis is not completely defined. In recent years, it has become apparent that neuropeptide expression may play a role in the development of psoriatic lesions. Since Farber et al. suggested the concept of neurogenic inflammation, other studies have explored the neuropharmacology and psychoneuroimmunology of psoriasis [1–3]. It is well recognized that psoriasis is exacerbated by stress [1]. There is also some clinical evidence that focal denervation can lead to clearing of lesions in the anatomic region previously innervated by the damaged nerve [4, 5].

Substance P (SP) has been shown to be overexpressed in nerves within psoriasiform lesions by immunochemistry and radioimmunoassay [6, 7]. In contrast, decreased levels of SP in psoriatic lesions have also been found [8]. It is known that SP degranulates mast cells and activates lymphocytes [9]. Mast cell-derived histamine appears to be important in the SP-evoked intradermal flare reaction [10]. SP has also been shown to be mitogenic for connective tissue and epithelial cells [11]. It has also been shown that capsaicin, by depleting SP, is effective in inhibiting delayed-type cutaneous hypersensitivity reactions [11]. Capsaicin treatment has been shown by others to augment both delayed-type hypersensititiviy and contact hypersensitivity reactions in animal models [12, 13]. Capsaicin has also been evaluated in the treatment of psoriasis but is not considered

effective [14]. SP colocalizes with calcitonin gene-related peptide (CGRP) within cutaneous sensory nerves [15].

Vasoactive intestinal protein (VIP) has also been shown to be increased in psoriatic lesions compared with nonlesional skin from patients with psoriasis [8]. VIP is known to be mitogenic for keratinocytes, and to mediate vasodilation and mast cell degranulation. All of these functions may play some role in the development of psoriatic plaques. Further, peptide T, a VIP analogue is effective in treating some patients with psoriasis [16].

CGRP causes vasodilation when injected intradermally [17]. However, there is disagreement as to the degree of CGRP expression within lesions of psoriasis [18, 19]. CGRP-positive neurons are in scant numbers in psoriatic dermis, but intraepidermal nerve fibers expressing CGRP are not observed in psoriatic lesions [19]. Increased numbers of CGRP-positive nerves have been demonstrated within the papillary dermis of patients with high stress levels and psoriasis [20].

In order better to understand the role of neuropeptides in the pathogenesis of psoriasis, we examined lesions from patients with psoriasis and selected inflammatory dermatoses for the presence of epidermal and dermal SP, VIP, and CGRP. It was our hope to further define the location and relative numbers of nerve fibers expressing these neuropeptides in psoriasis and in a variety of other inflammatory conditions.

Materials and methods

Biopsies from 36 patients with psoriasis were included in this study. All patients were seen at the Psoriasis Research Institute (Palo Alto, Calif.) and biopsied as part of the diagnostic work-up and evaluation. Clinical data are summarized in Table 1. Tissue from the 3 mm biopsies was embedded in OCT medium and snap-frozen at –70° C and stored for later immunologic studies. In 36 patients, biopsies were taken from lesional skin. The 36 biopsies of lesional psoriatic skin included 33 biopsies of chronic plaque psoriasis, 2 biopsies of guttate psoriasis, and 1 biopsy of erythrodermic psoriasis. Additionally, 10 biopsies were obtained from nonlesional skin.

As one set of controls in this study 13 3-mm biopsies from patients with other inflammatory dermatoses. The tissue from these patients was taken from the frozen storage files of the Stanford University Medical Center Department of Pathology. All cases had been previously diagnosed by one of us (BRS), and these diagnoses were confirmed prior to inclusion in the study. There were three biopsies diagnosed as lichen planus, three as lichen simplex chronicus, six as spongiotic dermatitis and one as seborrheic dermatitis. The six cases of spongiotic dermatitis included one of each of pruritic urticarial papules and plaques of pregnancy, drug eruption, allergic contact dermatitis and photocontact dermatitis, and two of nummular eczema. All tissue had been previously snap frozen in a manner similar to that described above.

A final group of controls consisted of ten pieces of normal skin salvaged from surgical pathology specimens containing unremarkable skin, such as a reduction mammoplasty, an amputation, and abdominoplasties. These ten pieces of skin were snap-frozen as they were received, and stored for inclusion in this study.

The frozen specimens were cut into 20-μm cryosections. Serial sections were labelled with primary antibodies and incubated for 45 min at room temperature. The following primary antibodies were generously provided by Phoenix Pharmaceuticals (Mountain View, Calif.): anti-SP (1:80), anti-VIP (1:80) and anti-CGRP (1:80). Extensive studies have shown no cross-reactivity of these neuropeptide antibodies with each other (data not shown). Sections were rinsed in phosphate buffered saline followed by an incubation with fluroscein-isothiocyanate-conjugated antirabbit IgG (Accurate, NY) for 45 min.

Immunohistochemical negative controls were performed either by omitting the primary antibodies or by replacing the primary antibodies with a nonimmune rabbit serum.

All sections were coded and examined with a Nikon epiluminescence microscope. Three linear millimeters were examined for the presence of positive-staining nerve fibers within the epidermis and papillary dermis. All sections were examined by one investigator (JC) without knowledge of the clinical diagnosis and independent confirmation of the counting was performed by a second of us (BRS). Only linear structures with strong, continuous linear staining were counted as positive. With adjustments to the fine-tuning mechanism of the microscope, it was easy to detect the linear nature of the structures, given the relative thickness of the 20 m sections. The requirement of definite linearity excluded any neural structures cut in cross-section, as these were difficult to precisely identify. Nerve tangles were often observed. In these cases, free nerve endings observed were counted as single nerves. The same criteria were used for all specimens examined.

Numbers of nerves were compared using a One Factor Analysis of Variance *F*-test and a computer-based statistical data package.

Results

The results of intraepidermal neuropeptide expression in psoriatic skin and control groups are summarized in Table 2. Indirect immunofluorescence analysis revealed strong linear staining of putative nerves with SP, and less frequently VIP and CGRP. The vast majority of staining was present within the epidermis, with only scant positively staining papillary dermal nerve fibers seen in all of the conditions examined. Nonspecific adsorption of fluorescent antibody by the reticular dermal collagen obscured small nerve fragments in most cases. Larger nerve bundles were clearly identified in most cases. In the present study, we did not systematically examine the reticular dermis and no attempt was made to control for the amount of reticular dermal tissue within the biopsies, or to quench reticular dermal collagen staining.

Psoriatic lesional skin expressed a wide range of intraepidermal SP-positive nerves (0–19.3 nerves per 3-mm biopsy). The psoriatic lesional skin expressing higher amounts of intraepidermal SP also tended to express intraepidermal CGRP and VIP. While some biopsies of severe psoriasis showed high expression of all three neuropeptides, there was no correlation between neuropeptide expression and the clinical severity of psoriasis. Spongiotic dermatitis showed intraepidermal SP-positive nerves in the cases of pruritic urticarial papules and plaques of pregnancy, nummular eczema, contact dermatitis, and photocontact dermatitis. This was in contrast to the other, nonspongiotic conditions which failed to demonstrate intraepidermal SP-positive nerve fibers. In order to learn more about the differences between SP expression by nerves in psoriasis and inflammatory conditions other than spongiotic dermatitis, we excluded the cases of spongiotic dermatitis from further analyses. There was no significant difference between the SP-positive nerves seen in spongiotic dermatitis and in the other control specimens,

Table 1 Clinical features of the psoriasis patients

Patient	Age	Sex	Duration of psoriasis (years)	Biopsy site	Treatment[a]	Clinical features
1	31	Male	7	N/A	Oral retinoid; topical vitamin D analogue	Extensive plaques
2	26	Male	10	N/A	Methothrexate	Severe plaques
3	64	Male	N/A	N/A	None	
4	67	Male	7	N/A	Topical vitamin D analogue	Resolving plaques
5	27	Male	8	Arm	UVB; topical vitamin D analogue	Plaques
6	44	Male	20	N/A	Topical steroid	Plaques
7	36	Male	24	Trunk		
8	53	Male	N/A	N/A	None	Very severe plaques
9	36	Male	12	N/A	Anthralin; topical vitamin D analogue	
10	55	Male	15	Back	None	
11	39	Male	10	Elbow	None	
12	50	Female	5	Thigh	Topical vitamin D analgue; PUVA; tar	
13	49	Male	30	Abdomen	Methotrexate; tar; topical steroid	Very severe plaques
14	58	Male	2	Chest	Topical steroid	Severe plaques
15	63	Male	13	Arm	None	Severe extensive plaques
16	46	Male	16	Thigh	Anthralin; vitamin D analogue	Plaque with central clearing
17	23	Male	8	Thigh	Topical steroid	Flare
18	60	Female	12	Elbow	Topical steroid	Remission
19	39	Male	34	Back	Tar; topical vitamin D analogue	
20	52	Female	18	Shin	Tar; topical vitamin D analogue topical steroid	Remission
21	48	Male	30	Trunk	Topical vitamin D analogue	Resolving lesions
22	63	Female	34	Elbow	Tar; anthralin	Flare
23	39	Male	8	Elbow	Vitamin D analogue; UVB	Resolving plaques
24	32	Male	14	Knee	Topical steroid	
25	43	Male	15	N/A	None	Heavy plaques
26	71	Male	31	N/A	Topical steroid; vitamin D analogue	Worsening plaques
27	34	Male	3	Arm	None	Extensive plaques
28	38	Male	15	Knee	N/A	Extensive plaques
29	36	Male	15	Back	N/A	Mild plaques
30	39	Male	10	Elbow	N/A	Mild plaques
31	61	Female	6	Elbow	N/A	Moderate plaques
32	64	Female	30	Elbow	N/A	Moderate plaques
33	65	Male	35	Forearm	N/A	Extensive plaques
34	60	Male	20	Elbow	N/A	Mild plaques
35	35	Male	3	Forearm	N/A	Mild plaques
36	36	Female	13	Arm	None	Extensive plaques

[a] Treatment(s) affecting biopsy site

Table 2 Intraepidermal neuropeptide expression in cutaneous lesions. Values are mean number of nerves per 3 mm biopsy ± standard deviation

Disease	*n*	SP	CGRP	VIP
Psoriasis – lesional	36	8.4 ± 12.8	03.0 ± 6.1	2.2 ± 6.0
Psoriasis – nonlesional	10	2.6 ± 2.1	2.1 ± 1.7	0
Lichen planus	3	0	0	0
Lichen simplex chronicus	3	4.0 ± 6.9	0	0
Spongiotic dermatitis	6	17.5 ± 16.8	0	2.5 ± 5.9
Seborrheic dermatitis	1	63.0	0	21
Normal skin	10	2.0 ± 1.7	1.1 ± 1.1	0

in large part owing to the relatively low numbers of cases in each group of conditions. Nonlesional psoriatic skin, normal skin, lichen planus, and lichen simplex chronicus showed almost no intraepidermal SP positivity. There was no significant difference between these groups, and they were combined for additional comparative analyses with psoriasis. When compared with the group comprising nonlesional psoriatic skin, normal skin, lichen planus, and lichen simplex chronicus, the increase in intraepidermal SP positivity in psoriatic lesional skin attained statistical

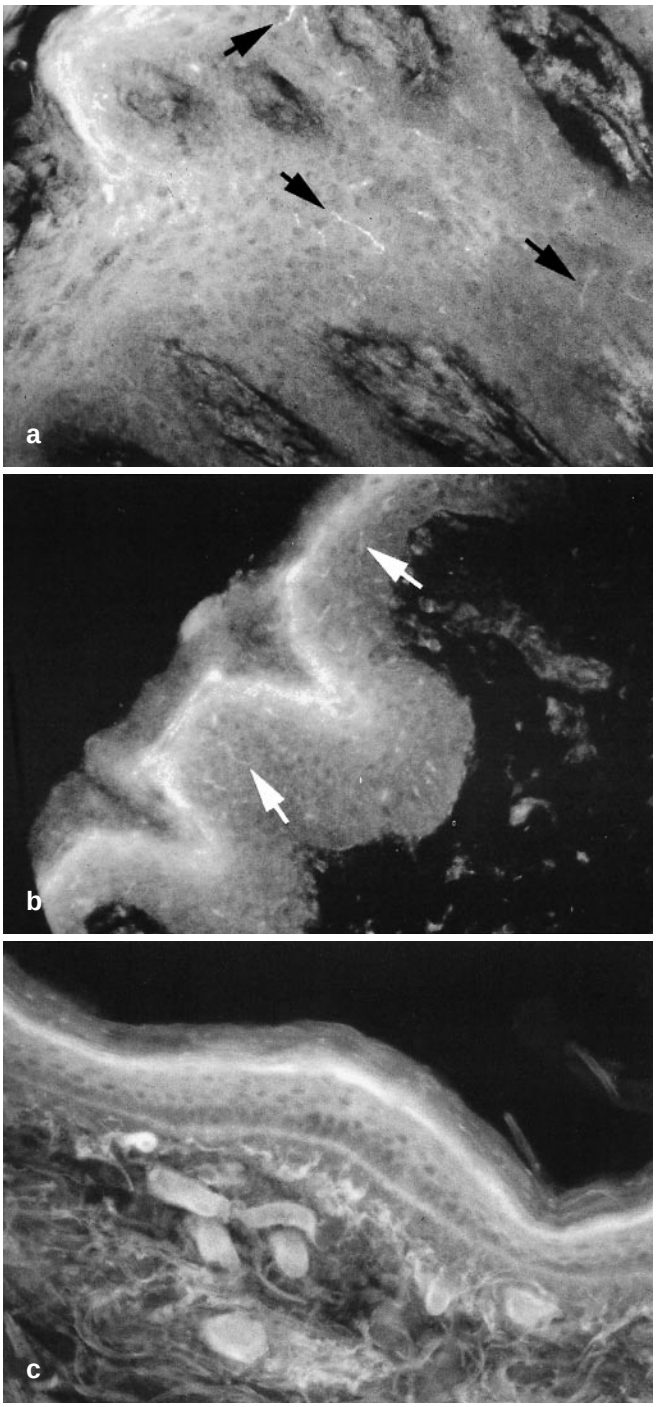

Fig. 1 **a** SP staining of putative nerve structures within the epidermis of psoriatic lesional skin (original magnification × 200). **b** SP staining of putative nerve structures within the epidermis of spongiotic dermatitis (original magnification × 200). **c** SP staining is not seen within the epidermis in a biopsy of normal skin the leg (original magnification × 200)

significance ($P < 0.013$). However, the qualitative differences were more striking than the quantitative data. Representative examples of SP staining in psoriatic lesional skin, spongiotic dermatitis, and normal skin are shwon in Fig. 1.

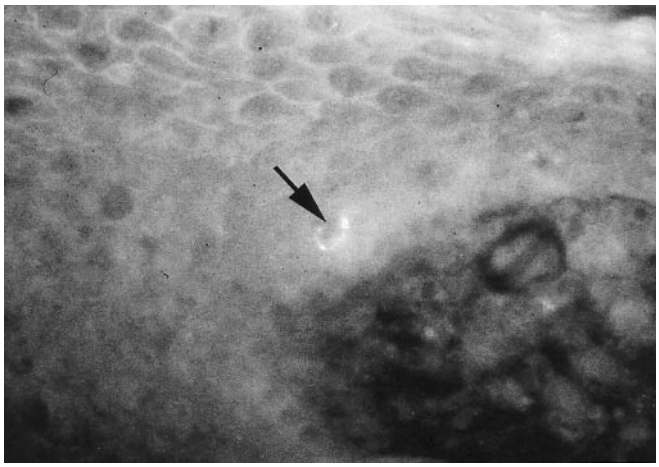

Fig. 2 Intraepidermal staining with antibody directed against VIP in lesional psoriatic skin (original magnification × 400)

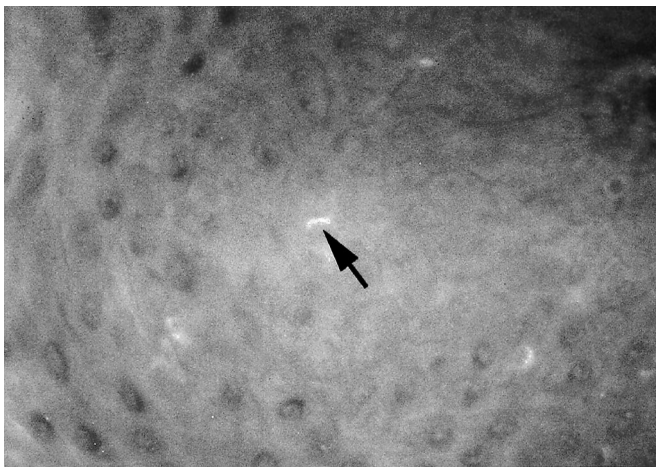

Fig. 3 Intraepidermal staining with antibody directed against CGRP in lesional psoriatic skin (original magnification × 200)

Intraepidermal VIP staining was observed in nine psoriatic lesional biopsies and in one biopsy of spongiotic dermatitis (nummular eczema). The magnitude of the difference in VIP staining in the epidermis between psoriatic lesional skin and the group comprising all other specimens tested was not significant. The difference increased but still did not attain significance when spongiotic dermatitis was excluded. In no case of normal skin or of nonlesional psoriatic skin was any intraepidermal staining detected, whereas in 9 of the 36 biopsies from lesional psoriatic skin VIP staining was identified. In 5 of these cases, there was also significant staining with SP and CGRP. Intraepidermal VIP staining is shwon in Fig. 2.

No siginificant difference was detected in CGRP staining between psoriatic lesional skin and all other conditions examined. However, as with SP and VIP staining, the difference between psoriasis and the other conditions became more pronounced when spongiotic dermatitis was excluded. There was staining with anti-CGRP antibodies in only two of the control specimens, one biopsy each of

nonlesional psoriatic skin and of spongiotic dermatitis. However, in 7 of the 36 lesional biopsies taken from patients with psoriasis, focal staining was seen in linear patterns (Fig. 3). Again, this staining was seen in biopsies which also demonstrated concomitant staining with SP.

Discussion

In this study, we demonstrated CGRP-positive nerve fibers within the epidermis of lesional psoriatic skin. CGRP fibers have been demonstrated within the papillary dermis of psoriatics [17,18]. However, to our knowledge, CGRP fibers have not been observed previously within the epidermis of psoriatics. The demonstration of the presence of CGRP intraepidermal expression in lesional psoriatic skin suggests a role for CGRP in the pathogenesis of psoriasis. Specifically, CGRP may play a role in the vasodilation of capillary beds that is characteristic of psoriasis. Intradermal CGRP has been previously shown to act directly on blood vessels to produce vasodilation in normal skin [21]. Despite CGRP colocalization with SP, intradermal CGRP does not potentiate SP-induced wheal and flare, and SP does not potentiate CGRP vasodilation [21]. However, other workers have suggested that CGRP, in the presence of SP, will potentiate SP-inducced edema [22]. CGRP may also play a role in the inflammation seen in psoriasis through modulation of cytokines. CGRP fibers have been observed in intimate association with Langerhans cells in the epidermis of normal skin, and CGRP has been found on the surface of Langerhans cells [23]. CGRP has been recently shown to alter cytokine expression in Langerhans cells. CGRP has been noted to decrease IL-10 and IL-12 production by Langerhans cells [24]. In addition to its role in inflammation, increased CGRP may also contribute to the hyperkeratotic state of psoriasis. CGRP has been shown to stimulate DNA synthesis and proliferation of human keratinocytes [25]. While the finding of CGRP-positive nerve fibers within the epidermis was not seen in all cases (hence the observed large standard deviation), their presence in some cases suggests a role for this neuropeptide in a subset of cases.

SP-positive nerve fibers were the most frequently observed type of nerve fiber in this study. SP fibers appeared primarily within the epidermis. SP fibers have been previously reported to be contained primarily beneath the epithelium [15]. There are several possible explanations for this difference in localization of SP expression. One possibility would be that we examined primarily well-developed plaque lesions of psoriasis, in which the SP expression is most intense. A previous study has demonstrated that pan-neuronal marker gene product and CGRP expression within the epidermis and papillary dermis is time-related in a rapidly developing suction blister [26]. Perhaps a similar time-dependent localization of SP expression is involved in the life cycle of a psoriatic plaque. In previous studies this point has not been specifically addressed and similar types of lesions may not have been investigated. In addition, we maximized visualization of fluorescence expression in the regions of the epidermis and the papillary dermis. We did not examine the deeper portions of the dermis because of high levels of background adsorption by the surrounding dermal collagen. We were thus limited in our ability to detect dermal SP expression. The epidermis of psoriatic lesional skin and spongiotic dermatitis contained the richest supply of SP fibers. Lichen simplex chronicus and normal skin demonstrated only minimal intraepidermal SP. Nonlesional psoriatic skin and lichen planus had no demonstrable intraepidermal SP. An isolated case of seborrheic dermatitis showed the highest number of intraepidermal SP.

Like SP-postive nerves, CGRP-positve nerves fibers and VIP-positive nerve fibers were observed primarily within the epidermis. There were no significant differences in CGRP or VIP expression by intraepidermal nerve fibers between the groups. However, in several cases of lesional psoriatic skin high numbers of intraepidermal CGRP and VIP were expressed. Thus, even though statistical significance was not achieved, suggesting that these observations are not uinformly observed in psoriatic skin, the presence of nerves expressing neuropeptides, especially within the epidermis, is a potentially significant finding.

Lesional psoriatic skin was the only group to demonstrate nerve fibers expressing SP, VIP, and CGRP within the papillary dermis as compared with the controls. However, nerve fibers were most abundant within the epidermis of lesional psoriatic skin. In contrast, nerve fibers have been previously seen predominantly within the papillary dermis of psoriatic skin [6, 8]. The novel observation of intraepidermal nerve fibers in this study may be a result of differences in technique, i.e. we did not use the avidin-biotin-peroxidase system of Naukkarinen et al. or in the sensitivity of the antineuropeptide antibodies [6]. The relatively few papillary dermal nerve fibers observed in this study may also be due to a difference in the population of psoriatic skin that was tested. Nerve fibers are reportedly fewer in the papillary dermis of psoriatic skin of nonstressed individuals as compared with the papillary dermis of psoriatic skin of stressed individuals [20].

Intraepidermal CGRP and VIP appeared only when intraepidermal SP was present. Colocalization of SP and CGRP beneath the epithelium has been previously demonstrated in normal skin [13]. However, VIP has not been reported to colocalize with SP or CGRP. Moreover, nerve fibers storing VIP have been associated with the deeper dermis, below SP- and CGRP-positive nerve fibers, in normal skin [21]. The findings of this study suggest that the three neuropeptides colocalize within the epidermis, with CGRP and VIP expression seen only in the presence of SP. Alternatively, expression of CGRP and VIP within epidermal nerve fibers may be dependent upon SP expression but occur within proximally located, but not identical, nerve fibers. As we did not perform double-labeling experiments, it is not possible to state with any degree of certainty whether or not the same nerve fibers contained each of the neuropeptides expressed.

Our results suggest that altered neuropeptide expression may be important in the pathogenesis of psoriasis in

a subset of patients. In five biopsies of lesional psoriatic skin, concurrent expression of SP, CGRP, and VIP was observed. Expression of all three neuropeptides was not seen within biopsies of normal skin, nonlesional psoriatic skin, or the other inflammatory disorders. Thus, in a subset of psoriasis, there is a unique increase in SP, CGRP, and VIP expression. There was no correlation between this high neuropeptide expression and the clinical severity of the psoriasis. Biopsies expressing all three neuropeptides were associated with a range of clinical severity, from mild to severe. The findings suggest that in a subset of patients with psoriasis, neuropeptides may be behaving in a synergistic manner to contribute to the clinical and histologic changes observed in this condition. As has been discussed, there is a wide range of proliferative and proinflammatory characteristics which have been attributed to SP, CGRP and VIP, many of which may contribute to the pathogenesis of psoriasis.

For all three of the neuropeptides examined, a wide range in the extent of expression was observed in lesional psoriatic skin. Some psoriatic biopsies displayed no neuropeptide positivity while other psoriatic biopsies expressed the majority of neuropeptide positivity, especially for SP. Given this wide range of neuropeptide expression, it is not surprising that our data did not reach statistical significance. However, the range of expression of neuropeptide positivity again suggests that neuropeptides may play a role in some patients with psoriasis. The conflicting nature of previous reports regarding neuropeptide expression in psoriatic skin further supports the hypothesis that neuropeptides are important in a subset of psoriasis, a multifactorial disease [7–9, 16, 17].

In conclusion, this study shows that intraepidermal expression of neuropeptides is altered in lesional psoriatic skin. These findings suggest that SP, CGRP, and VIP may be important mediators in the complex and multifactorial pathogenesis of psoriasis and play a role in the maintenance of the mature psoriatic plaque.

References

1. Farber EM, Nickoloff BR, Recht B, Fraki JE (1986;. Stress, symmetry and psoriasis: possible role of neuropeptides. J Am Acad Dermatol 14:305–311
2. Raychauduri SP, Rein G, Farber EM (1995) Neuropathogenesis and neuropharmacology of psoriasis. Int J Dermatol 34: 685–693
3. Farber EM, Lanigan SW, Rein G (1990) The role of psychoneuroimmunology in the pathogenesis of psoriasis. Cutis 46:314–316
4. Farber EM, Lanigan SW, Boer J (1990) The role of cutaneous sensory nerves in the maintenance of psoriasis. Int J Dermatol 29:418–420
5. Raychauduri SP, Farber EM (1993) Are sensory nerves essential for the pathogenesis of psoriasis? J Am Acad Dermatol 28:488–489
6. Naukkarinen A, Nickoloff BJ, Farber EM (1989) Quantification of cutaneous sensory nerves and their substance P content in psoriasis (comments). J Invest Dermatol 92:126–129
7. Eedy DJ, Johnston CF, Shaw C (1991) Neuropeptides in psoriasis; an immunohistochemical and radioimmunoassay study. J Invest Dermatol 96:434–438
8. Pincelli C, Fantini F, Romualdi P, Sevignani C, Lesa G, Benassi L, Giannetti A (1992) Substance P is diminished and vasoactive intestinal peptide is augmented in psoriatic lesions and these proteins exert disparate effects on the proliferation of cultured human keratinocytes. J Invest Dermatol 98:421–427
9. Payan DG, Goetzl E (1986) Mediation of pulmonary immunity and hypersensitivity by neuropeptides. Eur J Res Dis 68 [Suppl 144]:77—103
10. Foreman JC (1987) Peptides and neurogenic inflammation. Br Med Bull; 43:386–400
11. Wallengren J, Ekman R, Sundler F (1986) Occurrence and distribution of neuropeptides in the human skin. Acta Derm Venereol (Stockh) 67:185–192
12. Girolomoni G, Tigehaar RE (1990) Capsaicin-sensitive primary sensory neurons are potent modulators of murine delayed-type hypersensitivity reactions. J Immunol 145:1105–1112
13. Wallengren J, Ekman R, Moller H (1991) Capsaicin enhances allergic contact dermatitis in guinea pigs. Contact Dermatitis 24:30–34
14. Ellis CN, Berberian B, Sulica VI et al. (1993) A double-blind evaluation of topical capsaicin in pruritic psoriasis. J Am Acad Dermatol 29:438–442
15. Wallengren J (1991) Substance P antagonist inhibits immediate and delayed type cutaneous hypersensitivity reactions. Br J Dermatol 124:324–328
16. Farber EM, Cohen EN, Trozak DJ et al. (1991) Peptide T improves psoriasis when infused into lesions in nanogram amounts. J Am Acad Dermatol 25:658–664
17. Pietrowski W, Foreman JC (1985) Some effects of calcitonin gene-related peptide in human skin and on histamine release. Br J Dermatol 114:37–46
18. Elder JT (1995) Cytokine and genetic regulation in psoriasis. Adv Dermatol 10:99–133
19. Naukkarinen A, Harvima I, Paukkonen K, Aalto M-L, Horsmanheimo M (1993) Immunohistochemical analysis of sensory nerves an neuropeptides, and their contacts with mast cells in developing and mature psoriatic lesions. Arch Dermatol Res 285:341–346
20. Harvima IT, Viinamaki H, Naukkarinen A, Paukkonen K, Neittaanmaki H, Harvima R, Horsmanheimo M (1993) Association of cutaneous mast cells and sensory nerves with psychic stress in psoriasis. Pyschother Psychosom 60:168–176
21. Wallengren J, Hakanson R (1987) Effects of substance P, neurokinin A and calcitonin gene-related protein in human skin and their involvement in sensory nerve-mediated responses. Eur J of Pharmacol 143:267–273
22. Brain SD, Williams TJ (1988) Neuropharmacology of peptides in skin. Sem Dermatol 7:278–283
23. Hosoi J, Murphy GF; Egan CL, Lerner EA, Grabbs S, Asahina A, Granstein RD (1993) Regulation of Langerhans cell function by nerves containing calcitonin gene-related peptide. Nature 363:159–163
24. Hosoi J, Torii H, Fox F, Yan Z, Rook AH, Granstein RD (1995) Alteration of cytokine expression by calcitonin gene-related peptide (Abstract). J Invest Dermatol 105:859
25. Takahashi K, Nakamishi S, Imamura S (1993) Direct effects of cutaneous neuropeptides on adenyl cyclase activity and proliferation in keratinocyte cell line; stimulation of cyclic AMP formation by CGRP and VIP/PMH and inhibition by NPY through G-protein coupled receptors. J Invest Dermatol 101:646–651
26. Gu XH, Ternghi G, Purkis PE, Price DA, Leigh IM, Polak JM (1994) Morphological changes of neural and vascular peptides in human skin suction blister injury. J Pathol 172:61–72