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# Psoriasis and the Nervous System

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**Both clinical and experimental evidence is accumulating on the role of the nervous system in the pathogenesis of psoriasis. Sporadic reports as well as extensive studies indicate that emotional stress can act as an exacerbating event in psoriasis. Moreover, that neurogenic mechanisms are operating in psoriasis is suggested by clinical, pharmacologic and experimental data. We have focused our investigations on the role of vasoactive intestinal peptide (VIP) and substance P (SP) in psoratic lesions using a variety of experimental approaches: 1) receptor autoradiography; 2) immunohistochemistry; 3) radio-imunoassay; 4) human keratinocytes cultures. Our results indicate that an imbalance of VIP and SP exists in psoriatic lesions, and that these neuropeptides exert different and specific effects on human keratinocytes. At present, however, the finding of psoriasis being exacerbated by psychological factors cannot be satisfactorily explained merely by alterations of neuropeptides in the skin.** ***Key words: stress; vasoactive intestinal peptide; substance P.***

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Several observations have been reported in the literature concerning the correlation between psoriasis and the nervous system. Psychogenic or neurogenic mechanisms have alternatively been claimed to act as provoking or exacerbating factors, either in the onset or in the maintenance of psoriatic lesions.

Indeed, it is common experience in dermatologic practice to observe a stressful event being strictly associated with a psoriatic rash. In these cases, it is obviously tempting both to the clinician and to the patient to think of a causative linkage, with the emotional stress acting as a trigger. Although most reports in the literature are just anecdotal and the concept of "stress" as related to clinical conditions is still vague, some studies have shown with standardized and statistical methods a correlation between stress and psoriasis. Gaston et al. were able to demonstrate a statistically significant relationship between adverse life events and severity of psoriasis (1). In 132 psoriatic patients followed over a 3-year period, Seville found that a specific stress occurred within a month before the first psoriatic attack in 39% of the subjects (2). Interestingly the prognosis for these patients was better than for patients who could not recall such a stressful event. Moreover, classic psychologic therapeutic tools, such as the "insight" of the patients (3), hypnosis (4), biofeedback (5) and psychotherapy (6) have been successfully used in psoriasis. However, at present the pathomechanisms connecting psychologic factors with the appearance of the psoriatic lesions are completely unknown, and a direct relationship is still to be demonstrated.

As far as neurogenic mechanisms are concerned, clinical and experimental evidence points to a role of peripheral nerves and neural molecules in the pathogenesis of psoriasis. For example surgical denervation (7), dermabrasion (8), and skin injury (9) have been reported to induce local remission of psoriasis, possibly as a consequence of peripheral nerve damage. Neuropeptides (NP) have been considered the peripheral mediators of the neurogenic component underlying the pathogenesis of psoriasis (10). Indeed, these neural peptides are known to be antidromically released by sensory nerve fibres in the skin, where they are able to induce local inflammatory reactions (11). Several functions and cells, which are modulated by NP, such as vasodilation (12), mast cell activation (13), keratinocyte proliferation (14), play a basic role in the pathology of psoriasis (15, 16). Furthermore, several NP affect the function of immune cells involved in the pathogenesis of psoriasis, such as lymphocytes, neutrophils, and mast cells (17). The neurotoxin capsaicin, which depletes cutaneous sensory nerves of their neurotoxin content (18), is effective when topically applied to psoriatic lesions (19). Intravenous infusion of somatostatin, an inhibitor of the NP substance P (SP) (20), is beneficial in severe psoriasis (21). An accelerated turnover of neural elements (22), an increased innervation (23), and a greater number of SP-containing intra-epidermal nerve terminals (24) have all been reported in psoriatic lesions.

In recent years, our group has been evaluating the role of two important cutaneous NP, vasoactive intestinal peptide (VIP) and SP, in the pathomechanisms of psoriatic lesions, using a variety of experimental approaches. Using receptor autoradiography, we were able to detect SP receptors, on both normal and psoriatic skin (25). Specific SP-biding sites were found, both evenly distributed in the epidermis and also focally clustered in the dermis, in a location corresponding to the possible SP dermal target structures (microvessels, mast cells, keratinocytes). Quantitative computerized analysis revealed no significant differences in receptor density or receptor affinity between lesional and normal skin. Similarly, immunohistochemistry showed a comparable density and distribution pattern of SP– and VIP-positive fibres in psoriatic lesional, non-lesional and normal skin sections (26). It should be noted that SP and VIP appeared to be contained not only in cutaneous nerve fibres, but also in the cytoplasm of neutrophils in the infiltrate, thus suggesting another possible source of these NP in psoriatic lesions.

A third approach was to measure VIP and SP cutaneous levels in psoriatic lesional, non-lesional and normal skin. A radioimmunologic technique was employed on tissue homogenates. The local content of VIP was consistently increased in psoriatic lesions as compared with both non-lesional and normal skin. These data would be confirmed by the observation that larger amounts of capsaicin are needed to induce neurogenic inflammation in psoriatic vis-à-vis control skin (27).

Finally, since keratinocyte hyperproliferation is a feature of psoriasis, we evaluated the effects of VIP and SP on cultured normal human keratinocyte proliferation. We demonstrated that



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the VIP carboxy-terminal fragment was responsible for the dose-dependent growth-promoting effect on keratinocytes (26). By contrast, SP and SP fragments failed to stimulate keratinocyte proliferation. Furthermore, SP was shown to significantly block the VIP-stimulated proliferation.

The changes in SP and VIP skin content in psoriasis indicate participation of these NP and cutaneous nerves in the mechanisms underlying the production or the maintenance of psoriatic lesions. Their specific effects on keratinocyte proliferation, as well as their antagonistic action on the cells of the immune-inflammatory system seem to reflect a different role of SP and VIP in the pathogenesis of psoriatic lesions. In conclusion, two distinct series of evidence would seem to indicate a role for the nervous system in psoriasis. On the one hand, emotional stress has long been recognized as acting as a precipitating factor in psoriasis. On the other hand an increasing body of observations indicates that at least some NP intervene at a local level in the pathogenesis of psoriatic skin lesions. However, evidence of a direct connection between psychological stress and peripheral NP release is still lacking. Therefore, at present, these concepts should be regarded as two different components in the pathomechanism of psoriasis.

## REFERENCES


1. Gaston L, Lassonde M, Bernier-Buzzanga J, Hodgins S, Crombez JC. Psoriasis and stress: a prospective study. J Am Acad Dermatol 1987; 17: 82–86.
2. Seville RH. Psoriasis and stress. Br J Dermatol 1977; 97: 297–302.
3. Seville RH. Sress and psoriasis: the importance of insight and empathy in prognosis. J Am Acad Dermatol 1989; 20: 97–100.
4. Frankel FH, Misch RC. Hypnosis in a case of long standing psoriasis in a person with character problems. Int J Clin Exp Hypn 1973; 21: 121–130.
5. Hughes HH, England R, Goldsmith DA. Biofeedback and psychotherapeutic treatment of psoriasis: a brief report. Psychol Rep 1981; 48: 99–102.
6. Cobb S. Social support as a moderator of life stress. Psychosom Med 1976; 38: 300–314.
7. Farber EM, Lanigan SW, Boer J. The role of cutaneous sensory nerves in the maintenance of psoriasis. Int J Dermatol 1990; 29: 418–420.
8. Gold MH, Roenigk HH. Surgical treatment of psoriasis: a review including a case of dermabrasion of hypertrophic psoriatic plaque. J Dermatol Surg Oncol 1987; 13: 1326–1331.
9. Eyre RW, Krueger GG: Response to injury of skin involved and uninvolved with psoriasis, and its relation to disease activity: Koebner and "reverse" Koebner reactions. Br J Dermatol 1982; 106: 153–159.
10. Farber EM, Nickoloff BJ, Recht B, Fraki JE. Stress, symmetry and psoriasis: possible role of neuropeptides. J Am Acad Dermatol 1986; 14: 305–311.
11. Maggi CA, Meli A. The sensory-efferent function of capsaicin-sensitive sensory neurons. Gen Pharmacol 1988; 19: 1–43.
12. Wallengren J, Håkanson R. Effects of substance P, neurokinin A and calcitonin gene-related peptide in human skin and their involvement in sensory nerve-mediated responses. Eur J Pharmacol 1987; 143: 267–273.
13. Piotrowsky W, Foreman JC. On the actions of substance P, somatostatin, and vasoactive intestinal polypeptide on rat peritoneal mast cells and in human skin. Naunyn Schmiedeberg's Arch Pharmacol 1985; 331: 364–368.
14. Haegerstrand A, Jonzon B, Dalsgaard CJ, Nilsson J. Vasoactive Intestinal Polypeptide stimulates cell proliferation and adenylate cyclase activity of cultured human keratinocytes. Proc Natl Acad Sci USA 1989; 86: 5993–5996.
15. Pinkus H, Mehregan AH. The primary histologic lesion in seborrheic dermatitis and psoriasis. J Invest Dermatol 1966; 46: 109–116.
16. Schubert C, Christophers E. Mast cells and macrophages in early relapsing psoriasis. Arch Dermatol Res 1985; 277: 352–358.
17. O'Dorisio MS. Neuropeptide modulation of the immune response in gut associated lymphoid tissue. Intern J Neurosci 1988; 38: 189–198.
18. Buck SH, Burks TF. Capsaicin: hot new pharmacological tool. Trends Pharmacol Sci 1983; 4: 84–87.
19. Bernstein JE, Parish LC, Rapaport M, Rosenbaum MM, Roenigk HH. Effects of topically applied capsaicin on moderate and severe psoriasis vulgaris. J Am Acad Dermatol 1986; 15: 504–507.
20. Brodin GE, Olgart L, Panopoulos P. Evidence that substance P is a mediator of antidromic vasodilation using somatostatin as a release mediator. Acta Physiol Scand 1984; 113: 155–159.
21. Weber G, Klughardt, Neidhart M. Psoriasis and human growth hormone: aetiology and therapy. Arch Dermatol Res 1981; 270: 361–365.
22. Weddel G, Cowan MA, Palmer E, Ramaswamy S. Psoriatic skin. Arch Dermatol 1965; 91: 252–266.
23. Armagni C, Di Francesco C, Schaltegger H. Electron microscopy studies on dermal nerves in psoriasis. Acta Derm Venereol (Stockh) 1979; Suppl 87: 68–70.
24. Naukkarinen A, Nickoloff BJ, Farber EM. Quantification of cutaneous sensory nerves and their Substance P content in psoriasis. J Invest Dermatol 1989; 92: 126–129.
25. Pincelli C, Fantini F, Giardino L, Zanni M, Calza L, Giannetti A. Autoradiographic detection of substance P receptors in normal and psoriatic skin. J Invest Dermatol 1993; 101: 301–304.
26. Pincelli C, Fantini F, Romualdi P, Sevignani C, Lesa G, Benassi L, Giannetti A. Substance P is diminished and vasoactive intestinal peptide is augmented in psoriatic lesions and these peptides exert disparate effects on the proliferation of cultured human keratinocytes. J Invest Dermatol 1992; 98: 421–427.
27. Glinski W, Glinska-Ferenz M, Pierozynska-Dubowska M. Neurogenic inflammation induced by capsaicin in patients with psoriasis. Acta Derm Venereol (Stockh) 1991; 71: 51–54.