

# Neurogenic Inflammation Induced by Capsaicin in Patients with Psoriasis

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**Increasing doses of capsaicin were applied topically to the forearm skin of 30 patients with psoriasis, 16 patients with systemic scleroderma and 16 healthy volunteers. Only one-third of the patients with psoriasis responded with neurogenic inflammation to capsaicin doses of 0.125 and 0.25  $\mu\text{g}/\text{cm}^2$  in contrast to 81% of scleroderma patients and all the normal controls, who showed a positive cutaneous reaction. Higher doses of capsaicin (0.5–4  $\mu\text{g}/\text{cm}^2$ ) were required to induce erythema and flare in patients with late-onset psoriasis (after 21 years of age) as well as in patients with more than 40% of skin surface involved with psoriatic lesion. Key word: *Neuropeptides*.**

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A triple response of skin – local redness, flare and wheal – after external application of capsaicin is mediated by substance P (SP) (1–3). This neuropeptide is generated in the dorsal root ganglia and is transported to peripheral sensory nerve endings where upon trauma SP is released by antidromic activation through the axon collaterals, resulting in neurogenic inflammation (2, 4–6). SP is able to induce histamine release from human skin mast cells in a dose-dependent manner (7, 8). This reaction is due to the polybasic structure of SP and it is receptor mediated, since SP analog exhibits antagonist activity (9).

It is known that capsaicin enhances the release of SP from the sensory neurons and nerve terminals in the central and peripheral nerve system (1, 6), as well as inducing tachyphylaxis after repeated applications (10, 11).

0.025% capsaicin ointment has been reported to improve psoriatic plaques when applied for 4 weeks (12). This is consistent with the hypothesis that skin neuropeptides (including SP) may play an important role in the induction of psoriatic lesions (13). Two reports on the disappearance of psoriasis after cutaneous nerve sectioning (13, 14), which resulted in the depletion of SP from the skin area innervated by the sensory nerve endings seemed to support this theory.

However, to our knowledge no experimental data are available on the quantitative capsaicin-induced SP-mediated erythematous skin response in psoriasis. This compound has been previously utilized as a 0.1% solution in the concentration of 4  $\mu\text{g}/\text{cm}^2$  of skin either for skin testing or for induction of tachyphylaxis. This capsaicin concentration induces the reaction in almost all patients studied (11).

The purpose of the present paper was to determine the dose responsiveness to topical capsaicin in patients with psoriasis, as compared with normal controls.

## MATERIAL AND METHODS

The studies were performed on groups of 30 patients with psoriasis, 16 healthy volunteers and 16 patients with systemic scleroderma. The results were analysed according to clinical criteria previously used (15), such as disease activ-

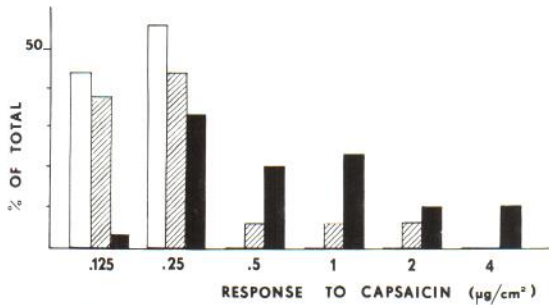


Fig. 1. Distribution of patients with psoriasis (■), patients with systemic sclerosis (▨) and healthy controls (□) by the intensity of neurogenic response to capsaicin.

ity, extent of psoriatic lesions, duration of recent relapse, age at onset of psoriasis, and present age of patients.

Capsaicin [trans-8-methyl-N-vanillyl-6-nonenamide, prod. Sigma] in 95% ethanol was applied on the forearm in concentrations increasing in geometric progression from 0.125 to 4.0 µg/cm<sup>2</sup>.

After evaporation of the solvent, the test site was covered with parafilm and adhesive tape, and inspected every 30 min for 3 h. The lowest dose of capsaicin inducing erythema was determined and expressed in a 6-grade score: 6 = 0.125 µg, 5 = 0.25 µg, 4 = 0.5 µg, 3 = 1 µg, 2 = 2 µg, and 1 = 4 µg. The mean capsaicin response index was calculated as the sum of individual scores in the group divided by the number of those tested.

## RESULTS

Amounts of capsaicin of 0.5 µg/cm<sup>2</sup> or more were needed to induce erythema in about two-thirds of the patients with psoriasis (mean index, 3.64 ± 1.40). In contrast, all normal volunteers responded to either 0.125 µg or 0.25 µg of capsaicin/cm<sup>2</sup> (mean index, 5.44 ± 0.51). The distribution of erythematous response in patients with systemic sclerosis did not differ from that of normal controls (mean index, 5.00 ± 1.15) (Fig. 1).

Larger doses of capsaicin had to be applied to provoke the erythematous skin response in patients with onset of psoriasis later than 21 years of age (mean index, 2.93 ± 1.39) (Fig. 2). In contrast, patients with early onset of psoriatic lesions had a reaction to capsaicin (mean index, 4.46 ± 0.88) similar to that of normal controls (mean index, 5.44) (Table I). No correlation has been found between the erythematous response to capsaicin and the clinical parameters, except for age at onset of psoriasis. Moreover, patients with widespread psoriatic lesions over more than 40% skin surface seemed to be unresponsive

to low capsaicin doses (mean index, 1.67 ± 0.95) (Table I).

## DISCUSSION

The neurogenic inflammation induced by topical application of capsaicin is mediated by SP released from peripheral sensory nerve terminals, which in turn stimulates specific receptors on the dermal mast cells and results in their degranulation (1–8). The subsequent vasodilatation is provoked by histamine, leukotrienes, and possibly mast cell neutral proteinases (16).

SP may be involved in the pathogenesis of inflammatory skin diseases in several different ways. Primary sensory neurons could be stimulated by trauma or inflammatory mediators. SP could be present in higher concentrations in the primary sensory neurons of the patients and/or could be released more readily. Continuous release of SP into the skin could account for the reduced flare response in patients with atopic dermatitis (17).

Larger doses of capsaicin were required in patients with psoriasis than in normal subjects in order to induce the triple cutaneous response. The unresponsiveness of psoriatic patients to low capsaicin doses may be related to: 1) a lower content of SP in the nerve fibres; 2) a lower content of inflammatory mediators in mast cells; 3) lesser affinity of specific receptors for SP on the mast cell membrane, and 4) faster degradation of SP by tissue endopeptidases in intercellular space, etc.

Since the erythematous response in psoriasis, when occurring after the application of a certain capsaicin dose, was usually of maximum intensity, the unresponsiveness to low doses of capsaicin was neither

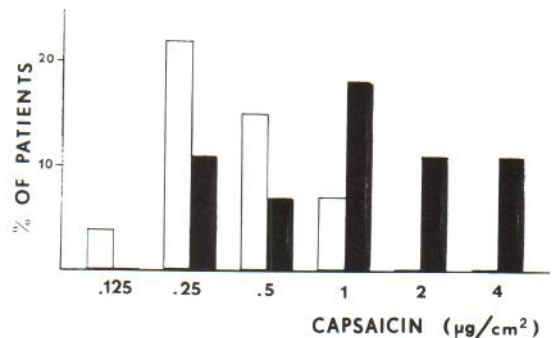


Fig. 2. Erythematous reaction to different doses of topically applied capsaicin in patients with early (≤ 20 y, □) and late (> 20 y, ■) onset of psoriatic lesions.



Table I. Mean capsaicin response index as related to some clinical parameters of the disease in 30 patients with psoriasis

Clinical parameter	Mean capsaicin index $\pm$ SD			
Extent of lesions	10% 3.00 $\pm$ 0.71	11–20% 4.36 $\pm$ 0.67	21–40% 3.6 $\pm$ 1.21	40% 1.67 <sup>a</sup> $\pm$ 0.95
Duration of relapse	1 mo 3.83 $\pm$ 1.46	1–2 mo 4.00 $\pm$ 0.82	2–4 mo 2.8 $\pm$ 1.17	4 mo 3.67 $\pm$ 1.11
Activity of disease <sup>b</sup>	2 3.89 $\pm$ 1.05	1 3.55 $\pm$ 1.40	0 4.00 $\pm$ 0.89	
Present age of patient	20 yr 4.14 $\pm$ 0.83	21–40 yr 3.5 $\pm$ 1.44	40 yr 3.17 $\pm$ 1.07	
Age at onset	20 yr 4.46 $\pm$ 0.88	20 yr 2.93 <sup>a</sup> $\pm$ 1.39		

<sup>a</sup>Significantly different from the remaining patients, *t*-test, *p* < 0.05.

<sup>b</sup>A2, guttate psoriasis; A1, active plaque psoriasis; A0, stationary plaque psoriasis.

dependent on tachyphylaxis (depletion of SP in sensory nerves) nor on previous degranulation of mast cells by SP or other stimuli (5, 11, 18, 19). An increased threshold response of nerve endings to capsaicin as well as decreased affinity of SP receptors is a more probable explanation for our findings.

It is possible that in patients with psoriasis who were responsive to high doses of capsaicin, only the tissue concentration of SP might be markedly reduced by proteolytic enzymes. The candidates are neutral serine proteinases of neutrophils, elastase and cathepsin G (15), or dermal mast cells, tryptase and chymotryptase (16). These enzymes may contribute to the inactivation of SP when continuously released from activated mast cells or stimulated neutrophils in the presence of degranulative agents. The mast cells were found to be altered both in psoriatic plaques and in symptom-free skin in psoriasis (18, 20).

An increased activity of proteinases responsible for the decreased response to capsaicin seems unlikely, since the unresponsiveness to small capsaicin doses was found in psoriatic patients with late onset who usually have high serum  $\alpha_1$ -proteinase inhibitor activity, in contrast to patients with early onset who show reduced  $\alpha_1$ -proteinase inhibitor levels (21). Thus, only the decreased activity of tissue proteinase inhibitor other than  $\alpha_1$ -proteinase inhibitor could be responsible for the enhancement in the SP degradation.

Since the capsaicin-induced SP-mediated erythematous skin response is reduced in more than half of the patients with psoriasis, it is unlikely that SP is re-

sponsible for the maintenance of psoriatic plaque (13). However, some beneficial effect of topical capsaicin on psoriatic lesions (12) might be explained only by the reduction of inflammatory process in the skin due to repeated applications of capsaicin as shown by Wallengren & Möller (11). It may be related at least in part to prostaglandins or other soluble factors which are known to be released upon application of capsaicin and can modify the psoriatic process (22). Furthermore, Naukkarinen et al. (23) showed that psoriatic lesions, but not uninvolved skin, were significantly more densely innervated with SP-containing nerve fibres.

Our data demonstrated an abnormal response of uninvolved psoriatic skin to SP, which presents yet more evidence that the psoriatic process involves not only psoriatic plaques but even the whole skin (24). The mechanism of this reaction is presumably related to secondary alteration (18, 20) of mast cells, but this is not yet clear.

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