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The Effect of Capsaicin on Some Experimental Inflammations in Human Skin

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Topical application of capsaicin is thought to deplete substance P from local sensory nerve terminals. In experiments on human skin inflammation was induced by injection of substance P (SP) or histamine intradermally, UV irradiation, non-immunologic contact urticaria, tuberculin reaction, contact allergens and benzalkonium chloride with or without capsaicin pretreatment. The flare response to SP and histamine was suppressed by capsaicin pretreatment whereas the wheal was enlarged. Interestingly, capsaicin pretreatment enhanced the responses to all other inflammatory agents. *Key words: Substance P; Contact dermatitis; Urticaria.* (Received March 7, 1986.)

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Trauma to the skin—mechanical, chemical, or thermal—induces a triple response (1) composed of local redness, flare and wheal. The triple response can be reproduced by intracutaneous injection of histamine. The flare is dependent upon an axon reflex mediated by sensory nerve fibres. Mast cell histamine may play a role in the vasodilatation since most mediators of "neurogenic inflammation" are capable of releasing histamine and since there is a close proximity between sensory nerve fibres and dermal mast cells (2).

The neuropeptide substance P has been demonstrated in sensory nerve fibres in the skin by immunocytochemistry (3, 4) and has been suggested to be the main mediator of neurogenic inflammation (5, 6). Intracutaneously injected substance P induces itch and triple response; itch and flare can be reduced by a histamine H_1-receptor antagonist (7, 8). Actually, substance P is 200–500 times more potent than histamine in producing flare (9).

Capsaicin has been found to be a useful tool in studies of the neurogenic component of inflammation. Capsaicin is a homovanillic acid derivative (8-methyl-N-vanillyl-6-nonenamide) and the principal pungent agent of hot pepper. Parenteral and local administration of capsaicin is followed by reduced traumatic flare reactions and heat pain thresholds while pricking pain tresholds are less affected (10, 11).

Local pretreatment with capsaicin reduces the flare response to injected histamine while the wheal is unaffected (12, 13). The flare and wheal response to substance P is similarly influenced (9, 10, 13).

With this background we found it of interest to examine the effect of capsaicin pretreatment on different inflammatory reactions in human skin.

MATERIAL AND METHODS

The study was performed on 29 subjects, 13 patients and 16 healthy volunteers; the latter were divided in two experimental groups. Ten of the patients had a history of contact allergy verified by patch test; they were in-patients treated for non-eczematous disorders, mainly leg ulcers. Informed consent was obtained in all cases.

Capsaicin pretreatment

In all subjects the ventral aspect of the left forearm was painted with freshly prepared capsaicin dissolved 0.1% in 95% ethanol. An amount of 0.1 ml was spread over the same 5×5 cm area once a

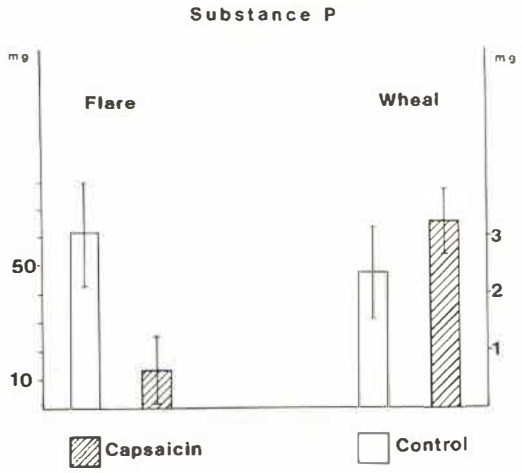

Fig. 1. The response to i.c. injection of substance P in eight subjects. Flare was registered after 3 min and wheal after 15 min. The mg unit on the vertical axis refers to the weight of paper corresponding to the skin area of flare or wheal. Mean values and standard deviations are given.

day for three days. On a corresponding skin area a control solution of ethanol was painted. All following experiments were performed indentically on pretreated and control skin.

Substance P and histamine

Substance P 10^{-7} M, 0.05 ml was injected intracutaneously in a saline solution. In the first experimental group of eight volunteers we used a refrigerated (−20°C) stock solution stored for two months. Flare and wheal responses were registered 15 min after the injection. The borders were marked with ink and transferred to transparent plastic, which was copied to regular paper and weighed. In the second group of eight volunteers we used freshly prepared solutions of substance P. The flare response was registered 3 min after injection when maximal, the wheal after 15 min when maximal (7).

Histamine hydrochloride 10^{-6} M 0.05 ml was injected intracutaneously in a saline solution in eight volunteers. Flare and wheal responses were registered as above 15 min after the injection.

Ultraviolet-evoked erythema

In 16 volunteers ultraviolet-evoked erythema was induced on a skin are of 1.0 diameter. The light source was a non-filtered 150 W xenon arc lamp (Osram XBO) giving medium wave ultraviolet light (UVB). The exposure time was 16 sec corresponding to about 2–3 MED. The inflammatory response after 24 h in the capsaicintreated site was compared to the control site with regard to intensity of erythema and inflitration by inspection and palpation.

Non-immunologic contact urticaria (NICU)

In the first volunteer group NICU was induced by benzoic acid, in the second group by cinnamic acid and sorbic acid (14). All compounds were dissolved 5% in petrolatum and applied to the skin by Finn chambers® on Scanpor® for 45 min. The urticarial reactions were registered immediately after removal of the chambers as for UV-evoked erythema.

Irritant delayed reaction

In all patients except one we used benzalkonium chloride in water, 0.5% in five patients, and 1% in the other seven patients. The compound was applied for 48 h as above (see NICU). The reaction was examined after a further 24 h. The response area was estimated by measuring two right-angled diameters.

Tuberculin reaction

All patients were tested with 2 TU PPD (Statens Serum Institut, Copenhagen, Denmark) 0.1 ml being injected intracutaneously. The response area was estimated after 72 h by measuring two right-angled diameters.

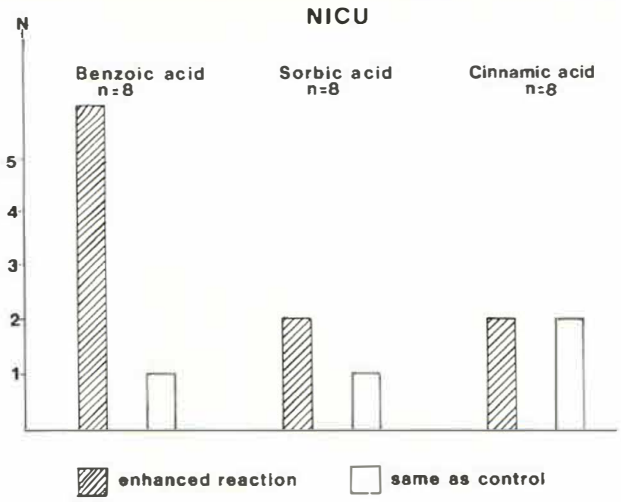

Fig. 2. Non-immunologic contact urticaria induced by benzoic acid, sorbic acid and cinnamic acid. The vertical axis shows the number of subjects. The columns express a comparison between capsaicin-pretreated skin and control site.

Allergic contact dermatitis

By patch testing allergic contact dermatitis was induced in 10 patients with a previous positive test to various allergens (fragrance-mix, tetramethylthiuramdisulfid, Vioform®, nickel sulfate, ethylenediamine, colophony, polymyxin B, wool alcohols). The individual allergen was applied as a regular patch test as above for 48 h and read after a further 24 h. The response are was estimated by measuring two right-angled diameters.

Statistics

In the studies on substance P and histamine mean values for each group were used for statistical evaluation. This was performed with the Student's *t*-test. For all other studies the Wilcoxon Rank Sum test was used.

RESULTS

Capsaicin

Erythema and burning pain was induced within 10–20 min. These reactions had vaned after 1–2 h. Erythema and pain could be provoked by a second but not by a third application of capsaicin. These reactions could be provoked also by contact with hot water after the first two capsaicin applications. Some subjects reported cough during exposure to capsaicin.

Substance P

In the first volunteer group of six subjects there was a flare at the control site after 15 min in only two; the flare was absent at the capsaicin pretreated site. In the second group of eight subjects the flare was read after 3 min when maximal, and after 15 min. In all eight cases the flare of 3 min was smaller at the capsaicin site (Fig. 1, $p<0.001$).

The wheal response was registered at 15 min in all 16 volunteers. In the first group the wheal was larger on the capsaicin site in all cases, in the second group it was larger in six of eight subjects, smaller in the other two. This difference in wheal size between capsaicin and control site in the first group was statistically significant ($p<0.01$) (Fig. 1).

Histamine

There was a flare at the control site in all eight subjects. At the capsaicin-pretreated site the flare was absent in six subjects and smaller than on the control site in the other two

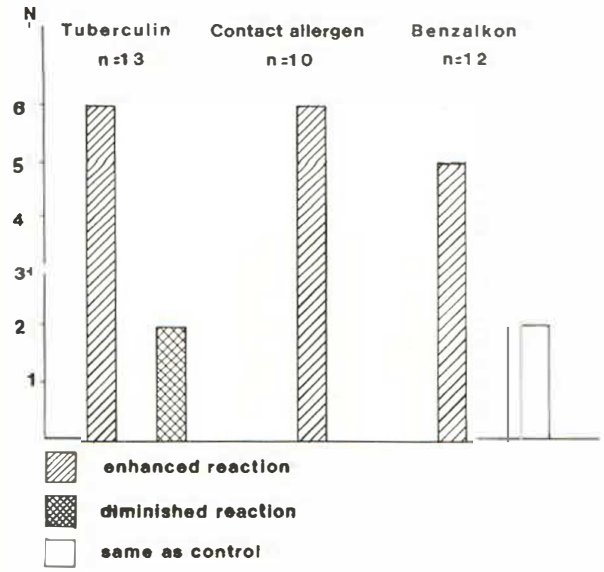

Fig. 3. Delayed allergic (contact and tuberculin allergy) and non-allergic (benzalkon) reactions. The vertical axis shows the number of subjects. The columns express a comparison between capsaicin-pretreated skin and control site.

subjects. This difference in flare size between capsaicin and control site was statistically significant ($p<0.001$).

The wheal response varied individually: it was larger on the capsaicin site in four subjects, smaller in three subjects, and identical in one. Statistically, there was no difference between the two sites.

Ultraviolet-evoked erythema

An erythema appeared in response to UVB in 11 of 16 subjects. It was intensified on the capsaicin site in eight subjects, diminished in one subject, and the same in two ($0.01<p<0.05$).

NICU

Benzoic acid was the most effective in inducing contact urticaria (Fig. 2). The enhancement of the reaction on the capsaicin site compared to the control site was significant ($p<0.01$). Sorbic acid and cinnamic acid were poor inducers of contact urticaria and the results of the experiments were not significant.

Allergic contact dermatitis and irritant delayed reaction

These reactions were significantly enhanced ($p<0.01$) on the capsaicin site compared with the control site (Fig. 3).

Tuberculin reaction

The PPD reaction was mostly larger on the capsaicin site compared with the control site (Fig. 3). The enhancement was, however, not significant.

DISCUSSION

In the present study we found that local pretreatment with capsaicin eliminates or diminishes the flare response from intracutaneously injected substance P and histamine. This is in agreement with earlier reports (9, 10, 12, 13).

With regard to the wheal response, however, substance P induced a larger reaction in capsaicin-treated skin than in control skin (Fig. 1). A similar tendency, although not significant, was seen with histamine. Previous authors have not observed such enhancement when working with substance P in capsaicin-treated skin (10, 13), or with histamine (9, 12, 13).

Capsaicin pretreatment seemed to intensify also other experimental inflammations. Thus, we have confirmed an earlier report on the response to UV light in capsaicin-pretreated skin (12). There is one recent report on IgE-mediated allergy (prick test) (15). In capsaicin-pretreated skin itch and flare were reduced, while the edematous response was not influenced. The results are thus similar to histamine and SP reactions. The NICU reactions studied by us resemble the effects of substance P and histamine in being urticarial although somewhat delayed (a difference of half an hour). The delay in time could be an important difference between NICU and type I cutaneous allergy. The two types of reactions may thus be effected by different mediators. We also studied two forms of delayed allergy (contact allergy and tuberculin reaction) and one non-allergic delayed reaction (benzalkon). In all inflammatory types there was a tendency to an enhancement of the reactions in capsaicin-treated skin. Capsaicin is known to deplete substance P from primary afferent neurons. However, capsaicin can release also other peptides such as somatostatin; also the release of acetylcholine and prostaglandins have been reported (16).

The fact that capsaicin depletes neuronal peptides other than substance P may explain the paradoxical enhancement by capsaicin pretreatment of the inflammatory response in most of our experiments. Thus, somatostatin for instance is known to inhibit the release of substance P from peripheral terminals of primary afferent neurons (17). Furthermore, somatostatin specifically inhibits immunologically important activities of human T lymphocytes (18). As a consequence, other factors promoting the inflammatory process may predominate.

Alternatively, the findings may be explained if locally administered capsaicin acts not only as a neurotoxin but also exerts toxic effects on endothelial cells (19). Although not macroscopically inflamed the capsaicin-treated skin may respond with exaggerated inflammatory reactions to noxious stimuli because of vascular damage. It is also possible that the reduction of blood flow (flare) prevents dispersal of antigen/irritant/ drug, thus leading to higher local concentrations and consequent enhancement of the wheal.

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