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Short communication

Cutaneous field stimulation of sensory nerve fibers reduces itch without affecting contact dermatitis

Background: A new technique, cutaneous field stimulation (CFS), which activates electrically unmyelinated C-fibers, is used to treat localized itch. Its action is similar to that of capsaicin, the pungent agent in hot peppers, which enhances delayed allergic reactions. The aim of the study was to investigate how experimental contact dermatitis responds to CFS.
Methods: Twelve patients with contact dermatitis in response to nickel were treated by CFS for 1 h each for four consecutive days. A flexible plate containing electrodes was applied to a test area on the upper arm and was stimulated by a constant current (0.8 mA). On the fifth day, patients were provoked by epicutaneous application of nickel sulfate (allergic contact dermatitis) and benzalkonium chloride (irritant contact dermatitis), and by intradermal tuberculin (delayed immunologic reaction). Twelve other patients with IgE-mediated allergy were treated by CFS on the lower arm for 1 h and were then pricked with histamine and allergen extracts (wheal volume was measured) and were tested using benzoic acid (nonimmunologic contact urticaria; closed test). Ten of these patients were also treated by CFS for four days, and experiments were performed on the fifth day.
Results: Test reactions to nickel, benzalkonium, and tuberculin were found to be unaffected by CFS treatment. Although allergic prick test reactions were enhanced (by 28%) after a single CFS treatment, the associated itch was significantly reduced both after single and repeated CFS treatments (by 65% and 38%, respectively).
Conclusions: Repeated use of CFS to reduce itch has no adverse effects on contact dermatitis.

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Key words: contact allergy; contact dermatitis; cutaneous field stimulation nickel; patch test; prick test; sensory nerves.

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Allergic skin diseases such as eczema and urticaria are characterized by inflammation of the skin and by itch. Stress-related exacerbation of the symptoms reflects the interaction between the skin and the nervous system.

Itching is transmitted by special C-fibers located in the dermoepidermal junction. Recently, a new technique, cutaneous field stimulation (CFS), involving electrical stimulation of the C-fibers, was reported to inhibit histamine-induced itch (1). We have also been successful in using it to treat patients with localized itch on noninflamed areas of skin (2). CFS has also been employed to combat chronic itching eczema, but its effects on delayed immunologic and irritative reactions have not been studied. The issue was whether CFS should be used to reduce itch from inflamed eczematous skin. Atopic eczema, an example of a delayed immunologic reaction, is often accompanied by itch (3). Scratching eczematous skin tends to prolong the healing process, so relieving itch is important for successful treatment.

The aim of this study was to evaluate the effects of CFS on modulation of the elicitation phase of both immediate and delayed immunologic, as well as nonimmunologic, reactions in human skin.

Material and methods

A group of 24 patients took part in the study. Twelve of them (all women, aged 35–78 years, mean 52 ± 10 years) had histories of contact dermatitis in response to nickel (delayed reactions) as verified by patch test. The other 12 (11 women and 1 man aged 22–67 years, mean 44 ± 14) had immediate, IgE-mediated allergy, as verified by prick test (4). Informed consent was obtained in all cases. The Ethics Committee of the the Medical Faculty of Lund University approved the study.

The experiments involving delayed reactions to nickel were performed on the dorsal surface of the upper arms. CFS (Fig. 1) was applied for 1 h a day for four days to one arm; the other arm served as a control. Allergic contact dermatitis, irritant contact dermatitis, and tuberculin reactions were then provoked on both upper arms on the fifth day.

The experiments involving IgE-mediated allergy were performed on the ventral part of the lower arm. CFS was applied to one arm for 1 h (the other arm was the control). After 30 min, prick tests

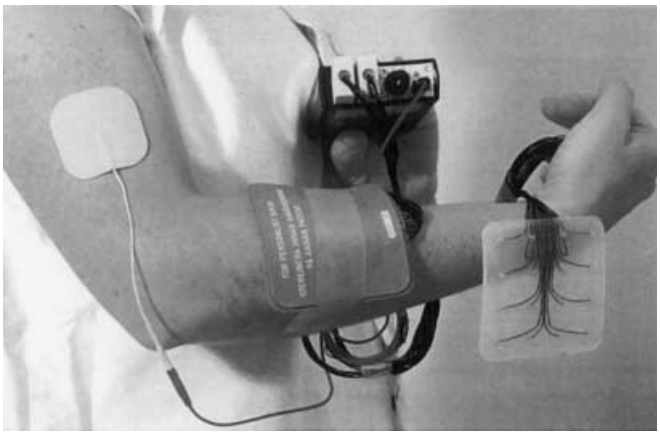

Figure 1. Cutaneous field stimulation (CFS) device consisting of a flexible electrode rubber plate (8 × 8 cm) to be fastened on the itchy patch or the area to be tested, a flat reference electrode (5 × 5 cm) to be placed on the same part of the body, and a stimulator (9 V battery). The pulse amplitude is adjustable from 0 to 10 A to control stimulus intensity.

were performed using histamine, allergen extract (nickel sulfate) or physiological saline, as well as a closed test using a nonimmunologic contact urticaria agent. Ten of the 12 patients in this group continued to use CFS for another three days and returned on the fifth day for tests as described above.

Cutaneous field stimulation (CFS) device

We used a CFS device consisting of a flexible rubber electrode plate (8 × 8 cm), a flat reference electrode (5 × 5 cm) placed on the same area, and a stimulator (a 9 V battery) (1) (Fig. 1). The CFS electrode plate was covered by needle-like electrodes (0.3 mm in diameter) surrounded by a "stop-device" protruding by 2 mm from the plate. The plate was pressed gently onto the area of skin to be treated and the electrode tips were positioned in the epidermis and in the superficial layer of the dermis. A constant current (0–0.1 mA, 64 pulses/s) was applied to the electrodes (1). The pulse amplitude was adjustable from 0 to 10 so that the intensity of the stimulus could be either increased or decreased.

Allergic contact dermatitis

Allergic contact dermatitis was induced in the 12 patients with nickel allergy by means of a patch test (Al-test, Imeco AB, Södertälje, Sweden) with a solution of 0.4% or 0.8% nickel sulfate in water. Testing was performed on the dorsal aspect of the upper arm, the patch test remained fastened for 48 h, and results were evaluated 24 h later using a clinical scoring system and planimetry. The scoring system followed the guidelines of the International Contact Dermatitis Research Group, providing information on the intensity of the allergic reaction (+ erythema, ++ infiltration or papules, +++ infiltration and vesicles) as well as the size of the afflicted skin area.

Tuberculin reaction

A tuberculin reaction was tested on the volar aspect of the forearm of the same 12 patients by intracutaneous injection of 0.1 ml of 2TU (0.04 μg) of Mycobacterium tuberculosis PPD (Statens Serum Institut, Copenhagen, Denmark). The area of the response was estimated 72 h later by planimetry.

Irritant contact dermatitis

In the same 12 subjects, a 1% in water solution of benzalkonium chloride was applied to the skin of the back, using Al-tests on Scanpor (Norgeplast, Vennesla, Norway). The compound was applied for 48 h, and the reaction was examined after another 24 h, using planimetry to estimate the area of the response.

Allergic IgE-mediated allergy

The 12 patients with positive prick test reactions to an allergen extract, either from cat hair (5 patients), mugwort (3), birch (2), shrimp (1), or from timothy grass (1), were tested during the autumn season. The prick tests were applied to the ventral surface of the lower arms 30 min after pretreatment by CFS on one arm. In additional tests, 10 of these patients received CFS once a day for four days and were tested on the fifth day, 12–24 h after the last treatment.

Extracts of a specific allergen (Soluprick, ALK, Denmark), histamine, and physiological saline were "pricked" into the volar aspect of the lower arm of each patient. Evaluation on the basis of erythema and infiltration was performed 20 min later. The volume of the wheal was calculated as the product of the area and depth (skinfold thickness − baseline/2) of the wheal. The skinfold thickness was measured using a low-tension spring-loaded caliper (Mitutoyo, Neuss, Germany).

Nonimmunological contact urticaria (NICU)

All 12 of the patients with IgE-mediated allergy also participated in experiments involving benzoic acid. Fifteen minutes after pretreatment of the one lower arm by CFS, 5% benzoic acid in petrolatum was applied epicutaneously to the skin of both lower arms using Al-tests on Scanpor. The patch tests were removed after 45 min and the area of reaction estimated by planimetry. In addition, 10 subjects used CFS once daily for four days and were tested on the fifth day, 12–24 h after the last CFS treatment.

Assessment of itch

The degree of itch was assessed by subjects in this group in the experiments concerning type-1 reactions and NICU. In each experiment, subjects evaluated the level of itching on each arm by placing a mark on a 100-mm horizontal visual analog scale (VAS) with the labels "least possible itch" and "worst possible itch" at the two extremes. Visual scales of this type have been employed by many other investigators and are regarded as reliable.

Statistical analysis and presentation of the results

The Wilcoxon signed-rank test was used for statistical analysis of intraindividual differences in response. Exact two-sided P values were computed in each case. Box-whisker plots were used for clarifying the differences in response when comparing pretreatment with CFS and control arms, boxes containing the 50% of the "most central values" (the upper limit corresponding to the 75th percentile and the lower limit to the 25th percentile). The upper whisker extends to the largest value that does not exceed the 75th percentile, to which 1.5 times the height of the box is added. The lower whisker

extends to the smallest value that does not exceed the 25th percentile, minus 1.5 times the height of the box. The reaction areas are given in $mm^2 \pm$ SEM, the reaction volumes in $mm^3 \pm$ SEM, and the itch intensity as a percentage ± SEM.

Results

A single 1-hour stimulation with CFS induced a flare under the rubber plate, which disappeared within 30 min. Flare sometimes remained in the area of the electrodes, seen in some patients 12–24 h after the last CFS treatment.

Allergic contact dermatitis

CFS treatment did not affect area or score for the allergic reactions evoked by nickel, the mean area being 228 ± 193 (SEM) mm^2 after pretreatment by CFS and 156 ± 155 mm^2 without pretreatment. The mean reaction score ± SEM was 3 ± 0.3 *vs.* 2 ± 0.8 in controls.

Irritant contact dermatitis

Benzalkonium chloride induced a sharply demarcated erythema in all 12 patients in that group, with edema in eight people and blisters in three. CFS pretreatment had no marked effect on the outcome, the mean reaction area being 96 ± 155 mm^2 after CFS and 107 ± 117 mm^2 in controls.

Tuberculin reaction

Seven of these 12 patients showed positive tuberculin reactions. CFS treatment had no discernible influence on the response, the mean reaction area being 171 ± 85 mm^2 after CFS and 199 ± 98 mm^2 in controls.

Histamine reaction

Neither single nor repeated CFS treatments had an appreciable effect on the area or the volume connected with the prick test reactions to histamine. The mean response areas were 879 ± 284 mm^2 after a single CFS application *vs.* 733 ± 196 mm^2 in controls, and 721 ± 322 mm^2 after repeated application of CFS *vs.* 663 ± 101 mm^2 in controls. The mean response volumes were 105 ± 49 mm^3 after a single application of CFS *vs.* 98 ± 56 mm^3 in controls, and 86 ± 54 mm^3 after repeated CFS application *vs.* 75 ± 37 mm^3 in controls.

IgE-mediated allergy

After a single application of CFS to people in this group, the mean response area (prick test reaction) was 675 ± 227 mm^2 after CFS treatment *vs.* 657 ± 312 mm^2 in controls. The mean response volume was increased significantly after CFS treatment to 80 ± 46 mm^3 *vs.* 58 ± 34 mm^3 in controls ($P = 0.049$) (Fig. 2).

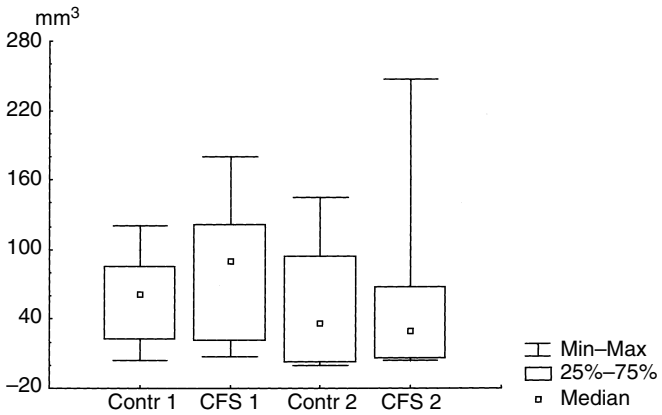

Figure 2. IgE-mediated responses to provocation by allergen extracts. The distribution of the differences in volume (mm^3) between skin pretreated by cutaneous field stimulation (CFS) and control skin are shown. 1) Reactions after 1 h of treatment with CFS administered 30 min prior to provocation ($n = 12$). 2) The reactions after four daily treatments with CFS administered one day before provocation ($n = 10$). The boxes represent half of the total responses that occurred.

Repeated CFS treatment did not change the outcome of the IgE-mediated allergy, with a mean response area of 490 ± 273 mm^2 after CFS treatment *vs.* 588 ± 276 mm^2 in controls, and mean response volume of 62 ± 30 mm^3 after CFS treatment *vs.* 59 ± 48 mm^3 in controls.

Nonimmunological contact urticaria (NICU)

All of these subjects responded to benzoic acid, all but three developing erythema (two of these developed erythema and infiltration). Neither single nor repeated CFS treatments had any appreciable effect on the test reactions: the mean response areas were 160 ± 51 mm^2 after a single application of CFS *vs.* 145 ± 33 mm^2 in controls, and 152 ± 17 mm^2 after repeated applications of CFS *vs.* 147 ± 28 mm^2 in controls.

Assessment of itch

Itch was significantly reduced after both treatments in this group (Fig. 3). After a single treatment by CFS it was reduced from 69 ± 11 (in controls) to 24 ± 18% (after treatment) ($P = 0.033$), and after repeated treatment by CFS itch was reduced from 62 ± 15% to 38 ± 24% ($P = 0.028$).

Discussion

A single application of CFS was found to produce erythema. This can be explained in terms of the release of

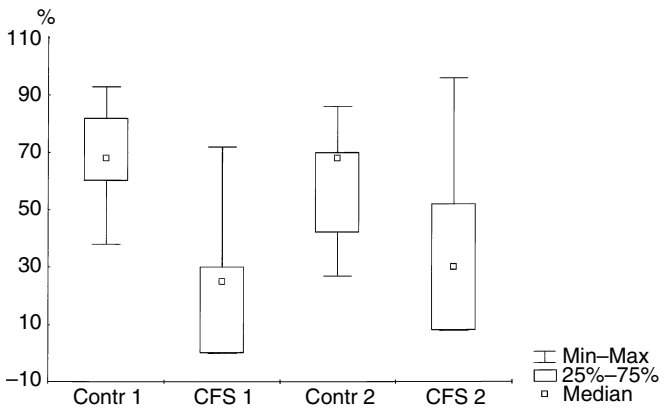

Figure 3. Itch in response to prick tests involving histamine, physiological saline, allergen extracts, and closed tests with benzoic acid, respectively. The distribution of differences in the mean values on the visual analog scale (%) between skin pretreated by cutaneous field stimulation (CFS) and control skin is shown. 1) Reactions after 1 h of treatment by CFS administered 30 min prior to provocation ($n = 12$). 2) Reactions after four daily treatments by CFS, the last treatment given one day before provocation ($n = 10$). The boxes represent half of the total number of responses that occurred.

vasoactive transmitters from the stimulated nerve fibers. Many of these transmitters act as inflammatory mediators. High concentrations of substance P, vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), neuropeptide Y, and somatostatin are found in spontaneous blisters from a variety of pathogenetically different inflammatory diseases (5). This emphasizes the fact that sensory and autonomic nerves often play an important role in the inflammatory process.

Although CFS treatment did not influence the flare-and-wheal response to intracutaneous histamine, it did reduce the itch. This is in line with reports from earlier studies showing that CFS, mechanical vibratory stimulation, and certain frequencies of transcutaneous electrical nerve stimulation, inhibit histamine-induced itch without affecting the flare response (1,6).

Suppression of the itch sensation probably reflects the fact that nerve fibers that are depleted of their transmitters are refractory.

After a single pretreatment by CFS, the prick test response to the allergen extract was found to be enhanced, and itch was suppressed. During treatment, the electrodes, which extend about 2 mm into the skin, stimulate the substance P- and CGRP-immunoreactive nerve fibers both within the epidermis and at the dermoepidermal junction (7). The vascular effects of the substance P and CGRP that are released may explain the enhanced prick test response to the allergen extract (8). In an earlier study we found that the substance P inhibitor, spantide, suppresses contact urticaria reactions (9). The potentiation of the IgE-mediated response was only seen after a single treatment with CFS, and was not found after repeated administration of CFS. Repeated treatment with CFS is associated with tachyphylaxis, which may explain why the vascular effects of neurotransmitters disappear, and why itch conduction is interrupted.

The effects of repeated CFS treatment are of particular interest since CFS is recommended for daily use in the case of severe pruritic disorders. Allergic contact dermatitis, tuberculin reaction, and irritative contact were unchanged here by treatment with CFS. There is evidence that substance P enhances delayed immunologic reactions and that CGRP inhibits such reactions (9,10). A possible explanation could be that the effects of the two neuropeptides tend to balance out.

Recently, we found that daily use of CFS for five weeks reduced localized itching and was associated with loss of epidermal nerve fibers (2). There are also reports that topical treatment with capsaicin induces a loss of epidermal nerve fibers and leads to a reduction in pain (11). Thus, there are some similarities in the pharmacological actions of capsaicin and of CFS, both compounds acting to deplete the sensory nerve fibers of their mediators (12). However, capsaicin affects immunologic reactions in the skin. Administered systemically to guinea pigs and mice, it enhances allergic reactions of a delayed type (13,14). The topical administration of capsaicin for three days also enhances contact dermatitis and tuberculin reaction in people (15). How can these diverging effects be explained? Capsaicin in an ethanol solution can diffuse and penetrate deep into the dermal layer and influence not only sensory nerve fibers at the dermoepidermal junction but also autonomic nerve fibers around blood vessels. Neuropeptides such as VIP and somatostatin are released, which have been shown to inhibit immunologic reactions (16). This cascade of events also involves other cell-derived mediators such as cytokinins (17). Capsaicin may also have its own immunological effects that are not simply related to neuropeptide release. CFS, on the other hand, probably operates where sensory nerve fibers are located both within the epidermis and at the dermoepidermal junction.

The results of this study indicate that repeated CFS treatment suppresses itch without increasing the degree of contact dermatitis, making it a useful tool for treating itchy, inflammatory skin disease.

Acknowledgments

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