Acta Derm Venereol (Stockh) 1996; 76: 48–51

Two-point Discrimination of Itch in Patients with Atopic Dermatitis and Healthy Subjects

CARL-FREDRIK WAHLGREN[1] and ANDERS EKBLOM[2]

Departments of [1]Dermatology and [2]Anaesthesiology and Intensive Care, Karolinska Hospital and Institute, Stockholm, Sweden

The ability to perceive two pruritic stimuli as separate depending on the distance between them (two-point discrimination of itch) was determined in a single-blind study of 20 patients with atopic dermatitis and 20 healthy subjects. Itch was induced with pairs of histamine injections (0.1 μg each) given on the upper arm, either along its axis (longitudinally within a dermatome) or at right angles to it (transversally involving more than one dermatome). The interinjection distances were varied in 3-cm steps until the shortest distance at which the two itching stimuli could be perceived as separate was found. Pairs consisting of one injection of histamine (0.1 μg) and one of saline served as controls.

The two-point discrimination of itch was significantly better in the atopic dermatitis patients than in the healthy controls, both longitudinally (atopic dermatitis: median 12 cm, range 3–21 cm; healthy controls: 15 cm, range 9–21; $p<0.01$) and transversally (atopic dermatitis: median 6 cm, range 3–18; healthy controls: 12 cm, range 6–21; $p<0.001$). The two-point discrimination of itch did not correlate with the subject's age, two-point discrimination of touch, or, for the atopic dermatitis patients, with their eczema scores or serum IgE levels. The quality, intensity or spatial summation of itch did not differ significantly between the two groups of subjects. *Key words: histamine; pruritus; sensory perception; spatial summation; tactile discrimination.*

(Accepted August 21, 1995.)

Acta Derm Venereol (Stockh) 1996; 76: 48–51.

C.-F. Wahlgren, Department of Dermatology, Karolinska Hospital, P.O. Box 120, S-171 76 Stockholm, Sweden.

The skin is a complex sensory organ with the ability to respond to touch, pressure, warmth, cold, pain and itch. In contrast to other sensory modalities, many basic features of the physiology of itch are still unexplored and unknown.

Methods for the induction and assessment of the sensation to be studied are prerequisites in somatosensory research. Various psychophysical techniques have been evaluated for the experimental investigation of itch and found useful (1–5). In this kind of experiment, histamine is frequently used as itch inducer (2–5) and the subject rates itch intensity with the visual analogue scale (3–5). The validity of the different methods of inducing and rating itch is strongly supported by the fact that significant dose-response relationships are obtained (1–5).

Atopic dermatitis (AD) is an inflammatory, chronically relapsing skin disease accompanied by intense itch. The pathomechanism of the itch in this disease is still unknown and controversial. For example, some authors report that AD patients, by comparison with healthy subjects, are unable to distinguish between itch induced by weak and strong histamine stimulation (6), whereas others cannot find such a difference between patients and controls (7). In contrast to these studies of temporal summation of itch, less, or even nothing, is known about the two-point discrimination or spatial summation of itch either in AD patients or in healthy subjects. Since patients with AD frequently have more than one pruritic lesion, it is of interest to investigate their ability to discriminate between closely located itch-provoking stimuli and to explore how they perceive or "sum" pruritic stimuli occurring at the same time at separate spots.

The aim of the present study was to determine the two-point discrimination of experimentally induced itch, and to elucidate some aspects of the spatial summation of pruritic stimuli in AD patients and in healthy subjects.

MATERIAL AND METHODS

Study protocol

All subjects were asked about their medical history. The AD patients were examined clinically. The extension and intensity of AD were scored according to a "twenty-area severity chart" (8), where the severity of eczema in each of the 20 areas was assessed semiquantitatively on a 0–3 scale (no, mild, moderate or severe), giving a total score of 0–60 arbitrary units. The serum IgE level was determined (Pharmacia CAP System IgE FEIA, Pharmacia, Uppsala, Sweden) in the AD patients but not in the healthy controls. Two-point discrimination of pruritic and tactile stimuli was examined on the upper arm, both longitudinally along the axis of the arm (lateral aspect) and transversally at right angles to it. The intention with this procedure was to involve ideally a single dermatome (C_6) and more than one dermatome (C_5 to T_1), respectively. The dermatomes in the region were outlined with a pen on the skin according to a dermatome map (9). The circumferences of the upper arms did not differ significantly between the two groups of subjects.

Subjects

Twenty patients with AD (9 males and 11 females; median age 25 years, range 19–43 years) and 20 healthy controls (9 males and 11 females; median age 28 years, range 18–43 years) participated in the study, which was approved by the Ethics Committee of the Karolinska Hospital.

The AD patients, all fulfilling the diagnostic criteria of Hanifin & Rajka (10), had a chronic stable eczema with a duration exceeding the previous 12 months. Their median age at initial eczema onset was 0.5 (range 0.25–8) years. At the investigation, the AD patients had a median eczema score of 13.5 (range 2–42) arbitrary units, a median serum IgE level of 610 (range 110–17300; reference value 1.6–122) kU/l and 15 out of 20 showed white dermographism. Thirteen out of 20 patients had a past or present history of hay fever and/or asthma. Emollients, but no topical corticosteroids, were permitted on the arms the week before the study. Exclusion criteria were pregnancy or lactation, unstable AD, skin infection or any other disease than atopy, internal pharmacotherapy for the previous week, ultraviolet therapy/sunbeds or systemic corticosteroids for the previous 3 months.

The healthy controls had no personal or family history of atopy or skin disease. Otherwise the exclusion criteria were identical to those for the AD patients.

 ISSN 0001-5555

Two-point discrimination of itch

Itch was provoked by intradermal injections of 10 µl histamine solution (10 µg/ml), prepared by diluting histamine hydrochloride (ACO Läkemedel AB, Solna, Sweden) with sterile pyrogen-free physiological saline containing 10% Sørensen phosphate buffer ($Na_2HPO_4 + KH_2PO_4$, 67 mM), pH 7.40. The study was single-blind with coded solutions for the subjects. An introductory test injection with histamine was given to ensure that it provoked itch in the subject. Since several histamine injections were required in the experiment, both arms were used alternately. Half of the subjects in each group started with the right arm and the others with the left. Injection needles with a diameter of 0.4 mm were used. Based on pilot studies, the two-point discrimination of itch was determined with pairs of histamine injections given at fixed distances (multiples of 3 cm), always starting with a distance of 12 cm between the two injection sites. If the two simultaneous injections provoked itch at one point, the distance between the next two injections was increased to 15 cm; but if itch was perceived at two points at 12 cm, the distance was instead reduced to 9 cm. After the two-point discrimination of itch had been determined in this way, the result was checked by injecting histamine and buffered saline (negative control) at the distance obtained. If the subject then perceived itch at one point, the result of the two-point discrimination test was accepted, but if two points were perceived as itching, the determination had to be repeated.

Two-point discrimination of touch

Two-point discrimination of tactile stimuli was determined using the ends of two blunt metal pins (diameter 1.3 mm), which were pressed concomitantly and gently against the skin of the lateral aspect of the dominant upper arm. Determinations were made both longitudinally and transversally. The minimal distance at which the two touch stimuli could be perceived as separate was measured in mm.

Recording of itch

The subjects were asked about the quality of the experimentally induced itch sensations ("pure itch", "burning itch", "pricking itch"). The intensity was recorded continuously until itch had stopped for at least 2 min, using a linear potentiometer equipped with a 100-mm visual analogue scale (VAS) (11). The potentiometer lever, sliding along the VAS, controlled the position of a pen on a plotter out of sight of the subject. The endpoints of the VAS were defined as "no itch" (=0 mm) and "maximal itch" (=100 mm). The technique allowed the calculation of itch duration (ID, sec), peak value of itch (maximal itch intensity = Imax, mm), and a total itch index (Tii = area under the curve, mm^2) reflecting both the intensity and the duration of itch.

Spatial summation of itch

To study the spatial summation of itch, the quantitative itch responses (ID, Imax, Tii) for the following pairs of injections, given longitudinally (see study protocol), were analysed: (a) histamine 0.1 µg and histamine 0.1 µg given at the two-point discrimination distance, i.e. inducing itch at two points with a total histamine dose of 0.2 µg, (b) histamine 0.1 µg and histamine 0.1 µg given at an interinjection distance 3 cm shorter than the two-point discrimination, i.e. inducing itch at one point with a total histamine dose of 0.2 µg, and (c) histamine 0.1 µg and buffered saline given as a control at the two-point discrimination distance and perceived as itch at one point.

Statistics

All statistics were non-parametric. The Wilcoxon signed ranks test was used for analysing related (matched) samples, and the Wilcoxon-Mann-Whitney test for independent samples. The Spearman rank-order correlation coefficient was determined as measure of association. The Friedman two-way analysis of variance by ranks was used for analysis of spatial summation within each group of subjects (related samples). A p-value < 0.05 denotes a statistically significant result.

RESULTS

Two-point discrimination of itch

All the patients and healthy controls perceived itch following the histamine injections. The two-point discrimination of histamine-induced itch was significantly shorter in the AD patients than in the healthy controls, both longitudinally and transversally. In both groups of subjects, the discrimination was better transversally. The data are summarised in Table I. There was a significant correlation between the results of the longitudinal and transversal values, both in the AD patients ($p < 0.01$) and in the healthy controls ($p < 0.05$). The two-point discrimination of itch did not correlate with the subject's age, two-point discrimination of touch, or, for the AD group, with the eczema score or serum IgE level.

Two-point discrimination of touch

The two-point discrimination of tactile stimulation was significantly shorter transversally in the AD patients than in the healthy controls, whereas the results of the longitudinal determinations did not differ significantly between the two groups. The data are summarised in Table II. Both for the AD patients and the healthy controls, a significant ($p < 0.001$) correlation was shown between the values obtained longitudinally and those obtained transversally.

Table I. *Two-point discrimination of itch*

Two-point discrimination (cm) of itch in 20 patients with atopic dermatitis (AD) and in 20 healthy controls (HC). Itch was induced with pairs of histamine injections given intradermally on the upper arm, either along its axis (longitudinally) or at right angles to it (transversally). For practical reasons, the interinjection distances were multiples of 3 cm (see "Material and methods"). Figures denote median values with ranges in brackets

Subjects	Two-point discrimination of itch (cm)		Longitudinal vs Transversal
	Longitudinal	Transversal	
AD	12 (3–21)	6 (3–18)	$p < 0.001$
HC	15 (9–21)	12 (6–21)	$p < 0.05$
AD vs HC	$p < 0.01$	$p < 0.001$	

Table II. *Two-point discrimination of touch*

Two-point discrimination (mm) of tactile stimulation was tested on the dominant upper arm, either along its axis (longitudinally) or at right angles to it (transversally), in 20 patients with atopic dermatitis (AD) and in 20 healthy controls (HC). Figures denote median values with ranges in brackets. NS = not significant

Subjects	Two-point discrimination of touch (mm)		Longitudinal vs Transversal
	Longitudinal	Transversal	
AD	47 (20–97)	27 (10–48)	$p < 0.001$
HC	42 (25–85)	40 (15–100)	NS
AD vs HC	NS	$p < 0.001$	

Spatial summation of itch

The quality of the histamine-induced itch responses did not differ between the AD patients and the healthy controls, or with respect to whether itch was perceived at one point or two.

The quantitative itch responses are shown in Table III. There was no significant difference between the AD patients and the healthy controls, although the Imax tended to be higher in the AD patients than in the controls (p-values 0.07–0.12). Thus the spatial summation of itch did not differ significantly between the two groups of subjects. Within each group, the only significant difference between the three combinations of injections (Table III) occurred for the ID in the AD group ($p<0.001$). Here a total histamine dose of 0.2 μg, irrespective of whether itch was perceived at one or two points, gave a significantly longer ID than 0.1 μg ($p<0.01$). The Imax and Tii did not differ significantly within the two groups.

DISCUSSION

The most appropriate method of inducing itch in AD patients would probably be to use the pruritogenic mediator of the disease, but it is still unidentified. Instead histamine was chosen, being the most thoroughly studied pruritogenic agent, although we do not consider it of major importance as an itch mediator in AD patients (11, 12). Histamine was injected intradermally and not administered iontophoretically, as no significant dose-response relationship was shown in AD patients with the latter technique (6). The histamine dose per injection was 0.1 μg given in a volume of 10 μl, leading to flare responses ranging between approximately 3 and 18 cm^2. This implies that the C-fibres were activated within relatively large skin areas although the histamine bumps were small (≤ 0.25 cm^2).

Insertion into the skin of spicules of the Mucuna pruriens plant (cowage), where the spicula tip diameter is about 5–10 μm (13), would stimulate a smaller area, but this technique was rejected for several reasons. First, the dose of the pruritogen (mucunain) in the spicule is not standardized or known; secondly, a mechanical skin stimulation induced by the remaining spicules interacting with the perception of itch cannot be excluded; thirdly, the cowage spicules do not provoke itch if they are inserted too superficially or deeply into the skin, and even with a correct spicule insertion itch is not always provoked (13), which is required in our study.

The two-point discrimination of itch was significantly better – i.e. involved a shorter distance between stimuli – in the AD patients than in the controls, both longitudinally and transversally. The two-point discrimination of touch was significantly better in the AD group when tested transversally. It is not known whether these data are valid also for other body regions than the upper arm. The quantitative itch responses provoked by histamine were not related to whether itch was perceived at one or two points, and furthermore, they did not differ significantly between the AD patients and the controls. The significant difference in the ID induced by the different pairs of injections in the AD patients (Table III) was related to the total histamine dose, since there was a significant difference between ID induced by 0.1 versus 0.2 μg histamine. However, this difference was not related to whether itch was perceived at one point or two. Most of the data in Table III suggest that the spatial summation of itch is of little importance for the magnitude of the itch perception.

The explanation of our present findings is uncertain. The AD patients' shorter two-point discrimination of itch may hypothetically be explained by peripheral and/or central nervous system (CNS) mechanisms.

In the periphery, pruritic and tactile stimulation activates different afferent nerve fibres in the skin: C-fibres (3, 13, 14) and Aβ-fibres (15), respectively. The receptive fields of the C-fibre population activated by pruritic stimuli are unknown, as is the dermatomal distribution of these fibres. Concerning peripheral nerve fibre densities, increased amounts of immunoreactive protein gene product 9.5 (16, 17), i.e. a general neuronal marker, and of the neuropeptides substance P(SP) (16–18) and calcitonin gene-related peptide (16, 17), i.e. neuropeptides of sensory nerves, have been reported in lesional skin of AD patients compared with skin of healthy controls. Our own tests were performed in non-lesional AD skin. Concerning peripheral nerve fibre function, to our knowledge other sensory modalities than itch have not been systematically explored in AD patients. It has, however, been suggested that unmyelinated afferent cutaneous nerve fibres are desensitized to histamine and SP, since these substances have been reported

Table III. *Spatial summation of experimentally induced itch*

Quantitative itch responses induced by three different pairs of injections in 20 patients with atopic dermatitis (AD) and in 20 healthy controls (HC). Each pair was given with one injection proximally and the other distally along the axis of the upper arm, i.e. longitudinally. For the two simultaneous histamine injections, itch was perceived at either two points (=two-point discrimination distance) or at one point (3 cm shorter interinjection distance than the two-point discrimination). Histamine and buffered saline were given at the two-point discrimination distance and perceived as itch at one point. Figures denote mean values ± standard deviations. ID = Itch duration, Imax = maximal itch intensity (peak value of itch), Tii = Total itch index (area under the curve, reflecting both duration and intensity)

Pairs of injections	Itch at	ID (sec)[a]		Imax (mm)[a]		Tii (mm^2)[a]	
		AD[b]	HC	AD	HC	AD	HC
Hi (0.1 μg) + Hi (0.1 μg)	two points	247.5 ± 168.9	255.3 ± 150.2	46.1 ± 28.8	32.6 ± 21.8	5697 ± 4096	5153 ± 4427
Hi (0.1 μg) + Hi (0.1 μg)	one point	239.5 ± 163.7	222.3 ± 157.0	43.4 ± 23.4	31.0 ± 25.6	5077 ± 3014	4321 ± 4867
Hi (0.1 μg) + Saline	one point	159.0 ± 110.1	207.6 ± 109.4	40.6 ± 31.1	26.6 ± 13.7	4461 ± 4591	3599 ± 3166

[a]No significant differences between the itch responses of AD and HC (Wilcoxon-Mann-Whitney test)
[b]Significantly differing ID provoked by the pairs of injections within this group of subjects (Friedman two-way analysis of variance by ranks)

to induce less itch in AD patients than in controls (6, 19). On the other hand, our own results as well as those of others have not shown any decreased itch response to histamine (7, 20) or SP (20) in patients with AD.

A second possibility is that CNS mechanisms explain the shorter two-point discrimination of itch in AD patients. Studies of nociception in the rat have shown that activity in peripheral C-fibres induces increased excitability and responsiveness in dorsal horn neurones activated by noxious stimuli (21). Changes in receptive field characteristics, including enlargement of area, can be demonstrated. Activity in C-fibres resulting in itch perception might theoretically result in a central sensitization changing the properties of CNS neurones, as has been described for spinal cord neurones activated by nociceptive afferents (22). We are, however, unaware of data providing evidence that such a shift in response characteristics of central neurones could increase the two-point discrimination capacity. Humans can localize cutaneous pain and itch stimuli with a high precision (23), suggesting that there is a somatotopical representation for noxious inputs in the brain similar to that found for tactile stimuli. This ability would be of interest to study in AD patients as well. We can only speculate that the difference in two-point discrimination of itch between AD patients and healthy subjects might be a consequence of different CNS mechanisms. Further investigations are needed to elucidate relevant explanations.

ACKNOWLEDGEMENTS

This study was supported by grants from the Karolinska Institute, the Swedish Medical Research Council, the Smedby Foundation and the Edvard Welander–Finsen Foundation.

REFERENCES

1. Tuckett RP. Itch evoked by electrical stimulation of the skin. J Invest Dermatol 1982; 79: 368–373.
2. Simone DA, Ngeow JYF, Whitehouse J, Becerra-Cabal L, Putterman GJ, LaMotte RH. The magnitude and duration of itch produced by intracutaneous injections of histamine. Somatosens Res 1987; 5: 81–92.
3. Handwerker HO, Magerl W, Klemm F, Lang E, Westerman RA. Quantitative evaluation of itch sensation. In: Schmidt RF, Schaible HG, Vahle-Hinz C, eds. Fine afferent nerve fibers and pain. Weinheim: VCH Verlagsgesellschaft, 1987: 461–473.
4. Magerl W, Handwerker HO. A reliable model of experimental itching by iontophoresis of histamine. In: Dubner R, Gebhart GF, Bond MR, eds. Proceedings of the Vth world congress on pain. Amsterdam: Elsevier, 1988: 536–540.
5. Wahlgren CF, Ekblom A, Hägermark Ö. Some aspects of the experimental induction and measurement of itch. Acta Derm Venereol (Stockh) 1989; 69: 185–189.
6. Heyer G, Hornstein OP, Handwerker HO. Skin reactions and itch sensation induced by epicutaneous histamine application in atopic dermatitis and controls. J Invest Dermatol 1989; 93: 492–496.
7. Wahlgren CF, Hägermark Ö, Bergström R. Patients' perception of itch induced by histamine, compound 48/80 and wool fibres in atopic dermatitis. Acta Derm Venereol (Stockh) 1990; 71: 488–494.
8. Zachary CB, MacDonald DM. Quantitative analysis of T-lymphocyte subsets in atopic eczema, using monoclonal antibodies and flow cytofluorimetry. Br J Dermatol 1983; 108: 411–422.
9. Kandel ER, Schwartz JH, eds. Principles of neural science. New York: Elsevier, 1985.
10. Hanifin JM, Rajka G. Diagnostic features of atopic dermatitis. Acta Derm Venereol (Stockh) 1980; Suppl 92: 44–47.
11. Wahlgren CF. Itch and atopic dermatitis: clinical and experimental studies. Acta Derm Venereol (Stockh) 1991; Suppl 165: 1–53.
12. Wahlgren CF. Pathophysiology of itching in urticaria and atopic dermatitis. Allergy 1992; 47: 65–75.
13. Shelley WB, Arthur RP. The neurohistology and neurophysiology of the itch sensation in man. Arch Dermatol 1957; 76: 296–323.
14. Torebjörk HE, Ochoa JL. Pain and itch from C fiber stimulation [abstract]. Soc Neurosci Abstr 1981; 7: 228.
15. Lynn B. Structure, function and control: afferent nerve endings in the skin. In: Greaves MW, Shuster S, eds. Pharmacology of the skin I. Berlin: Springer-Verlag, 1989: 175–192.
16. Tobin D, Nabarro G, Baart de la Faille H, van Vloten WA, van der Putte SCJ, Schuurman HJ. Increased number of immunoreactive nerve fibers in atopic dermatitis. J Allergy Clin Immunol 1992; 90: 613–622.
17. Al'Abadie MSK, Senior HJ, Bleehen SS, Gawkrodger DJ. Neuropeptides and neuronal marker in atopic dermatitis: a quantified immunohistochemical study. Eur J Dermatol 1994; 4: 394–398.
18. Pincelli C, Fantini F, Massimi P, Girolomoni G, Seidenari S, Gianetti A. Neuropeptides in skin from patients with atopic dermatitis: an immunohistochemical study. Br J Dermatol 1990; 122: 745–750.
19. Heyer G, Hornstein OP, Handwerker HO. Reactions to intradermally injected substance P and topically applied mustard oil in atopic dermatitis patients. Acta Derm Venereol (Stockh) 1991; 71: 291–295.
20. Giannetti A, Girolomoni G. Skin reactivity to neuropeptides in atopic dermatitis. Br J Dermatol 1989; 121: 681–688.
21. Cook AJ, Woolf CJ, Wall PD, McMahon SB. Dynamic receptive field plasticity in rat spinal cord dorsal horn following C-primary afferent input. Nature 1987; 325: 151–153.
22. Simone DA, Sorkin LS, Oh U, Chung JM, Owens C, LaMotte RH, *et al.* Neurogenic hyperalgesia: central neural correlates in responses of spinothalamic tract neurons. J Neurophysiol 1991; 66: 228–246.
23. Koltzenburg M, Handwerker HO, Torebjörk HE. The ability of humans to localise noxious stimuli. Neurosci Lett 1993; 150: 219–222.