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Electrically evoked itch in humans

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Abstract

We compared itch sensations and axon reflex flare induced by transcutaneous electrical (0.08–8 ms, 2–200 Hz) and chemical (histamine iontophoresis; 100 μC) stimulation. Stimuli were applied to non-lesional volar wrist skin in 20 healthy human subjects and 10 patients with atopic dermatitis. Intensity of evoked itch and pain sensations were rated on a numerical rating scale (NRS) of 0 (no sensation) to 10 (the maximum sensation imaginable). The axon reflex erythema was measured by laser Doppler imager and areas of alloknesis (itch evoked by light brushing) and hyperknesis (itch evoked by pricking) were assessed psychophysically. Electrical stimulation was most effective for stimulus durations ≥ 2 ms and frequencies ≥ 50 Hz. It evoked pure itch as threshold sensation in 80% of the subjects that was perceived with a delay of approximately 1 s. Itch intensities of up to 7/10 were not accompanied by an axon reflex flare. In contrast, histamine provoked a massive increase of axon reflex erythema and maximum itch ratings of 3.1 ± 0.2. The extention of alloknesis areas (2.3 ± 0.5 cm) evoked by electrical stimulation clearly exceeded those induced by histamine (0.7 ± 0.3 cm). Healthy subjects and patients with atopic dermatitis did not differ significantly in their response to either stimulation. We conclude that C-fiber activation underlies the electrically evoked itch sensation. The low electrical thresholds and the absence of an axon reflex flare suggest that these fibers are not identical with the previously described mechano-insensitive histamine responsive C fibers, but represent a separate peripheral neuronal system for the induction of itch.

Keywords: Pruritus; Axon reflex erythema; Nociception; Central sensitization; Alloknesis

1. Introduction

Histamine and mast cell degranulating mediators have been used since decades to induce itch in experimental models (Hägermark et al., 1978; Keele and Armstrong, 1964). Histamine sensitive, mechano-insensitive unmyelinated afferent nerve fibers have been identified that convey histamine-induced itch and it has become clear that a specialized neuronal pathway for itch distinct from pain processing exists (Andrew and Craig, 2001; Schmelz et al., 1997). However, anti-histamines do not relief chronic itch in many patients, suggesting that histamine is not the main mediator. Moreover, in atopic dermatitis, one of most abundant pruritic diseases, itch can often be induced mechanically (Wahlgren et al., 1991), which contrasts the mechano-insensitivity of the histamine-sensitive C-fibers (Andrew and Craig, 2001; Schmelz et al., 1997). Activation of mechano-insensitive fibers also has been shown to evoke a widespread axon reflex erythma (Schmelz et al., 2000a), which is absent in itch induced by papain (Hägermark, 1973) and also in some clinical itch conditions ('pruritus sine materia'). Thus, there is evidence to suggest that activation of histamine-sensitive C-fibers is not sufficient to explain all the clinical itch phenomena.

Also electrically evoked itch can be regarded as argument for another class of pruriceptive nerve fibers: as electrical thresholds of mechano-insensitive C-fibers are particularly high (Weidner et al., 1999), one would expect transcutaneous electrical stimulation to provoke pain rather

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than itch. Electrically evoked itch has been reported also in early studies (Edwards et al., 1976; Shelley and Arthur, 1957; Tuckett, 1982), but the reproducibility and intensity of itch were not very high. In this study, a newly developed method to evoke intense itch electrically was used. We assessed the effect of duration, intensity and frequency of the electrical stimulus on the intensity of the evoked itch and measured the accompanying axon reflex erythema. Flare size and itch intensity was compared to the traditional histamine iontophoresis, which is known to activate a subpopulation of pruriceptive mechano-insensitive C fibers.

2. Material and method

2.1. Subjects

Twenty healthy human subjects (11 females and nine males aged at 33.1±4.6, mean±SD) and 10 patients with atopic dermatitis (five females and five males aged at 24.7±3.6, mean±SD) participated in this study. All the atopic dermatitis (AD) patients had typical characteristics of AD which are listed in Hanifin and Rajka's diagnostic criteria (Hanifin and Rajka, 1980). They had chronic itch in their lesional skin areas, mostly around the neck, antecubital fossae and popliteal fossae. None of them had lesions in the forearm except for fingers and antecubital fossae. The healthy human subjects had no atopic factors (AD, allergic rhinitis and asthma). None of the subjects had used any antipruritic or analgesic drugs for a week prior to the experiments. The study was approved by the ethic committee in Erlangen and Kyoto and the subjects participated after giving their informed consent in writing.

2.2. Electrical stimulation

An electrode of 0.1×7 mm consisting of stainless steel wire (diameter 0.1 mm, Vogelsang, Hagen, Germany) was attached to the wrist skin so that the long axes of the electrode and arm were orthogonally positioned. The electrode was fixed onto the skin by an insulating tape of 3×20 mm which covered the whole electrode. A saline-soaked gauze pad (3×7 cm) served as the reference electrode (anode). Constant current stimuli of different duration (0.08–8 ms) and frequency (2–200 Hz) were applied from the stimulator (DS7, Digitimer Ltd, Hertfordshire, UK and SEN7203, Nihon-Koden Ltd, Tokyo, Japan) to the skin through the electrode.

2.3. Electrical stimulation, effect of duration and frequency

Ten healthy subjects participated in the experiment investigating the effect of pulse duration and frequency. The test was performed at the left wrist of each subject. Trains of 50 pulses (2 ms duration) were applied at 50 Hz every 30 s. The current intensity (mA) was gradually increased to a level, which induced the desire to scratch. The subjects were asked to take the intensity of this itch sensation as 100%. Thereafter, the frequency was varied between 2 and 200 Hz (2, 10, 20, 50, 100 and 200 Hz) at a duration of 2 ms or the duration was varied between 0.08 and 8 ms (0.08, 0.4, 0.8, 2, 4 and 8 ms) at a frequency of 50 Hz. These permutations were applied in randomized order at intervals of 30 s. Each test stimulus was followed by a reference stimulus (50 Hz, 2 ms). The subjects were instructed to rate the itch intensity of each stimulus relative to the initial reference stimulus. They were informed that every other stimulation was the reference stimulus, but were unaware of the parameters of the remaining stimuli.

2.4. Comparison with histamine-iontophoresis

Ten healthy human subjects and 10 AD patients participated in a protocol comparing electrical stimulation and histamine iontophoresis. The test was performed at both wrists of each subject. Trains of 50 pulses (50 Hz, 2 ms) were applied at an intertrain interval of 3 s for 90 s (Fig. 1). The areas of alloknesis, allodynia, hyperknesis and hyperalgesia were assessed immediately after the stimulation ended. This was followed by the measurement of flare performed 60 s after the end of stimulation. This whole procedure was repeated at intervals of 60 s on the same skin area using the same stimulation electrode. The intensity of flare was measured also before the beginning of the first procedure as the baseline.

The stimulation intensity in the beginning of the experiment was set to a level that evoked a just noticeable sensation of itch, pain or/and tapping. In the subsequent trials, the stimulation intensity was gradually increased at a rate of 0.01 mA/s until the subjects reported a change of intensity ratings. During the 90 s of stimulation the subjects were asked to give intensity ratings at 15-s intervals. In case of a decrease in sensation rating, the stimulation intensity was increased to keep the original level of sensation. The maximum increase during the stimulation was set to 0.05 mA. For statistical analysis maximum current intensity during each stimulation period was recorded. In addition, the absolute current intensities were expressed as order of subsequent levels: with level '0' for no stimulation (0 mA) and levels '1–7' for the increased intensities of the seven subsequent stimulation periods.

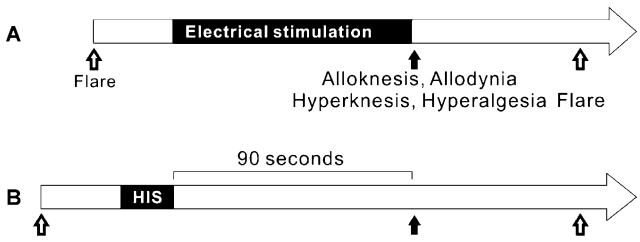

Fig. 1. Upper panel (A), Trains of 50 electrical pulses (50 Hz, 2 ms duration) were applied to the wrist skin through an electrode of 0.1×7 mm with an intertrain interval of 2 s every 3 s for a total stimulation period of 90 s (black bar). Assessments of alloknesis, allodynia, hyperknesis and hyperalgesia were performed immediately after the end of the stimulation (black arrow). Axon reflex flare was measured before and 60 s after the stimulation (opern arrow). The electrical stimulation protocol was repeated seven times using increasing stimulus intensities, starting with the threshold intensity (see Section 2) Lower panel (B), histamine iontophoresis: 1% histamine solution was applied by iontophoresis (black bar) to a 0.1–0.2× 7 mm area of the wrist skin. Assessments of alloknesis, hyperknesis, allodynia and hyperalgesia (black arrow) and measurement of axon reflex flare (open arrow) were performed according to the schedule for the electrical protocol taking into consideration the delay of the maximum itch sensation (about 60 s) following iontophoresis.

2.5. Histamine iontophoresis (Fig. 1)

Ten healthy human subjects participated in a protocol using histamine iontophoresis. The test was performed at both wrists of each subject. An insulating tape of 3×20 mm with a 0.1×7 mm gap in its center was placed on the wrist skin and a cotton fiber soaked with histamine solution (1%, dissolved in water) was placed above the gap. A stainless steel wire (diameter 0.1 mm), which was connected to an electrical stimulator (A360, World Precision Instruments, Inc., Sarasota, FL, USA) and served as anode, was attached to the cotton fiber. A saline-soaked gauze pad (3×7 cm) served as cathode and was attached to forearm skin 15 cm proximal from the insulating tape. Constant current of 5 μA was applied for 10 s. If the rating of the evoked itch did not reach three or more, the same procedure was performed with a current application for 20 s on another spot of the same wrist. The same procedure with saline instead of histamine solution was also performed with a current application for 20 s on the same spot before the histamine iontophoresis in order to investigate the influence of the current application on the flare intensity. Itch ratings were given by the subjects at 15 s intervals following the end of iontophoresis for 90 s. The measurement of alloknesis, allodynia, hyperknesis and hyperalgesia was performed 90 s after the end of iontophoresis, while that of flare was performed before iontophoresis as the baseline and 150 s after the end of iontophoresis.

2.6. Psychophysics

To compare electrical stimulation and histamine iontophoresis, the subjects were asked to report intensities of itch, pain and tapping sensation separately on a numerical scale from 0 (no sensation) to 10 the maximal sensation imaginable). Only in the experiment investigating effects of various pulse durations and train frequencies, subjects were asked rate the itch intensity relative to the intensity of a standard stimulus of 2 ms and 50 Hz, i.e. a stimulus inducing half the itch intensity of the reference stimulus should be rated as 50%. Itch was defined as a sensation provoking the desire to scratch while pain as a sensation provoking the desire to withdraw. A tapping sensation was defined as sensation that was not itching, painful or otherwise noxious and was perceived as pulsing. The stimulator for electrical stimulation was equipped with an external LED, which indicated the stimulation (on during stimulation). To investigate the latency of electrically evoked sensation, the subjects were asked to report the onset of the sensation in relation to the light signal, which they were allowed to see during this particular experiment.

2.7. Itch and pain caused by central sensitization

The areas of alloknesis, allodynia, hyperknesis or hyperalgesia were measured psychophysically. Alloknesis and allodynia were tested by light brushing with a cotton-headed stick (diameter 5 mm), while hyperknesis and hyperalgesia were tested by pin-pricks with a hand-held cylinder probe (diameter 1 cm) in which a steel pin (round tip, diameter 0.3 mm) with a load of 12 g could move smoothly (Baumgartner et al., 2002).

2.8. Flare

Axon reflex erythema was analyzed in an area of 6×20 mm around the stimulation electrode or iontophoresis site. The intensity of flare in this area was measured by a laser Doppler imager (LDI, Moor Instrument Ltd, Devon, UK) according to the manufacturer's instruction. It took 20 s for the LDI to scan the area and finish one image. The mean flux values in the area were calculated and expressed relatively to the control flux assessed before the respective stimulation. In case of histamine iontophoresis, the flux increase caused by a 20 s saline iontophoresis (5.7±4.3%, mean± SEM) was subtracted from each value obtained after histamine iontophoresis in order to control for the pure current effect.

2.9. Statistics

Mann–Whitney *U*-tests were used for the comparisons of itch and pain ratings of AD patients and healthy human subjects. Wilcoxon matched pairs tests were applied to compare itch intensities and areas of alloknesis, punctate hyperknesis, allodynia and hyperalgesia. Correlations were analyzed by Spearman *R* correlation coefficient. $P<0.05$ was recognized as statistically significant.

3. Results

Electrical stimulation evoked itch, pain and tapping sensations, axon reflex erythema and secondary areas of alloknesis, hyperknesis, and punctate hyperalgesia; atopic dermatitis patients and healthy control subjects did not differ significantly in any of the above reaction.

3.1. Latency of electrically evoked itch

At electrical stimulation for 1 s, the tapping sensation, if any, was perceived by the subjects in parallel to the stimulation without delay. On the contrary, itch sensation started just when the stimulation was coming to an end, i.e. at a latency of about 1 s. The duration was about 1–2 s. In those cases in which the subjects reported pain, burning pain was felt with a same delay as the itch sensation, whereas for stabbing pain no delay was perceived.

3.2. Effects of stimulation frequency and pulse duration

At a stimulus frequency of 50 Hz and pulse duration of 2 ms, pure itch at an intensity of three or more could be evoked in all the 10 subjects. A current intensity of 0.05± 0.04 mA (mean±SD) was required to increase the itch sensation to a level which incited the subjects to scratch.

A massive reduction of itch ratings was observed when pulse duration was reduced from 2 to 0.5 ms (reduction to 21.5±8.2%) and 0.08 ms (8.5±5.3%). Increased pulse durations (4 and 8 ms) only slightly increased the itch intensity (121±6.5 and 133±5.3%) resulting in a sigmoid

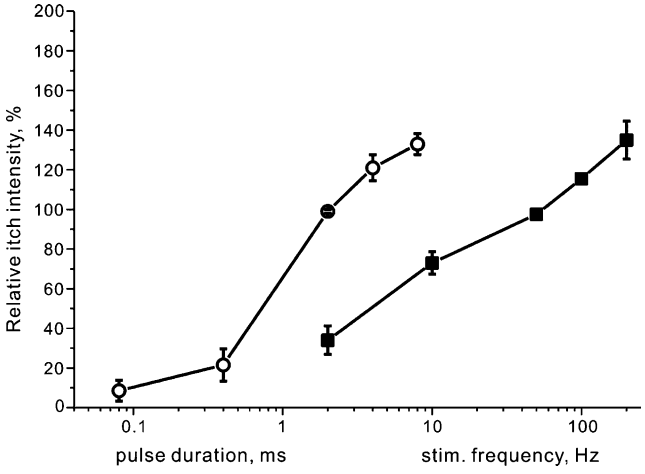

Fig. 2. Effects of pulse duration (open circles) and stimulation frequency (black squares) on itch intensity are shown.

stimulus–response function (Fig. 2). In contrast, increasing stimulation frequencies from 2 to 200 Hz gradually augmented the intensity of itch sensation in a log-linear fashion. Changes of pulse duration and frequency modified the intensity of the perceived itch. However, in none of the subjects the quality of itch converted to pain or other sensations.

3.3. Effect of current intensity

The threshold sensation evoked by the electrical stimulation (50 Hz, 2 ms) was itching in 88% ($n=44/50$ trials in 30 subjects). Electrical stimulation evoked pure itch in the rating of one or more without any other sensations including pain and tapping sensations in 84% ($n=42/50$). Pure itch in the rating of two or more was evoked in 74% ($n=37/50$) and an intensity of three or more was evoked in 68% ($n=34/50$). When increasing current intensity in just notable steps, the itch ratings increased for five subsequent steps. However, in 80% of the trials ($n=32/40$) itch ratings decreased when the current level was increased above 0.12 ± 0.01 mA ('level 5'; Fig. 3). At these higher current intensities, tapping and pain sensation were frequently reported which further increased with current intensity. Itch and burning pain sensations were perceived with a delay of about 1 s and lasted for 1–2 s, whereas tapping sensation and sharp pricking pain was directly linked to the periods of electrical stimulation. In addition, vague sensations with intensities rated below 1/10 remained in 20% ($n=8/40$) for 5 s to 2 min after the end of stimulation.

3.4. Central sensitization for itch and pain

The electrical stimulation caused alloknesis and hyperknesis that was dependent of stimulus intensity (Fig. 4). There were no significant differences between the development of alloknesis and hyperknesis. Again, AD patients and controls did not differ significantly, although

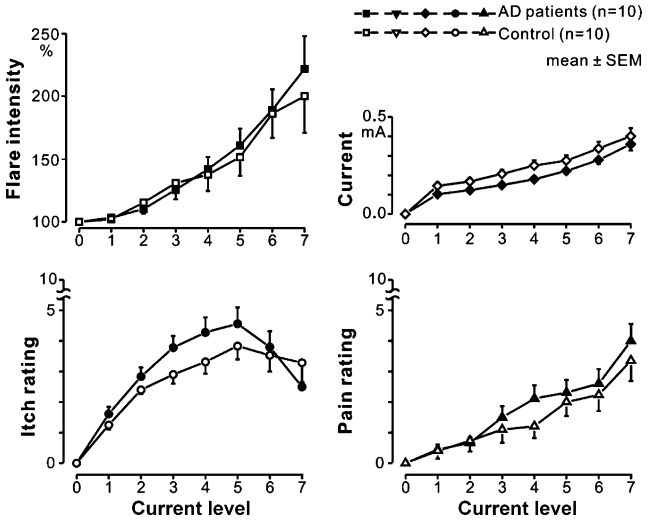

Fig. 3. Effects of increasing stimulation intensity on itch (lower left panel) and pain ratings (lower right panel) and on flare intensity (upper left panel) are shown for healthy volunteers (open symbols) and for patients with atopic dermatitis (filled symbols). Absolute values for the current levels are given in the upper right panel.

there was a trend for smaller areas of hyperknesis in AD. While low current intensities evoked alloknesis and hyperknesis, even strong electrical pulses did not produce significant allodynia. At the highest level of stimulation (0.38 ± 0.03 mA) a small area of punctate hyperalgesia was induced in control subjects. Interestingly, at this high stimulus intensity itch ratings and areas of alloknesis and hyperknesis did not increase further, but instead diminished.

The diameters of areas of alloknesis and hyperknesis were correlated to the itch intensity (Spearman $R=0.41$, $P<0.001$, Spearman $R=0.27$, $P<0.001$, respectively). This was also true of the correlation between the extent of allodynia and hyperalgesia and the pain intensity (Spearman $R=0.14$, $P<0.05$, Spearman $R=0.27$, $P<0.001$, respectively). The extent of alloknesis was negatively correlated to the pain intensity (Spearman $R=-0.14$, $P<0.05$).

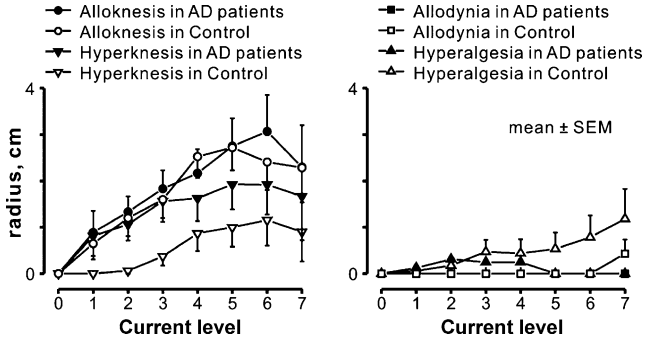

Fig. 4. The effect of increasing stimulus intensities on the extension of secondary sensitization for itch (alloknesis and punctate hyperknesis-left panel) and for pain (allodynia and punctate hyperalgesia) are shown for healthy volunteers (open symbols) and for patients with atopic dermatitis (filled symbols).

3.5. Histamine iontophoresis

Histamine iontophoresis evoked pure itch sensation that reached the maximum intensity (rating of 2.7±0.2, mean± SEM) within 30 s after iontophoresis ended and then diminished gradually. It took 184±18 s (mean±SEM) to vanish completely. During the initial 20 s of the iontophoresis an additional slight burning pain sensation (rating of one) was perceived in 15% ($n=3/20$).

3.6. Axon reflex flare induced by electrical stimulation and by histamine iontophoresis

Electrical stimulation which only evoked pure itch sensation did not increase flare intensity and consequently no correlation between flare intensity and the itch ratings was found (Spearman $R=0.22$, not significant) (Fig. 5). On the contrary, histamine iontophoresis evoked itch sensations that were combined with an intense flare reaction. The flare intensity and itch ratings following histamine application correlated significantly (Spearman $R=0.71$, $P<0.001$) (Fig. 5).

3.7. Induction of alloknesis by electrical stimulation and histamine iontophoresis

Histamine iontophoresis evoked no allodynia or hyperalgesia, but provoked areas of alloknesis and hyperknesis that correlated to the intensity of the itch sensation (Spearman $R=0.45$, $P<0.001$). However, the extent of alloknesis and hyperknesis was less pronounced as compared to electrical stimulation. Even when compared at

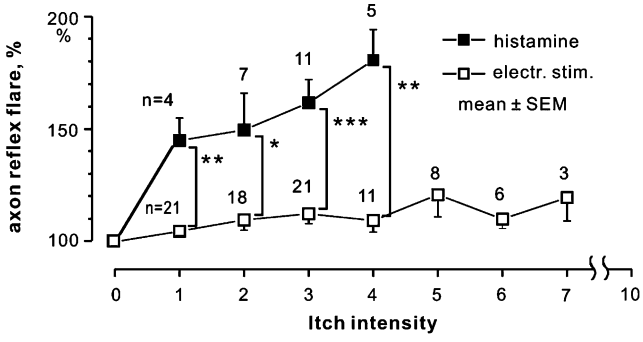

Fig. 5. The correlation of itch and flare intensity is shown in healthy volunteers for electrical stimulation (open squares) and histamine iontophoresis (filled squares). Flare intensity is given as flux value normalized to the pre-stimulation baseline value set to 100%. Only those subjects were included which reported a pure itch. For histamine iontophoresis flare increased with itch intensity (Spearman $R=0.71$, $P<0.001$), whereas electrical stimulation failed to induce a flare even at highest evoked itch ratings. There were statistically significant differences between electrical stimulation and histamine iontophoresis at each itch rating of one to four (at one: 104.4±1.5 vs 144.8±10.0, $P<0.01$, at two: 109.4±4.7 vs 149.5±16.4, $P<0.05$, at three: 112.1±4.4 vs 161.6±10.4, $P<0.001$, at four: 109.1±5.2 vs 180.6±13.6, $P<0.01$, mean ± SEM, %).

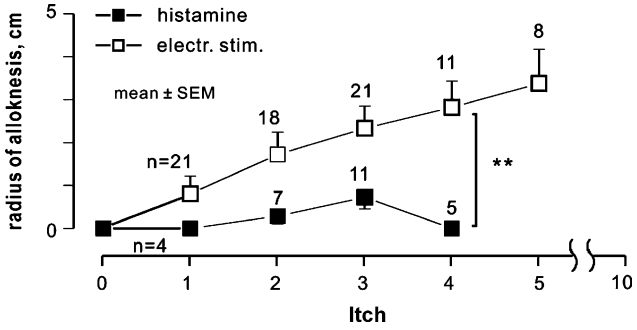

Fig. 6. The correlation of itch intensity and alloknesis is shown for electrical stimulation (open squares) and histamine iontophoresis (black squares). The extension of alloknesis increased with increasing itch ratings induced by electrical stimulation, whereas histamine ionotophoresis induced only small areas of alloknesis despite similar itch ratings.

corresponding itch levels, electrical stimulation evoked a larger extent of alloknesis (Fig. 6).

4. Discussion

Our knowledge about the neurophysiology of histamine-induced itch has been greatly increased by recent studies on a specialized pathway consisting of peripheral and spinal neurons, that are identified by their long lasting response to histamine and are characterized by low conduction velocities, high electrical thresholds, mechano-insensitivity, distinct thalamic projection and absent spontaneous activity (Andrew and Craig, 2001; Schmelz et al., 1997). Spontaneous activity in these pruriceptive fibers has been verified in a patient with chronic itch suggesting that these fibers are also involved in chronic pruritus (Schmelz et al., 2003). Yet, mechanically- (Wahlgren et al., 1991) and electrically-evoked (Shelley and Arthur, 1957) itch suggest, that the mechano-insensitive pruriceptive fibers with their high electrical thresholds cannot account for the entire itch perception.

In this study, we provoked intense itch without the generation of an axon reflex flare by low intensity, high frequency transcutaneous electrical stimulation using very localized electrodes. The delayed perception and the long pulse duration required for its induction implicate that unmyelinated afferents underlie the electrically evoked itch. Thus, our study provides evidence that there is another neuronal system of afferent C-fibers involved in the generation of itch that is characterized by lower electrical threshold, high following frequency and lack of involvement in generation of the axon reflex flare.

Electrical stimulation on wrist and ankle has been reported to provoke itch already half a century ago (Shelley and Arthur, 1957). In that study, constant current of 25 Hz and 5 ms duration was applied through an intracutaneous electrode (diameter 0.1 mm). This stimulation evoked itch in about 50% of the tested spots in

the wrist of the author, that was perceived with a delay of about 1 s (Shelley and Arthur, 1957). Also larger electrodes were used to provoke itch (Edwards et al., 1976; Tuckett, 1982), however, no data about the maximum intensity of itch were given in these manuscripts. In our study, a different type of surface electrode was used and the effects of stimulus intensity and frequency on itch intensity were systematically investigated. The study resulted in a new method to reproducibly provoke itch sensation under well controlled conditions. Sixty-eight percent of the subjects perceived pure intense itch with an intensity rating of three out of 10 or higher, which is higher than the itch induced by histamine or histamine releasing substances in healthy human subjects in this and a previous study (Rukwied et al., 2000).

The subjects perceived the itch with a delay of about 1 s and pulse durations of >0.5 ms were required to produce intense itch sensations. This pattern would suggest that C fibers having a slow conduction velocity and long chronaxy underlie the electrically evoked itch. In contrast, the high frequencies of 50–200 Hz needed to provoke intense itch appear to be too high for unmyelinated fibers. However, this is true only for polymodal and mechano-insensitive nociceptors: although they can reach instantaneous frequencies exceeding 150 Hz (Weidner et al., 2002), they cannot sustain this high frequency for more than a few action potentials. However, there are also low threshold mechanoreceptive C-fibers in human skin that can be activated by slightly stroking the skin and discharge at surprisingly high frequencies of up to 100 Hz upon weak mechanical stimulation (Vallbo et al., 1999) and have been hypothesized to have a role in grooming behavior (Olausson et al., 2002). Thus, the high stimulation frequency required to produce the electrically evoked itch does not necessarily preclude that unmyelinated afferent fibers are involved. Low threshold mechanoreceptive C fibers have been mainly found in the face and proximal limb regions and their activation is not linked to itch (Nordin, 1990; Olausson et al., 2002; Vallbo et al., 1999) so they are no candidates for explaining the electrically evoked itch.

Histamine sensitive 'itch fibers' have been found among the human C fibers (Schmelz et al., 1997). However, as their transcutaneous electrical threshold is about 10 times above the one of mechano-sensitive nociceptors (Weidner et al., 1999), they cannot produce a threshold sensation of itch as observed in this study. Moreover, application of histamine is also linked to the generation of an widespread axon reflex (Magerl et al., 1990), which has been attributed to the mechano-insensitive subpopulation of C-nociceptors (Schmelz et al., 2000a). The generation of itch without axon reflex flare shown in our study has been reported before: upon injection of papain intense itch without flare reaction was found (Hägermark, 1973). The papain-induced itch was not reduced by antihistamines, whereas itch induced by the proteinase activated receptor (PAR-2) agonist trypsin was accompanied by a flare and was sensitive to antihistamines (Hägermark, 1973). PAR-2 agonists have been implicated in the generation of itch (Steinhoff et al., 2003) and have renewed interest in proteases as pruritics; however, the pathway by which papain can produce itch is unclear yet.

The electrically induced itch was accompanied by an area of touch-evoked itch (alloknesis) and of pinprick-induced itch (hyperknesis). These phenomena, called alloknesis (itchy skin) (Bickford, 1938; Simone et al., 1991) and hyperknesis (Atanassoff et al., 1999; Brull et al., 1999) have been observed primarily in skin areas surrounding a histamine application site. It is interesting to note, that electrically induced itch provoked larger areas of alloknesis even when compared to histamine stimuli that provoked the same itch intensity. The exact mechanism of these types of sensitization are unclear, however, they correspond to the sensitization phenomena of allodynia and punctuate hyperalgesias in pain processing (Atanassoff et al., 1999; Brull et al., 1999; Ikoma et al., 2003). Sensitization of spinal processing has been assumed as underlying mechanism (Klede et al., 2003; Koltzenburg, 2000), however, a contribution of peripheral sensitization has also been claimed (Light, 2004; Serra et al., 2004). Mechano-insensitive C nociceptors with high electrical thresholds have been implicated in the generation of the central sensitization leading to punctate hyperalgesia and allodynia (Klede et al., 2003; Koppert et al., 2001; Schmelz et al., 2000b). As can be expected from their high electrical thresholds, only at the highest intensities of electrical stimulation pain and punctate hyperalgesia were elicited in our study. Interestingly, the generation of pain and punctate hyperalgesia was combined with a reduction of itch ratings and areas of alloknesis. This observation confirms the itch suppression by painful stimuli and in the area of secondary punctate hyperalgesia as described earlier (Atanassoff et al., 1999; Brull et al., 1999; Nilsson et al., 1997, 2004).

Although hypersensitivity in patients with chronic pruritus like atopic dermatitis has been reported before (Fisher, 1996), no significant differences in the electrical thresholds, the evoked flare and the evoked itch and pain sensations between atopic dermatitis patients and healthy human subjects were found when investigating non-lesioned skin sites. Thus we have no evidence for a general hypersensitivity to itch of uninvolved wrist skin of patients with atopic dermatitis. This result is in agreement with unchanged or even reduced sensitivity to histamine stimulation in non-lesioned skin in these patients (Heyer et al., 1998; Wahlgren et al., 1991). Our results therefore do not contribute to clarify the pathogenesis of itch in atopic dermatitis.

Normally painful stimuli can evoke pruritus in chronic itch patients when stimulated in lesioned skin (Ikoma et al., 2004; Nilsson et al., 2004). This phenomenon can be explained by centrally changed processing of pain and itch in these patients. However, in our study electrical stimulation at an intensity that was not perceived as painful

in either controls or patients with atopic dermatitis provoked an itch sensation. At higher intensities pain was perceived by both groups and with increasing pain itch ratings were reduced in both groups suggesting a physiological central inhibition of itch by pain.

We conclude that this newly developed method of electrical stimulation on human wrist skin induces well controlled itch and areas of alloknesis. The low intensity of the required electrical stimulation and the absence of an axon reflex erythema suggest, that this type of itch is not mediated by histamine sensitive mechano-insensitive C fibers. The long delay between stimulation and perception as well as the long stimulus duration of the stimulus suggest, that C fibers are underlying the itch sensation. In ongoing studies, the nature of these fibers and the resulting activation patterns in functional magnetic resonance experiments are investigated.

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