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INVESTIGATIVE REPORT

Gender Differences in Itch and Pain-related Sensations Provoked by Histamine, Cowhage and Capsaicin

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Cowhage, capsaicin and histamine, all applied via spicules, were used to induce itch and pain-related sensations in 15 male and 15 female subjects. Sensory qualities were assessed by questionnaire; intensities and time courses of the "itching" and "burning" sensation were measured alternately, but continuously on a VAS. In addition, axon reflexes were assessed. Only histamine and capsaicin produced a clear axon reflex flare (histamine > capsaicin, male = female). The 3 types of spicules caused mixed burning and itching sensations with different time courses. In the beginning burning prevailed, in the following minutes histamine induced mostly itching, capsaicin predominantly burning, cowhage both sensory components equally. Female subjects experienced more pain-related sensations (questionnaire), and their ratings leaned more toward burning than those of males. These findings indicate that the mixed itching and burning sensations are differentially processed by both genders. No indications were found for gender-specific differential processing in the primary afferents as reflected by nearly identical flare responses. ***Key words: itch; gender difference; capsaicin; histamine; cowhage.***

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Although the definition of itch as the sensation that causes the urge to scratch, was already established in the 17th century (Samuel Hafenreffer, Ulm 1660), itch is still enigmatic to some extent. Neurophysiological studies have revealed different "itch pathways" in the periphery, grossly divided into histaminergic and non-histaminergic (1). Interestingly, capsaicin, a substance known for eliciting strong pain may also induce itch when applied in minute amounts through spicules (2, 3). These different itch pathways are composed of distinct afferent nerves. Histamine excites a subpopulation of mechano-insensitive C-fibres (4), cowhage, the prototype of a non-histaminergic itch stimulus, activates a population of polymodal nociceptors and A-delta fibres (5, 6). Capsaicin activates a large population of mechano-insensitive and polymodal C-nociceptors (7).

The central nervous processing of itch is also still in the focus of research (8–12). Thereby, the boundaries to the sensation of pain and the interactions with pain are of particular interest (1, 10). When dealing with the psychophysiology of itch, the relationship between itch and superficial pain is of particular interest. These 2 factors, the descriptors of itching also relating to pain sensations, and the different neuronal underpinnings of itch sensations, have to be regarded when dealing with gender differences in the itch perception. It has been well established that females are more sensitive to experimental pain stimuli (reviewed in 13), but the literature on gender differences in itch sensations is scarce.

In this study we investigated differences in the qualities and intensities of itching induced by the different agents histamine, cowhage and capsaicin.

MATERIALS AND METHODS

Participants in the study

Thirty healthy young subjects (15 females [22–28 years] and 15 males [20–29 years]) took part in the study. None of the subjects reached more than 6 points (atopic disposition unlikely) in the Diepgen Atopy Score.

The subjects were informed about the aim and procedures of the experiment and were advised not to take any anti-histaminergic drugs for at least one week before the experiment. The subjects gave their informed consent to participate in the study and did not receive financial compensation for taking part. The study was approved by the local Ethics Committee.

Stimulus

For stimulation we used cowhage spicules from pods of *mucuna purinens*, which were inserted into the skin of the lower forearms. In part of the spicules mucunain, the itching agent of the spicules was inactivated by autoclaving and the spicules were prepared with histamine or capsaicin (see below).

Preparation. For application the spicules were affixed to a cotton bud with a drop of glue, their sharp ends pointing to the tip. Each carrier was equipped with approximately 30 spicules. For cowhage-stimulation we took active cowhage spicules. For histamine stimulation inactivated spicules were coated with histamine by dipping them several times into a 1% histamine solution (histamine supplied by Sigma Aldrich (Nr. H7250) dissolved in distilled water for a 1% solution). Capsaicin was applied by inactivated cowhage spicules dipped in a capsaicin solution (capsaicin (N-vanillyl-nonanamide), supplied by Sigma Aldrich (Nr. V9130). To this purpose, 500 mg were dissolved in 3.5 g ethanol and titrated to 10% solution. This procedure was repeated 3 times with drying periods of at least

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20 min in between. Since the ethanol evaporated quickly, it had no influence on the capsaicin stimuli. Histamine and capsaicin spicules were prepared several hours before application.

Application. The stimulus was applied by pressing the spicule-carrying head of the cotton bud against the skin of the subjects' lower forearms for about 2 s, so that approximately 15 spicules were inserted superficially into the skin on an area of approximately 10 mm². The number of inserted spicules was controlled after the experiment using a dissecting microscope.

Every subject received stimuli with all 3 substances histamine, cowhage and capsaicin in randomised order. Subjects and operator were blinded, since applicators looked identical. The subjects were also prevented from seeing the application site throughout the observation time. Therefore they could not see an erythema or wheal that might have been developing after application.

After the end of the observation time all applied spicules were removed from the skin by repeated stripping with an adhesive tape. The stripping was not painful.

Experimental protocol

Cowhage spicules and spicules coated with capsaicin or histamine were inserted into the skin of the lower forearms. In each session all 3 stimuli were applied alternating between both forearms. At least 20 min elapsed between the applications which should have been sufficient for any effects such as "diffuse noxious inhibitory control" to dissipate. The 3 agents were employed in randomised order; the first agent was always applied on the left arm, the second on the right arm and the third on the left arm again, but at least 10 cm away from the first application site.

The subjects used the hand of the uninvolved arm to manipulate an electronically controlled visual analogue scale (VAS) for rating the itch and burning sensations (see below). At the end of the 7-min observation time the spicules were removed from the skin and the subjects were asked to assess the qualities of the experienced sensations using a questionnaire containing 24 items (see below).

Continuous assessment of itching and burning during the experiment. The participants were asked to distinguish between the itching and burning sensations evoked by the stimulus and to rate the intensity of these perceptions alternately, when prompted by a visual cue. For rating, an electronic VAS was manipulated by moving a lever. The VAS ranged from 0% (no sensation at all) to 100% (unbearable itching and unbearable burning, respectively). The participants were instructed to rate the maximum of their momentary perception when prompted and then to set the VAS back to zero. The prompts were green and red lights switched on for 5 s, alternately. The green light was the prompt for rating "itching", the red light for "burning". The first itch rating was retrieved 10 s after the stimulus application, followed 10 s later by rating of burning. Each rating period lasted for 5 s, followed by a 5-s pause. The whole observation time lasted 7 min comprising 42 rating periods (21 each for burning and itching).

The VAS scale for itch had a mark at 30% of its length. The subjects were instructed that for the rating of itch this point on the scale should represent the itch intensity inducing a strong urge to scratch. The scale for "burning" had a mark at 70% of its length. This point should indicate that the sensation became strongly painful, inducing the urge to withdraw the arm from the stimulus.

The marks within the scale were introduced to prevent the subjects from clustering their ratings close to the zero points. The "scratch threshold" is equivalent to "moderate itch" in a categorical scale whereas the "withdrawal-threshold" in the pain scale is equivalent to "strong pain". This scale construction led to mean ratings between 20 and 40%.

Statistical analyses of the ratings. The ratings of itch and burning were extracted from the maxima of the lever movements and used for further analyses. Time courses of the itching and burning sensations during the 7-min observation periods were computed. Further, the fraction of "itching" in the mixed perception was computed as percentage of the total sensation (itching plus burning): itch percentage = itching*100/(itching+burning). These data were analysed by an analysis of variance (ANOVA) with repeated measure design, with the factors "gender", "substance" (capsaicin, cowhage, histamine, repeated factor) and "time course" (repeated factor). For control we computed also ANOVAs with the same models but dependent variables itching and burning ratings (though they are not independent of each other).

Flare responses scanned by laser Doppler imaging. A 4.0 × 8.5 cm area (145 × 70 pixels resolution, scan time: 4 ms/pixel) surrounding the application site was scanned by a laser Doppler imager (Moor LDI2-VR, Moor Instruments, Axminster, UK) 2 min before the application (baseline image) and 1 and 5 min after the stimulus application for measuring blood flow increases in the surroundings of the test stimuli. For further analyses only the baseline image and the image recorded 5 min after application were used, when the flare reaction was fully developed.

Image analyses. For the analysis of the Doppler imaging scans the Moor scanner software was used. The baseline image was subtracted from the image scanned after 5 min. An increased blood flux was assumed when the increase of the perfusion was higher than the mean flux plus 2 standard deviations within a reference which was clearly area outside the erythema. All pixels with increased blood flow determined the area of the flare reaction. An analysis of variance with repeated measure design was performed with the factor gender and "substance" (capsaicin, cowhage, histamine, repeated factor).

Qualitative assessment of itch- and burning-related sensations. After the 7-min observation period, when the spicules had been removed, the participants completed a questionnaire on itch- and pain-related sensory qualities. We used the shortened version of the "Eppendorfer Juckreizfragebogen" as used before by Kosteletzky et al. (14). The questionnaire consisted of 24 items describing sensory qualities of itch and pain. The participants rated each item from 0 ("not appropriate") to 4 ("absolutely appropriate") on an ordinal scale, ticking the appropriate figure.

Statistical analysis

The questionnaire data were analysed with an ANOVA, repeated measure design with the factor "substance" (capsaicin, cowhage, histamine, repeated factor). Sheffe's *post hoc* tests were applied to reveal differences between the single types of spicules. Gender differences were assessed with Mann-Whitney *U* tests.

For all statistical analyses the software package STATISTICA (data analysis software system), version 8.0, was used (StatSoft, Inc.). A p-value < 0.05 was considered to be significant.

RESULTS

Blood flow increases scanned by laser Doppler imaging. After application of any type of spicule the blood flow at the application site increased in all subjects. However, the size of the area of increased blood flow showed significant differences between the type of spicules (ANOVA $p < 10^{-6}$).

After 5 min, when the flare reaction was completely developed, its size in female subjects was on average 6.18 cm² for histamine, 2.87 cm² for capsaicin and 1.21 cm² for cowhage. In male subjects the average flare was 5.40 cm² for histamine, 2.97 cm² for capsaicin and 1.51 cm² for cowhage. Histamine was the only substance to cause

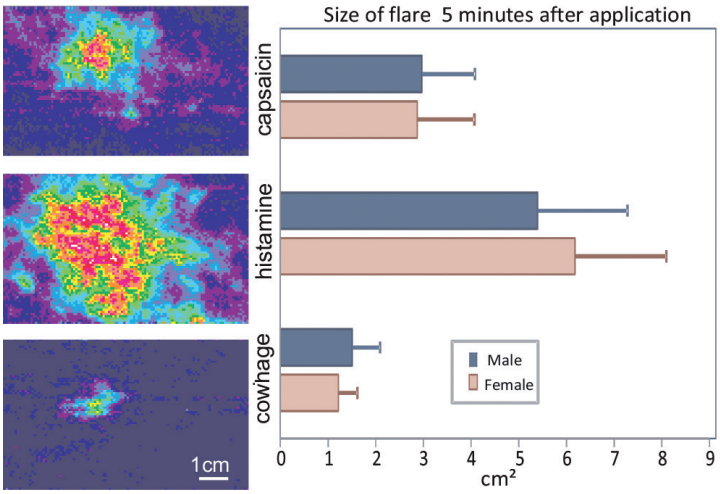

Fig. 1. Increase of skin blood flow (flare reaction) after spicule application. The left part shows specimen records of increased blood flow after application of the pruritic agents capsaicin, histamine and cowhage. Laser Doppler scanning of the volar side of the forearm was used, the upper side of the scans shows to the proximal part of the arm. Scans were recorded 5 min after stimulus application. The bars on the right side depict the sizes of the areas with increased blood flow. Statistical analysis revealed significant differences of the flares induced by the different substances (ANOVA $p<0.0001$). These substance specific differences in the flare reactions were found in both genders, but there were no differences between the genders.

a wheal. The axon reflex flare reactions to capsaicin and histamine were significantly different in size in males as well as in females (*t*-tests, male: $p_{caps\ vs\ hist}<0.01$; female: $p_{caps\ vs.\ hist}<0.003$). However, there were no significant differences in the sizes of the flare reactions between the genders (Fig. 1). This finding matches the results of a previous study where no gender differences for flare reactions were found, though the local wheal responses were significantly larger in females (15).

Qualitative assessment of itch and burning related sensations. All 3 substances induced itching and burning sensations in the subjects. For qualitative evaluation we used the items of the "Eppendorfer Juckreizfragebogen" which are depicted with an English translation in a previous paper (Kosteletzy et al., 14). As found in this previous work, only a minority of the items differentiated between the stimulating agents: "itching", "sharp", "burning", "biting" and "painful". The attribute itching was rated highest for histamine, followed by cowhage and capsaicin. The pain-related attributes burning, biting, painful and sharp were rated highest for capsaicin (ANOVA and *post hoc* Scheffé test, $p<0.05$ for the ANOVA and the *post hoc* tests).

Gender differences in the qualitative ratings. Gender-related significant differences were found for the ratings of the more pain-related qualities: "biting", "burning", "prickling", "pointed", "stinging" and "annoying" (Mann-Whitney test, $p<0.05$). All these qualities were rated higher by female subjects. The attribute "biting" describes the more dissipating character of the stimulus while "stinging" is more pointed. Fig. S1[1] shows the most relevant gender differences. The "pain-related" items revealed significant differences between the genders in 2 or all 3 spicule applications (Fig. S1 A–C[1]) whereas the differences in "itching" were not significant.

Time courses of itching and burning after application of the 3 types of itching agents. As revealed by the qualitative tests, subjects felt a mixture of itching and pain-related sensations following the application of all 3 types of spicules, even after histamine.

The time courses of the itching and burning ratings are shown in Fig. 2. Though the gender differences were not significant for the itching-scale (ANOVA), it was close to significant in the burning scale (ANOVA $p<0.055$). The *post hoc* analysis revealed significant differences of burning in the histamine experiments.

Fig. S2[1] shows the proportion of itching in the itch/burn-mixture. In both genders the burning component prevailed in the beginning of each test, probably as a consequence of the minimal trauma by the spicule insertion. However, subsequently the itch component grew, most conspicuously in the histamine, least in the capsaicin tests. In both genders the burning component was more pronounced following cowhage compared to histamine. After capsaicin, "bur-

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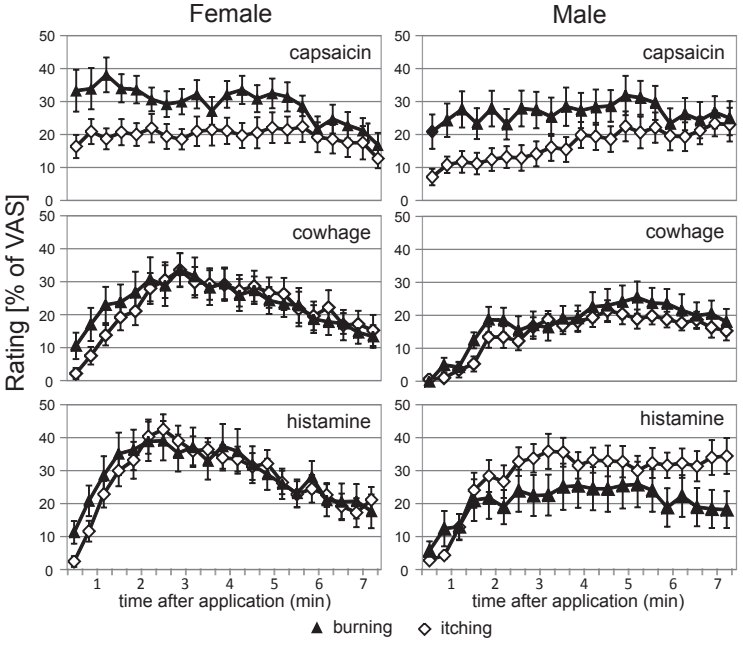

Fig. 2. Rating of "itching" and "burning" after application of the 3 substances in male and female subjects (mean ± SEM). The rating was performed using a visual analogue scale (0–100%) with marks at 30% for the itch scale indicating moderate itch and at 70% for the pain scale indicating strong pain (see Methods).

ning" remained the dominant quality throughout the whole observation time.

When these data were evaluated for gender differences (ANOVA, Table I), significant rating differences between male and female subjects were found. A (*post hoc*) planned comparison revealed a significant difference in the time courses of the ratings after histamine between males and females ($p < 0.04$).

DISCUSSION

In this study we dealt with qualities, intensities and time courses of the sensations provoked by the 3 irritant stimuli capsaicin, cowhage and histamine. To corroborate the different stimulus mechanisms we also studied the axon reflex flares induced by capsaicin and histamine. The focus of the study was on gender differences.

Differential peripheral input. The axon reflex flare provides an indication about the type of nerve fibres which are activated by the stimulus. It has been known for decades that histamine (e.g. applied by iontophoresis or pricking) provokes a pronounced flare reaction 8 (14–16). On the other hand, it has been shown repeatedly that cowhage does not induce such a flare reaction in spite of provoking pronounced itching (17). These findings were replicated with spicule application (2, 14). Cowhage induced only a short lived local reaction which had almost disappeared after 5 min. As in the study of Sikand et al. (2), the flare induced by capsaicin was smaller than the flare caused by histamine. It resembled the histamine flare and is very likely do to an axon reflex as the latter. Capsaicin has been established as one of the key substances in pain research. Its action, binding to the TRP V1-receptor of nociceptive nerve terminals, is related to the induction of burning pain. In contrast, histamine has been the key substance for itch induction. In human microneurography experiments it has been shown to activate selectively a group of mechano-insensitive C-fibres (CMI) with very large receptive fields, which release CGRP from their terminals upon excitation (4, 18). However, to some extent these "itch fibres" are also weakly responsive to capsaicin and are probably equipped with the TRP V1 receptor (7). This notion is supported on the molecular level since the G-protein coupled HR1-receptor to which histamine binds in the membrane of the nerve terminals activates the TRP V1 receptor through a second messenger pathway ([19], for a review see [1]). In the light of this lack of specificity, itch processing has been explained by a "selectivity hypothesis" (20–22): Excitation of the small population of "itch fibres" by histamine will induce itch (due to the central connection of these fibres), whereas activation of the much larger population of nociceptors by capsaicin will induce pain. This hypothesis seems to be supported by the finding of Sikand and coworkers (2, 3) where capsaicin-coated spicules provoked itch accompanied by stinging and burning pain. In this stimulus paradigm a very small population of primary afferents is affected and among them the "itch" receptors may have a greater impact on central projection neurons than "pain" nociceptors which may require more spatial summation. The finding that the histamine flare is significantly larger than the capsaicin flare provoked in the same skin region indicates that the latter is due to the excitation of the capsaicin sensitive nociceptors and not due to the weakly capsaicin sensitive histamine responsive pruriceptors (7).

Cowhage, the third agent in this study, became the prototype of a "non-histaminergic" itch stimulus. It does not release histamine from mast cells and does not provoke the typical axon reflex flare. The active agent is mucunain which binds to PAR 2 and PAR 4 receptors in nerve membranes (23). Via a second messenger pathway it probably activates the TRP A1 channel (24). It is important to note that the primary afferents excited by cowhage and by histamine belong to different populations of C-fibres (5, 25). Furthermore, the differentiation of the pathways can be followed in the CNS, different dorsal horn neurons are excited by cowhage and histamine (26).

In a study with painful intracutaneous capsaicin injections in the trigeminal region, Gazerani et al. described larger flares in females (27). However, this is not comparable to our results on histamine induced flare on the forearms. The results of Magerl et al. and of the present study may indicate a similar distribution of receptors and nerve fibres mediating the histamine induced axon reflex flare in both genders. This is remarkable since Magerl et al. (15) had described significantly larger wheal reactions in females. Since wheals are determined by local skin conditions whereas flare reactions depend on the arborisation of histamine sensitive fibres, this indicates that there is probably no difference between the sexes in arborisation of these afferent nerves. In this study we show that there are no gender related differences in flare sizes.

Thus our present and previous findings (14) indicate that any differences in itch sensitivity are probably not due to differences in the composition of excited peripheral nerve fibre populations, or in the densities and arborisation of primary afferents.

Gender-related differences in sensations caused by capsaicin, histamine and cowhage. The 3 itching agents were applied with the same carrier, a bundle of spicules, to avoid confounders due to the way of application. This

Table I. *ANOVA table of the analysis of the percentage of itch. The effects of gender and applied substances on the amount of itch in the general perception as calculated by: itch-rating/(itch-rating+burn-rating). The respective time courses are shown in Fig. 1*

ANOVA of "percentage of itch "	F	*p*
Gender	5.16	<0.028
Substance	3.43	<0.041
Time	5.92	<0.001
Interactions		
Sex*substance	0.94	n.s.
Time*sex	0.79	n.s.
Time*substance	1.03	n.s.
Time*sex*substance	1.24	n.s.

way of application has been used before by others and by our group. In contrast to the Sikand group (2, 3) we did not apply single, but a small group of spicules. As with the single spicule application capsaicin induced a mixed itch and burning sensation, in contrast to intracutaneous or epicutaneous application of capsaicin to a larger area, which generally provokes a pure painful, burning sensation. These higher doses of capsaicin have been used to suppress itch (28, 29).

Our group has reported that cowhage induced itch was more stinging and prickly than the itch induced by histamine (14), and Sikand et al. (3) reported that the spicule application of capsaicin was followed by higher ratings for pricking/stinging than histamine and that the latter had been rated highest for itching. Those findings correlate nicely with the results of the experiments described here and are extended to the quality of "burning": Capsaicin induced sensations were dominated by burning throughout the observation time of several minutes, whereas histamine induced sensations were dominated by the itching component shortly after the spicule application. Cowhage-induced sensations were in between, which tails the microneurography findings that they are mainly induced by the excitation of polymodal C-nociceptors (5) and by mechanoresponsive A-delta-nociceptors (6) (Fig. 2).

Significant differences were found between female and male subjects, in the questionnaire assessment of sensory qualities and in the composition of the mixed itching and burning sensations in the continuous ratings (Fig. S1 and S2[1]).

In the questionnaire evaluation, female subjects gave higher values to pain related items. Likewise, a higher burning and lower itching proportion was observed in the continuous ratings. Female subjects tended to indicate higher rating values for the painful components of itching, whereas the itching itself is sensed equally in the two genders. The significantly lower percentages of the itching component in the ratings of the female subjects, in particular in the histamine experiments (see ANOVA of the percentage of itch, Table I), are due to a higher proportion of the burning component. In the last years many groups have studied gender and sex differences in the perception of acute and chronic pain (for reviews see [13, 30]). In studies on acute, experimentally induced pain different stimuli like heat, cold, pressure and ischaemia have been used. Studies on pressure and heat pain may come closest to our study of chemically induced sensory irritations in the spectrum of activated fiber classes. Though there are some studies in which gender differences are questioned (31), most authors agree that the pain threshold and tolerance during acute heat pain is significantly lower in female than in male subjects. Furthermore, female ratings of heat pain expressed more intense and unpleasant perceptions (13). There are also some studies that concentrate on pain induced by capsaicin. In all these studies, female subjects rated pain items higher than male subjects (13, 32).

These data match the tendency of our results. Even though the gender differences that we found are based on ratings of intensity and quality of perception, they reflect a greater sensitivity to the pain component of the sensation in female subjects. Perhaps this is also relevant for clinical itching diseases, since Ständer et al. (33) found female patients to experience more stinging and painful attacks in chronic pruritus.

There is a wide range of explanations for the different perception of pain in male and female subjects. Many studies have concentrated on gonadal steroid hormones, both in adulthood and during development. In adulthood, oestrogens, progesterone metabolites and testosterone have to be considered (for reviews see [34, 35]). A variety of studies have concentrated on the different mechanisms how oestrogens interfere with pain modulation and found activations of the Mu-opioid system via oestrogens, also in brief experimentally induced pain (35, 36). On the other hand, oestrogens suppress adrenergic antinociceptive mechanisms (34, 37). Progesterone metabolites are known to show GABAergic effects (35, 38) and therefore may modulate pain. The sex specific differences in pain perception may also be attributed to the pain protective effect of testosterone: a sexual differentiation of pain is known to already happen during the early neonatal period in rodents, when stress induced antinociception mediated via NMDA or morphine induced antinociception depend on testosterone exposure (35, 39). In adulthood testosterone is known to activate adrenergic antinociceptive mechanisms (40), attenuate nociception after a variety of noxious stimuli, and also attenuate acute thermal nociception (35). Of course, also gender differences based on psychosocial factors have to be considered.

In contrast to the great number of studies on gender differences in acute pain, there are few studies so far that concentrate on the gender differences in acute pruritus. Ständer et al. (33) reported in a study on chronic itch that women reported more often localised itching occurring during attacks, with stinging, warmth and painful qualities. In a more recent study Stumpf et al. (41) found that females reported more itching after histamine-application to the lower leg, but not to the lower arm (the location of our stimulus applications). The burning component in these itching sensations was not assessed, however.

We conclude from our results that those differences may be mainly caused by a more painful component in itch sensed by females.

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