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ORIGINAL ARTICLE

Generalized and symptom-specific sensitization of chronic itch and pain

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Abstract

Background Physicians are frequently confronted with patients reporting severe itch and pain. Particularly in patients suffering from persistent itch and pain, central and peripheral sensitization processes are assumed to be involved in the long-term maintenance and aggravation of the symptoms. The present study explores generalized and symptom-specific sensitization processes in patients suffering from persistent itch and pain. Specifically, it examines whether patients with chronic itch and pain are more sensitive to somatosensory stimuli (generalized sensitization) and simultaneously perceive somatosensory stimuli as a symptom of their main physical complaint, e.g. pain in chronic pain patients (symptom-specific sensitization).

Methods Thresholds for different mechanical and electrical sensory stimuli of Quantitative Sensory Testing were determined in 15 female patients suffering from chronic itch associated with atopic dermatitis, 15 female chronic pain patients diagnosed with fibromyalgia, and 19 female healthy controls. Intensities of itch and pain sensations were rated on a visual analogue scale.

Results As expected, the patient groups had significantly lower tolerance thresholds for the somatosensory stimuli applied than the healthy controls, supporting generalized sensitization. Moreover, patients with chronic itch consistently reported more itch, while patients with chronic pain partly reported more pain in response to analogous somatosensory stimuli than the healthy controls and the other patient group, indicating symptom-specific sensitization.

Conclusion The present study provides preliminary support that both generalized and symptom-specific sensitization processes play a role in the regulation and processing of somatosensory stimulation of patients with chronic itch and pain.

Introduction

Physicians are frequently confronted with patients with high symptom reports that lack a clear pathophysiological aetiology, driving up healthcare costs due to lengthy diagnostic procedures and ineffective treatment. Central and peripheral sensitization (i.e. enhanced sensory sensitivity) has been proposed as one of the mechanisms responsible for these high symptom reports. Particularly in patients suffering from chronic physical symptoms such as persistent itch and pain, sensitization processes are assumed to be involved in the long-term maintenance and aggravation of the symptoms.

Consistent with basic psychophysiological theories on the regulation and processing of somatosensory and affective stimuli, two processes are distinguished with respect to physical sensations: the tendency of an individual to react with various degrees of intensity and the tendency to ascribe a specific quality to the sensation.[1–3] The first tendency concerns the quantification of sensations and

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solely regards intensity independently of the type of sensation. The second is a qualitative interpretation that labels the sensations primarily based on their incorporation into contextual information. Sensations are perceived in a specific sensory modality, a classification parameter according to which the brain habitually organizes information. New input of sensory information matching the modality has a higher probability of being processed than information from a mismatching modality. Consequently, both processes might be involved in sensitization and altered in patients with chronic physical complaints, resulting in *generalized sensitization* – a tendency to experience an overall lowered threshold to somatosensory stimuli; and *symptom-specific sensitization* – a tendency to perceive sensory stimuli in correspondence with the main physical symptom. Patients with chronic itch or pain may hence be more sensitive to all kinds of somatosensory stimuli than healthy individuals and may tend to perceive sensory stimuli in terms of their primary symptom, e.g. pain in chronic pain (CP) patients.[1–7]

There is a longstanding history of research into sensitization processes in CP patients, mainly focused on either generalized or symptom-specific sensitization processes. Quantitative Sensory Testing (QST) is a validated and frequently applied assessment method for sensitization with various sensory stimulus modalities.[8–12] Numerous QST studies have shown that patients with chronic pain, including patients with fibromyalgia or rheumatoid arthritis, have lowered tolerance thresholds and an altered sensation perception in comparison to healthy controls, suggesting generalized sensitization.[13–19] There is also some preliminary support for symptom-specific sensitization in CP: when asked to describe the quality of a mechanical stimulus, patients with fibromyalgia used more pain-related descriptors for the stimulus than healthy controls.[20] In addition, histamine iontophoresis resulted in burning pain instead of itch in patients with neuropathic pain.[21,22]

Less attention has been directed to sensitization processes in chronic itch (CI) sufferers, although itch and pain bear many similarities.[23] Despite specific neurophysiological differences, both use the lateral spinothalamic tract, in two separate, centrally located systems, and the pattern of brain activation shows a broad overlap.[24,25] Furthermore, both concern adverse body conditions that generate reflexive autonomic and motor responses under central control.[23,26] Ikoma and colleagues have recently delivered evidence for symptom-specific sensitization in CI patients.[15,27] They showed that by varying the electrical stimulus intensity, QST could induce both pain and itch and that CI patients experienced itch to a stimulus healthy subjects experienced as pain. Consequently, the QST paradigm seems to allow the investigation of both generalized and symptom-specific sensitization processes in both populations of chronic itch and pain. However, to date, comparative research examining the two sensitization processes in patient groups with different physical symptoms is lacking.

With the present study, both sensitization processes were explored in patients suffering from chronic pain and itch. We hypothesized that in reaction to a somatosensory stimulus, the patients with CP and CI would show an overall lower tolerance threshold than the controls consistent with the hypothesis of generalized sensitization. Following the symptom-specific sensitization hypothesis, we expected the CP patients to report more pain and the CI patients more itch in response to the same stimuli relative to the other patient group and the controls.

Methods

Participants

Fifteen female CP patients (mean age = 44.5; SD = 7.9) diagnosed with fibromyalgia by a rheumatologist (American College of Rheumatology criteria, Wolfe *et al.*[28]) and 15 female CI patients (mean age = 33.2; SD = 12.5) diagnosed with atopic dermatitis by a dermatologist were recruited from two hospitals in the Netherlands. Mean symptom duration for the CP and CI patients was 13.7 years (SD = 9.0) and 23.0 years (SD = 13.2), respectively. Inclusion criteria were a minimum age of 16 years and a diagnosis of either fibromyalgia or atopic dermatitis. Exclusion criteria were comorbid conditions (e.g. multiple sclerosis, diabetes mellitus and arthritis psoriatica), double diagnoses with regard to the conditions investigated, severe psychiatric disorders and pacemaker use. In addition, 19 healthy female controls (mean age = 43.3; SD = 12.1) were recruited via advertisements.

The protocol was approved by the regional medical ethics committee and all participants gave their informed consent prior to the investigation. Upon arrival to the test facility, participants were informed about the procedure and asked about their menstruation cycle, cigarette smoking and intake of medication, caffeine and alcohol over the previous 24 h. Participants had earlier been asked not to alter their regular medication usage on the day of testing. Five CP patients and eight CI patients had not taken any medication at the time of testing. Two CP patients and two CI patients took selective serotonin reuptake inhibitor/serotonin-norepinephrine reuptake inhibitor antidepressants, one CP patient took corticosteroids, seven CP patients and one CI patient took (combinations of) nonsteroidal anti-inflammatory drugs (NSAID). Five of the CI patients took antihistaminics (of whom one patient took a combination with antidepressants) and one healthy control took beta blockers as treatment for high blood pressure. In the CI patients, the severity and extent of the skin disease was measured using a validated skin severity scale,[29]

showing that all patients had at least one body area affected by the skin disease and that 73% of the patients had at least one body area that was severely affected. In addition, the baseline degree of itch and pain of all participants was determined before the start of the experiment by having the patients indicate the current level of itch and pain on a visual analogue scale (VAS) ranging from 0 to 10. As expected, the CI patients reported a significantly higher baseline level of itch (M = 3.0, SD = 1.9) than the controls (M = 0.7, SD = 1.1) ($t = 4.27$, $P < 0.001$) and the CP patients (M = 0.6, SD = 0.8) ($t = –4.56$, $P < 0.001$), while patients with CP reported significantly more pain (M = 5.4, SD = 2.0) than the patients with CI (M = 0.8, SD = 0.9) ($t = 8.13$, $P < 0.001$) and the controls (M = 1.0, SD = 1.5) ($t = 7.48$, $P < 0.001$). No significant differences were found for the itch level between the CP patients and the controls ($t = –0.19$, $P = 0.85$) nor for the baseline pain level between the CI patients and the controls ($t = –0.45$, $P = 0.66$).

General procedure

The QST was performed using von Frey filaments for mechanical stimulation as well as electrical stimulation.[15–18,30] All tests were administered by the same investigator in the same order. On the test day the subjects were informed about the tests and familiarized with the procedure in a pretest trial. They were told that the stimuli could provoke different sensations, for example, itch and pain. After each stimulus, they were asked to rate down their sensation using a 10-point VAS for both itch and pain ranging from no itch/pain to the worst itch/pain imaginable. Measurements were made at two sites: 2 cm distal to the epicondylus of the humerus on the non-dominant forearm (corresponding to dermatome C5) and at the midpoint of upper trapezius on the dominant side (corresponding to dermatome C4). The first area is a tender point in fibromyalgia and a frequently affected site in patients with atopic dermatitis, while the latter is not a tender point and only infrequently affected in patients with atopic dermatitis.[28,31] In the present study, 12 of the CI patients had lesions on the target site at the forearm and three at the trapezius.

Mechanical stimulation

At both sites mechanical stimuli were delivered using 20 Semmes-Weinstein von Frey calibrated filaments in the range of 0.0045 to 447.0 g.[32] The filaments were applied vertically once, with increasing force and avoiding contact with body hair. Subjects were asked to report the Aδ-fibre threshold, defined as 'the moment that the stimulus perception changed into an unpleasant, stinging sensation' (specified by the hair number out of at total of 20 hairs).

Electrical stimulation

Cutaneous electrodes (4 × 3.5 cm, 3M Red Dot) were applied at both body sites. The electrical stimuli consisted of 0.3-ms pulses with a 100-Hz frequency with a continuous increasing intensity of 0.2 mA/s, delivered by a nerve stimulator (Pajunk, Germany). Stimulus intensity was increased at a rate with a maximum of 25 mA.[33] After a pretest trial at the trapezius, tolerance measurements were started at the forearm. The electrical tolerance threshold was defined as 'the moment that the subject did not wish to experience a higher intensity and wanted to stop'. The means of two repeated thresholds (three in those cases where both values differed more than 0.5 mA) were defined. Interstimulus time was set at at least 30 s.[27]

Statistics

The reported threshold intensities and VAS ratings for itch and pain were analysed with one-tailed analyses of variance (ANOVA) using SPSS 13.0 for Windows. Between-group differences were taken as the independent variable. To test the hypothesis of generalized sensitization, the healthy controls were compared to the merged CP/CI patients group. To evaluate symptom-specific sensitization, the patient group matching the modality of the stimulus under investigation (e.g. pain in CP) was compared to the merged group of the controls and the other patient group that thus mismatched the modality of the stimulus tested (e.g. pain in CI). The dependent variables were the threshold values for generalized sensitization and the patients' itch and pain VAS ratings for symptom-specific sensitization. Post-hoc testing included a pairwise multiple comparison test of the least significant difference (LSD) with statistical significance set at $P < 0.05$.

The same procedure was applied with the repeated measures analyses of covariance (ANCOVA) with the control variables age, educational level, menopausal status, disease duration, smoking and current medication intake for patients with CP and CI as well as VAS pain and itch at the day of testing. Menopausal status was found to be a significant covariate in three, disease duration in one and medication use in two of the 12 ANCOVAS. However, when the results were corrected for these variables by ANCOVA, no significant differences emerged with regard to the main effects. Consequently, the results reported are based on the ANOVAS only.

Results

Mechanical stimulation

Table 1 summarizes the means and standard deviations and ANOVA results for the QST thresholds and the pain and

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Table 1 Analysis of variance results of Quantitative Sensory Testing (QST) at the forearm and the upper trapezius of patients with chronic itch (CI), chronic pain (CP) and healthy controls (HC)

		CP (*N* = 15)	CI (*N* = 15)	HC (*N* = 19)	*F*	Post hoc
Tactile stimulation		M (SD)	M (SD)	M (SD)		
Forearm	Threshold	13.13 (5.76)	13.20 (5.36)	**16.00 (4.91)**	6.75*	HC > CI, CP
	VAS itch	1.31 (1.69)	**2.21 (2.10)**	0.85 (1.07)	10.62*	CI > HC, CP
	VAS pain	1.23 (1.44)	1.08 (2.11)	0.87 (0.94)	0.95	
Trapezius	Threshold	11.27 (5.81)	11.87 (3.44)	**16.79 (4.24)**	30.92***	HC > CI, CP
	VAS itch	1.63 (1.51)	**2.91 (2.85)**	0.32 (0.61)	23.90***	CI > HC, CP
	VAS pain	**2.00 (2.48)**	1.40 (1.35)	0.68 (0.93)	9.26*	CP > HC, CI
Electrical stimulation						
Forearm	Threshold	4.07 (2.51)	3.72 (1.59)	**7.34 (7.36)**	11.79**	HC > CI, CP
	VAS itch	0.89 (1.09)	**2.48 (2.56)**	1.60 (1.61)	8.76*	CI > HC, CP
	VAS pain	**2.30 (1.09)**	1.56 (1.20)	1.40 (1.52)	10.58*	CP > HC, CI
Trapezius	Threshold	6.74 (6.64)	5.25 (2.48)	**8.08 (4.51)**	6.21*	HC > CI, CP
	VAS itch	0.95 (1.27)	**3.31 (3.30)**	1.59 (1.59)	17.64***	CI > HC, CP
	VAS pain	3.21 (2.30)	3.21 (2.74)	3.04 (1.86)	0.03	

*$P = 0.05$, **$P = 0.01$, ***$P = 0.001$; one-tailed; bold values indicate significant differences between groups for thresholds (HC vs. CP and CI), VAS itch (CI vs. CP and HC) and VAS pain (CP vs. CI and HC).

itch ratings. As to generalized sensitization, the patients reported lowered thresholds for mechanical stimulation at both the forearm and the trapezius ($F(1,48) = 6.75$, $P < 0.05$; $F(1,48) = 30.92$, $P < 0.001$, respectively) relative to controls. Regarding symptom-specific sensitization, the CI patients reported more itch than the other two groups at both sites (forearm: $F(1,48) = 10.62$ $P < 0.05$; trapezius: $F(1,48) = 23.90$, $P < 0.001$). In contrast, the CP patients reported more pain at the trapezius than the other groups ($F(1,48) = 9.26$, $P < 0.05$). Only at the forearm was this result not significant for pain ($F(1,48) = 0.95$, $P = 0.25$).

Electrical stimulation

With regard to generalized sensitization, the CI and CP patients reported lower electrical tolerance thresholds than the controls both at the forearm ($F(1,48) = 11.79$ $P < 0.01$) and at the trapezius ($F(1,48) = 6.21$, $P < 0.05$). With respect to symptom-specific sensitization, the patients with CI reported significantly more intense itching sensations at both sites than the other two groups (forearm: $F(1,48) = 8.76$ $P < 0.05$; trapezius: $F(1,48) = 17.64$ $P < 0.001$), while the patients with CP reported significantly more pain in the forearm in comparison with the other groups ($F(1,48) = 10.58$, $P < 0.05$). Only at the trapezius was this result not significant for pain ($F(1,48) = 0.03$, $P = 0.45$) (see Table 1).

Discussion

The results of the current study suggest that both generalized and symptom-specific sensitization processes are implicated in the symptom regulation of the two patient samples suffering from chronic physical complaints. In line with our expectations regarding generalized sensitization, patients with chronic pain (CP) and itch (CI) have lower thresholds for the applied somatosensory stimuli than the healthy controls. At the same time, we found indications for symptom-specific sensitization as the CI patients report more intense itching and the CP patients partly more intense pain sensations in response to similar stimuli than the other patient group and the healthy controls.

With regard to generalized sensitization, our findings underpin earlier studies that showed patients with CP and CI to have lower electrical tolerance thresholds than healthy controls.[17,34] With our paradigm we also demonstrate corresponding effects in response to mechanical stimulation. More importantly, as both our patient groups proved to have lowered tolerance thresholds for electrical as well as mechanical stimulation relative to the healthy controls, it is likely that corresponding generalized sensitization mechanisms play a role in the regulation and processing of somatosensory stimulation of patients with different chronic physical symptoms. Our results thus seem to support the assumption of a common sensitization process in a wide range of chronic complaints, including sensitization processes of adverse bodily conditions that are under central and peripheral control.[7,23,26,35]

The current study has also provided preliminary support for symptom-specific sensitization in the two patient populations investigated: the CI patients reported higher levels of itching following all four somatosensory stimuli and the CP sample reported more intense pain for two of the four stimuli. These findings are relatively consistent

with earlier studies, e.g. Berglund and her colleagues found that mechanical stimulation was perceived with more pain-related descriptors in fibromyalgia patients than in healthy controls.[20] Ikoma and colleagues[15] demonstrated that in CI patients with atopic dermatitis mechanical and electrical stimulation evoked itchy sensations, in contrast to the painful sensations reported by the healthy subjects. By comparing patients with two different chronic symptoms with the same paradigm, preliminary support for the symptom-specific sensitization was for the first time found in patients with different physical symptoms; demonstrating that a patient's sensation report to somatosensory stimuli tend to be in accordance with his or her main physical complaint.

Taken together, the study results deliver preliminary support for altered sensitization processes in patients with chronic pain and itch, suggesting that these patients are more sensitive to somatosensory stimuli in terms of a lowered sensory tolerance threshold, i.e. generalized sensitization, and largely tend to perceive the same somatosensory stimulus as a symptom of their main physical complaint, i.e. symptom-specific sensitization.

Several limitations need to be taken into account. First, although the stimuli in our study were mostly experienced according to the patient's main physical symptom within its matching sensory modality, suggesting that the applied stimuli were ambiguous and interpretable in different ways, the symptom-specific pain ratings in the CP patients were not as clear as the itch reports in the CI patients. In future research, it might be important to vary the stimulus intensity, duration and sensory modality as well as to study the responses to other stimuli (e.g. cold, warm, acoustic).[27] Second, alternative explanations for the symptom-specific sensitization processes have to be taken into account. For example, it has been suggested that central sensitization of itch pathways might upset the regular mechanism that pain inhibits itch in CI patients.[23] Third, although we observed corresponding effects for both the lesioned (forearm) and non-lesioned (trapezius) sites in most patients and the level of baseline daily itch and pain proved not to have affected our results, a generally non-affected body site is to be preferred.[15] Additional measurements of erythema and flare reactions should also be carried out to obtain more insight into the basis of central and peripheral (e.g. nerve growth factor, C-fibre damage and sensitization of neuroreceptors) sensitization processes.[15,27] Fourth, there is some evidence that sensitization processes appear to differ depending on the pathophysiological aetiology for the patients' symptoms,[34] which makes it worthwhile to compare groups with different pathophysiological origins of their symptoms (e.g. fibromyalgia and rheumatoid arthritis). Fifth, although the use of pain- or itch-relieving medication generally did not affect the main results, future studies should address the issue of possible (side) effects of specific medication (e.g. corticosteroids, selective serotonin reuptake inhibitors) on psychophysiological responses. The same was the case for our analyses of menopausal status, and possible influences of this and other hormonal factors (e.g. phase of the menstrual cycle) as well as gender differences should be taken into account in future studies.[36] Finally, specific affective, cognitive and central processes, such as negative affectivity, cognitive expectations and central processing of sensory information, have been put forward as factors affecting both sensitization phenomena.[4,6,37,38] For example, negative affectivity have been shown to impinge on the conditioning processes of symptoms in patients with chronic physical complaints, possibly due to their attentional bias towards internal sensations, catastrophizing expectations towards aversive stimuli or interpretation bias to attribute ambiguous symptoms to their main symptom.[7] Further scrutiny of these mechanisms might provide deeper insights into the generalized and symptom-specific sensitization processes in patients suffering from chronic physical symptoms of pain and itch. On the long-term, insight into these sensitization processes might contribute to improvements in diagnostics, such as the clinical use of QST to screen for patients at risk as early as possible, and the development of new desensitization treatments for patients with chronic pain and itch.

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