Pain 118 (2005) 215–223

PAIN

www.elsevier.com/locate/pain

Impairment of pain inhibition in chronic tension-type headache

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Received 3 November 2004; received in revised form 2 July 2005; accepted 15 August 2005

Abstract

Evidence has been accumulated suggesting that a dysfunction in pain inhibitory systems, i.e. in 'diffuse noxious inhibitory controls' (DNIC)-like mechanisms, might be—amongst other factors—responsible for the development of anatomically generalized chronic pain like fibromyalgia. The aim of the present study was to look for similar impairments in chronic tension-type headache (CTTH) as a regionally specific pain syndrome. Twenty-nine CTTH patients and 25 age- and sex-matched healthy control subjects participated in the study. After baseline assessment of electrical detection and pain thresholds, tonic heat stimuli were concurrently applied by a thermode to the thigh to induce DNIC-like pain inhibition. Tonic heat stimuli were applied either slightly above ('pain' condition) or slightly below ('heat' condition) pain threshold. For determination of electrical detection and pain thresholds, electrocutaneous stimuli were administered either to the forearm (extra-cranial site) or to the temple (cranial site), using a multiple staircase procedure. The increase in the electrical detection and pain thresholds induced by concurrent tonic heat stimulation was significantly smaller in the CTTH patients than in the control subjects. This group difference was present during the 'pain' as well as the 'heat' condition. Furthermore, the electrical detection and pain thresholds were affected in this group-specific manner both at the forearm and at the temple. These findings suggest that patients with CTTH suffer from deficient DNIC-like pain inhibitory mechanisms in a similar manner, as do patients with anatomically generalized chronic pain like fibromyalgia.

Keywords: Diffuse noxious inhibitory controls (DNIC); Chronic tension-type headache; Pain inhibition

1. Introduction

Chronic tension-type headache (CTTH) is characterized by mild to moderate bilateral pain occurring either in episodes of variable duration or continuously. The diagnostic criteria require an occurrence of more than 15 days per month (180 days per year) for more than 3 months; furthermore, they postulate a type associated with tenderness of the pericranial muscles and a second type without such an association (Headache Classification Committee, 2004).

Since a clear somatic pathology in the myofascial cranial tissue or a damage to the trigeminal branch of the nervous system have not been found, chronic tension-type headache is regarded a functional pain syndrome. Changes in nociceptive signal transmission and pain processing are thought to be critical pathogenic factors, which are due to peripheral and central sensitization and deficiencies in pain inhibitory systems (Olesen, 1991).

In a series of studies on the exteroceptive suppression of the masseter and temporalis muscle and on the trigemino-cervical reflex it has been demonstrated that these brain stem reflexes, which are thought to be indicative of the trigeminal pain inhibitory functions, is weakened in patients

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0304-3959/$20.00
doi:10.1016/j.pain.2005.08.019

with tension-type headache (e.g. Milanov and Bogdanova, 2003; Schepelmann et al., 1998; Tataroglu et al., 2002). Since Schepelmann et al. (1998) observed decreased exteroceptive suppression only in patients with tension-type headache but not in fibromyalgia patients, this type of deterioration of the anti-nociceptive systems might be specific for headache.

Deficiencies in diffuse noxious inhibitory controls (DNIC)-like mechanisms have been alleged to be responsible for the development of chronic pain in general (Lautenbacher and Rollman, 1997). The DNIC allow that the activity of pain-signaling neurons in the spinal dorsal horn and in trigeminal nuclei can be inhibited by noxious stimuli applied to body areas far remote from the excitatory fields of these neurons (Le Bars et al., 1979a,b; Schouenborg and Dickenson, 1985). In studies on DNIC-like mechanisms in man a reduction of sensitivity to phasic pain have repeatedly been found while a concurrent tonic pain stimulus was applied (Lautenbacher et al., 2002; Price and McHaffie, 1988; Willer et al., 1984). Functionally seen, DNIC-like mechanisms act like a barrier against the uncontrolled spread of pain and keep pain regional and bearable.

In a few studies dysfunctions of DNIC-like mechanisms have been observed in fibromyalgia patients (Julien et al., 2005; Kosek and Hanson, 1997; Lautenbacher and Rollman, 1997), rendering an impairment of DNIC-like mechanisms a candidate for being a pathogenetic factor. Due to contrasting findings in patients with rheumatoid arthritis and trapezius myalgia (Leffler et al., 2002a,b), it is still unclear of whether an impairment of DNIC-like mechanisms is a universal finding in conditions with chronic pain or is confined to certain conditions. The aim of the present study was to search for deficiencies in DNIC-like mechanisms in patients with chronic tension-type headache in order to expand the basis of evidence of whether this type of pain inhibitory control system is universally weakened in chronic pain and has also to be considered in the pathogenesis of CTTH as a form of regionally specific chronic pain.

2. Methods

2.1. Subjects

Twenty-nine patients suffering from chronic tension-type headache (CTTH) and 25 healthy control subjects were investigated. The sex distribution was not different in the two groups (CTTH: 16 men, 13 women; control: 14 men, 11 women; $\chi^2 = 0.004$, $P = 0.951$). The mean age was 37.1 years (SD = 13.5) in the headache group and 38.5 years (SD = 12.9) in the control group ($t = 0.382$, $P = 0.704$ for group differences). According to these data, sex and age could not be confounded with the differences between headache patients and healthy control subjects.

The patients were in-patients in a hospital for psychosomatic disorders. The hospital is specialized in the treatment of neurotic and psychosomatic patients by behavior therapy with an emphasis on self-management and, in some cases, by psychopharmacological medication. Physicians and psychologists of all wards were asked to inform their patients about the study. Patients, who were interested in participating, were provided with further information about the study by the investigator (AP). The healthy control subjects were pain-free volunteers recruited from the staff of the hospital.

The patients entered the study not later than 2 weeks after admission. All patients passed a routine neurological examination. The investigator, who had been trained in pain management of headache patients, assessed the pain history. All patients fulfilled the diagnostic criteria of the IHS for chronic tension-type headache (Headache Classification Committee, 2004). They were free of any analgesic drug for a minimum of 14 days and did not use other medications on a regular basis. In a semi-structured interview based on the ICD-10 criteria, subjects with psychiatric disorders were excluded, except those with depression who were included because of the very high co-morbidity with tension-type headache. Of the headache patients 15 subjects (51.7%) suffered from mood disorders.

Furthermore, dermatosis at the site of the nociceptive stimulation, cardiac pacemakers, pregnancy and neurological or endocrine disorders known to affect somatosensitivity led to exclusion. The same exclusion criteria were applied for recruiting the healthy control subjects, who were of course carefully screened not to suffer from tension-type headache. Since only minor and infrequent pain experiences were allowed for inclusion into the control group, the healthy volunteers described themselves as being habitually pain-free.

Currently the patients suffered on average from moderate headache according to a score of 3.5 cm (SD = 2.3) on a 10 cm visual analog scale (VAS) and had experienced pain for 116.7 months (SD = 9.7). On the day of assessment only 5 subjects were completely pain-free according to their ratings on the VAS.

The study was approved by the local ethical committees of the Bayerische Landesärztekammer and of Medical School of the University of Marburg (Germany). All subjects gave their written informed consent.

2.2. Apparatus and procedure

2.2.1. General procedure and questionnaires

The investigation took place in a sound-attenuated room, from which all distracting visual stimuli had been removed. The time of investigation was always in the afternoon. The same investigator (AP) conducted all assessments. The subjects were carefully familiarized with the methods to be used before the start of each assessment. During the whole session, which lasted for approximately 3 h, subjects sat upright at a small table. First, the subjects (patients only) completed a number of pain questionnaires, which are not all reported here (e.g. Berner Pain Questionnaire, West-Haven-Yale Multidimensional-Pain-Inventory). The questionnaire of interest for the present study was designed for the assessment of headache strength and consists of two maps showing the head in sagittal views from the left and right side. The patients were instructed to mark each painful area and to rate the average pain intensity for each painful area on a 7-point scale ranging from ‘not at all’ to ‘very strong’. The headache scores obtained were the number of painful sites and the accumulated rating over all sites. This type of quantification of chronic pain with potentially

multiple sites was used for example by Lautenschläger et al. (1991), who designed a similar assessment tool called the Localized Pain Rating.

2.2.2. Somatosensory and pain threshold assessment

Second, a series of experimental tests of somatosensitivity and pain sensitivity were run, which made only use of the left body-side. It has been reported from several studies that the left side is more sensitive to pain stimuli than the right side (Schiff and Gagliese, 1994; Spernal et al., 2003).

The sensory tests started with the assessment of the detection and pain thresholds for electrocutaneous stimuli. These were also used as starting values for the multiple staircase procedure applied later in the session. An electro-stimulator (Toennies, Jäger-Medizintechnik GmbH, Würzburg, Germany) delivered the stimuli either to the forearm or to the temple. Each stimulus consisted of a train of 15 monophasic square-wave pulses (duration: 4 ms) with a stimulus onset asynchrony of 10 ms (100 Hz). These parameters resulted in duration of 144 ms per stimulus. For safety reasons the intensity of stimulation was limited to 10 mA. The skin was cleaned and abraded. Then two monopolar electrodes (13L20) with a surface area of 0.3 cm^2 were attached 2–3 cm from each other, slightly to the left and to the right of the middle of the volar forearm or of the center of the temple. A light signaled the start of each stimulus. Detection and pain thresholds were measured in three ascending series with discrete steps of 0.1 mA. The subjects were instructed to report the very first sensation and the first sensation of pain. The average of the three series was taken as the corresponding threshold value.

Heat pain thresholds were measured using a computer-controlled thermal stimulator with a contact thermode of 1.6×3.6 cm^2 (Galfe et al., 1990). The thermode was attached with a constant pressure of 0.4 N/cm^2 to the thigh. Beginning at a temperature of 38 °C, eight heat stimuli were applied with a rate of temperature change of 0.7 °C/s. The inter-stimulus interval was 15 s. Subjects signalled pain by pressing a button, at which time the temperature returned to baseline. There were eight trials, which were visually and acoustically announced. The measure of the pain threshold was the mean calculated during the last five trials. This value serves as the reference temperature for the subsequent tonic heat stimulation (conditioning stimulus) in the experimental DNIC paradigm.

2.2.3. Assessment of DNIC-effects—experimental protocol

After assessment of the electrical detection and pain thresholds and the heat pain thresholds the experimental DNIC paradigm followed, consisting of four experimental blocks (four assessments of the effects of conditioning stimulation preceded each time immediately by a baseline assessment) (see Fig. 1). Between blocks subjects had always a short break of 1 min. In each block, the sensitivities to non-painful (detection threshold) and painful (pain threshold) electrical stimuli were tested in parallel by use of a multiple staircase method (see below for details), once at the forearm and once at the temple (see Fig. 1). The two sites were chosen in order to test once a non-cranial site being not affected by the pathophysiology of CTTH and once a cranial site being affected. Forty electrical stimuli per experimental block were administered; twenty electrical stimuli were delivered during baseline assessment and 20 during subsequent conditioning stimulation by a concurrent tonic heat stimulus. During baseline assessment a temperature of 38 °C was applied to the thigh via the thermode. During conditioning stimulation either a tonic non-painful heat stimulus ('heat' condition) or a tonic painful heat stimulus ('pain' condition) was applied to induce pain inhibitory effects (for the experimental definitions of the conditions 'heat' and 'pain' see below). Thus the effects of four experimental conditions were tested in each individual: (1) the effect of tonic 'pain' at the thigh on the electrical sensitivity at the temple, (2) the effect of tonic 'heat' at the thigh on the electrical sensitivity at the temple, (3) the effect of tonic 'pain' at the thigh on the electrical sensitivity at the forearm and (4) the effect of tonic 'heat' at the thigh on the electrical sensitivity at the forearm. The sequence of the four conditions was administered in random order to control for order effects.

2.2.4. Assessment of DNIC-effects—conditioning stimulus

The tonic heat stimuli for induction of pain inhibitory effects (conditioning stimuli) were applied by a thermode to the thigh. We chose the thigh because we assumed that nociceptive processing originating in the lower limb is still intact in headache sufferers, which at least might guarantee an undisturbed induction of pain inhibition. The exact site of thermode placement at the dorsal thigh was changed in a random manner between conditioning stimulations.

Each conditioning stimulus consisted of a series of small heat pulses with a constant frequency of 30 pulses per minute and an amplitude of 1.3 °C (Lautenbacher et al., 1995). In the two 'pain' conditions the pulses were tailored to have a peak temperature of 1 °C above the individual pain threshold and in the two 'heat' conditions of 0.3 °C below the individual pain threshold (see Fig. 1). This approach was designed for comparing the conditioning effects of a still tolerable tonic heat pain ('pain') with the conditioning effects of a strong but non-painful tonic heat stimulus ('heat'). Since we used the individual pain threshold as point of reference, the induction of painful and non-painful sensations as intended was very likely. Conditioning stimulation was maintained until all 20 electrical test stimuli had been delivered for the given intensity, resulting in a period of tonic stimulation of about 5 min.

To assess the subjective intensity of the conditioning stimuli, the subjects were instructed to rate the heat sensation in regular intervals (after each 5th electrical test stimulus) on a 10 cm visual analogue scale (VAS) with a verbal anchor ('slightly painful') just in the middle. The scale was designed to allow for assessment of painful and non-painful sensations by one tool (Marchand et al., 1991). The four ratings of conditioning stimulation per condition were averaged for further analysis.

2.2.5. Assessment of DNIC-effects—test stimulus

The electrocutaneous test stimuli were administered either to the forearm or to the temple (for the exact sites of electrode placement see above), using a multiple (double) staircase procedure with two staircases, one for assessing the electrical detection threshold and one for assessing the electrical pain threshold. The electrical stimuli were ordered in pairs over the series of 160 stimuli, with one stimulus tracking the detection threshold and the second one tracking the pain threshold. The position of these two stimuli in the pair was randomized. The stimulus intensities varied depending on the subject's ratings on a 6-point verbal scale. The scale categories were: 1, no sensation; 2, slight sensation; 3, moderate sensation; 4, strong

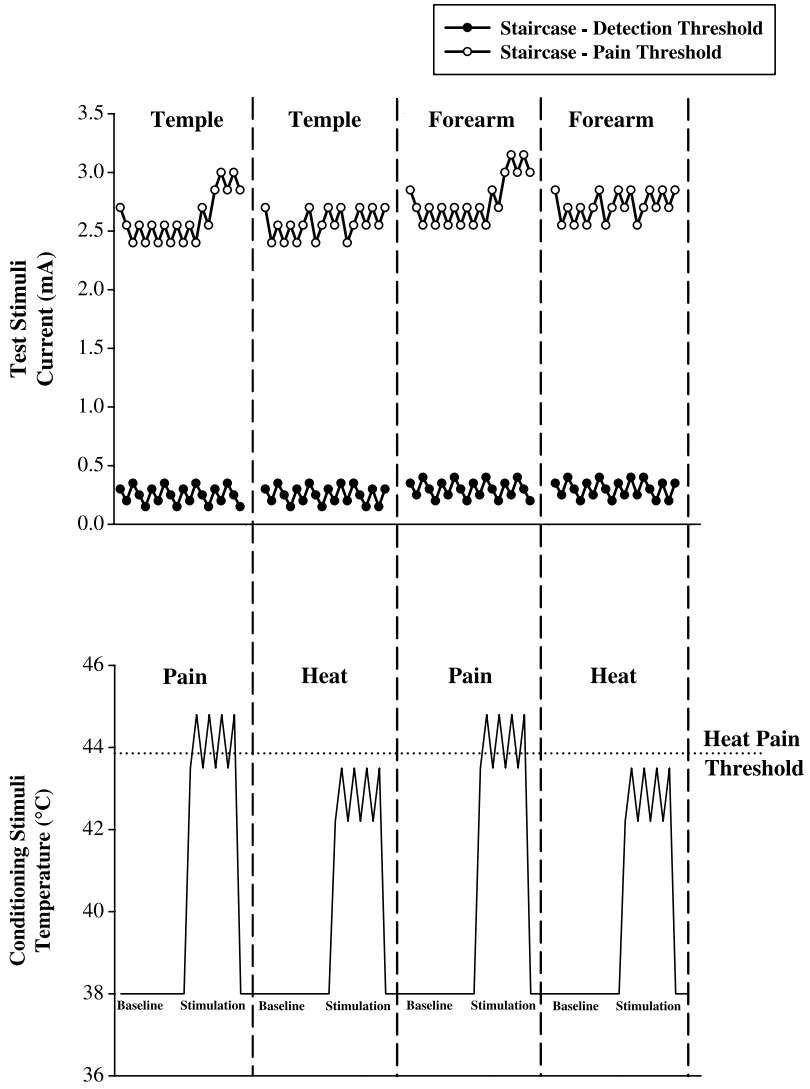

Fig. 1. Schematic representation of the experimental protocol for induction and assessment of DNIC-like effects; the order of the site of application of the test stimuli (temple, forearm) and of the intensity of the conditioning stimuli ('heat', 'pain') is exemplary and varied due to random.

sensation; 5, slight pain; and 6, moderate pain. The tracking algorithms for the detection and the pain threshold staircases are described in Table 1. By use of these algorithms the two staircases were kept close to the detection threshold and close to the pain threshold, respectively. The electrocutaneous detection and pain thresholds determined at the beginning of the session were used as starting points of the two staircases.

2.3. Evaluation

In order to calculate the electrocutaneous detection and pain thresholds under baseline or under conditioning stimulation the 10 electrical stimuli per staircase were averaged, resulting into one detection and one pain threshold value per baseline as well as one detection and one pain threshold value per conditioning stimulation. Further analysis of the inhibitory effects was based on differences, i.e. electrical detection or pain threshold under baseline (just preceding conditioning stimulation) minus electrical detection or pain threshold under conditioning stimulation. This approach was used to allow assessing effects of conditioning stimulation relative to baseline immediately preceding conditioning stimulation. A negative sign of the difference indicates an inhibitory effect under conditioning stimulation; a positive sign a facilitatory effect. The difference scores were analyzed using a three-way ANOVA with repeated

Table 1
Tracking algorithms for the electrical detection and pain thresholds in the multiple staircase procedure

If the rating is	For a stimulus from the 'detection' staircase then go	For a stimulus from the 'pain' staircase then go
6 = moderate pain	0.15 mA lower	0.30 mA lower
5 = slight pain	0.15 mA lower	0.15 mA lower
4 = strong sensation	0.15 mA lower	0.15 mA higher
3 = moderate sensation	0.15 mA lower	0.30 mA higher
2 = slight sensation	0.10 mA lower	0.30 mA higher
1 = no sensation	0.15 mA higher	0.30 mA higher

measures on two factors. Besides the group factor (CTTH patients vs. control subjects) the factors of repeated measurements were 'condition' with the two levels 'heat' and 'pain' and 'site of assessment' with the two levels 'forearm' and 'temple'. This analysis allows for assessing group differences in DNIC-like effects and differences due to the site of application of the test stimuli and due to the intensity of the conditioning stimuli. Paired and unpaired t-tests were performed for simple comparisons of group and condition differences. The magnitude of the inhibitory effects elicited by the conditioning stimuli is given as effect size (Cohen's d). Correlations were computed by use of Pearson coefficients. Two-tailed tests were used throughout. Statistical significance was accepted at $P \leq 0.05$.

3. Results

3.1. Sensory thresholds

The mean heat pain threshold at the thigh of the headache sufferers was 43.7 °C (SD = 1.9) and that of the healthy control subjects 44.2 °C (SD = 1.6), which resulted into a non-significant difference ($t = -1.036$, $P = 0.305$). Since the temperatures of the conditioning stimuli were tailored afterwards to the individual pain threshold, the conditioning stimuli both below ('heat') and above ('pain') pain thresholds were comparable in the two groups. Therefore, it is not surprising that the two groups did not differ in their ratings of the conditioning stimuli applied later in the session (for the 'heat' condition: $t = -0.842$, $P = 0.404$; for the 'pain' condition: $t = -0.222$, $P = 0.825$). As intended, ratings in the 'heat' condition were on average below 5, those of the 'pain' condition above 5, with 5 marking a 'slightly painful' sensation (see Fig. 2). Means ratings over blocks ranged from 4.3 to 4.6 in the 'heat' condition and from 5.7 to 6.2 in the 'pain' condition. In summary, the conditioning stimuli appeared comparable between the CTTH patients and the control subjects.

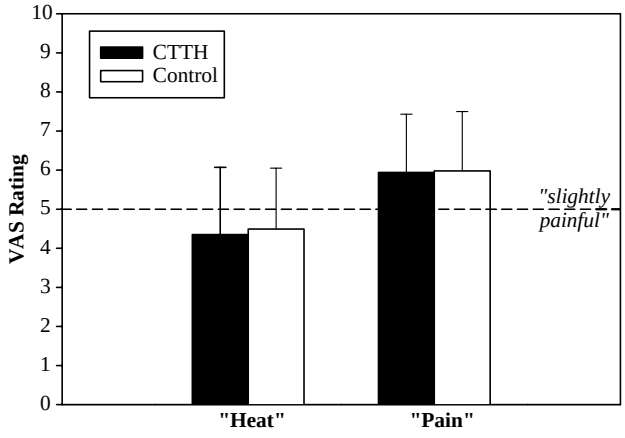

Fig. 2. Subjective ratings (mean + SD) for the conditioning (tonic heat) stimulation in the 'heat' and in the 'pain' condition of patients with CTTH and control subjects

Table 2
Electrical detection and pain thresholds of the CTTH patients and the control subjects at the forearm and at the temple

Threshold	Site	CTTH (in mA)	Control (in mA)	*t*-test
Detection	Forearm	0.39 ± 0.15	0.37 ± 0.09	$t = 0.837$, $P = 0.203$
Detection	Temple	0.45 ± 0.17	0.41 ± 0.20	$t = 0.790$, $P = 0.216$
Pain	Forearm	2.01 ± 1.41	1.85 ± 1.09	$t = 0.496$, $P = 0.311$
Pain	Temple	1.63 ± 1.33	1.49 ± 1.01	$t = 0.452$, $P = 0.326$

Electrical detection and pain thresholds, which were later used as starting values for the multiple staircase procedure in the session, did also not differ between the two groups. This was true both at the forearm and at the temple (see Table 2). Accordingly, also the test stimuli appeared comparable at the beginning between the headache patients and the healthy control subjects. This means that similar antecedents for the evaluation of the inhibitory effects of the conditioning stimuli on the test stimuli were given in the two groups.

3.2. DNIC-like effects

The differences in the DNIC-like effects between CTTH patients and control subjects, which are of critical relevance in this study, were evaluated by means of analyses of variance, the results of which are shown in Table 3. The significant effects of the group factor on both the detection threshold and the pain threshold, confirm that the increase in the thresholds induced by the conditioning heat stimuli was

Table 3
Results of the analyses of variance for the influence of the group type (CTTH patients vs. control subjects), condition ('heat' vs. 'pain') and site of assessment (forearm vs. temple) on the inhibitory effect of the conditioning stimulation on the electrical detection and pain thresholds assessed by multiple staircase procedure

	Df	*F*-value	*P*-value
Electrical detection threshold			
Group (G)	1/52	9.062	0.004
Condition (C)	1/52	0.913	0.344
Site of assessment (S)	1/52	0.084	0.773
G×C	1/52	0.035	0.851
G×S	1/52	0.001	0.978
C×S	1/52	2.503	0.120
G×C×S	1/52	0.201	0.656
Electrical pain threshold			
Group (G)	1/52	10.985	0.002
Condition (C)	1/52	0.093	0.761
Site of assessment (S)	1/52	6.623	0.013
G×C	1/52	0.679	0.414
G×S	1/52	6.623	0.013
C×S	1/52	4.011	0.050
G×C×S	1/52	0.098	0.755

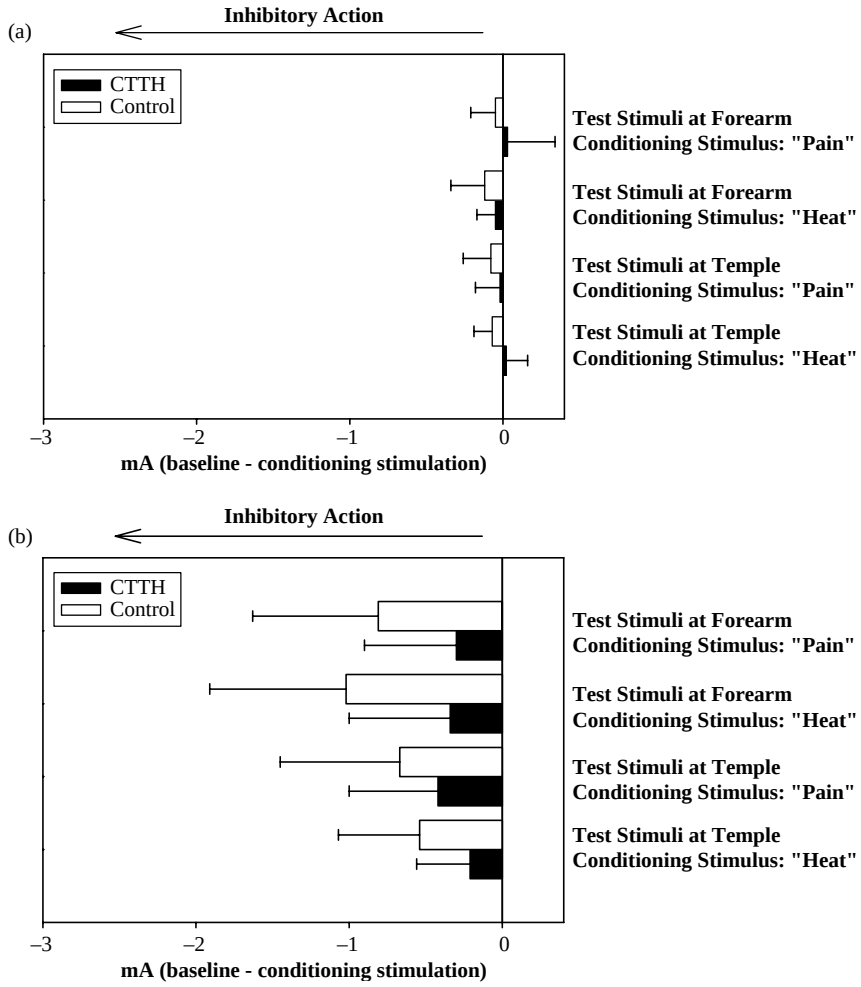

Fig. 3. (a) Inhibitory actions (difference baseline—conditioning stimulation) (mean + SD) of conditioning stimulation of different intensities ('heat', 'pain') on the electrical detection threshold (non-painful test stimuli) assessed at the forearm and at the temple. (b) Inhibitory actions (difference baseline—conditioning stimulation) (mean + SD) of conditioning stimulation of different intensities ('heat', 'pain') on the electrical pain threshold (painful test stimuli) assessed at the forearm and at the temple.

throughout greater in control subjects than in CTTH sufferers. The results are depicted graphically in Fig. 3a and b. The inhibitory action of the conditioning heat stimuli was stronger in control subjects than in CTTH patients, irrespectively of whether the test stimuli were non-noxious (see Fig. 3a) or noxious (see Fig. 3b).

The sizes of the inhibitory effects in both groups are given in Table 4. The effect size computation demonstrated large inhibitory effects ($-0.78 < d < -1.15$) of the conditioning stimuli on the electrical pain threshold in the healthy control subjects. Although inhibitory action on the electrical pain threshold was also consistently observed in the CTTH sufferers, effects were only moderate ($-0.47 < d < -0.73$) in this case. The effects on the electrical detection threshold were much smaller throughout.

The significant effect of the factor 'site of assessment' and the interaction of the factor 'site of assessment' with the factor 'group' seen only in the analysis for the electrical pain threshold (see Table 3) was probably due to the fact that mainly in the healthy control subjects the increase in the electrical pain thresholds induced by the conditioning heat stimuli appeared greater when the thresholds were assessed at the forearm than at the temple (see Fig. 3b). Correspondingly, post-hoc analyses revealed significant group

Table 4
Effect sizes (Cohen's d) of the inhibitory action of the two conditions ('heat', 'pain') assessed by means of the two thresholds (detection, pain) at the two sites (forearm, temple)

Conditions	Threshold	Site	CTTH	Control
'Heat'	Detection	Forearm	−0.35	−0.55*
'Heat'	Detection	Temple	0.15	−0.71**
'Heat'	Pain	Forearm	−0.56*	−1.15***
'Heat'	Pain	Temple	−0.60*	−1.05***
'Pain'	Detection	Forearm	0.14	−0.31
'Pain'	Detection	Temple	−0.08	−0.33
'Pain'	Pain	Forearm	−0.47*	−1.03***
'Pain'	Pain	Temple	−0.73**	−0.78**

Significance of effects: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

differences between the groups with the two intensity levels of the conditioning stimulus at the forearm ($t > 2.970$, $P < 0.004$) but at the temple only when tonic heat slightly below heat pain threshold was applied ($t = 2.985$, $P = 0.004$) but not when tonic heat slightly above pain threshold was used ($t = 0978$, $P = 0.332$).

The just significant interaction of 'condition' and 'site of assessment' suggest that the effect of the intensity of the conditioning stimulation on the electrical pain threshold is modulated by the site of assessment. However, post hoc analyses did not show differences in effect between the conditioning stimuli 'heat' and 'pain', neither at the temple ($t = 1.651$, $P = 0.104$) nor at the forearm ($t = -1.152$, $P = 0.254$).

In a correlation analysis we tested whether the inhibitory effects were associated with any characteristics of the headache pain as assessed by questionnaire. Since all correlations were close to zero ($-0.205 < r < 0.126$) and not significant, such a relationship could not be demonstrated.

4. Discussion

The present study was the first to examine pain inhibitory mechanisms in patients with chronic tension-type headache (CTTH) by use of an experimental 'diffuse noxious inhibitory controls' (DNIC) paradigm. In accordance with our hypothesis on DNIC deficiencies in chronic pain, the patients with CTTH showed significantly less pain inhibition both at cranial and at extra-cranial sites tested than healthy control subjects. This result suggests that the DNIC-like pain inhibitory mechanism is deficient when suffering from CTTH.

This finding matches results in other chronic pain syndromes, for which a deficient DNIC-like pain inhibitory mechanism could be proven. Kosek and Hansson (1997) found a significant increase in pain thresholds for pressure stimuli in healthy control subjects but not in fibromyalgia patients under concurrent stimulation using the submaximal effort tourniquet test. Lautenbacher and Rollman (1997) found that strong heat stimuli increased the pain thresholds for electrical stimuli in healthy control subjects whereas fibromyalgia patients did not show any changes in pain thresholds. The electrical detection thresholds remained unchanged in both groups. Recently, these observations were corroborated by Julien et al. (2005), who did not find evidence for the recruitment of inhibitory systems by cold-pressor pain in fibromyalgia patients in contrast to healthy control subjects. These authors interpreted their findings as evidence for a dysfunction in endogenous pain inhibitory systems of fibromyalgia patients.

A dysfunction of the DNIC-type anti-nociceptive system can now be assumed also for CTTH. Accordingly, a dysfunction in an anatomically generalized inhibitory mechanism as DNIC can exist also in a regional pain syndrome. Interestingly, other forms of anatomically generalized inhibitory mechanisms like pain habituation, which have been shown to fall short in other chronic pain conditions, have appeared to be intact in CTTH (Flor et al., 2004; Valeriani et al., 2003). Earlier attempts of providing evidence for a deficit in DNIC-like pain inhibition in a regional pain syndrome failed in the case of trapezius myalgia (Leffler et al., 2002b). It is difficult to explain the discrepant results of the study of Leffler et al. and of the present study given that differences both in methods and in patients exist.

Our observation requires the assumption of additional causative factors for explaining the regional predilection of pain in CTTH. Algogenic alterations in cranial structures, such as muscular irritations, might be assumed to be one of these additional causative factors. However, numerous studies did not produce unequivocal evidence for a specifically stronger tension of the head and neck musculature in CTTH patients than in healthy control subjects (Pielsticker and Lautenbacher, 2004). However, a deficient pain inhibitory system might even not handle trivial muscular irritations sufficiently and assign them with noxious relevance (Olesen, 1991).

Another additional causative factor responsible for the regional nature of pain in CTTH might be a deficit in anti-nociceptive circuits specific for the trigeminal pain system, which has been made likely by studies on the exteroceptive suppression of the masseter and temporalis muscle and on the trigemino-cervical reflex (e.g. Milanov and Bogdanova, 2003; Schepelmann et al., 1998; Tataroglu et al., 2002).

The deficient DNIC-like pain inhibition appeared to be only weakly correlated with the size of the headache area and the intensity of the headache in CTTH patients with full-blown syndromes. However, this deficiency in pain inhibition might constitute a pre-disposition for developing CTTH out of more episodic forms, which is not similarly relevant for sustaining CTTH later on. Although it is tempting to assume an impairment of DNIC-like pain inhibition as predisposition for pain chronification in general, evidence for this argument is scarce. Even the opposite route of causation is conceivable as suggested by a study conducted by Kosek and Ordeberg (2000) on patients with painful osteoarthritis. These patients presented first with a deficient DNIC-like pain inhibition but show normal inhibition after surgery in a pain-free state. This observation suggests that the chronic pain maintained the dysfunction of DNIC. More longitudinal studies are necessary to prove the direction and the temporal pattern of the relationship between deficient pain inhibition and chronic pain.

Our results suggest that apparently DNIC-deficient individuals like the headache sufferers do not necessarily present with pain thresholds lower than those of pain-free individuals. This might appear puzzling at first glance. However, our methods of pain threshold assessment did not include stimuli suitable to condition pain inhibition to a relevant extent. Therefore, DNIC-like pain inhibitory mechanisms were not sufficiently activated during pain

threshold assessment to produce individual differences in pain threshold due to individual differences in DNIC-like mechanisms. Unchanged pain thresholds in CTTH were also observed by others (de Tommaso et al., 2003; Flor et al., 2004).

A limitation of our findings might result from the fact that half of our headache sufferers were co-morbid with mood disorder. However, in an analysis of subgroups no differences in DNIC-like pain inhibition between headache patients with and without mood disorder were found. Similar rates of depression were also reported by Juang et al. (2000) from a headache clinic, demonstrating that our sample can be considered representative in this respect.

The finding that both temperatures slightly below ('heat') and slightly above ('pain') pain threshold triggered similarly the DNIC-like pain inhibition may seem surprising at first glance but replicates observations made in earlier studies (Lautenbacher and Rollman, 1997; Lautenbacher et al., 2002). The sensation of pain is obviously no necessary prerequisite for the induction of DNIC-like pain inhibition. Apparently, a sufficient number of nociceptive afferents is stimulated already slightly below pain threshold to activate the DNIC. However, an ultimate conclusion cannot be drawn from our data because a few subjects may have experienced even our 'heat' conditioning stimulation at times as painful. Considering the ratings of our subjects, 'heat' and 'pain' conditioning stimulation were subjectively clearly distinct but 'heat' conditioning stimulation produced sensations close to pain threshold. We had originally introduced these two intensity levels of conditioning stimulation to demonstrate compellingly the pain specificity of its inhibitory effect by including physically similar but subjectively distinct conditioning stimuli but have now repeatedly failed to do so.

Also the inhibition of non-painful sensations - as shown by the effect on the electrical detection thresholds in the healthy control subjects - had already been observed in an earlier study (Lautenbacher et al., 2002). There were no hints for facilitatory effects of the conditioning stimulation as observed sometimes by others under similar experimental conditions (Edwards et al., 2003).

Of course, the experimental DNIC paradigm used is open to other physiological and psychological influences besides DNIC. Attention has often been claimed to be of importance in this context. However, constant conditioning stimuli applied over an extensive period of time without any challenging response requirements are no good distractors because they lack essential features in this context, i.e. novelty, complexity and response challenges. Furthermore, such an objection applies to all experimental studies of DNIC in humans, which do not allow assessing selectively only one inhibitory mechanism.

In summary, the present study provides evidence that patients with chronic tension-type headache (CTTH) suffer from deficient pain inhibitory mechanisms in an experimental DNIC paradigm. However, this impairment of pain inhibition appears not to be related to the severity of headache in the full-blown syndrome of CTTH.

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