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Pain sensitivity and descending inhibition of pain in Parkinson's disease

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ABSTRACT

Background: Patients suffering from Parkinson's disease (PD) often complain about painful sensations. Recent studies detected increased subjective pain sensitivity and increased spinal nociception, which appeared reversible by dopaminergic treatment. Possibly, reduced descending pain inhibition contributes to this finding.

Objective: We investigated subjective pain thresholds as well as nociceptive reflex thresholds to isolate potential loci of the pathophysiological changes within the pain pathway. In addition, the diffuse noxious inhibitory control (DNIC) system as one form of descending control was assessed.

Method: Fifteen patients with PD and eighteen controls participated in the study. Electrical and heat pain thresholds as well as the nociceptive flexion reflex (NFR) thresholds were determined. Thereafter, the electrical pain thresholds were measured once during painful heat stimulation (conditioning stimulation) and twice during innocuous stimulation (control stimulation).

Results: The PD patients exhibited lower electrical and heat pain thresholds as well as lower NFR thresholds. The suppression of the electrical pain thresholds during painful heat stimulation (conditioning stimulation) compared to control stimulation did not differ significantly between the groups. No differences of the thresholds between PD patients with and without clinical pain were seen.

Conclusions: Finding the NFR threshold to be decreased in addition to the decreased electrical and heat pain thresholds indicates that the pathophysiological changes either already reside at or reach down to the spinal level. A reduced activation of the DNIC system was apparently not associated with increased pain sensitivity, suggesting that DNIC-like mechanisms do not significantly contribute to clinical pain in PD.

The majority of patients suffering from Parkinson's disease (PD) complain about the intermittent occurrence of painful sensations.^{1 2 3} In most patients the pain is of musculoskeletal or dystonia-associated origin and often associated with motor fluctuations, whereas primary, i.e. central, pain is less frequent.^{1 2 3 4} Furthermore, the additional occurrence of chronic pain has been considered relevant by some authors.³

To investigate the underlying mechanisms, studies on experimentally-induced pain were performed. They reported increased pain sensitivity and spinal nociception in PD patients without clinical pain during the "off-phase" that were normalized by L-dopa.^{5 6} Mainly two mechanisms were discussed which are thought to contribute to increased sensitivity towards experimentally-induced pain and to the high prevalence of intermittent pain in PD. One explanation is a diminished activity of the descending inhibitory control system. The electrical stimulation of the substantia nigra has been found to modulate the impending pain within the dorsal horn of the spinal cord, which is probably mediated by a dopaminergic descending inhibitory pathway originating in the midbrain.^{7 8} A tool for the detection of the activity of the endogenous pain-inhibitory system is the diffuse noxious inhibitory controls (DNIC) system. The DNIC system allows for the inhibition of afferent nociceptive neurons at the dorsal horn of the spinal cord by noxious stimuli applied to far remote body areas.⁹ Deficiencies of DNIC-like mechanisms have so far been mainly investigated in association with the development of chronic pain (e.g. osteoarthritis, tension type headache and fibromyalgia).^{10 11 12} The second explanation is mainly based on dopaminergic pathways involving the basal ganglia and the lateral and medial pain pathways.¹³ A Positron Emission Tomography (PET) study showed an increased brain activity induced by experimental pain within the right insular, right prefrontal and left anterior cingulate cortices during "off" condition, which could be reduced by L-dopa suggesting an increased nociceptive input induced by a deficiency of the dopaminergic system.⁵

Inspired by these previous data, the aim of the present study was twofold. First, by comparing subjective pain and spinal nociception, we aimed at isolating potential loci of the pathophysiological changes within the pain pathway. Second, we intended to determine whether a deficiency of the diffuse noxious inhibitory control (DNIC) system as a part of the descending inhibitory control system might contribute to the altered pain sensitivity and thereby to PD-related pain. Since mutual effects between clinical pain and pain sensitivity have to be assumed, patients with and without clinical pain related to PD were compared.

METHODS

Subjects

All participants were screened and examined for conditions that could affect pain sensitivity by a neurologist (e.g. neuropathy by sural neurography, neurological and psychiatric disorders). The participants were further screened for potential dementia by use of the Mini Mental Status Examination (MMSE; exclusion criterion; cut-off < 25) and for potential depression by use of the Geriatric Depression Score (GDS; exclusion criterion; cut-off >5). None of the subjects took any analgesic medication for at least 24 hours prior to the test sessions. Antidepressants, opioids, antineuropathic drugs, neuroleptic drugs, and long-lasting dopamine agonists were not allowed for inclusion into the study. The patients with the clinical diagnosis of PD according to the criteria of the United Kingdom PD Society Brain Bank were recruited from the Department of Neurology of the University of Marburg.¹⁴ The control group was pain-free, while in the group of PD patients only clinical pain related to PD was allowed. However, the additional occurrence of chronic back pain - possibly not related to PD - could not be excluded in two patients. The PD-related pain was then classified into the five different forms according to Ford et al.¹: dystonia-associated (n=1), dystonia-associated and musculoskeletal (n=3), musculoskeletal and akathitic discomfort (n=2), musculoskeletal and radicular (n=1) and musculoskeletal and central (n=1). PD-related pain was responsive to dopaminergic treatment in two patients with dystonia-associated pain. In the group of PD patients without pain 3 out of 7 patients had a history of rare PD-related pain of the musculoskeletal type. Informed consent was obtained from all subjects before participation in the study. The study protocol was approved by the local Ethics Committee of the University of Marburg.

Apparatus and Procedure

Electrical stimulation and EMG recording were performed using a standard electro-diagnostic device (Viking IV D, VIASYS Healthcare) with modified software. Thermal pain was measured using a Peltier based contact stimulation device (Medoc TSA-2001, Ramat Yishai, Israel) with a 30 x 46 mm² contact thermode.

General procedures and questionnaires

The control subjects and the patients completed a MMSE and a GDS to exclude patients with dementia and depression.^{15 16} The participants rated their pain on a horizontal visual analogue scale (VAS), which was labeled with verbal anchors from 'no sensation' (0) to 'extremely strong pain' (100) with a verbal anchor in-between of 'slightly painful' (50). In addition they provided information on their clinical pain by completing a pain questionnaire (e.g. frequency, duration, localization and relation to medication). The Hoehn and Yahr stage and the UPDRS motor score were assessed in the PD patients. For the determination of the heat pain threshold, the subjects were seated upright in an armchair. For the further examination the subject lay supine on an examination table with knees flexed at 130° by using a pillow. The investigation took place in the morning after overnight withdrawal of all dopaminergic medication at 6-9 am (practically defined "off" state) and had a duration of 2-3 hours.

Pain threshold and NFR threshold assessment

In order to localize the sural nerve for reflex stimulation sural neurography was performed. For recording of the nociceptive flexion reflex (NFR) and the assessment of the electrical pain threshold, surface electrodes were attached at the same localization as for sural nerve neurography, i.e. at the left calf. The recording electrode was attached ipsilaterally

over the short head of the biceps femoris muscle, and the reference electrode was fixed near the tendon of the biceps femoris muscle at the head of the fibula. Stimulation of the sural nerve elicits two responses in the biceps femoris muscle, the first is of short latency (40-70 ms, RII) and low threshold reflecting a tactile reflex, the second of longer latency (80-150 ms, RIII) and higher threshold corresponding to a nociceptive reflex.¹⁷ At the spinal level the peripheral input is processed and subjected to segmental and descending control in a polysynaptic pathway before it triggers the motor response. Since the NFR - as a marker for spinal nociception - has appeared to correlate well with subjective pain perception, it has been widely used in experimental pain research.¹⁸ A time window of 80 - 150 ms was selected in order to exclude RII responses and voluntary limb movements.^{17 19} Furthermore, an amplitude of at least 50 μ V (corresponding to a level of 150 % of baseline fluctuations) within 100 ms after reflex onset was required to distinguish reflex responses from baseline fluctuations with certainty.

For the determination of the subjective pain threshold and the nociceptive flexion reflex (NFR) threshold, a stimulus train of five impulses of 1 ms duration at a frequency of 250 Hz was used.²⁰ Stimulus trains were applied at intervals varying from 10 to 20 seconds in order to avoid habituation. The NFR threshold was assessed using the up-down staircase method.^{19 21} Stimulation intensity was increased in 3 mA increments until the flexion reflex RIII component was detected the first time. Next, we lowered the stimulus intensity in 2 mA steps until the reflex disappeared. Subsequently, steps of 1 mA were used, and the procedure was repeated until the reflex appeared and subsided two more times. Mean values of three peaks (current intensity that just elicited a reflex) and three troughs (current intensity that no longer elicited a reflex) determined the reflex threshold. The electrical pain threshold was then determined by using the same stimulus paradigm and the same staircase method as during the NFR threshold measurement but with a subjective estimation of pain (painful or non-painful sensation).

The thermal heat pain thresholds were assessed by using the method of adjustments. The participants were instructed to indicate the point at which the sensation of warmth turned into pain by tapping two mouse keys that increased or decreased stimulus intensity, respectively. Two trials were performed to familiarize the subjects with the procedure before the threshold was determined three times. The means of the three trials were used for further analysis.

Assessment of DNIC-like effects - experimental protocol

For assessment of DNIC-like effects in humans the paradigm of heterotopic noxious conditioning stimulation (HNCS) has been regularly used.^{22 23} In this paradigm the effects of a conditioning, mainly tonic and intense pain stimulus on the sensation elicited by a second, mainly phasic and less intense pain stimulus, which is classified as test stimulus, are assessed. The stimuli have to be applied to remote sites, which do not activate nociceptive pathways to the same spinal segment. HNCS was used also in the present study and controlled by baseline stimulation (control stimulation). There were three experimental blocks. Before and following the conditioning stimulation by painful heat two stimulations under control conditions with 37° C (baseline temperature) were performed. In each block the electrical pain threshold was determined as measure of the sensitivity for the test stimulus.

Conditioning stimulus: The tonic heat stimuli (conditioning stimuli) for the induction of pain-inhibitory effects were applied by a thermode to the forearm contra-lateral to the stimulated sural nerve at the side that was more affected by PD. The 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.¹² The pulses were tailored to have a peak temperature of 1° C above the individual heat pain threshold. For control stimulation 37° C with an amplitude of 1.3° C were employed as baseline. To assess the subjective intensity of the conditioning stimuli, the subjects were instructed to rate the heat sensation before

and following the determination of the electrical pain threshold on a VAS. Conditioning stimulation was maintained until the test stimulus was applied, resulting in a period of tonic stimulation of about 6 min per block.

Test stimulus: The electrocutaneous test stimuli were administered to the sural nerve as previously determined by neurography at the back of the lower limb on the more affected side in PD patients or on the left side in the control group. The electrical pain threshold was determined after one minute of conditioning stimulation and twice under control stimulation (37° C), i.e. before and after the conditioning stimulation. A staircase method using the previously determined electrical pain threshold – 2 mA as starting value was employed. Stimulation intensity was increased in 1 mA increments until the stimulation was perceived at least as slightly painful. Next, we lowered stimulus intensity in 1 mA steps until the stimulation was no longer perceived as painful. This procedure was repeated two more times. Mean values of three peaks (current intensity that was just perceived as painful) and three troughs (current intensity that was no longer perceived as painful) determined the electrical pain threshold. The mean of the two electrical pain thresholds determined during control stimulation was used for further analysis.

Statistical Analysis

For statistical analysis the Statistical Package for the Social Sciences (SPSS) version 12 was used. A MANOVA was applied to assess the effect of the factor ‘disease (Parkinson’s disease and control group)’ on the NFR and the electrical and heat pain thresholds. A MANOVA with the same design but the factor ‘clinical pain (PD patients with and PD patients without clinical pain)’ was applied to investigate the effect of clinical pain on the thresholds. A two-way analysis of variance including the inner-subject factor ‘condition (pain threshold during control and conditioning stimulation)’ and the between subject-factor ‘disease (PD patients and control group)’ was performed to determine whether ‘condition’ had a significant effect on the pain threshold and whether there was an interaction with ‘disease’. Simple group comparisons were conducted using Student’s t-tests for independent variables. Descriptive statistics were given as mean \pm standard deviation; statistical significance was set to $\alpha=0.05$.

RESULTS

Clinical parameters

The sample characteristics of the PD patients and the pain-free control group are presented in table 1. Eighteen control subjects (11 female and 7 male) between the ages of 42 and 80 years (mean \pm SD; 67.1 ± 10.4 years) and fifteen PD patients (6 female and 9 male) between the ages of 45 and 83 years (mean \pm SD; 63.4 ± 11.2 years) participated in the study. The difference of 3.7 years was not significant ($T(31)=0.974$; $P=0.338$; CI [-4; 11.3]). The PD patients had a mean MMSE score of 29.1 ± 1.1 and the control subjects of 29.4 ± 0.7 ($T(31)=0.933$; $P=0.358$). The GDS score was 2.9 ± 1.6 in the group of PD patients and 0.9 ± 0.9 in the control group ($T(31)=-4.200$; $P<0.001$). The Hoehn and Yahr stage ranged from 1-3 (2.3 ± 0.7). Eight PD patients reported clinical pain related to PD while seven did not. The mean pain intensity (VAS) score in the group of PD patients with clinical pain was 57.5 ± 8.0 . Disease duration, the UPDRS motor score and the dopaminergic treatment did not differ significantly between the PD patients with and without clinical pain (L-dopa equivalents were calculated according to Möller et al.)²⁴ (Table 1).

Threshold determination

Pain thresholds and NFR thresholds

A MANOVA with the group factor 'disease' and the NFR, the electrical and the heat pain thresholds as dependent variables showed a significant main effect of 'disease' [$F(3,29) = 6.883$, $P = 0.001$] with significantly lower NFR thresholds [$F(1,31) = 17.968$, $P < 0.001$] and electrical and heat pain thresholds in the group of PD patients [$F(1,31) = 4.401$, $P = 0.044$; $F(1,31) = 6.426$, $P = 0.017$] (Table 1).

Influence of clinical pain on threshold determination

A MANOVA with the group factor 'pain' and the NFR, the electrical and heat pain thresholds as dependent variables did not show an influence of pain in the group of PD patients [$F(3,11) = 0.227$, $P = 0.875$] (Table 1).

DNIC-like effects

Since the temperatures of the conditioning stimuli were adjusted to the individual heat pain thresholds, no significant group differences of the VAS ratings of the conditioning stimulation were seen (controls: 50.2 ± 17.2 vs. PD: 58.1 ± 14.9), ($T(31) = -1.294$; $P = 0.205$). A two-way analysis of variance including the inner-subject factor 'condition' and the between-subject factor 'disease' revealed a significant main effect of 'condition' [$F(1,31) = 44.665$, $P < 0.001$], which indicates an activation of the DNIC system in both groups, but no differences in the DNIC effect between PD patients and controls [disease \times condition, $F(1,31) = 0.013$, $P = 0.908$] (Figure 1, Table 2). The thresholds of the test stimuli were again lower in PD patients, but not found to differ significantly between the groups [$F(1,31) = 2.829$, $P = 0.103$].

Table 1.

Sample characteristics as well as heat, electrical and NFR thresholds; descriptive statistics and ANOVA results

	PD total (PD) N=15	Control group (CG) N=18	PD vs CG <i>P</i>	PD with pain (PDP) N=8	PD without pain (PDN) N=7	PDP vs PDN <i>P</i>
Age, years	63.4 ± 11.2	67.1 ± 10.4	0.338	61.8 ± 12.2	65.3 ± 10.5	0.560
Disease duration, years	11.0 ± 5.4			11.5 ± 2	10.4 ± 7.9	0.740
UPDRS Part III	28.3 ± 9.4			30.3 ± 7.6	26.1 ± 11.3	0.418
L-dopa, mg	1207 ± 806			1427 ± 844	956 ± 738	0.274
Threshold determination						
Electrical pain threshold, mA	7.8 ± 3.6	12.1 ± 7.2	0.044	7.7 ± 3.3	8.0 ± 4.2	0.870
Heat pain threshold, °C	43.9 ± 1.3	44.9 ± 0.9	0.017	43.8 ± 1.6	44.2 ± 1.0	0.597
NFR threshold, mA	9.8 ± 3.6	18.1 ± 6.8	0.001	10.3 ± 4.5	9.2 ± 2.4	0.576

Data are given as mean ± SD; significant effects are marked as bold.

Table 2.
Electrical pain thresholds of the DNIC experiment

Electrical pain thresholds	Pre-heat control stimulation	Conditioning stimulation	Post-heat control stimulation
PD patients	7.83 \pm 3.5	9.17 \pm 3.7	7.73 \pm 3.6
Control group	11.37 \pm 6.9	12.69 \pm 7.8	11.33 \pm 7.5

Data are given as mean \pm SD

DISCUSSION

The present study investigated subjective and objective parameters of pain perception as well as the integrity of the DNIC system in PD patients before the intake of the first

medication in the morning. The main findings were: 1) We confirmed that the heat pain threshold is decreased in PD patients.²⁵ 2) We provided further evidence that spinal nociception as measured by the NFR threshold is altered in PD patients. This is altogether the second of three studies that investigated the NFR in PD patients and found a lower threshold than in controls.^{6 26} 3) Furthermore, this is apparently the first study to provide experimental data on a decreased electrical pain threshold in PD. 4) However, the investigation of DNIC-like effects in PD patients compared with controls revealed a similar activation of the DNIC system in both groups. 5) Besides, the presence of PD-related pain had no effect on neither electrical and heat pain nor the NFR thresholds.

The pain system and PD

In PD both spinal and cerebral components of pain perception were proposed to be affected: 1) A connection of the basal ganglia with spinal nociception has been suggested by the stimulation of the substantia nigra in animals, which probably results in an inhibition of the nociceptive input by an activation of spinal cord neurons through dopaminergic descending pathways.^{7 8} 2) PET data in PD patients yielded an increased cortical neuronal activity provoked by experimentally-induced pain within structures that belong to the medial pain system.⁵ 3) Furthermore animal models provide evidence for anti-nociceptive effects of the dopaminergic treatment mainly via spinal and striatal D2 receptors.^{27 28} Fittingly, it was recently reported that PD patients have decreased thermal pain and NFR thresholds, which can be normalized by dopaminergic medication in two studies.^{5 6 25} Altogether our data support the notion that the pain sensitivity and spinal nociception in PD are increased in the medication-free period. In light of the apparently early augmentation of nociception at the spinal level, we therefore assume that the pathophysiological mechanisms of increased pain sensitivity in PD patients either reside at or reach down to the spinal level. Since recent studies in chronic painful disorders confirmed high pain sensitivity towards experimentally-induced pain^{29 30}, the high pain sensitivity in PD patients may predispose to PD-related pain or even to chronic pain.

The DNIC system in PD

The DNIC-like mechanisms represent an endogenous pain control system whose deficiency is assumed to contribute to chronic pain.^{10 11 12} The DNIC system originates from the serotonergic subnucleus reticularis dorsalis in the caudal medulla, is activated by nociceptive afferents and in turn modulates the impending noxious input by the inhibition of WDR neurons in the dorsal horn.⁹ It can be facilitated by serotonergic agents and inhibited by opioidergic agents, opioid antagonists and serotonin antagonists, respectively.^{31 32 33} Since the pathophysiological changes in PD also include the serotonergic system, an impaired DNIC system could contribute to the high prevalence of pain.³⁴ A loss of serotonergic neurons within the dorsal and the median raphe nuclei and a reduction of the respective biochemical markers were shown by post mortem studies.^{35 36 37} However, since no alterations of the DNIC system were seen in our PD patients, we suggest that DNIC-like mechanisms do not play a relevant role in PD and pain. Although PD is characterized by the intermittent occurrence of different types of acute pain, the prevalence rates of chronic pain are apparently similar to those in ageing people.^{1 2 38} This clinical observation can possibly be explained by the unchanged DNIC system, which is particularly important for the development of chronic pain. However, because other parts of the descending inhibitory control system (e.g. the periaqueductal gray and the nucleus raphe magnus) were not found to mediate DNIC effects, an unchanged DNIC system does not exclude that changes of further descending inhibitory control systems (e.g. dopaminergic, serotonergic and noradrenergic)^{35 36 39} occur - as proposed by the increased spinal nociception - and that diverse mechanisms may predispose to pain in PD.⁹

Pain perception in PD patients with and without pain

The present study revealed no significant differences of the objective and subjective pain thresholds between PD patients with and without PD-related pain. In contrast, one previous study observed a greater sensitivity towards heat pain in PD patients with clinical pain compared to PD patients without clinical pain.²⁵ The larger sample size of the precedent study or the different pain characteristics may account for this discrepancy. The present observation supports the notion that intermittent PD-related pain has less impact on the pain pathway compared to its alteration in chronic pain (e.g. central sensitization). Also we did not observe relevant additive effects on the cognitive level of pain evaluation in this sample.⁴⁰

Limitations of the present study are the unequal sex distribution within the groups and that because of the low statistical power no sub-group analysis of the different clinical pain types (i.e. particularly with respect to primary central pain) could be performed. Besides, in general, psychological aspects such as cognitive decline and depression may bias pain perception in PD (e.g. by effects on attention) and should be more thoroughly assessed in further studies. In addition, neuroimaging studies can be employed to detect a deterioration of further descending control systems.

The increases in spinal nociception and pain sensitivity in experimentally-induced pain corroborate the hypothesis that the pathophysiological mechanisms reach down to the spinal level. Since no significant alteration of the DNIC system was detected, we conclude that DNIC-like mechanisms do not significantly contribute to clinical pain in PD. However, the observed higher experimental pain sensitivity may predispose to intermittent PD-related pain and hypothetically also increase the risk for the development of chronic pain.

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Figure legend

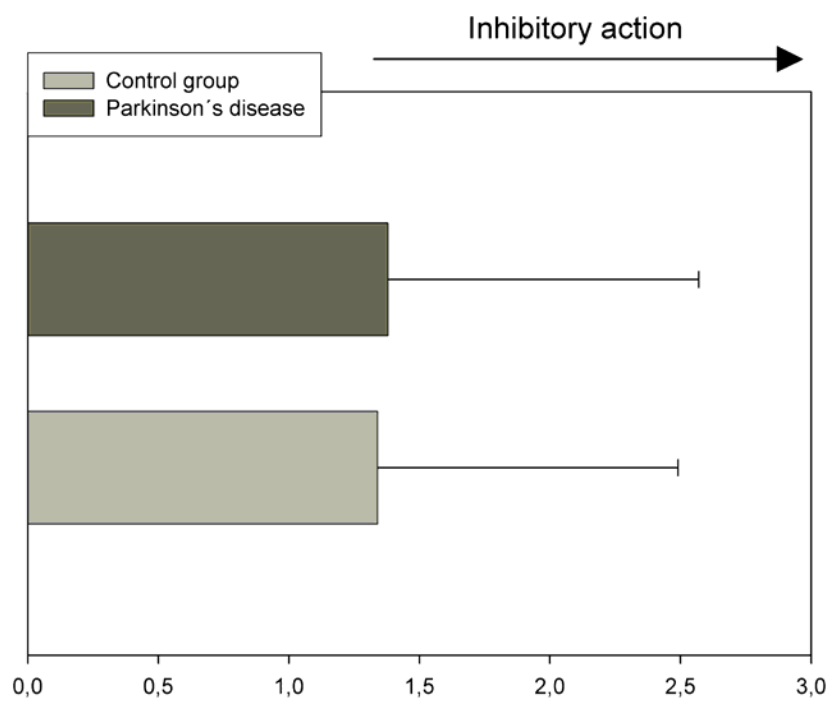
Figure 1.

Differences of the electrical pain thresholds during conditioning heat stimulation and control stimulation in the group of PD patients and the control group (mean+SD).

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Difference of the electrical pain threshold (conditioning stimulation - control stimulation) in mA