Supporting Data

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ABSTRACT: Background: Of patients with Parkinson’s disease (PD), 30% to 85% report pain. However, mechanisms underlying this pain remain unclear. In line with known neuroanatomical impairments, we hypothesized that pain in PD is caused by alterations in emotional-motivational as opposed to sensory-discriminative pain processing and that dopamine recovers the capacity for endogenous emotional-motivational pain modulation in patients with PD.

Methods: A total of 20 patients with PD played a random reward paradigm with painful heat stimuli in addition to assessments of pain sensitivity once with and once without levodopa.

Results: Levodopa increased endogenous pain inhibition in terms of perceived pain intensity and un/pleasanthness compared with a medication off state. Higher clinical pain was associated with higher increases in pain inhibition. Levodopa did not affect heat pain threshold, tolerance, or temporal summation.

Conclusion: Patients with PD seem to be predominately impaired in emotional-motivational as opposed to sensory-discriminative pain processing. A differential

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understanding of pain in PD is urgently needed because effective treatment strategies are lacking. © 2020 The Authors. Movement Disorders published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society

Key Words: Parkinson’s disease; endogenous pain modulation; dopamine; emotional-motivational pain processing; medial pain system

Introduction

Of patients with Parkinson’s disease (PD), 30% to 85% report chronic pain,1 with dopamine-relieving musculoskeletal pain only in about one third of patients.2 However, the mechanisms of pain and altered pain perception in PD are not fully understood. In healthy volunteers, dopamine has not only simple antinociceptive effects3,4 but also can act pro-nociceptive.5 In line with the finding from patients with PD that dopamine does not always show effects on the perception of experimental pain stimuli,6 the modulation of dopamine in healthy volunteers does not affect sensory-discriminative pain perception of mild to moderately painful stimuli.7,8 Rather, dopamine modulates motivation to endure or avoid pain.9 For patients with PD, hyperactivity and the accumulation of Lewy bodies in brain regions of the medial pain system—processing predominantly emotional-motivational aspects of pain10—have been described.11-13 Based on these considerations, we hypothesized that patients with PD are mainly impaired in emotional-motivational as opposed to sensory-discriminative pain processing. Thus, we tested with a wheel-of-fortune game combined with painful stimuli whether the capacity for endogenous emotional-motivational pain modulation in patients with PD improves with dopamine with no effects on baseline pain sensitivity, indicating sensory-discriminative pain processing.

Materials and Methods

Participants

A total of 20 patients with PD (mean age, 61.5 years; SD, 7.87 years; range, 42–75 years; 4 women) were recruited for the experiment. Exclusion criteria were dementia and current depression. The study was approved by the local ethics review board (University Hospital Düsseldorf, study number 6068R) and informed written consent was obtained from all participants according to the revised Declaration of Helsinki (2014).

Experimental Design

All patients participated in 2 testing sessions on the same day. The first session was in a medication off state, that is, after withdrawal of antiparkinsonian medication for at least 12 hours. The second testing was in a medication on state, that is, after the intake of 1.5 times the regular morning dose of levodopa (l-dopa; l-dopa equivalent dosage; mean, 188.75 mg; SD, 63.07 mg; range, 100–350 mg). Within each testing session, participants’ thermal pain threshold, thermal pain tolerance, and temporal summation of pain to 10 repeated thermal stimuli were assessed,7 followed by a wheel-of-fortune game to assess endogenous pain inhibition by monetary wins.

Heat stimuli were applied to the thenar eminence of participants’ nondominant hand using a 30 × 30 mm contact thermode (Medoc Ltd. Advanced Medical Systems, Ramat Yishay, Israel). Participants’ pain thresholds were assessed using a modified staircase method14 with verbal feedback on perceived pain intensity to avoid distortions because of PD-related prolonged reaction times. The following 3 stimulation intensities were used in the wheel of fortune: (1) low, individual pain threshold minus 1.5°C; (2) medium, pain threshold plus 1.5°C; and (3) high, pain threshold plus 2.5°C. The low intensity was used as a nonnociceptive control condition. Strongest effects are expected with medium intensity (5).

Patients performed on a computer screen the same wheel-of-fortune game as described in Becker and colleagues5 to modulate participants’ perceptions of painful thermal stimuli by receiving monetary wins and losses between 5.10 and 9.80 € corresponds to 6.10 and 11.70 US dollar (Fig. 1A).

A total of 9 trials per condition (win, loss, neutral) were presented in pseudorandom order. After each thermal stimulus, participants rated the perceived intensity and un/pleasantness on a visual analog scale.5

For clinical characterizations, the patients completed the following: Mattis Dementia Rating Scale,15 Beck Depression Inventory,16 King’s Parkinson’s Disease Pain Scale (KPPS),17 and painDETECT questionnaire,18 off and on medication on the Positive and Negative Affect Schedule,19 and the Unified Parkinson’s Disease Rating Scale Part III was assessed20 (Table S1 in Appendix S1).

Statistical Analysis

Participants did not choose a wheel color in 44 of 1753 trials (2.5%), which were excluded before aggregating the data.

Main outcome of the wheel of fortune was pain modulation induced by receiving wins and losses with painful stimuli, which was calculated as the difference of the average ratings in win minus loss outcomes for each stimulation intensity within each subject.5,14 To analyze changes from off to on medication, this pain modulation...
of perceived intensity and un/pleasantness was compared using analysis of variance design linear mixed models with the within-subject factor “condition” (off, on) for each stimulation intensity. Neutral trials were not included in the analyses because they only aim at increasing engagement through a higher game diversity. Within these linear mixed models, it was tested whether clinical characteristics indicated by scores in the Mattis Dementia Rating Scale, Beck Depression Inventory, painDETECT, Positive and Negative Affect Schedule, Unified Parkinson’s Disease Rating Scale, KPPS, dose of L-dopa (L-dopa equivalent dosage in experiment), PD duration (time since diagnosis) as well as sex explained significant portions of variance by including them as covariates. Significant covariates were included in the further analysis, which was only the case for the KPPS. To test whether the domains of the KPPS modulated the results, the domains of the KPPS, that is, musculoskeletal, chronic, fluctuation related, nocturnal, radicular pain were included as covariates. Oro-facial pain and discoloration/edema/swelling were not included because only 1 and 2 patients, respectively, reported values >0. Pain threshold, pain tolerance, and temporal summation were compared between off and on medication states with analysis of variance design linear mixed models.

For all outcome variables, we removed outliers bigger than 1.5 times the interquartile range of the respective variable. The significance level was set to 5%. Effect sizes in terms of Cohen’s d were calculated. All statistical analyses were performed using Predictive Analytics Software Statistics 26 (SPSS Inc., Chicago, IL).

Results

Recovery of Endogenous Pain Modulation by L-Dopa

Dopamine in patients with PD improved endogenous pain modulation via winning and losing money in the wheel of fortune: the perceived intensity (“condition” $F_{1,32} = 4.92, P = 0.034, d = 0.68$) as well as un/pleasantness (“condition” $F_{1,16} = 5.53, P = 0.031, d = 0.62$) of the medium intensity pain stimuli changed significantly in the on compared with the off state. In the on state, pain modulation for intensity ratings was negative on average and positive for unpleasantness ratings, indicating pain modulation due to reward (Fig. 1B,C; Table 1). The negative estimate ($-0.20; P = 0.046$) of the covariate KPPS indicates that the higher the KPPS score, that is, the more pain patients indicated attributed to PD, the stronger was
the endogenous pain modulation in the wheel of fortune. This association was not different between the off and on conditions (interaction “condition × KPPS total” $F_{1,31} = 0.09$, $P = 0.768$). Interestingly, the KPPS domains did not influence the change in pain modulation from the off to on condition.

No significant changes in pain modulation between the off and on states were found for low and high intensity stimuli for both intensity and unpleasantness ratings (Table 1).

**No Effects of L-Dopa on Baseline Pain Sensitivity**

Neither heat pain threshold nor heat pain tolerance or temporal summation differed between the off and on states (Table 1). Moreover, pain threshold, pain tolerance, and temporal summation were not correlated with pain modulation in the wheel of fortune from the off to on medication state (all $r < 0.18$ and $P > 0.49$).

**Discussion**

Our results on dopamine effects in patients with PD are consistent with our 2 hypotheses. Dopamine improved emotional-motivational pain inhibition, whereas baseline pain sensitivity was unaffected. Thus, our findings support the notion that dopamine has a more complex role in pain perception related to emotional-motivational aspects that goes beyond simple antinociceptive effects. They are also consistent with patients with PD being predominately impaired in emotional-motivational pain processing as opposed to sensory-discriminative processing.

Attempts to distinguish emotional-motivational and sensory-discriminative pain perception typically rely on self-reports of intensity and unpleasantness ratings. However, these ratings are highly correlated and response biases can be expected, leading to an incomplete/insufficient dissociation. In contrast, we used a paradigm where pain was modulated by reward, assessing emotional-motivational pain processing and not just baseline pain sensitivity (targeting sensory-discriminative pain processing). In line with previous results from healthy volunteers, emotional-motivational pain modulation of perceived intensity and unpleasantness improved while on compared with off medication. Importantly, although dopamine improved mood assessed with the Positive and Negative Affect Schedule, this change in mood did not significantly modulate pain perception. Therefore, our results highlight the importance of dopamine in restoring emotional-motivational pain processing in PD.

Increased baseline pain sensitivity and the restoring effects of L-dopa on this sensitivity have previously been reported in patients with PD, although the results are variable. For example, some studies using methods that incorporated substantial emotional-motivational pain processing showed restoring effects of L-dopa on pain sensitivity, whereas others with a stronger sensory-discriminative focus did not find such effects. Furthermore, the presence and type of clinical pain might influence the exact characteristics of altered pain processing in PD. Thus, it appears that in line with our findings, both emotional-motivational and sensory-discriminative pain processing can be affected in PD.

Interestingly, the higher the reported pain by the KPPS, the stronger was the endogenous pain inhibition by monetary rewards, independent of the intake of L-dopa. In contrast, chronic pain is often accompanied by deficient pain modulatory capacity. Potentially, pain in PD is qualitatively different and can be dissociated from PD-independent pain. However, including KPPS subdomains in the analyses did not reveal further insights.

Dopamine had only an effect on medium stimulation intensities, aiming at mildly painful sensations, in line with previous findings. In particular, with higher intensities, modulatory effects on pain typically decline, presumably because pain becomes more dominant and an increasingly stronger motivator, as also shown in...
the context of pain modulation by attention. 32 Furthermore, the present study does not allow a conclusion of whether l-dopa led to a normalization of emotional-motivational pain modulation compared with healthy individuals.

Summarizing, our results indicate that patients with PD are predominately impaired in emotional-motivational pain processing as opposed to sensory-discriminative pain processing. Such a differential understanding of pain is urgently needed in PD because effective treatment strategies are lacking, even though a high number of patients with PD experience pain. Results from pain research suggest that such a differential view is very important because many clinical trials were unsuccessful because of a focus on sensory-discriminative pain processing. 33,34 Accordingly, strategies from pain research focusing on emotional-motivational pain processing could be adapted to patients with PD, including pain-specific psychological approaches known to be effective in pain patients. Future studies should incorporate brain imaging techniques to investigate whether impaired cognitive-emotional pain modulation is accompanied by altered processing in the medial as opposed to the lateral pain system. In addition, the present paradigm could be used to assess differential placebo effects on different components of pain processing in patients with PD, promising novel mechanistic insights.

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Paroxysmal Cranial Dyskinesia and Nail-Patella Syndrome Caused by a Novel Variant in the LMX1B Gene

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ABSTRACT: Background: In a Danish family, multiple individuals in five generations present with early-onset paroxysmal cranial dyskinesia, musculoskeletal abnormalities, and kidney dysfunction. Objective: To demonstrate linkage and to identify the underlying genetic cause of disease. Methods: Genome-wide single-nucleotide polymorphisms analysis, Sequence-Tagged-Site marker analyses, exome sequencing, and Sanger sequencing were performed. Results: Linkage analyses identified a candidate locus on chromosome 9. Exome sequencing revealed a novel variant in LMX1B present in all affected individuals, logarithm of the odds (LOD) score of z = 6.54, predicted to be damaging. Nail-patella syndrome (NPS) is caused by pathogenic variants in LMX1B encoding a transcription factor essential to cytoskeletal and kidney growth and dopaminergic and serotonergic network development. NPS is characterized by abnormal musculoskeletal features and kidney dysfunction. Movement disorders have not previously been associated with NPS. Conclusions: Paroxysmal dyskinesia is a heretofore unrecognized feature of the NPS spectrum. The pathogenic mechanism might relate to aberrant dopaminergic circuits. © 2020 International Parkinson and Movement Disorder Society

Key Words: dyskinesia; paroxysmal dyskinesia; dystonia; nail-patella syndrome

Paroxysmal dyskinesia (PxD) was first described in 1940 by Mount and Reback1 and was initially termed paroxysmal dystonic choreathetosis. PxDs are clinically and genetically heterogeneous movement disorders characterized by recurrent attacks of abnormal movements, mainly dystonia or chorea, without loss of consciousness. They have traditionally been grouped phenomenologically according to precipitating factors into kinesigenic, nonkinesigenic, and exercise induced. With an increasing number of underlying genetic causes being identified, significant genotypic and phenotypic variability is becoming evident, hence challenging traditional classification.2

The nail-patella syndrome (NPS) is an autosomal dominantly inherited disorder caused by variants in LMX1B (NPS [MIM: 161200]), encoding the transcription factor LMX1B, known to be important for normal cytoskeletal and kidney development.3,4 It has also been demonstrated that LMX1B is a key regulatory gene in neuronal development of, for example, serotonergic and dopaminergic neurons in the mammalian CNS,5–8 and it plays an important role in the development of dopaminergic circuits.9 Clinical hallmarks of this