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Cerebrospinal fluid-orexin levels and sleep attacks in four patients with Parkinson's disease

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ABSTRACT

Objectives: Sleep attacks (SAs) in Parkinson's disease (PD) are rare, but clinically important because they significantly impair the daily lives of patients. Causes of SAs include long-term activation of dopaminergic (especially D3) receptors. Recent studies suggest that SAs in PD may be related to impairment of hypothalamic orexin neurons, similar to narcolepsy. Whether orexin is associated with long-term activation of dopaminergic receptors remains uncertain.
Patients and methods: We measured levels of orexin in samples of spinal cerebrospinal fluid (CSF) from 25 patients with PD, including 9 with excessive daytime sleepiness and 4 with SAs. Furthermore, in the four patients with SAs, the selective dopamine D1/D2 agonist pergolide was substituted for the causative drugs with D3 stimulatory activity, and CSF-orexin levels were measured before and after switching treatment.
Results: In the 25 patients with PD, including the 4 patients with SAs, lower CSF-orexin levels were associated with a longer disease duration, which has been linked to a higher incidence of SAs. Switching treatment to pergolide significantly increased CSF-orexin levels and completely resolved SAs in the four patients with PD.
Conclusion: Despite the small number of patients studied, our results suggest that orexin transmission is most likely involved in SAs in PD and that abrogation of D3 receptor stimulation may increase orexin and thereby inhibit SAs.

1. Introduction

Sleep disturbances occur in 15–50% of patients with Parkinson's disease (PD). Most of these patients have excessive daytime sleepiness (EDS), but some have diurnal "sleep attacks" (SAs) [1]. SAs are characterized by the sudden and irresistible onset of sleep, which significantly impairs the daily lives of patients [2]. Probable clinical causes of SAs in PD include long-term activation of dopaminergic (especially D3) receptors [3], but the precise mechanism remains unknown. Several recent studies suggest that SAs in PD may involve impairment of hypothalamic orexin neurons [4–6], associated with dysfunction in narcolepsy, because lower orexin levels in ventricular CSF or decreased numbers of orexin neurons are found in advanced PD. This notion is supported clinically, since SAs in PD share several characteristics with narcolepsy, including fragmented nocturnal sleep and rapid-eye-movement-sleep behavioral disorders [7]. However, whether orexin is associated with long-term activation of dopaminergic (especially D3) receptors remains uncertain, although previous SPECT studies have suggested that sleep is regulated by D3 receptors in the nucleus accumbens [8,9], a region from which hypothalamic orexin neurons receive inputs [10]. In addition, dopaminergic regulation of orexin neurons has also been demonstrated in rats [11]. On the basis of these clinical and experimental findings indicating a link between orexin and D3 stimulation, we clinically studied whether reducing D3 stimulation would change orexin levels in patients with SAs.

In this study, we measured spinal CSF-orexin levels in 25 patients with PD, including 9 with EDS and 4 with SAs. Furthermore, in the four patients with SAs the selective dopamine D1/D2 agonist pergolide [12] was substituted for the causative drugs with D3 stimulatory activity, and CSF-orexin levels were measured before and after switching treatment.

2. Methods

2.1. Patients

The study group comprised 25 consecutive patients with PD (14 men and 11 women) who fulfilled the United Kingdom Brain

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Table 1
Clinical characteristics of PD subgroups.

	Total PD ($n=25$)	PD without sleep disturbance ($n=12$)	PD with EDS ($n=9$)	PD with SAs ($n=4$)
Age at onset (year)	66.2 ± 8.6	67.5 ± 7.5	65.2 ± 8.9	60.0 ± 5.8
Disease duration (year)	6.4 ± 2.6	6.3 ± 2.3	5.7 ± 2.8	7.9 ± 2.9
Epworth sleepiness scale	8.4 ± 5.9	5.6 ± 2.8	13.9 ± 2.0*	4.5 ± 1.3
Orexin levels (pg/ml)	285.2 ± 77.4	302.3 ± 71.1	286.1 ± 47.6	232.4 ± 12.4

* Significantly higher than other subgroups.

Bank criteria [13] and gave informed consent for lumbar puncture (Table 1). Age at disease onset and the duration of disease were 66.2 ± 8.6 years (mean ± S.D.) and 6.4 ± 2.6 years, respectively. Mean Hoehn and Yahr stage were 3.6 ± 1.4. SAs in PD were diagnosed according to Homann's criteria [14] as follows: "an event of overwhelming sleepiness that occurs without warning or with a prodrome that is sufficiently short or overpowering to prevent the patient from taking appropriative measures" (Frucht's definition) plus "as confirmed by a reliable source". EDS was diagnosed on the basis of the Epworth Sleepiness Score (≥10). According to these criteria, nine patients had EDS. Four patients (patients 1, 2, 3, and 4) had SAs as described below.

2.2. Measurement of CSF-orexin levels

Spinal CSF collection and orexin assay were performed as described previously [6]. Briefly, 5 ml of CSF was taken by lumbar puncture from 25 patients before breakfast, frozen immediately, and kept at −80 °C until measurement. Orexin in crude CSF was measured in duplicate, using a commercially available radioimmunoassay kit (Phoenix Pharmaceuticals, Belmount, CA). Samples from 12 healthy controls (7 men and 5 women; mean age = 37.0 ± 15.0 years) [15] and those from 56 patients who had narcolepsy with cataplexy (30 men and 26 women; mean age = 28.5 ± 20.6) were also assayed. Inclusion criteria for the healthy controls were no history of neurologic, psychiatric, renal, or cardiac disorders; no apparent family history of neurologic or psychiatric disorders; and informed consent for lumbar punctures. The detection limit of the orexin assay was 40 pg/ml and intra-assay/inter-assay variation was 4.3%/3.7%, respectively. A second CSF sample was collected from the four PD patients with SAs 5–10 days after the initiation of pergolide-replacement therapy. For statistical analysis, we used analysis of variance to compare CSF-orexin levels among PD without sleep disturbances, PD with EDS, and PD with SAs. We also used paired t tests to compare CSF-orexin levels before and after pergolide-replacement therapy. Relations of orexin levels to disease duration and to the Epworth Sleepiness Score were examined by linear regression analysis.

3. Results

3.1. Efficacy of pergolide-replacement therapy in four PD patients with SAs

3.1.1. Patient 1

A 65-year-old man with a 9-year history of typical PD received 150 mg/day of L-dopa/dopa-decarboxylase inhibitor (DCI) and 2 mg/day of pramipexole. Within a week after increasing the dose of pramipexole from 2 to 2.5 mg/day, he developed SAs 2–3 times a day. Pramipexole was switched to an equivalent dose of pergolide (2.25 mg/day) and his motor function was unchanged [16]. SAs completely disappeared within a week and did not recur for more than 2 years. The Epworth Sleepiness Score slightly improved after switching to pergolide (from 4 to 2).

3.1.2. Patient 2

A 70-year-old man with an 8-year history of typical PD received 450 mg/day of L-dopa/DCI. Within a week after starting treatment with 1 mg/day of pramipexole, he developed SAs 4–5 times a week. Pramipexole was changed to an equivalent dose of pergolide (0.9 mg/day) and his motor function was unchanged [16]. SAs completely disappeared within a few days and have not recurred for more than 2 years. The Epworth Sleepiness Score slightly improved after switching to pergolide (from 8 to 6).

3.1.3. Patient 3

A 70-year-old man with a 4-year history of PD received 700 mg/day of L-dopa/DCI. He had severe aspiration pneumonia and was admitted to a hospital. Within a week after starting 150 mg/day of L-dopa by intravenous infusion (equivalent to 3000 mg/day of oral L-dopa/DCI [17]) instead of orally, he developed SAs. He was then admitted to our neurological ward. After recovering from pneumonia, he received 1.25 mg/day of pergolide (equivalent to 113.7 mg/day of oral L-dopa/DCI [18]) concomitantly with oral L-dopa/DCI (700 mg/day). His motor function did not change appreciably as compared with that during intravenous infusion of L-dopa. He has remained free of SAs for more than 3 years. The Epworth Sleepiness Score changed slightly after switching to pergolide (from 6 to 8).

3.1.4. Patient 4

A 64-year-old woman with a 10-year history of typical PD received 400 mg/day of L-dopa/DCI. Within a week after the initiation of pramipexole (0.25 mg/day), she developed SAs 2–3 times a week, but did not complain for 4 months. However, because she reported a sudden episode of sleep while she was in the bathtub, she was admitted to our hospital. Pramipexole was switched to an equivalent dose of pergolide (0.2 mg/day) and her motor function was unchanged [16]. SAs completely disappeared within a week, and have not recurred for more than 2 months. The Epworth Sleepiness Score did not change after switching to pergolide (from 0 to 0).

3.2. Results of CSF-orexin levels

The normal range of CSF-orexin levels is defined as the range within the mean ± 2S.D. (167–419 pg/ml) of the levels in control subjects [15]. CSF-orexin levels did not significantly differ between PD without sleep disturbances (302.3 ± 71.1), PD with EDS (286.1 ± 47.6), and PD with SAs (232.4 ± 12.4), but were apparently decreased in patients with narcolepsy (94.8 ± 109.6, Fig. 1a). Orexin levels negatively correlated with disease duration ($p < 0.05$, $r = -0.51$, Fig. 1b). Orexin levels did not correlate with Epworth Sleepiness Score ($p = 0.98$, $r = -0.67$), suggesting the absence of a positive correlation between orexin levels and EDS. Pergolide-replacement therapy significantly increased CSF-orexin levels from a baseline value of 232.4 ± 12.4 to 312.7 ± 41.0, $p = 0.034$ (Fig. 1c).