

## LETTER TO THE EDITOR

## Parkinson's disease, sleepiness and hypocretin/orexin

Christian R. Baumann,<sup>1,2</sup> Thomas E. Scammell<sup>2</sup> and Claudio L. Bassetti<sup>1</sup><sup>1</sup>Department of Neurology, University Hospital Zurich, Switzerland and <sup>2</sup>Department of Neurology, Beth Israel Deaconess Medical Center, Harvard Institutes of Medicine, Boston, USA

Correspondence to: Christian R. Baumann

E-mail: c.r.b@swissonline.ch; christian.baumann@usz.ch

doi:10.1093/brain/awm220

Advance Access publication September 26, 2007

Sir, Sleepiness and disrupted sleep substantially impair quality of life in people with Parkinson's disease (PD) (Arnulf *et al.*, 2000). The hypocretin/orexin neuropeptides stabilize wakefulness and sleep, and in two recent studies, Fronczek *et al.* (2007) and Thannickal *et al.* (2007) showed that patients with late-stage PD have a 38–45% loss of the hypothalamic hypocretin-producing neurons. These studies provide novel and important insights into the neuropathology of PD, but several questions remain about whether this partial loss of hypocretin neurons actually causes the sleep–wake disturbances of PD.

First, are the sleep-related symptoms of PD consistent with a loss of hypocretin neurons? Narcolepsy is caused by a 90–95% loss of the hypocretin neurons and is characterized by excessive daytime sleepiness and cataplexy (sudden loss of muscle tone with strong emotions), with fragmented sleep, sleep paralysis (immobility either at sleep onset or upon awakening), hypnagogic hallucinations and sleep-onset REM sleep (SOREM) during daytime naps (Bassetti and Aldrich, 1996; Peyron *et al.*, 2000). Certainly, PD patients often have fragmented sleep, daytime sleepiness, SOREM, and hallucinations (Arnulf *et al.*, 2000). Our own clinical experience, however, is not in agreement with the statements by Thannickal *et al.* that the daytime sleep attacks in PD resemble sleep attacks in narcolepsy, nor do we agree that sleep–wake disturbances are often more disturbing for PD patients than their motor symptoms. Furthermore, narcoleptics may have hypnagogic hallucinations at the transitions between wakefulness and sleep, but PD patients often have delusions and illusions rather than dream-like hallucinations (Aarsland *et al.*, 1999). Last, cataplexy has not been reported to occur in PD. Therefore, while there are some similarities, the sleepiness and other symptoms of PD differ in many ways from those seen in narcolepsy.

Second, do patients with PD have a physiologically significant loss of hypocretin signalling? In narcolepsy with

cataplexy, the almost complete loss of hypocretin neurons is accompanied by severe reductions in lumbar CSF hypocretin levels (Peyron *et al.*, 2000; Thannickal *et al.*, 2000; Nishino *et al.*, 2000). However, most studies have found normal hypocretin levels in PD (Ripley *et al.*, 2001; Overeem *et al.*, 2002; Yasui *et al.*, 2006). In fact, we found normal CSF concentrations of hypocretin even in PD patients with objectively confirmed severe excessive daytime sleepiness, hallucinations and SOREMs (Baumann *et al.*, 2005a).

One group reported very low hypocretin levels in ventricular CSF of late-stage PD patients (Drouot *et al.*, 2003), raising the question of whether ventricular or lumbar CSF more accurately reflects the integrity of the hypocretin system. Fronczek *et al.* found that hypocretin levels in ventricular CSF of PD patients are slightly reduced compared to controls and correlate with the loss of hypocretin neurons, but in the absence of normative data, it is unclear whether these levels are physiologically low. In two patients with simultaneous sampling of lumbar and ventricular CSF, we found no significant differences in hypocretin levels (Baumann *et al.*, 2005b). Overall, it appears that in patients with PD, hypocretin signalling as measured in CSF appears normal.

Third, does PD selectively injure the hypocretin neurons? Thannickal *et al.* found that hypothalami of PD patients also have fewer neurons producing melanin concentrating hormone. This supports the assumption that PD kills many types of hypothalamic neurons, and loss of non-hypocretin neurons may contribute to the sleep–wake disturbances of PD.

Overall, we suspect that the moderate loss of hypocretin neurons in PD is accompanied by compensation in the remaining cells to achieve relatively normal hypocretin signalling. Furthermore, hypocretin cell loss may be a non-specific finding of late-stage PD, in which injury to many neuronal systems produces sleep–wake disturbances different from those seen in narcolepsy.

**References**

- Aarsland D, Larsen JP, Lim NG, et al. Range of neuropsychiatric disturbances in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1999; 67: 492–6.
- Arnulf I, Bonnet AM, Damier P, et al. Hallucinations, REM sleep, and Parkinson's disease: a medical hypothesis. *Neurology* 2000; 55: 281–8.
- Bassetti C, Aldrich MS. Narcolepsy. *Neurol Clin* 1996; 14: 545–71.
- Baumann C, Ferini-Strambi L, Waldvogel D, Werth E, Bassetti CL. Parkinsonism with excessive daytime sleepiness—a narcolepsy-like disorder? *J Neurol* 2005a; 252: 139–45.
- Baumann CR, Stocker R, Imhof HG, et al. Hypocretin-1 (orexin A) deficiency in acute traumatic brain injury. *Neurology* 2005b; 65: 147–9.
- Drouot X, Moutereau S, Nguyen JP, et al. Low levels of ventricular CSF orexin/hypocretin in advanced PD. *Neurology* 2003; 61: 540–3.
- Fronczek R, Overeem S, Lee SY, et al. Hypocretin (orexin) loss in Parkinson's disease. *Brain* 2007; 130: 1577–85.
- Overeem S, van Hilten JJ, Ripley B, Mignot E, Nishino S, Lammers GJ. Normal hypocretin-1 levels in Parkinson's disease patients with excessive daytime sleepiness. *Neurology* 2002; 58: 498–9.
- Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. *Lancet* 2000; 355: 39–40.
- Peyron C, Faraco J, Rogers W, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. *Nat Med* 2000; 6: 991–7.
- Ripley B, Overeem S, Fujiki N, et al. CSF hypocretin/orexin levels in narcolepsy and other neurological conditions. *Neurology* 2001; 57: 2253–8.
- Thannickal TC, Moore RY, Nienhuis R, Ramanathan L, Gulyani S, Aldrich M, et al. Reduced number of hypocretin neurons in human narcolepsy. *Neuron* 2000; 27: 469–74.
- Thannickal TC, Lai YY, Siegel JM. Hypocretin (orexin) cell loss in Parkinson's disease. *Brain* 2007; 130: 1586–95.
- Yasui K, Inoue Y, Kanbayashi T, Nomura T, Kusumi M, Nakashima K. CSF orexin levels of Parkinson's disease, dementia with Lewy bodies, progressive supranuclear palsy and corticobasal degeneration. *J Neurol Sci* 2006; 250: 120–3.