LETTER TO THE EDITOR

Hypocretin (orexin) loss and sleep disturbances in Parkinson’s Disease

Rolf Fronczek,1,2 Sebastiaan Overeem,1,3 Sandy YY. Lee,2 Ingrid M. Hegeman,1 Johannes van Pelt,4 Sjoerd G. van Duinen,5 Gert Jan Lammers1 and Dick F. Swaab2

1Department of Neurology, Leiden University Medical Center, Leiden, 2Netherlands Institute for Neurosciences, Amsterdam ZO, 3Department of Neurology, Radboud University Nijmegen Medical Center, Nijmegen, 4Department of Clinical Chemistry and 5Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands

Corresponding to: Rolf Fronczek, Department of Neurology, Leiden University Medical Center, Leiden, Netherlands Institute for Neurosciences, Amsterdam ZO, The Netherlands
E-mail: r.fronczek@lumc.nl
doi: 10.1093/brain/awm222

Received August 5, 2007. Accepted August 20, 2007.

We would like to thank Baumann et al. for their interest in our paper (Fronczek et al., 2007). The questions raised are all relevant and mainly entail the relationship between the partial hypocretin loss in PD (Fronczek et al., 2007; Thannickal et al., 2007) and actual sleep disturbances. Furthermore, the selectivity of the hypocretin cell loss in PD is questioned. We fully agree with these remarks and therefore prominently discussed them in our original paper (Fronczek et al., 2007). However, two of the issues warrant a more detailed reply.

First, Baumann et al. state that the daytime sleep attacks in PD do not resemble those seen in narcolepsy. However, after listing those symptoms that are similar between the two disorders, the authors do not specify what the exact differences may be, and do not provide any studies on this topic. One of the few published studies that addressed this exact topic stated that the combination of excessive daytime sleepiness (sometimes culminating in sleep attacks), hypnagogic hallucinations, REM-sleep behaviour disorder (RBD) and daytime sleep-onset REM periods, is similar to narcolepsy (Arnulf et al., 2005). Note, that these are all symptoms that can occur without a complete loss of hypocretin.

Second, the authors consider hypocretin-1 levels in the cerebrospinal fluid (CSF) to be a measure of physiological relevance, and that therefore the normal lumbar CSF levels in PD suggest that hypocretin-1 signalling is normal. The study by Baumann et al. assessed lumbar and ventricular CSF levels in just two non-PD patients with already undetectable or very low hypocretin levels, and can thus not prove the point that was made (Baumann et al., 2005).

In general, the functional meaning of hypocretin in the CSF is unclear. Most likely, it does not have any role at all. It could be seen as a marker without an actual physiological function or even be considered as ‘waste’ that is leaving the brain by the spinal fluid after performing its function, showing only a drop when the number of hypocretin neurons is severely reduced. Because of these uncertainties regarding the role of CSF peptide levels, we used tissue hypocretin-1 concentrations and — most importantly — actual hypocretin-1 cell counts to test the integrity of the hypocretin system in PD.

To conclude, there is a partial but significant loss of hypocretin neurons in PD. In rodent studies, a 60–70% reduction in hypocretin readily led to REM-sleep disturbances (Gerashchenko et al., 2003; Chen et al., 2006). Further studies may shed more light on the relationship between hypocretin defects and sleep disturbances in human PD. When available for human use in the future, hypocretin agonists may be the best tool to answer this fundamental question.

References

