LETTER TO THE EDITOR

Hypocretin (orexin) and melanin concentrating hormone loss and the symptoms of Parkinson’s disease

Thomas C. Thannickal, Yuan-Yang Lai and Jerome M. Siegel

Department of Psychiatry, University of California at Los Angeles, Los Angeles, CA 90095, Neurobiology Research (IS1A3), Veterans Administration Greater Los Angeles Healthcare System, North Hills, CA 91343 and Brain Research Institute, University of California at Los Angeles, Los Angeles, CA 90095

Correspondence to: Jerome M. Siegel, PhD, UCLA/V AGLAHS – Sepulveda, Neurobiology Research (IS1A3), 16111 Plummer Street, North Hills, CA 91343, USA
E-mail: jsiegel@ucla.edu
doi: 10.1093/brain/awm221

Keywords: Parkinson; narcolepsy; sleep; hypocretin; orexin; melanin concentrating hormone

Advance Access publication September 26, 2007

We reported that Parkinson’s disease (PD) patients have a substantial loss of hypocretin (Hcrt) cells (Thannickal et al., 2007). As two of the authors of the letter to which we are responding have emphasized in their prior publication (Baumann et al., 2005), and as other groups have reported, the sleep disturbances associated with PD are a major complaint in a large proportion of these patients (Arnulf et al., 2002; Onofrj et al., 2003; Arnulf et al., 2006; Frucht et al., 2002; Thannickal et al., 2003). Surviving Hcrt cells may increase their output of Hcrt or the Hcrt cells that release peptide into the CSF may be relatively less affected in the early stages of PD, accounting for the normal levels of Hcrt seen in some reports. Fronczek et al. and Drouot et al. (2003) reported reduced Hcrt levels in CSF samples drawn from the ventricular system of PD patients (Fronczek et al., 2007). Injection of massive amounts of Hcrt into the CSF is arousing (Hagan et al., 1999; Ida et al., 1999; Sweet et al., 1999; Yamanaka et al., 1999; Espana et al., 2001; Kiyashchenko et al., 2001; Ishizuka et al., 2002; Kotz et al., 2002; Milejkovskiy et al., 2002; Peever et al., 2003; Walling et al., 2004; Fadel et al., 2005). However, there is no evidence we are aware of that indicates that Hcrt normally acts through the ventricular system rather than through axonal-dendritic communication, or that the presence of normal Hcrt levels in the CSF levels indicates normal Hcrt function.

We reported that Hcrt cell loss ranged from 23 to 62%, with the loss increasing with the severity of PD according to the Hoehn and Yahr scale. The loss of melanin concentrating hormone cells ranged from 12 to 74%, also increasing with disease progression (Thannickal et al., 2007). Prior work has reported that PD patients have a loss of 2–3% of dopaminergic cells in the central gray, 40–50% of dopaminergic cells in VTA and 80–90% of neuromelanin containing substantia nigra pars compacta cells (Hartmann, 2004). It is well established that many areas of the brain degenerate in PD, although a prior systematic review did not note anatomical damage to the dorsomedial and perifornical

© 2007 The Author(s)
This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/2.0/uk/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.
hypothalamic regions, the location of Hcrt and MCH cells, in their model of PD progression (Braak et al., 2003). In our study we found that the degenerative changes in the Hcrt cells was better correlated with disease progression than that in neuromelanin cells of the substantia nigra. The latter loss was correlated with disease duration. We did not state that PD is associated with ‘selective’ injury to Hcrt cells.

It is to be expected that any slow disturbance linked to the loss of hypocretin cells will interact with the other degenerative changes in PD, with this interaction determining the expression of symptoms. For example, one might expect that hallucinations linked to PD in patients with MCH, substantia nigra and other cell loss would not mirror those of narcolepsy caused solely by much more specific Hcrt cell loss. This is why we stated at the conclusion of our paper that while hypocretin cell loss may be a clinically important cause of the major sleep disturbances and certain other symptoms seen in PD, the only way to test this hypothesis would be by administering hypocretin or suitable analogs to PD patients and determining the extent to which these symptoms reversed. We look forward to seeing such clinical trials.

Acknowledgements
Supported by NS14610, HL41370, MH64109 and the Medical Research Service of the Department of Veterans Affairs. Funding to pay the Open Access publication charges for this article was provided by the National Institutes of Health NS14610.

References