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

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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.*, 2000; Frucht *et al.*, 2000; Arnulf *et al.*, 2002; Frucht, 2002; Onofrj *et al.*, 2003; Arnulf, 2005; Abbott *et al.*, 2005; Arnulf, 2006; Benbir *et al.*, 2006; Rye, 2006; Savitt *et al.*, 2006) and resemble the sleep complaints of narcoleptics. These disturbances can include not only sleep attacks and nocturnal insomnia, but also REM sleep behaviour disorder, which can lead to severe injury.

In our prior study of narcoleptics, the loss of Hcrt cells, in patients who had been symptomatic for an average of 41 years (range 31–51 years), was on average 91% (range from 86 to 94%) (Thannickal *et al.*, 2000). Published data have not determined the threshold level of Hcrt cell loss for the onset of symptoms in narcolepsy, or if the loss of Hcrt cells is progressive after the initial appearance of symptoms. Moreover, the relatively small number of human narcoleptic brains that are available for study limits conclusions regarding relationship of the percent and pattern of Hcrt cell loss to the presence, nature and severity of each of the symptoms in narcolepsy, including cataplexy, hallucinations, sleep paralysis, REM sleep behaviour disorder, daytime sleep attacks and nocturnal insomnia, all of which are known to be associated with narcolepsy. The presence of cataplexy is not necessary for a diagnosis of narcolepsy (Billiard, 2007).

Hcrt CSF levels have been shown in an experimental study in rats to not be linearly related to the number of Hcrt cells lost. Rats with 56–86% loss of Hcrt cells had marked sleep

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abnormalities (Gerashchenko *et al.*, 2003). The loss of Hcrt cells in human narcoleptics is accompanied by a reduced innervation of cell groups that receive Hcrt (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; Mileykovskiy *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 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 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 sleep 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. The widespread degeneration characterizing PD may either potentiate or ameliorate the deficits caused by 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.

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