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Hypocretin-1 (orexin A) levels are normal in Huntington's disease

Received: 24 August 2005
Received in revised form: 9 January 2006
Accepted: 24 January 2006
Published online: 5 April 2006

Sirs: Sleep-wake disturbances are common in Huntington's disease (HD), and include disturbances of the sleep-wake cycle, insomnia/disturbed night sleep with nocturnal awakenings, and more rarely excessive daytime sleepiness, and disturbed REM sleep [1–3]. Furthermore, alteration of nutrition status and energy balance (including weight loss and altered plasma concentrations of ghrelin and leptin) are common in HD [4, 5].

At the present time, there are no biochemical markers for the diagnosis of HD.

Hypocretins (orexins) are hypothalamic neuropeptides which are involved in the regulation of arousal, feeding behavior and energy expenditure (i.a. via

interactions with ghrelin and leptin). In the sleep-wake disorder narcolepsy-cataplexy, which is associated with altered energy expenditure, cerebrospinal fluid (CSF) hypocretin-1 levels are decreased due to a loss of hypothalamic hypocretin neurons [6, 7]. Petersen et al. recently reported a significant loss of hypocretin neurons and dramatically decreased CSF hypocretin-1 levels in the best studied rodent model of HD [8]. Furthermore, the authors observed a decrease of hypocretin-immunopositive neurons in the hypothalamus of five human HD patients. In our preliminary study, therefore, we intended to test whether CSF hypocretin-1 levels are decreased in human HD patients.

In seven genetically confirmed HD patients (mean age 51 years, range 35–74 five men), we assessed duration of disease (defined as time from onset of first symptom to lumbar puncture), body mass indices and sleep-wake disturbances by standardized sleep questionnaires (including Epworth Sleepiness Scale=ESS; available in six patients). CSF hypocretin-1 levels were determined in all patients in a single radioimmunoassay as previously described [9]. Levels were compared with those of controls without neurological or other sleep-wake disorders (n=20), and with patients with other neurodegenerative disorders (Parkinson's disease, n=6, mean age 71 years; dementia with Lewy bodies, n=9, mean age 73 years; Alzheimer's disease, n=7, mean age 72 years).

In the HD patients, mean duration of disease was 4.1 years (range 1–10). Mean BMI was 26.3 (range 22–33). Four patients reported unintentional weight loss. Sleep-wake disorders were com-

mon complaints, and included insomnia (n=4), fragmented night sleep without daytime tiredness (n=1), and REM sleep behavior disorder (n=1). Excessive daytime sleepiness (defined as ESS score>10) was not reported (mean ESS score 6.3, range 4–8).

CSF hypocretin-1 levels were normal in all HD patients (mean 441 pg/ml, range 326–583) (Fig. 1). Levels did not differ significantly from those of patients with Parkinson's disease (487 pg/ml, range 307–654 pg/ml), dementia with Lewy bodies (504 pg/ml, range 382–667), and Alzheimer's disease (474 pg/ml, range 333–564). There were no associations between the presence of sleep-wake disorders, Epworth Sleepiness Scale, duration of the disease, body mass index, unintentional weight loss, and CSF hypocretin-1 levels.

We could not find a hypocretin neurotransmission deficiency – as assessed by determination of CSF hypocretin-1 levels – in human HD. However, Petersen et al. reported an approximate 27 % loss of hypocretin neurons in human HD [8]. We think that this discrepancy may be due to quantitative effects: Gerashchenko and colleagues [10] found that an average loss of 14 % of rodent hypocretin neurons was not followed by a decrease of CSF hypocretin levels. An average loss of 73 %, however, was associated with a significant 50 % decline in CSF hypocretin levels. The authors assumed that surviving hypocretin neurons might compensate for hypocretin neuronal loss by increased hypocretin ligand production. Thus, interpreting Petersen's finding together with the observations of Gerashchenko, it is conceivable that CSF hypocretin-1 levels are normal in HD patients.

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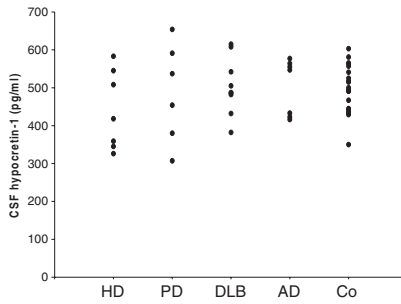


Fig. 1 CSF hypocretin-1 levels (in pg/ml) in Huntington's disease (HD, n=7), Parkinson's disease (PD, n=6), dementia with Lewy bodies (DLB, n=9), Alzheimer's disease (AD, n=7), and healthy controls (Co, n=20)

In conclusion, we found normal CSF hypocretin-1 levels in patients with Huntington's disease, independent of the presence of sleep-wake disorders, and independent of nutritional status. CSF hypocretin-1 determination may not be helpful in the diagnosis of HD. Further studies to evaluate hypocretin neuronal loss in HD are required.

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