Abstract

A recent publication suggested that hypocretin (Hcrt, orexin) may mediate the neuropathological process leading to Alzheimer’s disease (AD) and that antagonism of hypocretin receptors decreases this process. Narcoleptics have an approximately 90% loss of Hcrt neurons and commensurate reductions in the levels of Hcrt in their cerebrospinal fluid beginning at disease onset, usually before the age of 30. If Hcrt mediates the disease process, narcoleptics should be protected against AD. We examined the postmortem neuropathology and clinical records of 12 sequentially encountered cases of human narcolepsy. We found that AD was present in 4 of these narcoleptics, a prevalence that is similar to that of the general population.

1. Introduction

Kang and colleagues (Kang et al., 2009) recently reported that levels of amyloid-β in brain interstitial fluid are high during periods of wakefulness, suggesting that higher levels of neuronal activity during wakefulness may promote the development of AD. They also found that the wake-promoting neuropeptide Hcrt1 increases levels of amyloid-β, whereas an Hcrt antagonist reduces amyloid-β levels. If low Hcrt signaling reduces amyloid release, then people with narcolepsy, who have lost most of their Hcrt neurons (Blouin et al., 2005; Crocker et al., 2005; Peyron et al., 2000; Thannickal et al., 2000; Thannickal et al., 2007), should have a lower risk of developing AD.

2. Methods

All postmortem brain tissue was analyzed by pathologists using hematoxylin eosin and Sevier-Munger sections of frontal, lateral, inferior temporal, parietal, occipital cortex, thalamic surface, cerebellum, and medulla for identification of neuritic plaques and neurofibrillary tangles. Medical records were inspected for tests performed on memory function and for clinical notes concerning orientation, memory and drug treatment. Additional tests were performed as described below.

3. Results

We examined the brain of a 75-year male with narcolepsy with cataplexy since he was 12 and an 8 year history of AD. Neuropsychological testing was consistent with AD, MRI showed moderate cortical atrophy, and SPECT scan revealed hypoperfusion of the temporal and parietal lobes. He had 85% loss of the Hcrt neurons and extensive plaques and tangles in the hippocampus, frontal and temporal cortex (Braak Stage 5/6), findings consistent with narcolepsy and AD.

In a review of all 11 other individuals ages 69 to 95 (mean age 83; 6 male, 6 female) with narcolepsy with cataplexy for whom we have neuropathologic material, we found that 3 others, a 75 year old male, a 79 year old male and a 94 year old female, had clinical histories of dementia and neuropathology consistent with AD—an overall preva-
lence of 33%, similar to that of the general population (Evans et al., 1989; Hebert et al., 2003). All had amyloid deposition typical of AD (See supplementary data). This data set encompasses the majority of identified brains of narcoleptics in the literature (Blouin et al., 2005; Crocker et al., 2005; Honda et al., 2009; Thannickal et al., 2000).

4. Discussion

These observations suggest that chronic loss of Hcrt signaling does not protect against AD. We agree with Kang and colleagues’ conclusion that high levels of neuronal activity may promote release of amyloid-β, but we believe that Hcrt in normal amounts is unnecessary in the pathogenesis of AD. Thus our results do not give reason to encourage the use of Hcrt antagonists to retard the progression of AD.

Acknowledgments

Supported by the Ministry of Education, Science and Culture of Japan [Grants-in-Aid for Scientific research: 17390324 and 19390310] (MH); The Medical Research Service of the VA, NS14610 and MH64109 (JMS and TCT).

Appendix. Supplementary data


References


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