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Cerebrospinal Fluid Hypocretin and Nightmares in Dementia Syndromes

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Hypocretin · Alzheimer disease · Dementia · Nightmares · Dreams

Abstract
Background/Aims: Hypocretin promotes wakefulness and modulates REM sleep. Alterations in the hypocretin system are increasingly implicated in dementia. We evaluated relationships among hypocretin, dementia biomarkers, and sleep symptoms in elderly participants, most of whom had dementia. ***Methods:*** One-hundred twenty-six adults (mean age 66.2 ± 8.4 years) were recruited from the Emory Cognitive Clinic. Diagnoses were Alzheimer disease (AD; $n = 60$), frontotemporal dementia (FTD; $n = 21$), and dementia with Lewy bodies (DLB; $n = 20$). We also included cognitively normal controls ($n = 25$). Participants and/or caregivers completed sleep questionnaires and lumbar puncture was performed for cerebrospinal fluid (CSF) assessments. ***Results:*** Except for sleepiness (worst in DLB) and nocturia (worse in DLB and FTD) sleep symptoms did not differ by diagnosis. CSF hypocretin concentrations were available for 87 participants and normal in 70, intermediate in 16, and low in 1. Hypocretin levels did not differ by diagnosis. Hypocretin levels correlated with CSF total τ levels only in men ($r = 0.34$; $p = 0.02$). Lower hypocretin levels were related to frequency of nightmares (203.9 ± 29.8 pg/mL in those with frequent nightmares vs. 240.4 ± 46.1 pg/mL in those without; $p = 0.05$) and vivid dreams (209.1 ± 28.3 vs. 239.5 ± 47.8 pg/mL; $p = 0.014$). Cholinesterase inhibitor use was not associated with nightmares or vivid dreaming. ***Conclusion:*** Hypocretin levels did not distinguish between dementia syndromes. Disturbing dreams in dementia patients may be related to lower hypocretin concentrations in CSF.

Introduction

Disturbed sleep in dementia may result from cell loss in neuronal populations affecting circadian rhythms, homeostatic sleep regulation, and autonomic and respiratory functions [1]. The neurobiological substrates for these dysfunctions remain incompletely understood, with recent attention focusing on hypocretin-1 (orexin A). Hypocretin is a hypothalamic peptide that promotes wakefulness and regulates REM sleep, and hypocretin de-

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ficiency is the biomarker for sleepiness and REM-related phenomena, including vivid dreaming and hallucinations, in narcolepsy type 1 (NT1). Animal models indicate that hypocretin may impact β-amyloid 1–42 (Aβ42). In particular, higher hypocretin may prevent phagocytosis of Aβ42 by microglia, exogenous administration of hypocretin increases Aβ42 in brain interstitial fluid, and reductions in hypocretin signaling via hypocretin receptor antagonists or in receptor knockout animals reduce Aβ42 [2–4].

Consistent with this animal literature, human studies have generally, although not universally [5], concluded that patients with Alzheimer disease (AD) or mild cognitive impairment (MCI) with subsequent conversion to AD have higher hypocretin levels than controls [6, 7], than patients with non-AD dementia syndromes [8], or than people with other nondementing neurologic diseases [9]. However, studies examining associations between hypocretin and cerebrospinal fluid (CSF) AD biomarkers, such as Aβ42, have shown mixed results [6, 8–12] to date. CSF τ is more consistently associated with higher hypocretin [5, 6, 10], with evidence of effect modification by gender [11].

We examined CSF hypocretin across 3 dementia types (AD, dementia with Lewy bodies [DLB], and frontotemporal dementia [FTD]) and controls to examine associations between CSF-derived hypocretin and AD biomarkers. Because hypocretin deficiency is so strongly associated with excessive daytime sleepiness and abnormal dreaming experiences in NT1, we also examined relationships between hypocretin and patient/caregiver-reported sleepiness, sleep quality, and dream experiences.

Materials and Methods

Participants were recruited from our tertiary referral, university-based medical center [13–16]. Age-matched normal-cognition (NC) subjects were prospectively recruited for a biomarker study, which included detailed neuropsychological, imaging, and CSF biomarker analyses [13].

Diagnoses of NC and AD were made according to consensus [13]. People meeting the consensus criteria for MCI whose CSF biomarkers were consistent with pathologic AD were included in the AD group. Diagnoses of FTD (behavioral or language variant) [17] and DLB [18] were made by a board-certified cognitive neurologist (W.T.H.) with international consensus criteria.

CSF Biomarkers

CSF was collected using a 24-gauge atraumatic needle into polypropylene tubes using a modified ADNI protocol without overnight fasting [19] and immediately aliquoted, labeled, and frozen at –80 °C. CSF AD biomarkers, including Aβ42, total τ (t-Tau), and τ phosphorylated at threonine 181 (p-Tau_{181}), were measured using Alzbio3 kits (Fujirebio, Malvern, PA, USA) in the Luminex 200 platform [19]. Ratio values of t-Tau/Aβ42 >0.39 or p-Tau_{181}/Aβ42 >0.15 were used as AD cutoffs. When ratios were discordant, p-Tau_{181}/Aβ42 was used.

Hypocretin-1 (orexin-A) levels were measured in unextracted CSF using a highlysensitive, commercially available, 125-I radioimmunoassay kit (Phoenix Pharmaceuticals, Burlingame, CA, USA) on all participants with sufficient CSF volume available. Each run included a positive control from the kit and known low and normal reference samples from our biobank. Samples were blindly measured in 100-μL duplicates and values were averaged. The standard curve range was 10–1,280 pg/mL. We have demonstrated an excellent interassay correlation ($r = 0.79$) between samples measured at our lab and the Stanford University reference lab [20]. Hypocretin values were defined as: low (<110 pg/mL), intermediate (110–200 pg/mL), or normal (>200 pg/mL).

Sleep Symptom Questionnaires

The Neurodegenerative Disease Sleep Questionnaire (NDSQ) [21] was completed by the participant or by the participant and caregiver and was it available on a subset of participants. Daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) [22].

Statistical Analyses

CSF biomarkers, ESS scores, and sleep durations on the NDSQ were analyzed as continuous variables. For questions assessing frequency of symptoms, responses were dichotomized, with symptoms considered present if endorsed at least "sometimes" for 5-point scales and at least "often" for 4-point scales. "Don't know" responses were considered missing for question-specific analyses. For sensitivity analysis, we limited analyses for items responded to by the patient alone or by both the patient and the caregiver. Cholinesterase inhibitor exposure was determined by medical record review and based on taking a cholinesterase inhibitor at the time of lumbar puncture, questionnaire completion, or both.

Sleep symptoms were compared across diagnoses by a χ^2 or Fisher exact test for categorical variables and by a one-way, mixed-model ANOVA (to control for unequal sample sizes and variances) for continuous variables. For significant ANOVA results, pairwise multiple comparisons were performed via a Tukey test. For biomarker interrelationships Pearson correlations were used. Sleep symptoms and biomarker associations were examined via a *t* test (correcting for unequal variance). $p < 0.05$ were considered statistically significant.

Results

Participants were 126 adults (58 women) with a mean (±SD) age of 66.2 (±8.4) years. Participants' diagnoses were AD ($n = 60$), FTD ($n = 21$), DLB ($n = 20$), or NC ($n = 25$). There were significantly fewer women with DLB and FTD (Table 1). Except for reported sleepiness (ESS), worse in DLB than in controls, and nocturia, worse in DLB and FTD, sleep symptoms did not differentiate di-

Table 1. Demographic characteristics, sleep symptoms, and biomarker levels

Characteristic	AD (n = 60)	FTD (n = 21)	DLB (n = 20)	CTL (n = 25)	p value	Significant pairwise differences
Female gender	**29 (48.3)**	**7 (33.3)**	**5 (25.0)**	**17 (68.0)**	**0.02**	**CTL > FTD CTL > DLB**
Age, years	65.5 (7.7)	66.3 (9.2)	64.9 (9.8)	69.6 (9.2)	0.52	–
ESS score	**6.0 (4.7)**	**6.9 (6.3)**	**9.8 (3.7)**	**4.8 (3.1)**	**0.04**	**DLB > CTL**
Nightly sleep duration, h	7.7 (1.3)	7.6 (1.1)	8.8 (1.9)	7.6 (0.9)	0.45	–
Vivid dreams	7 (15.9)	4 (22.2)	3 (37.5)	3 (23.1)	0.51	–
Nightmares	3 (6.7)	1 (5.9)	2 (25)	2 (15.4)	0.22	–
Nocturia	**10 (20.8)**	**8 (42.1)**	**5 (62.5)**	**1 (7.7)**	**0.01**	**CTL < FTD = DLB; AD < DLB**
Snoring	24 (53.3)	12 (70.6)	7 (100)	6 (60.0)	0.09	–
Sleep onset insomnia	10 (20.4)	2 (11.1)	2 (25.0)	6 (46.2)	0.13	–
Sleep maintenance insomnia	20 (40.8)	10 (52.6)	6 (75.0)	4 (30.8)	0.20	–
Early morning awakenings	14 (28.6)	4 (21.1)	5 (62.5)	5 (38.5)	0.19	–
Leg restlessness at bedtime	2 (4.4)	0 (0)	1 (12.5)	1 (7.7)	0.36	–
Leg restlessness during nocturnal awakenings	2 (4.3)	1 (5.3)	2 (25)	1 (7.7)	0.16	–
CSF Aβ42	118.8 (63.1)	271.2 (148.4)	255.5 (90.4)	301.0 (137.5)	0.44[a]	–
CSF t-Tau	**93.8 (71.8)**	**61.0 (36.8)**	**33.1 (16.6)**	**37.9 (20.7)**	**0.01**[a]	**FTD > DLB = CTL**
CSF p-Tau$_{181}$	50.2 (26.0)	21.8 (13.6)	18.5 (8.0)	24.8 (19.6)	0.31[a]	–
CSF hypocretin	256.8 (59.0)	245.0 (50.5)	240.3 (60.2)	248.1 (53.3)	0.79	–

Values are reported as means (SD) or numbers (%). CTL, control. [a] Aβ42, t-Tau, and p-Tau$_{181}$ were used to assign an AD diagnosis and therefore differ between AD and other groups by definition; this p value is for the 3-group comparison of FTD, DLB, and CTL. Bold text indicates statistical significance with $p < 0.05$.

agnostic groups (Table 1). These differences were not modified meaningfully by whether the patient had completed the questionnaire alone or with caregiver assistance (data not shown).

AD participants had significantly lower Aβ42 and significantly higher t-Tau and p-Tau$_{181}$ values than NC and the other 2 patient groups (Table 1). Participants with FTD had higher t-Tau values than those with DLB or NC. Hypocretin (n = 87) was normal in 70, intermediate (range 143.8–198.0 pg/mL) in 16 (all 4 diagnoses), and low (106.8 pg/mL) in 1 patient (AD). Hypocretin did not differ by diagnosis. Across all of the participants, Aβ42 was negatively correlated with p-Tau$_{181}$ (r = –0.39; p < 0.0001) but not with t-Tau (r = –0.16; p = 0.08). The 2 τ biomarkers were strongly correlated (r = 0.53; p < 0.0001). Hypocretin levels were uncorrelated with Aβ42, t-Tau, or p-Tau$_{181}$ across all groups or in AD only. Among men, hypocretin and t-Tau were moderately correlated (r = 0.34; p = 0.02), particularly for AD (r = 0.68; p = 0.001), but hypocretin was unrelated to p-Tau$_{181}$ or Aβ42. Among women, no such associations were noted.

AD biomarkers were unrelated to sleep symptoms (all p values ns), except leg restlessness, which was was associated with lower t-Tau values (39.2 ± 14.7 vs. 75.8 ± 54.6). ESS and hypocretin were unrelated (r = –0.06; p = 0.66); however, REM-sleep dyscontrol symptoms correlated with hypocretin. Participants with frequent nightmares had significantly lower hypocretin levels than those without (203.9 ± 29.8 vs. 240.4 ± 46.1 pg/mL, t = 2.01; p = 0.05), and participants having frequent vivid dreams showed lower hypocretin levels than those without (209.1 ± 28.3 vs. 239.5 ± 47.8 pg/mL, t = 2.62; p = 0.014). The directionality of these differences was not impacted by whether the caregiver had assisted with questionnaire completion, although p values in those subanalyses became nonsignificant, likely reflecting smaller samples. No other questionnaire items were related to hypocretin.

Associations between hypocretin and reported dreaming were not mediated by cholinesterase inhibitors. Reported nightmares occurred in 10.0% of those receiving cholinesterase inhibitors and in 9.4% of those not receiving them (p = 1.00; Fisher exact test), whereas the corresponding proportions reporting vivid dreaming were 16.7 and 22.6%, respectively (p = 0.52; χ^2 test).

Discussion/Conclusions

Although biomarkers differentiated AD patients from controls [19], the absence of associations with hypocretin was unexpected. Among moderate-to-severe AD patients, Liguori et al. [6] reported moderate effects (r^2 values of 0.31–0.40) relating CSF hypocretin and p-Tau$_{181}$ and t-Tau (but not Aβ42). In a community-based, nondementia cohort, Osorio et al. [23] reported more modest positive relationships (r^2 values of 0.18–0.25) between hypocretin, t-Tau, and p-Tau$_{181}$, with a still weaker relationship with Aβ42. In lateral hypothalamic postmortem analyses, hypocretin immunoreactivity was reduced in AD relative to NC, while neuronal counts were robustly related to neurofibrillary stage ($r^2 = 0.45$) [24]. From these findings, one might expect AD to be associated with a greater neurofibrillary tangle count, elevated CSF t-Tau and p-Tau$_{181}$ levels, and decreased CSF hypocretin. Our and others' observation of a positive correlation between τ and hypocretin in AD thus suggests a functional upregulation independent of neuronal loss. Because CSF t-Tau levels in AD also mirror biology beyond tangle deposition [25], increased CSF hypocretin may reflect bystander effects with clinical consequences. Even stronger neuropathologic relationships were noted with hypocretin immunoreactivity in DLB [24], but we detected no relationship between τ and hypocretin in DLB. This could reflect a small sample, a floor effect associated with low CSF t-Tau and p-Tau$_{181}$ levels in DLB, different biological pathways activated in AD vs. DLB, or a stronger gender influence because of the DLB male predominance. Women have been shown to have higher postmortem ventricular CSF hypocretin levels than men [26]; this occurs in both AD and NC and could reflect estradiol's effects on hypocretin receptor expression [27]. Higher hypocretin in relation to higher τ was reported in a small-sample study comprised mainly of women [10].

We noted relatively few associations between sleep symptoms and AD biomarkers and, except for dreaming experiences, hypocretin. AD biomarkers show a complex relationship to sleep in human studies. For example, 1 night of experimentally induced slow-wave sleep fragmentation in controls elevated CSF Aβ40 [28] and decreased Aβ42 [29], suggesting that sleep disruption dysregulates the Aβ isoform. Paralleling these results are cross-sectional, observational studies demonstrating that a poorer self-reported sleep quality [30], a lower actigraphically defined sleep efficiency [31], and lower levels of slow wave sleep [32] were all associated with altered CSF Aβ42. Using neuroimaging, similar associations occurred between subjectively assessed poor sleep and a greater PET-based amyloid burden [33], and impaired overnight memory consolidation was related to both decreased slow-wave activity and prefrontal amyloid burden in a causally dependent manner [34].

In contrast to much of this research, however, Olsson et al. [35] reported that a 5-night restriction of 4 h in bed had no effect on Aβ isoforms in middle-aged adults, and a community-based study showed that Aβ42 levels were unrelated to incident AD in 2 cohorts totaling about 1,000 participants [36]. Among AD patients and patients with MCI with likely incipient AD, lower Aβ42 levels were associated with a longer, not a shorter, sleep duration [9]. A complex interaction between actigraphically assessed disturbed sleep measured antemortem and greater postmortem Aβ neuropathology has also been suggested, in which sleep per se may not directly mediate associations but may operate only within the context of apolipoproteinE4 [37] risk alleles.

Findings are also inconclusive regarding CSF τ and sleep, with some experimental studies in normals showing no effects of sleep deprivation/fragmentation [28, 29, 35] and several descriptive studies reporting associations between poor sleep and higher τ values [6, 30]. An observational study in a population with no or only very mild cognitive impairment demonstrated that a lower spectral power in slow-wave (1–4.5 Hz) activity was related to a widespread higher τ activity on PET across the amygdala and various cortical regions, as well as higher t-Tau and p-Tau$_{181}$ values in CSF (though not Aβ42) [38]. Additionally, mouse models have recently implicated τ deposition as a consequence of sleep loss [39].

Although it has been investigated in fewer studies, a similar lack of consensus occurs for hypocretin, where some reports have suggested higher CSF levels associated with poor nocturnal sleep in AD measured both subjectively [7] and polysomnographically [6], findings not reported by others [9, 23, 40]. One study reported that lower, rather than higher, hypocretin related to increased daytime napping, as assessed actigraphically [40], and total sleep deprivation had no effect on hypocretin in normal subjects [29]. Taken together, this literature shows a lack of uniformity between various measures of sleep disturbances and AD biomarkers or hypocretin, findings that likely vary depending on the biomarker under evaluation, the population studied, and how sleep was measured.

We found few differences in sleep-related symptoms across diagnoses, and perhaps most surprising was their lack of differentiation of AD and DLB. An analysis of

nearly 4,600 patients on the single NPI sleep item showed that DLB patients were reported by caregivers to experience disturbed sleep more often, and earlier in the disease course, compared to AD patients [41]. In the current much smaller sample, we found that the DLB patients reported more severe daytime sleepiness than all of the other groups, compatible with the sleepiness ascribed to the condition via diagnostic criteria [42]. Additionally, nocturia, both a cause and an effect of poor sleep [43], was more common in DLB and is compatible with both worse nighttime sleep and daytime sleepiness.

Disturbing dreams accompany many forms of dementia, particularly in cases with prior war exposures leading to PTSD [44]. Perhaps paradoxically, early studies (e.g., [45]) suggested that the lack of dream recall was an early predictor of incipient cognitive decline, and polysomnographic studies indicate that dream recall is less likely among more demented patients when awakened from REM [46]. Seminal polysomnographic studies of unmedicated AD patients have shown graded associations between a greater severity of cognitive impairment and lower amounts of REM (e.g., [47]), findings that may reflect disruption of REM cholinergic systems. These findings have a new impetus in a 12-year follow-up of elderly participants from the Framingham Heart Study, which showed that a 1% decrease in the REM percentage increased the incident dementia risk by 9% [48]. We did not document altered REM sleep here, but we noted associations between a biochemical marker related to REM sleep regulation and the frequency of adverse dream experiences. This could not be accounted for by cholinesterase inhibitors despite the fact that this medication class is often associated with increased REM [49] and despite reports of increased and distressing dream experiences in both case reports [50] and randomized clinical trials [51]. Insofar as we know, our data are the first to suggest that relatively low hypocretin levels might represent a transdiagnostic marker of dreaming across different types of dementia. Several small-scale studies (i.e., 15 or fewer patients) have reported reduced CSF hypocretin in relation to poor-quality sleep or increased daytime sleepiness in AD [40] or FTD [52], and one reported that increased hypocretin corresponded with REM without atonia [53] but none reported on abnormal dream experiences among those patients. In 26 MCI patients, Liguori et al. [7] reported higher, rather than lower, CSF hypocretin levels in relation to REM.

Despite novel findings, our study has clear limitations, including reliance on patient and/or caregiver reports about sleep rather than more objective measures. Also, our analyses did not adjust for multiple testing. We did not control for time of day of CSF collection, though the circadian amplitude of CSF hypocretin is small (11.5 pg/mL) and not different between those with and those without AD [12]. Dementia severity, dementia duration, and presence of an REM sleep behavior disorder might impact these findings and should be evaluated in future studies. We acknowledge that our reported associations between hypocretin and abnormal dreaming constituted relatively small effects, though they are compatible with the magnitude of effects seen in other studies involving subjective sleep measures in relation to AD biomarkers (e.g., [30]). Furthermore, our sample size did not allow a detailed assessment of these effects within each diagnosis. Within these interpretative constraints, however, these data imply that vivid and troubling dreams experienced by at least some dementia patients may have their origin not in pharmacology but rather in dysregulation of a neuropeptide controlling REM sleep.

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Statement of Ethics

This work was approved by the Emory University Institutional Review Board and all of the participants (and legal representatives, when appropriate) provided written informed consent.

Disclosure Statement

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Author Contributions

L.M.T., D.L.B., and W.T.H.: conception/design of this work. L.M.T. and D.L.B. drafting of this work. All authors: acquisition/analysis/interpretation of data, critical revision of this work for important intellectual content, final approval of the version to be published, and accountability for this work.

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