Orexinergic System Dysregulation, Sleep Impairment, and Cognitive Decline in Alzheimer Disease

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IMPORTANCE Nocturnal sleep disruption develops in Alzheimer disease (AD) owing to the derangement of the sleep-wake cycle regulation pathways. Orexin contributes to the regulation of the sleep-wake cycle by increasing arousal levels and maintaining wakefulness.

OBJECTIVES To study cerebrospinal fluid levels of orexin in patients with AD, to evaluate the relationship of orexin cerebrospinal fluid levels with the degree of dementia and the cerebrospinal fluid AD biomarkers (tau proteins and β-amyloid 1-42), and to analyze potentially related sleep architecture changes measured by polysomnography.

DESIGN, SETTING, AND PARTICIPANTS We conducted a case-control study from August 1, 2012, through May 31, 2013. We included 48 drug-naive AD patients referred to the Neurological Clinic of the University Hospital of Rome Tor Vergata. Based on the Mini-Mental State Examination score, 21 patients were included in mild AD group (score, ≥21), whereas 27 were included in the moderate to severe AD group (score, <21). The control group consisted of 29 nondemented participants of similar age and sex.

EXPOSURE Laboratory assessment of cerebrospinal fluid levels of orexin, tau proteins, and β-amyloid 1-42 and polysomnographic assessment of sleep variables.

MAIN OUTCOMES AND MEASURES Levels of orexin, tau proteins, and β-amyloid 1-42; macrostructural variables of nocturnal sleep (total sleep time, sleep efficiency, sleep onset and rapid eye movement [REM] sleep latencies, non-REM and REM sleep stages, and wakefulness after sleep onset); and Mini-Mental State Examination scores.

RESULTS Patients with moderate to severe AD presented with higher mean (SD) orexin levels compared with controls (154.36 [28.16] vs 131.03 [26.55]; P < .01) and with more impaired nocturnal sleep with respect to controls and patients with mild AD. On the other hand, in the global AD group, orexin levels were positively correlated with total tau protein levels (r = 0.32; P = .03) and strictly related to sleep impairment. Finally, cognitive impairment, as measured by the Mini-Mental State Examination, was correlated with sleep structure deterioration.

CONCLUSIONS AND RELEVANCE Our results demonstrate that, in AD, increased cerebrospinal fluid orexin levels are related to a parallel sleep deterioration, which appears to be associated with cognitive decline. Therefore, the orexinergic system seems to be dysregulated in AD, and its output and function appear to be overexpressed along the progression of the neurodegenerative process. This overexpression may result from an imbalance of the neurotransmitter networks regulating the wake-sleep cycle toward the orexinergic system promoting wakefulness.
Orexinergic Dysregulation in Alzheimer Disease

Methods

Patients and Study Design

Participants provided their written informed consent to the study, which was approved by the Independent Ethical Committee of the University Hospital of Rome Tor Vergata. We included in our study consecutive drug-naive AD patients referred to the Neurological Clinic of the University Hospital of Rome Tor Vergata who met the criteria for AD diagnosis according to the recently proposed version of the diagnostic guidelines for AD.1 All patients underwent a diagnostic and experimental study protocol, including history, physical and neurological examinations, laboratory tests, a standard neuropsychological evaluation, electroencephalography, polysomnography (PSG), magnetic resonance imaging of the brain, and lumbar puncture for CSF analysis.

We divided the AD patients into the following 2 subgroups on the basis of the assessed Mini-Mental State Examination (MMSE) profile: mild AD (MMSE score, ≥21) and moderate to severe AD (MMSE score, <21).16-19 The control group consisted of nondemented inpatients who underwent clinical neurological investigation, magnetic resonance imaging of the brain, and lumbar puncture for diagnostic purposes. In particular, controls were inpatients admitted for suspected subarachnoid hemorrhage or chronic polyneuropathy, which were ruled out after the diagnostic investigation. The subset of controls with suspected polyneuropathy also underwent a full nocturnal PSG study.

Patients and controls were required to fulfill the following entry criteria: no additional neurological or psychiatric disease, no intake of drugs active in the central nervous system, and no use of caffeine, tobacco, and/or alcohol at the time of the sleep laboratory investigation. Exclusion criteria for patients and controls were neoplastic or thyroid illness; diagnosis of primary sleep disorders or other conditions interfering with sleep quality, such as symptomatic obstructive pulmonary disease and uncontrolled seizures; and abnormal white blood cell count (>4/μL; to convert to 10^9 per liter, multiply by 0.001) at the CSF sample analysis.

Polysomnography

Patients with AD and controls underwent 2 consecutive video-PSG studies to evaluate their nocturnal sleep (SOMNOScreen; SOMNOmedics GmbH). The signal was stored on a flash card using a common mean reference and a time constant of 0.3 seconds. Electrodes were positioned according to the International 10-20 System.20 The montage consisted of 2 oculographic channels, 3 electromyographic channels (mental and anterior tibialis muscles), and 8 electroencephalographic channels (F4, C4, O2, A2, F3, C3, O1, and A1). Cardiorespiratory variables were assessed by recording oronasal flow, thoracic and abdominal movements (plethysmography), pulse oximetry, and electrocardiography. Patients and their caregivers were also instructed to maintain the usual sleep schedule and report it in a sleep diary during the week preceding the evaluation. The first night-sleep study was considered an adaptation period. Sleep analysis was performed at the second PSG monitoring according to standard criteria.21 The following standard variables were computed: time in bed (time spent in bed between lights off and lights on), sleep onset latency (the interval between lights off and the first sleep epoch), total sleep time (the actual sleep time without sleep onset latency and awakenings), sleep efficiency (the ratio of total sleep time to time in bed), REM sleep latency (the interval between sleep onset and the first epoch of REM), stage 1 of non-REM sleep (N1), stage 2 of non-REM sleep (N2), stage 3 of non-REM sleep (N3), REM sleep, and wakefulness after sleep onset (WASO). Sleep stage percentages were calculated during the total sleep time. The PSG scorers (C.L., S.Z., and F.P.) identified apnea/hypopnea events based on the international standard criteria of the American Academy of Sleep Medicine.21 Leg movements were scored according to standard criteria.21 Patients with obstructive sleep apnea (apnea-hypopnea index, >5/h) and a periodic leg movement index greater than 15/h at PSG recording were excluded.
CSF Collection and Analysis
All CSF samples were obtained by lumbar puncture performed in the decubitus position between 8 and 9 AM (range, 60-90 minutes from rise time) using an atraumatic needle. We performed lumbar puncture the day after the second PSG recording. Blood specimens were also obtained at the time of the lumbar puncture procedure. We collected CSF samples in polypropylene tubes using standard sterile techniques; the samples were centrifuged immediately after collection to eliminate cells and cellular debris and immediately frozen at −80°C until the time of analysis. Participants had no signs of structural sleep apnea, 5 had an abnormal white blood cell count according to previously published standard procedures using commercially available sandwich enzyme-linked immunosorbent assays (Innotest β-Amyloid 1-42, Innotest Phosphorylated T-tau and Innotest Phospho-T-tau 181 [Innogenetics] and Orexin A/Hypocretin-1 EIA Kit [Phoenix Pharmaceuticals, Inc]).

Statistical Analysis
For the statistical analysis, we used commercially available software (Statistica 10.0 program; Statsoft Inc). Because the Kolmogorov-Smirnov test showed normal distribution of CSF data, parametric tests were used throughout the analysis. We used the independent t test to compare AD biomarkers and orexin levels between the AD global sample and controls and between female and male AD patients. The Mann-Whitney test was used to compare sleep diary and PSG data between the AD and control groups. The 1-way analysis of variance was used to compare CSF orexin results and PSG data between more than 2 groups (patients with mild vs moderate to severe AD vs controls). The post hoc analysis was performed using the Tukey test for honestly significant difference.

In the global AD group, correlations among all the CSF data, PSG variables, and MMSE scores were performed separately using the nonparametric Spearman rank correlation test. We performed an additional multiple regression analysis. The significance level was set at P < .05 for all statistical analyses.

Results
Demographic and Clinical Data of Patients and Controls
Seventy-two consecutive eligible AD patients were enrolled in the study from August 1, 2012, through May 31, 2013. Twenty-four patients were excluded because 15 presented with obstructive sleep apnea, 5 had an abnormal white blood cell count at CSF analysis, and 4 showed a pathologic periodic leg movement index. Therefore, 48 AD patients completed the study. Using the MMSE profile, 21 patients were included in the mild AD group and 27 patients were included in the moderate to severe AD group. The control group consisted of 29 nonmedicated participants of similar age and sex. Demographic and clinical features of the patients and controls are summarized in Table 1.

CSF Data
As expected, AD patients showed significantly greater mean levels of t-tau and p-tau proteins in their CSF with respect to controls, whereas CSF levels of Aβ1-42 were significantly lower in the global AD group compared with the control group (Table 1). On the other hand, when we compared CSF AD biomarkers, we did not find statistical differences between patients with mild and moderate to severe AD (Table 1).

When we compared CSF orexin levels, we did not find significant differences between AD patients and controls (Table 1). However, patients with moderate to severe AD showed significantly higher CSF orexin levels with respect to controls, whereas CSF orexin levels did not differ statistically between patients with mild and moderate to severe AD or between patients with mild AD and controls (Table 1). Finally, we found no differences in mean (SD) CSF orexin levels between female (148.88 [35.20] pg/mL) and male (145.40 [26.16] pg/mL) AD patients.

Sleep Data and PSG Variables
When we analyzed sleep diaries, we found earlier mean bedtimes for the AD global sample (10:15 PM [SD, 1 h 23 min]; range,

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**Table 1. Demographic, Clinical, and CSF Data of AD Patient Groups and Controls**

<table>
<thead>
<tr>
<th>Demographic and Clinical Data</th>
<th>AD Group</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Global (n = 48)</td>
<td>Mild (n = 21)</td>
</tr>
<tr>
<td>Age, y</td>
<td>70.5 (7.6)</td>
<td>71.7 (6.3)</td>
</tr>
<tr>
<td>Sex, No. of participants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>9</td>
</tr>
<tr>
<td>MMSE score</td>
<td>19.36 (5.30)</td>
<td>24.53 (1.86)</td>
</tr>
<tr>
<td>Estimated disease duration, y</td>
<td>2.99 (1.84)</td>
<td>2.72 (1.40)</td>
</tr>
<tr>
<td>CSF data, pg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orexin</td>
<td>147.07 (30.54)</td>
<td>137.69 (31.56)</td>
</tr>
<tr>
<td>Total tau protein</td>
<td>670.33 (273.7)</td>
<td>607.14 (250.15)</td>
</tr>
<tr>
<td>Phosphorylated tau protein</td>
<td>96.60 (41.32)</td>
<td>84.95 (36.34)</td>
</tr>
<tr>
<td>β-Amyloid 1-42</td>
<td>323.46 (215.11)</td>
<td>355.14 (273.34)</td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; NA, not applicable.

* Unless otherwise specified, data are expressed as mean (SD).
* P < .01, moderate to severe AD vs control groups.
* P < .001, global AD vs control groups.
* P < .001, mild AD vs control groups.
* P < .001, moderate to severe AD vs control groups.
8:00-12:00 PM [P = .02]) and the moderate to severe AD subgroup (9:45 PM [SD, 1 h 31 min]; range, 8:00-11:30 PM [P < .01]) with respect to controls (11:30 PM [SD, 58 min]; range, 10:00-12:00 PM), whereas the mild AD subgroup (10:45 PM [SD, 1 h 36 min]; range, 8:00-12:00 PM [P > .05]) did not show a significant difference in bedtimes compared with controls. Moreover, patients with moderate to severe AD showed earlier bedtimes compared with those with mild AD (P = .04). On the other hand, we did not observe significant differences (P > .05) in mean rise times among the global AD (7:10 AM [SD, 56 min]; range, 6:30-8:00 AM), mild AD (6:55 AM [SD, 54 min]; range, 6:30-8:00 AM), moderate to severe AD (7:15 AM [SD, 55 min]; range, 6:30-8:00 AM), and control (7:00 AM [SD, 47 min]; range, 6:30-8:00 AM) groups.

From the PSG data, we found that AD patients showed reduced sleep efficiency, reduced N3 and REM sleep, longer REM sleep latency, and increased WASO compared with controls. On the other hand, when we considered the AD patient subgroups, we documented that patients with moderate to severe AD presented with significantly higher WASO and reduced sleep efficiency with respect to those patients with mild AD. All data are summarized in Table 2.

### Table 2. PSG Variables of AD Patients and Controls

<table>
<thead>
<tr>
<th>PSG Variable</th>
<th>Mean (SD)</th>
<th>Global (n = 48)</th>
<th>Mild (n = 21)</th>
<th>Moderate to Severe (n = 27)</th>
<th>Controls (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time, min</td>
<td>377.71 (62.25)</td>
<td>380.09 (46.26)</td>
<td>375.87 (73.15)</td>
<td>382.20 (32.95)</td>
<td></td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>71.87 (11.55)*</td>
<td>78.49 (9.16)*</td>
<td>66.73 (10.67)*</td>
<td>85.44 (2.26)</td>
<td></td>
</tr>
<tr>
<td>Sleep latency, min</td>
<td>20.58 (23.61)</td>
<td>15.38 (16.37)</td>
<td>24.63 (27.62)</td>
<td>11.67 (4.58)</td>
<td></td>
</tr>
<tr>
<td>LREM, min</td>
<td>225.52 (133.99)*</td>
<td>181.43 (125.47)</td>
<td>259.81 (132.50)*</td>
<td>101.93 (16.20)</td>
<td></td>
</tr>
<tr>
<td>WASO, min</td>
<td>150.87 (73.26)*</td>
<td>107.67 (51.57)*</td>
<td>184.48 (70.54)*</td>
<td>49.33 (8.46)</td>
<td></td>
</tr>
<tr>
<td>N1, %</td>
<td>34.57 (10.43)*</td>
<td>32.17 (8.53)*</td>
<td>34.44 (11.51)*</td>
<td>15.27 (3.55)</td>
<td></td>
</tr>
<tr>
<td>N2, %</td>
<td>51.73 (9.35)</td>
<td>50.78 (10.07)</td>
<td>52.48 (8.88)</td>
<td>51.60 (4.03)</td>
<td></td>
</tr>
<tr>
<td>N3, %</td>
<td>8.65 (7.23)*</td>
<td>10.73 (8.00)*</td>
<td>7.04 (6.25)*</td>
<td>17.87 (3.19)</td>
<td></td>
</tr>
<tr>
<td>REM sleep, %</td>
<td>5.03 (4.26)*</td>
<td>6.31 (4.35)*</td>
<td>4.04 (3.99)*</td>
<td>15.27 (3.22)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AD, Alzheimer disease; LREM, rapid eye movement (REM) sleep latency; N1, stage 1 of non-REM sleep; N2, stage 2 of non-REM sleep; N3, stage 3 of non-REM sleep; PSG, polysomnography; WASO, wakefulness after sleep onset.

### Correlations Between CSF Orexin and AD Biomarker Levels, MMSE, and PSG Data

The Spearman rank correlation test documented a positive correlation in the global AD group between CSF orexin and t-tau levels (r = 0.32; P = .03). On the other hand, the Spearman rank correlation test showed no correlation between CSF orexin and Aβ1-42 levels in the global AD group (P > .05 and r = −0.20; eFigure in the Supplement).

In moderate to severe AD in particular, a positive correlation was evident between CSF orexin and t-tau (r = 0.64; P < .001) and p-tau (r = 0.56; P = .02) protein levels (Figure 1). We found no correlation for CSF data in mild AD. The Spearman test found no correlation between MMSE scores and CSF levels of orexin, Aβ1-42, and t-tau and p-tau proteins in the whole AD group and in each subgroup.

When we correlated MMSE scores with PSG data in the global AD sample, we documented a correlation between decreased MMSE values and increased REM sleep latency (r = −0.38; P = .008) and WASO (r = −0.61; P < .001) (Figure 2). On the other hand, decreased MMSE scores correlated with decreased sleep efficiency (r = 0.60; P < .001) (Figure 2) and REM sleep (r = 0.3; P = .04). The additional multivariate
Discussion

The main result of our study is the increase of the CSF orexin levels found in AD patients with moderate to severe cognitive decline. This finding, achieved among a large cohort of drug-naive AD patients, suggests that the orexinergic system is involved and dysregulated with the advance and severity of the AD neurodegenerative process. Literature findings concerning CSF or plasma orexin levels in AD are scarce and conflicting, suggesting that the sleep-wake orexinergic-related structures are involved or preserved.13,17-24

In our study, significant differences in orexin levels between the global AD and control groups were not evident. This result is consistent with a few literature reports5,14-16 showing that CSF orexin levels were not decreased in AD samples compared with controls. However, these previous studies considered smaller samples of patients including, in some cases, patients receiving psychotropic medications, which may influence the orexinergic neuronal activity and output.14-16 When we analyzed the results by Schmidt et al,16 a trend in the increase of CSF orexin levels could be appreciated in patients with moderate to severe cognitive impairment (MMSE score, <20).

On the other hand, our results are in contrast to those of a single postmortem study13 reporting decreased orexinergic hypothalamic neurons and orexin levels in the ventricular CSF of AD patients. This discordance may be related to the fact that we performed an in vivo study, whereas samples in the study by Fronczek et al13 were drawn from postmortem brains with very advanced AD. Moreover, we found no differences in CSF orexin levels by sex, which contrasts with previous reports14,16 describing higher CSF orexin levels in female compared with male AD patients. This dissimilarity may be ascribed to the different sex distribution in our study.

The CSF AD biomarkers (Aβ1-42 and t-tau and p-tau proteins) reflect the neuropathologic process of AD.7 In particular, higher CSF t-tau protein levels mark the AD neurodegeneration, higher CSF p-tau protein levels represent the pathologic neurofibrillary tangles of hyperphosphorylated tau, and lower CSF Aβ1-42 levels are considered to reflect impaired Aβ clearance and deposition in the brain tissue.8 Increased t-tau protein levels represent a sign of rapid cognitive decline because they have been associated with faster and more pronounced neuronal degeneration,7 significantly supporting the transition from early to more advanced disease stages.25 In our study, CSF orexin levels were directly correlated with t-tau protein levels in the global AD sample and with t-tau and p-tau protein levels in the group with moderate to severe AD. This result, consistent with recent findings,26 suggests that the dysregulation of the orexinergic system, as expressed by the increased CSF orexin levels, could be related to the faster and more marked tau-mediated neurodegeneration in AD.

regression analysis revealed an association between MMSE scores and sleep efficiency ($\beta = 1.01; P < .001$) as well as REM sleep latency ($\beta = −0.18; P = .01$).

Levels of CSF orexin correlated directly with sleep onset latency ($r = 0.41; P = .004$), N1 ($r = 0.43; P = .002$), and WASO ($r = 0.47; P < .001$). Furthermore, increased CSF orexin levels were correlated with decreased sleep efficiency ($r = −0.38; P = .007$), N3 ($r = −0.32; P = .027$), and REM sleep ($r = −0.31; P = .03$) (Figure 3). The additional multivariate regression analysis revealed the association between CSF orexin levels and sleep onset latency ($\beta = 0.091; P = .03$).

Increased CSF t-tau protein levels correlated with increased N1 ($r = 0.47; P < .001$) and decreased N3 ($r = −0.41; P = .003$). The CSF p-tau protein levels directly correlated with N1 ($r = 0.41; P = .004$). On the other hand, decreased CSF levels of Aβ1-42 were correlated with decreased sleep efficiency ($r = 0.31; P = .03$) and REM sleep ($r = 0.32; P = .03$) and with increased sleep onset latency ($r = −0.32; P = .03$). Using multivariate regression analysis, we found no associations between CSF AD biomarkers and sleep data.
The previously reported association between CSF orexin and Aβ1-42 concentrations, described in animal model studies and in a small sample of AD patients, was not evident in our investigation. This lack of correlation, also reported in other studies, may be owing to a plateau of low Aβ levels reached by our AD patients. In fact, we found no differences in CSF Aβ1-42 levels between mild and moderate to severe AD.

The pathologic features of AD are well known to interfere with the physiological features of sleep. Although sleep disturbances are associated with a more evident cognitive impairment in patients with AD, PSG evidence that disturbed sleep is dependent on disease stage is scarce. In our study, AD patients presented with more compromised nocturnal sleep, which manifested as early bedtime, sleep fragmentation, and poor representation of N3 and REM sleep. Furthermore, sleep impairment was more severe in moderate to severe AD compared with mild AD.

Xie et al recently hypothesized that the restorative function of sleep has a critical role in ensuring the metabolite clearance in brain interstitial fluid via activation of the glymphatic system in a mouse model. In particular, this system seems to increase the rate of Aβ clearance during sleep and prevent the deposition of Aβ plaques. Therefore, the sleep impairment in AD could be considered an additional detrimental factor for pathologic Aβ findings, thus worsening the neurodegeneration of AD.

The association between sleep alterations and dementia is very likely owing to the AD neurodegenerative process and, in particular, the cholinergic depletion typical of the disease. In fact, the impairment of the cholinergic networks in AD, result of the advanced pathologic features of the disease, could be responsible for the sleep disruption and the NREM/REM sleep alterations. In this study, we have documented that the cognitive impairment correlates with sleep structure deterioration. Therefore, sleep is impaired proportionally to the severity of the cognitive dysfunction owing to the progression of the pathologic features of AD.

Orexin physiologically promotes arousal through activation of the wake-active monoaminergic system and the deactivation of the REM-on cholinergic groups. Therefore, orexin neurons show a wake-on and REM-off pattern of firing. In AD, the impairment of the cholinergic pathways may contribute to the derangement of the sleep homeostasis.

Figure 3. Correlations Between Cerebrospinal Fluid (CSF) Orexin Levels and Polysomnographic Data in Patients With Alzheimer Disease

A, Positive correlation of orexin level with wakefulness after sleep onset. B, Negative correlation of orexin level with sleep efficiency. C, Positive correlation of orexin level with sleep onset latency. D, Negative correlation of orexin level with rapid eye movement (REM) sleep. Data points represent individual patients; lines, the linear regression fit across all patients. Spearman rank correlation coefficients are shown.
Furthermore, increased wakefulness during the night is a hallmark of the breakdown in the normal sleep/wake rhythm that occurs in AD. Therefore, the sleep impairment may be caused by the imbalance between the cholinergic and the orexinergic systems, with overexpression of the latter because of the absence of the damaged cholinergic feedback. In fact, in vitro intracellular recordings from identified orexin neurons revealed that they have a depolarized resting membrane potential, leading to spontaneous firing in the absence of injected current or application of neurotransmitter agonists. On the other hand, REM sleep deprivation increases orexin levels in the CSF of rats, potentiating the orexinergic tone. Hence, the raised CSF orexin levels found in AD patients could be linked to reduced REM sleep and increased sleep-onset latency and fragmentation. In particular, this hypothesis seems to be significant because, in our sample of AD patients, increased CF orexin levels were significantly related to decreased sleep efficiency and REM sleep and increased WASO and sleep onset latency. In particular, beyond these simple correlations, our additional multivariate analysis revealed the significant influence of sleep onset latency in determining CSF orexin levels. Hence, we suppose that, in AD, as the neurodegenerative processes affect the cholinergic pathways, they may cause upregulation of the orexinergic system, which is possibly mediated by the lack of deactivation of the wake-on orexinergic neurons.

Animal studies have demonstrated that, after Aβ plaque formation, the sleep-wake cycle deteriorated severely with the marked reduction in sleep efficiency. In a sample of patients with AD ranging from mild to severe, we found that decreased CSF Aβ1-42 levels correlate with sleep deterioration. This finding is consistent with a previous report showing that lower CSF Aβ1-42 levels are associated with poorer sleep efficiency in patients with preclinical AD.

Conclusions

Our study has shown that, in AD, increased CSF orexin levels are linked to a parallel sleep deterioration, which appears to be related to cognitive decline. Hence, our results demonstrate that, in AD, orexinergic output and function seem to be overexpressed with disease progression and severity, possibly owing to an imbalance in the neurotransmitter networks regulating the sleep-wake cycle toward the orexinergic system promoting wakefulness. Finally, we hypothesize that, in the future, orexin receptor antagonists will be used as potential drugs targeting the downregulation of the orexinergic system in the management of sleep disturbances in AD patients.

REFERENCES


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