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Sleep in Alzheimer's Disease: Further Considerations on the Role of Brainstem and Forebrain Cholinergic Populations in Sleep–Wake Mechanisms

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Sleep disturbances are commonly reported in Alzheimer's disease (AD). They include primarily a low percentage of slow-wave sleep (SWS), a high percentage of stage 1 sleep and a high percentage of time spent awake in bed (1–5). However, other anomalies have been observed more specifically for rapid eye movement (REM) sleep. A low percentage of REM sleep has been reported, which worsens with the progression of cognitive dysfunctions (3). A highly variable latency to the first REM sleep period has also been found (1). Several studies have shown a slowing of electroencephalographic activity (EEG) during wakefulness in AD (3,6–9), but more recently, EEG slowing was found to be more prominent in REM sleep than in wakefulness (10–12). That initiation and maintenance of REM sleep depends upon cholinergic networks has been shown in animals (see reference 13 for review) and in humans (see reference 14 for review). Many components of REM sleep are thought to be under the command of executive cholinergic neurons located in the dorsolateral pontine tegmentum (DLPT). Two higher structures are nonetheless important in the cortical activation process, namely the thalamus (13,15,16) and the nucleus basalis of Meynert (NBM) in the basal forebrain (13,15,17). The NBM is the major source of cholinergic innervation to the cerebral cortex (18).

A deficit in the cholinergic system is one of the first and most marked biochemical changes in AD. In particular, a marked reduction in the number of cholinergic neurons in the NBM has been found in AD patients (19). No marked cell loss, however, has been reported in the cholinergic populations of the brainstem in patients with mild AD (20,21), although neurofibrillary tangles have been found (21,22).

The present study aimed to provide further information on nocturnal sleep of patients with AD. The results presented here will be discussed with respect to the role of brainstem and forebrain cholinergic populations in REM sleep for human subjects.

METHODS

Ten patients (mean age: 60.6 years) meeting the NINCDS-ADRDA criteria of probable Alzheimer's disease (23) were studied. All patients underwent a clinical neurological investigation, including a computerized tomographic scan. They had a modified Hachinski ischemia score of 4 or less. Patients were at mild to moderate stages of AD, that is, stages 3 and 4 of the Global Deterioration Scale (24), and had a mean score of 20.6 ± 5.3 on the Mini-Mental State examination (MMSE) (25). Blood analyses revealed no other causes of dementia. Ten volunteers (mean age: 58.3 years; MMSE: 29.3 ± 1.0) served as paired control subjects. The study was approved by the hospital ethics committee.

All subjects were recorded in the sleep laboratory for 2 consecutive nights; only data from the second night were used. In addition to standard sleep parameter analyses (26), amplitude spectral analyses were performed on artifact-free sections from both awake (eyes closed) and REM sleep EEG sections recorded from fronto-central (F3-C3, F4-C4), parieto-occipital (P3-O1, P4-O2) and temporo-temporal (T3-T5, T4-T6) leads. In two AD patients and their controls, temporal leads were not available. An index of EEG slowing was calculated as the ratio of slow frequencies (delta

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TABLE 1. *Sleep architecture in 10 AD patients and 10 controls*

	Controls (mean ± SEM)	AD (mean ± SEM)	p[a]
Total sleep time (minutes)	434.7 ± 13.78	431.0 ± 22.99	ns
Sleep latency (minutes)[b]	19.03 ± 5.75	15.23 ± 4.14	ns
Waking (%)	13.16 ± 1.67	15.95 ± 3.56	ns
Stage 1 (%)	15.23 ± 1.34	20.98 ± 4.06	ns
Stage 2 (%)	59.12 ± 1.98	61.66 ± 3.59	ns
K-complex density[c]	1.46 ± 0.11	0.77 ± 0.11	0.0015
Spindle density[c]	1.43 ± 0.20	0.37 ± 0.11	0.0015
SWS (%)	8.36 ± 2.03	5.10 ± 0.98	ns
REM sleep (%)	17.29 ± 1.00	12.26 ± 1.54	0.049
Number of periods	4.4 ± 0.31	4.3 ± 0.47	ns
Period duration (minutes)[d]	24.75 ± 2.47	17.68 ± 2.02	0.023
Efficiency (%)	73.1 ± 3.74	70.6 ± 5.02	ns
Latency (minutes)	86.0 ± 17.34	92.2 ± 18.27	ns
Density (%)[e]	30.3 ± 4.31	21.9 ± 2.56	ns
Atonia (%)	93.0 ± 2.44	94.9 ± 2.03	ns
Phasic EMG (%)[f]	9.85 ± 1.26	9.05 ± 2.42	ns
EEG slowing index[g]	1.27 ± 0.06	2.43 ± 0.24	0.0002

[a] Mann-Whitney rank sums.
[b] Sleep latency criteria = three consecutive epochs (1 minute) of stage 1 or one epoch of any other sleep stage.
[c] Mean number per minute of stages 2 + 3.
[d] Mean duration of REM periods.
[e] Calculated for REM periods of similar duration in both groups.
[f] Calculated for the same number of REM 2-second epochs in both groups.
[g] (delta + theta)/(alpha + beta).

+ theta) over fast frequencies (alpha + beta). Ratios from the three regions of both hemispheres were pooled to produce a single EEG slowing score.

RESULTS

As shown in Table 1, no differences were found between AD patients and controls for total sleep time, sleep latency, percentage of time spent awake, or percentage of time in any of the stages of NREM sleep. However, AD patients did show a decreased density of K-complexes and of sleep spindles. AD patients also showed a lower percentage of REM sleep and shorter REM sleep periods but did not differ from controls on other REM sleep variables.

The EEG slowing index was significantly greater for AD patients than for controls in both wakefulness (1.23 vs. 0.63; Mann-Whitney $p < 0.002$) and REM sleep (2.43 vs. 1.27; $p < 0.0002$). Moreover, a significant group (AD patients, controls) × state (wakefulness, REM sleep) interaction [$F(1,17) = 21.24$; $p < 0.0003$] indicated that the between-group difference was more pronounced for REM sleep than for wakefulness.

DISCUSSION

The most robust difference observed in our AD patients was the slowing of both waking and REM sleep EEGs. This EEG slowing in AD has been characterized in previous studies to be the result of both an increase in slow-frequency power and a decrease of fast-frequency power (11,12). The more prominent EEG slowing observed in REM sleep in AD patients can be explained by the heightened influence of cholinergic inputs for this state. Many of the noncholinergic inputs that are involved in cortical activation during wakefulness, namely noradrenaline, serotonin and histamine, are "silent" during REM sleep (27–29). Thus, cortical activation during REM sleep is more dependent (than during wakefulness) on the basalo-cortical cholinergic system, the system which is rapidly degenerating in AD. Although this explanation of EEG slowing in AD focuses on the NBM, the importance of the thalamus in EEG activation is not in dispute. Steriade and colleagues (13,30) have demonstrated the primordial role of glutamatergic thalamocortical neurons in EEG desynchronization for both wakefulness and REM sleep. However, because the thalamus does not seem to be significantly affected by AD (31), EEG slowing observed in AD probably reflects degeneration of the NBM. On the other hand, the EEG remained desynchronized in wakefulness and REM sleep compared with NREM sleep; this residual level of desynchronized activity probably reflects the integrity of the glutamatergic thalamocortical system.

The lower REM sleep percentage observed in AD patients could also be attributed to the degeneration of the NBM. The NBM ensures cortical desynchronization not only through direct activation of the neocortex, but also by suppressing the rhythm-generator mechanisms (spindling and slow rhythms) of the reticulo-thalamic system (17). If the NBM is impaired,

the inhibition it usually exerts on the rhythm-generator system might also be weakened, leading to the observed curtailment of REM sleep periods.

Variables related to the initiation of REM sleep (latency, number of REM periods) and to its characteristic features (atonia, EMG phasic activity, REMs) were unaffected in our AD patients. Because these variables are controlled by DLPT cholinergic populations, these negative findings likely reflect the fact that DLPT neurons are spared in early AD (20,21).

There is no simple explanation for the decrease in K-complex and sleep spindle density in our AD patients. On one hand, two studies have also reported a reduction in sleep spindles following lesions of the basal forebrain (32,33), but these lesions extended beyond the NBM to probably also affect noncholinergic NREM sleep-active neurons. On the other hand, because the impaired NBM in AD cannot fully inhibit the nucleus reticularis thalami—the spindle generator—one would expect, on the contrary, the number of sleep spindles to increase. In any case, a similar reduction in the number of K-complexes and sleep spindles has also been reported in other dementing disorders with different neurobiological characteristics (34,35).

Discrepancies in results for NREM sleep variables between previous studies and the present study may be due to the fact that our patients were less impaired than patients in many of these other studies, except the study by Vitiello et al. (4). Consideration of the severity of the disorder is critical because it has been demonstrated that the magnitude of sleep-related changes increases with increasing severity of the illness (3). However, it may also be that the relatively small sample size of the present study was unable to demonstrate more than statistical trends toward decreased SWS, increased stage 1 sleep and increased wakefulness during sleep.

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