The Circadian System in Alzheimer's Disease: Disturbances, Mechanisms, and Opportunities

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Alzheimer's disease (AD) is a devastating neurodegenerative condition associated with severe cognitive and behavioral impairments. Circadian rhythms are recurring cycles that display periods of approximately 24 hours and are driven by an endogenous circadian timekeeping system centered on the suprachiasmatic nucleus of the hypothalamus. We review the compelling evidence that circadian rhythms are significantly disturbed in AD and that such disturbance is of significant clinical importance in terms of behavioral symptoms. We also detail findings from neuropathological studies of brain areas associated with the circadian system in postmortem studies, the use of animal models of AD in the investigation of circadian processes, and the evidence that chronotherapeutic approaches aimed at bolstering weakened circadian rhythms in AD produce beneficial outcomes. We argue that further investigation in such areas is warranted and highlight areas for future research that might prove fruitful in ultimately providing new treatment options for this most serious and intractable of conditions.

Key Words: Alzheimer's disease, chronotherapy, circadian, dementia, SCN, sleep

Disturbances of daily behavioral and sleep patterns are commonly described in neurological and psychiatric disorders (1). In Alzheimer's disease (AD) such behavioral disturbance is a leading reason for institutional care in moderate to severe AD (2). There is considerable evidence that disturbances of sleep-wake cycles are related to alterations in the suprachiasmatic nucleus (SCN), the master circadian pacemaker (3). The SCN is a small nucleus of the anterior hypothalamus located directly dorsal to the optic chiasm (from which it receives direct retinal innervations) that is composed of a neurochemically and functionally heterogenous assembly of neurons (4). Circadian rhythms are generated as an output of the clock gene cycle, produced by a series of interlocking transcriptional feedback/feedforward loops of a panel of clock genes (e.g., *PER1,2, CRY1,2, CLOCK, BMAL1*). Such cycles drive the rhythmic expression of clock-controlled genes, and ultimately such molecular cycles are translated into physiological and behavioral circadian rhythms (3,5). Outside of the SCN there are circadian oscillators throughout the brain and periphery, and the circadian network normally functions as a complex and distributed system that imposes temporal architecture on physiology and behavior (5). There are also circadian rhythms in neurocognitive parameters (6,7) and disruption of circadian rhythms leads to cognitive impairments (8). Circadian dysfunction also impacts negatively on immune, metabolic, and cardiovascular systems (9,10). Such circadian alterations are increasingly being explored with regard to both functional decline during healthy aging and in age-related diseases (11). In this review we examine the evidence with regard to circadian alterations in AD and explore the therapeutic avenues that arise and the opportunities for advancement at the interface between dementia research and chronobiology.

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Functional Studies of Circadian Disruption in AD

Many studies to date have examined the relationship between aging and circadian function, with decreased amplitude but not period of the rhythm as well as alterations in circadian phase being commonly reported findings (12) (see the glossary of chronobiological terminology in Supplement 1). These alterations in circadian parameters are exacerbated in AD, the most apparent deficit being fragmentation of the sleep-wake cycle leading to increased nocturnal awakenings and increased daytime sleep bouts (13). The use of noninvasive actigraphy (usually via a wrist-worn accelerometer) has been beneficial in monitoring rest/activity cycles in dementia patients since the early 1990s (14,15). Later rest/activity cycles of home-dwelling AD patients were examined over one year, and those with mild dementia displayed rhythms not significantly different from those of control subjects, whereas those with moderate dementia displayed fragmentation of the rhythm and decreased amplitude, although these effects were not correlated with the severity of the dementia (16). Van Someren *et al.* (17) reported that rhythms were most fragmented in institutionalized AD patients and that higher levels of daytime activity predicted more coherent rhythms, whereas lower levels of daytime activity predicted rhythm fragmentation. Changes in circadian parameters are not equivalent across different types of dementias; there are differences in the nature and magnitude of rhythm disturbance in AD, frontotemporal dementia, and diffuse Lewy body disease (18). The overall locomotor changes that occur in AD seem to be related to more specific behavioral changes, for example in meal time, which in turn might be linked to poorer nutritional outcomes (19). Further evidence for the importance of circadian rhythms in AD is provided by the finding that higher daytime activity levels and lower nocturnal activity (i.e., consolidated, nonfragmented sleep/wake cycle organization), is strongly associated with increased wellbeing and functional status (20). Results from a large prospective study indicate that changes in circadian activity patterns (decreased

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rhythm amplitude, phase-delays) are significant predictors of subsequent AD or mild cognitive impairment, suggesting that compromised rhythms might be a preclinical phenomenon (21). Another point of interest is that anti-psychotic medication used in the clinical management of AD might impact on circadian rhythms (22), because these medications might impact on the molecular components of the circadian system (23).

General activity is not the only parameter that can be used to assess circadian rhythmicity at the gross level in AD. Skin temperature monitoring demonstrates that proximal but not distal skin temperature is raised in the daytime in AD patients compared with elderly control subjects, with no nocturnal difference in either distal or proximal skin temperature (24). Proximal skin temperature was also positively correlated with daytime sleepiness in both AD patients and healthy control subjects. One explanation for these findings is that alterations in proximal skin temperature in AD are functions of altered circadian clock control of autonomic processes involved in the regulation of skin temperature.

A potential consequence of disrupted circadian rhythms in AD is the manifestation of rhythms in behavioral agitation. Patients affected by AD often develop varying disruptive behavioral symptoms, such as agitation and restlessness, verbal outbursts, wandering, physical threats, and aggression (25). "Sundowning" is the term given to the occurrence of the aforementioned symptoms during the late afternoon or early evening (26,27). The prevalence of sundowning in AD is reported as being between 13% and 66% (28–30). The temporal nature of sundowning is suggestive of a circadian origin: nonlinear analyses of actigraphic data in AD show that higher levels of motor regularity, especially during the night, are associated with aggressive behavior in AD patients (31).

Insight into the nature of the circadian disturbances that occur in AD is provided through the analysis of actigraphic activity data for scale invariance of activity fluctuations, which was reduced in AD patients and most reduced in the oldest, most severely demented patients (32). This is of interest, because scale invariance in activity patterns is found in rodents to be dependent on the SCN (33), and so the changes observed in AD might be taken as indicative of changes occurring in the master clock that are then translated into gross patterns of behavior. This finding is in accordance with the findings from neuropathological studies discussed later.

There are some significant issues that limit the interpretation of functional studies of circadian rhythms in AD. First is the nature of the diagnosis commonly used to select study populations, that of dementia of the probable Alzheimer's type, which cannot be confirmed until postmortem examination (itself not routinely carried out). Given that dementia is a symptom of many other diseases of old age and that postmortem examination might not confirm a diagnosis of AD (e.g., 15% of diagnoses are not confirmed at autopsy [34]), it seems likely that the populations examined in the aforementioned studies represent a heterogeneous population representing both AD and non-AD dementias. Another caveat for actigraphy-based studies is the ease with which rhythms might be masked by environmental factors, such as nursing care, occupational therapies, and a host of societal factors for studies in AD patients in the home setting. Such concerns are not just limited to dementia studies and do not negate the usefulness of actigraphy to gain significant insight into circadian rhythm disturbance in AD, but they do highlight that care needs to be taken in the interpretation of results from such studies. Supplement 1 contains information on neuroendocrine changes in AD.

Postmortem and Neuropathology Studies

Postmortem studies have assessed neuropathological changes within the SCN in both healthy aging and in dementia and neurodegenerative disease (12). Stopa *et al.* (35) evaluated the degenerative changes in the SCN from patients with severe AD and found neuronal loss and tangles, indicating that the SCN is affected by AD, whereas amyloid plaques were only seldom noted in the SCN. Overall SCN volume has been reported to decrease in dementia of the Alzheimer's type (36), and the expression of the neuropeptide vasoactive intestinal polypeptide (VIP) was found to be decreased in the presenile male SCN (37). There is also a loss of rhythmicity of SCN arginine vasopressin (AVP) during aging (38), and in AD this loss of AVP neurons and rhythmicity is accelerated (39,40). Loss of neurotensin-expressing neurons in the SCN of AD patients is also reported along with increased astrocytes (35). Because VIP, AVP, and neurotensin are known to alter SCN neuronal function (41,42), their loss during AD might be of particular functional consequence. Interestingly, there is evidence to suggest that neuropeptide alterations in the SCN occur at early stages of AD and might preface cognitive decline (43). Harper *et al.* (44) also provide evidence that neuropathological progression (as measured by Braak stage) in postmortem AD brains is associated with the severity of circadian abnormalities, suggesting that the circadian rhythm disturbances in AD are directly linked to the central neuropathology of the disease. There is also evidence for neurodegeneration in the SCN in both AD and frontotemporal dementia, as determined by the neuron/glia ratio, and this degeneration correlates to the magnitude of circadian rhythm impairment in core body temperature and activity parameters (45). Loss of SCN neurotensin cells was also associated with dampened activity rhythm amplitude but not with increased fragmentation of the rhythm, although loss of AVP neurons in the dorsomedial SCN was associated with rhythm fragmentation but not dampened amplitude (45). Expression of the MT1 melatonin receptor in the SCN is also markedly decreased in late stage AD (40). Supplement 1 contains an overview of circadian influences on Aβ levels.

Another area that undergoes neurodegeneration in AD and might be important for circadian rhythm disturbance is the cholinergic basal forebrain. Cells of the nucleus basalis project to the SCN (46), there is cholinergic innervations of the SCN (47), and cholinergic agents act in the SCN to modulate circadian rhythms (48). The question should then be posed as to what effect the loss of cholinergic cells in the basal forebrain in AD might have on circadian function. Lesion of the cholinergic projection to the SCN in rats leads to alterations in the phase-shifting effects of light on circadian rhythms (49), although another study in using lesions of the cholinergic medial septum did not find alterations in circadian parameters (50). Differences between these studies might be due to the neuroanatomical locations of the lesion as well as differences in the behavioral paradigms examined. The study of Wisor *et al.* (51) reports that alterations in non–rapid eye movement sleep in the Tg2576 mouse model of AD might be due to alterations in cholinergic transmission. On balance, it seems reasonable to suggest that further studies examining the role of cholinergic depletion in circadian disturbance in AD (e.g., postmortem analysis of acetylcholine fibers in the SCN) are needed (Figure 1).