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Consequences of Circadian Disruption on Neurologic Health

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Abstract

Circadian rhythms have a major role in physiology and behavior. Circadian disruption has negative consequences for physiological homeostasis at molecular, cellular, organ–system and whole-organism levels. The onset of many cerebrovascular insults exhibit circadian temporal trends. Impaired sleep-wake cycle, the most robust output rhythms of the circadian system is significantly affected by neurodegenerative disorders, may precede them by decades, and may also impact their progression. Emerging evidence suggest that circadian disruption may be a risk factor for these neurological disorders. In this review, we discuss the implications of circadian rhythms in brain disorders, with an emphasis on cerebrovascular and neurodegenerative disorders.

Keywords

circadian; sleep; clock genes; cerebrovascular; stroke; Alzheimer’s; Parkinson’s; Huntington’s

Introduction

The relevance of circadian rhythms and timekeeping for human health has been increasingly recognized not only by sleep medicine but also by many other medical specialties. 24 hour diurnal fluctuations in symptom intensity, responsiveness to treatment modalities and survival have been well documented. Tremendous advances in the field of circadian biology over the past several decades provide an opportunity to systematically investigate relationships between diseases, endogenous circadian rhythms, and exogenous influences. Many neurological disorders exhibit fluctuating rhythms of symptoms and responsiveness to therapies. In this review we outline available literature pertinent to circadian function in

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common neurological disorders with an emphasis on cerebrovascular and neurodegenerative disorders.

Circadian Disruption in Cerebrovascular Disease

Stroke is the third leading cause of death in the United States. Sleep disorders are common in stroke victims. Sleep dysfunction has also been repeatedly linked with cardiovascular and cerebrovascular insults and implicated in post-stroke recovery. Although well recognized, the relationship between sleep, circadian disruption and stroke is not fully understood. Sleep and circadian dysfunction may lead to vascular events through direct or indirect mechanisms. Sleep loss, sleep disordered breathing and sleep-related movement disorders, such as restless legs syndrome (RLS) and periodic limb movements disorder (PLMD), may increase the risk of stroke, hypertension and cardiovascular disorders.[1] Sleep loss itself appears to be an independent risk factor for cerebrovascular events, likely due to alterations in the autonomic nervous system and immune homeostasis.[2]

Emerging evidence suggests important effects that circadian homeostasis has on cerebrovascular health. Major cardiovascular parameters such as heart rate (HR), blood pressure (BP), and endothelial function, known to impact wide range of cerebrovascular disorders, have intrinsic circadian properties. The onset of major cerebrovascular disorders frequently exhibits a unique diurnal pattern. Both epidemiological data and animal models' data strongly point to circadian disruption as a risk factor for cerebrovascular disease.

Circadian cardiovascular rhythms

Blood pressure, heart rate and baroreceptor sensitivity demonstrate robust physiological oscillations over a 24-hour period.[3] Normally BP "dips" overnight, increases shortly prior to awakening, and reaches its maximum during mid-morning hours. Individuals with "non-dipping" BP pattern have less than 10% decline/rise in systolic BP and/or diastolic BP during sleep relative to their mean daytime BP levels. Non-dipping BP rhythm is associated with cardiac ventricular hypertrophy, renal pathology, and alterations in the cerebral vasculature.[4] Individuals lacking the normal circadian rhythm of BP are therefore at increased risk for cerebrovascular events, which tend to occur in the early morning hours. Factors contributing to cerebrovascular insult, in particular ischemic events, follow a circadian pattern.

Circadian variation in stroke onset

Diurnal variation in stroke onset has been reported in numerous studies with higher frequency of stroke occurring in the morning.[5] Approximately 55% of all ischemic strokes, 34% of all hemorrhagic strokes, and 50% of all transient ischemic attacks (TIA) occur between 06:00 and 12:00 h.[6] Mortality from stroke remains high in strokes occurring in the morning hours.[7] While stroke exhibit this clustering in the morning, some studies reported a bimodal distribution of stroke onset in hemorrhagic strokes with the second peak being in the afternoon.[8–12] The effects of the recombinant tissue plasminogen activator rt_PA treatment on outcomes have been independent of time of day stroke onset.[13] Majority of investigations related to 24h patterns in stroke are centered on the "time of day" when stroke

occurred, lacking relevant determinants of exogenous influences such as the rest/activity rhythm and other known risk factors.

Pathophysiological factors that may explain diurnal pattern of stroke onset include early morning raise in BP ("morning surge"), increased platelet aggregation and prothrombotic factors as well as blunting of endothelial function in the morning hours. The peak level of circadian sympathetic activity also occurs in the morning, which along with the simultaneous increased activity of the renin-angiotensin-aldosterone activity influences the morning increase in BP and HR. Further, the propensity for REM sleep increase in early morning hours. This stage of sleep is associated with reduced coronary blood flow and increased occurrence of coronary spasm, which contributes to heightened sympathetic activity and rises in BP and HR. Additionally, primary sleep disorders, such as sleep disordered breathing, are yet another culprit, through repetitive intermittent overnight hypoxemia and sympathetic activation. The majority of available studies failed to demonstrate significant demographic and clinical differences between wake-up strokes and those occurring while awake.[5] Available studies have numerous methodological limitations, and better controlled prospective investigations are needed to distinguish between stoke present on awakening and those while awake. This is important as these differences may have potential implications for treatment.

Other circadian rhythms implicated in the pathophysiology of cerebrovascular disease include rhythms of plasma viscosity, blood flow volume, hematocrit, peripheral resistance, and platelets. Platelets numbers and aggregation both have rhythmicity, with peak number of platelets being in the afternoon. Platelet aggregation response to various stimuli tends to peak during the late night or early morning hours. Several factors within the coagulation pathways have its own circadian rhythms. For example, the peak activity of Factor II remains in close correlation with the peak incidence of thromboembolic events.

Aside from circadian rhythms, cerebrovascular events are also linked with periodicities longer than circadian. For example, fibrinolysis has circaseptan (approximately 7-day) rhythm with the lowest amplitude of the rhythm on Monday and the peak between Tuesday and Thursday. This pattern mirrors that of thromoembolic events during the week. Similarly, circannual variations in cardiovascular parameters may impact the pathophysiology of vascular events.[14] Numerous studies reported 7-day, and annual patters in stroke onset. It is important to emphasize that many exogenous stressors impact the occurrence of cerebrovascular events, likely through a complex interactions with endogenous circadian rhythms. These factors may include emotional stress, napping, physical activity, medication schedules etc.

Clock genes and cardiovascular function

Circadian transcription rhythms have been demonstrated in 4–6% of protein coding genes in mouse heart and aorta.[15–17] Similar oscillations persist in endothelial and vascular smooth muscle cells as well as in human cardiomyocites.[18–20] Recent investigations suggest a role of the nuclear receptor PPARγ in BP rhythm regulation, likely through its interactions with Bmal1, a major circadian clock gene. Cry1/2 genes have also been implicated in the development of hypertension.[21,22] Deletion of a core clock gene, Bmal 1 in heart and

endothelium results in arrhythmias and loss of diurnal blood pressure oscillation.[23,24] Internal desynchronization between the central circadian pacemaker and local cardiovascular clocks has been shown to affect cardiac structure and the expression of cardiac clock genes.[25] This internal desynchronization may arise from disruption of physiological sleep-wake cycles. The relationship between molecular regulation of circadian rhythms and the cardiovascular disease is likely bidirectional as cardiac hypertrophy and aortic constriction attenuate expression of several core clock genes throughout cardiovascular system[26,27] Recent investigations have suggested differential susceptibility to neuronal damage from an ischemic insult is dependent on the time of day when the insult occurs.[28] Although the mechanisms that underlie this susceptibility to ischemic damage remains unknown, the role of ERK, a MAPK (mitogen-activated protein kinase) molecule and its neuroprotection against glutamate toxicity on SCN neurons has been recently implicated.[29] Further investigations directed to understanding how circadian biology affects cerebrovascular and cardiovascular disorders on cellular and molecular levels and vice versa are much needed.

Circadian Rhythms in Aging and Neurodegeneration

Aging is associated with changes in the circadian system. Age-related changes in the circadian rhythmicity result in a reduced amplitude and period length of circadian rhythms, an increased intra-daily variability, and a decreased inter-daily stability of a rhythm.[30–36] The timing of the rhythm is disturbed as well, leading to changes in the time relationship of rhythms to each other, known as *internal desynchronization*. This loss of coordination has negative consequences on rest-activity cycles and other physiological and behavioral functions.[37] Numerous studies in humans have demonstrated reduced amplitudes of melatonin rhythms, and phase advance of body temperature and melatonin with ageing.[32,38–40] The circadian profile of cortisol in the elderly demonstrates higher plasma levels at night, which results in an elevated 24-hour mean cortisol level and a reduction in the rhythm amplitude.[40,41] These changes in circadian rythmicity of cortisol secretion have been associated with cognitive impairments, and increased propensity for awakenings with ageing.[42–45] Not all studies, however, demonstrate age related decline in the amplitude of the circadian markers.[46–48] This may be due to several shortcomings, including a small sample size, subject selection criteria, complex medication regimens, and absence of well controlled experimental conditions (i.e., constant routine). Clearly the human data are inadequate and further studies are warranted.

Disrupted rest/activity cycles are common in neurodegenerative disorders. Pathophysiological mechanisms that underlie disruption of circadian rhythmicity in Alzheimer's disease (AD) have been well established. Circadian biology of other neurodegenerative conditions such as Parkinson's (PD) and Huntington disease (HD) has not been systematically studied. In the following paragraphs we summarize current understanding of the function of circadian system in common neurodegenerative disorders, AD, PD and HD.

Circadian rhythms in Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disorder after Alzheimer's disease. Estimated prevalence of PD is over 1 million in the United States.[49,50] The prevalence of PD will likely double over the next few decades.[50] Motor hallmarks of PD, tremor, bradykinesia and rigidity, result from progressive loss of dopaminergic neurons and its projections with the nigro-striatal system. Neuronal cell loss and alteration of neurotransmission outside the basal ganglia loop contribute to development of non-motor manifestations of PD. These include disrupted sleep/wake cycles, autonomic dysfunction, cognitive decline and alterations in mood. Both motor and non-motor manifestations of PD demonstrate strong diurnal oscillations. These clinical observations coupled with current understanding of progression of the neurodegenerative process of PD raise the question is PD affected by chronobiology?

Diurnal rhythms of clinical features in PD

Examples of profound diurnal fluctuations in PD are oscillations in daily motor activity[51–54], autonomic function[55–60], rest-activity behaviors, visual performance, as well as fluctuating responsiveness to dopaminergic treatments for PD. It is plausible to suggest that these fluctuations may be reflective of modifications in circadian system in PD.

Actigraphy studies in PD patients demonstrate lower peak activity levels and lower amplitude of the rest-activity cycle compared to healthy older adults.[53,54,61] Increased levels of physical activity and shorter periods of immobility during the night, result in an almost flat diurnal pattern of motor activity in PD.[62,63] Fragmented pattern of activity with transitions from high to low activity periods leads to less predictable rest-activity rhythm in PD.[61] The circadian pattern of motor symptoms in PD is characterized by worsening of motor functioning in the afternoon and evening, present in both stable and patients with motor fluctuations.[51,64] This daily pattern occurs without relationship to the timing of dopaminergic medications, and may be related to circadian regulation of dopaminergic systems. Furthermore, responsiveness of PD motor symptoms to dopaminergic treatments declines throughout the day, despite the absence of significant changes in levodopa pharmacokinetics.[51,65] Non-motor manifestations of PD, such as neuropsychiatric symptoms of PD, seem to be independently associated with reduced inter-daily stability of the rest-activity cycle.[61]

Autonomic dysfunction is an important and common component of PD. Alterations in the circadian regulation of the autonomic system in have been reported in PD. Blood pressure monitoring in PD demonstrates reversal of circadian rhythm of blood pressure, increased diurnal blood pressure variability, postprandial hypotension, and a high nocturnal blood pressure load.[57,66–68] This is associated with a decrease of daily sympathetic activity with a loss of the circadian heart rate variability and a disappearance of the symphatetic morning peak.[56] Although these abnormalities are more prominent in advanced PD, suppressed 24-hour heart rate variability remains present in untreated patients with early PD as well[69] The prognostic significance and pathophysiological mechanisms leading to suppressed circadian HR variability in PD remain to be determined. While observed abnormalities may certainly arise from the peripheral autonomic ganglia, the influence of central networks such as the

hypothalamus, which remains affected by neurodegenerative process of PD, may be significant.[70–72] Impairments of several sensory systems, such as olfaction and visual functions, are also reported in PD. Similarly to motor performance, circadian fluctuations of visual performance, measured by contrast sensitivity, have been reported in PD.[73]

Impaired sleep and alertness are among the most common non-motor manifestations of PD, and affect up to 90% of PD patients.[74–76]. Sleep maintenance insomnia is the most common sleep disorders in this population. Other sleep disorders include sleep disordered breathing, parasomnias, and periodic limb movements disorder. Although sleep disturbances in PD worsen with progression of the disease, objective measures of sleep quality demonstrate alterations in sleep-wake cycles in de novo PD patients.[77] The etiology of sleep/wake disturbances in PD encompass influence of motor symptoms on sleep and alertness, adverse effects of antiparkinsonian medications and primary neurodegeneration of central sleep regulatory areas.[78–84], the role of circadian dysfunction has just recently started to be a focus of clinical studies in PD.

Markers of circadian system in PD

Several studies examined markers of circadian system in the PD population. Initial studies that focused on the secretion of melatonin reported phase advance of melatonin rhythm.[85,86,87] Plasma cortisol rhythms in these studies did not differ between the PD group and controls. In another study of 12 PD patients, 24-hour mean cortisol production rate was significantly higher and the mean secretory cortisol curve was flatter, leading to significantly reduced diurnal variation in the PD group relative to controls.[88] These studies did not control for exogenous factors that are known to influence endogenous circadian rhythms such as light exposure, timing of meals, ambient temperature and physical activity, and co-existent depression. Recent circadian investigations eliminated these methodological limitations. Using salivary dim light melatonin onset (DLMO) in 29 PD patients and 27 healthy controls, Bolitho et al. demonstrated a prolongation of the phase angle of melatonin rhythm in the medicated PD patients compared to the un-medicated PD group and controls.[89] Two other recent studies did not show alterations in the circadian phase of melatonin secretion.[90,91] Both studies, however reported decreased amplitudes of melatonin secretion. Further, compared with PD patients without excessive daytime sleepiness, patients with excessive sleepiness had significantly lower amplitudes and 24-hour melatonin area under the curve (AUC).

Temperature, perhaps the most valid marker of endogenous circadian system, was also examined in the PD population. While 24-hour rhythms of core body temperature remain similar in PD relative to healthy controls[92], basal body temperature is significantly lower in parkinsonian patients.[93] PD patients with coexistent depression have altered circadian rhythms of rectal temperature and lower amplitudes of core body temperature.[94].

Data on molecular circadian clock mechanisms in PD patients are scarce. Time-related variations in the expression of circadian clock genes have been recently reported in patients with PD.[95] Expression levels of the clock gene Bmal1 but not those of Per1 are dampened in total leukocytes of PD patients and correlate positively with PD severity.[95] Another study

conducted in a cohort of PD patients with early disease reported flattened expression rhythm of a major core clock gene, Bmal1.

Circadian rhythms in Huntington's Disease

Huntington's disease (HD) is a neurodegenerative movement disorder caused by an abnormal trinucleotide CAG expansion in the huntingtin (HTT) gene. HD affects approximately 14–16 individuals per 100,000.[96] This progressive disorder is characterized by abnormal involuntary movements, cognitive decline and behavioral/psychiatric dysfunction. Aside from these cardinal manifestations of the disease, impaired sleep and alertness are also common in the HD population.

Up to 90% of patients with HD endorse sleep problems.[97] In a cohort of 292 HD patients, 87% endorsed sleep problems, especially early morning awakening.[98] Despite these high numbers of HD patients affected by poor sleep, there is relatively small number of studies dedicated to sleep in HD. Available literature points to insomnia and excessive daytime somnolence. Few polysomnography studies reported reduced REM and slow wave sleep, prolonged sleep onset latency, sleep fragmentation, reduced sleep efficiency, and reduced total sleep time. Parasominas and sleep related movement disorders are rarely present in HD. Increased sleep spindle density in HD has also been reported.[99,100] It appears that HD patient may not recognize sleep problems as their reports on sleep instruments do not differ much from healthy controls.

Markers of circadian system in HD

Circadian rhythms in HD have not been systematically studied until recently. This is in part due to challenges related to the implementation of circadian protocols within the HD population effected by motor, cognitive and behavioral deficits as well as by lack of recognition of sleep and circadian dysregulation in this disorder. Circadian disruption in HD has a neuroanatomical correlates, as postmortem studies documented reduced expression of vasoactive intestinal peptide (VIP) and arginine vasopressin (AVP), characteristic peptides in the SCN.[101] Actigraphy studies in HD patients reveal decreased level of daytime activity and increased overnight activity, leading to abnormal night-day activity ratios. Delayed sleep phase and increased REM latency have been reported in HD patients.[102] Phase delay seems to be present in both premanifest HD mutation carriers and HD patients.[97] Later wakeup times correlate with more prominent depressive symptoms, lower functional scores and cognitive performance. Changes in melatonin secretion were also reported.[102] Dim light melatonin onset is quite variable in HD patients compared with controls. Moreover, concentrations of melatonin in serum are significantly decreased in HD patients, with manifest patients showing more significant reductions compared with premanifest HD mutation carriers.[103] Alterations in cortisol and adrenocorticotropic hormone have been found in HD.

Circadian homeostasis in animal models of HD

Very informative observations on circadian function in HD have emerged in recent years from animal models of the disease. The most commonly used HD model in circadian studies

has been transgenic R6/2 mice model. R6/2 mice exhibit profound disruptions of rest-activity cycles that worsen with disease progression.[104] This is coupled with abnormal expression of circadian core clock genes in the SCN and several other brain regions. Of interest is preserved molecular regulation of the SCN during in vitro experiments, which suggests a dysfunction within the circadian circuitry, rather than in the SCN itself.[105] Exciting emerging evidence from a transgenic sheep model of HD support the hypothesis that social factors/networks may influence circadian rest/activity cycles and behaviors in HD; circadian behavior seems to normalize when HD-sheep are kept with the normal sheep flock as opposed to the housing with HD flock only, in which circumstances circadian disruption persists.[106] Internal desynchrony between central and peripheral circadian rhythms may be relevant to HD, as peripheral liver clocks in R6/2 mice seem to be uncoupled from the SCN control.[107] This desynchrony may have negative impact on the metabolic state and energy homeostasis which in turn may impact the biology of HD. Changes in circadian function have also been reported in several other animal HD models such as HD rat, drosophila HD model, R6/1 HD mice and BAC mouse model of HD.[108–110]

Circadian rhythms in Alzheimer's disease

Alzheimer's disease (AD) is the most common form of neurodegenerative dementia and affects one in nine people aged ≥65 years.[111] This disease belongs to tauopathies and its pathological hallmark is the accumulation of amyloid-β (Aβ) and tau proteins. Sleep and circadian disruption are very common in AD, affecting up to 40% of patients with mild to moderate dementia.[112] Disruption of the rest-activity cycles may be predictive of cognitive impairment / dementia. A large epidemiological study demonstrated increased risk of developing AD in the setting of fragmented sleep and others reported associations between impaired cognition and poor sleep quality, low sleep efficiency, and frequent daytime napping.[113–116]

Circadian disruption in AD - pathophysiology

Circadian dysregulation has a major impact on quality of life and represents a major reason for the institutionalization among the AD population.[117] Pathophysiological mechanisms which underlie disruption of circadian rhythmicity in AD have been well established. Neuronal cell loss within the SCN and loss of pineal gland function are the main contributors to disrupted circadian rhythm in the AD population.[118,119] Atrophy of the SCN is associated with reduced numbers of neurons with melatonin receptors and presence of the neurofibrillary tangles.[119,120] Further, neurons that express peptide-defining SCN compartments such as intestinal polypeptide and neurotensin are also depleted in AD.[121,122] These neurochemical and neuropathological changes within the SCN become more prominent with the progression of AD. Lack of zeitgebers necessary for the entrainment of the circadian system and co-existance of primary sleep disorders such as sleep disordered breathing are additional cause of circadian and sleep disruption in PD.

Markers of circadian system in AD

While the changes in circadian markers in AD mimic those observed in aging, the magnitude of these changes is enhanced in AD. Circadian rhythm of temperature shows

phase delayed and dampened amplitude. The age related decline of melatonin is more pronounced in AD relative to healthy peers.[123,39] CSF melatonin levels are reduced in preclinical stages, and they continue to decrease with the progression of AD.[118,124,125] Alterations in amplitude and timing of cortisol and core body temperature are altered in AD as well.[126,127] There is a positive correlation between circadian rhythm disturbances and the degree of dementia in AD.[104,128,129] The amplitude of the rest-activity cycle is low in AD patient and circadian phase becomes progressively delayed throughout the course of the disease.[130] Further, sleep duration is reduced, fragmented and daytime becomes interspersed with frequent napping. Sleep interruption and naps during the daytime alter rest-activity rhythms leading to a reversal of the normal pattern of rest-activity, well documented in actigraphy studies conducted in the AD population.[129,131] Most prominent disruptions in the rest-activity cycles are evident in institutionalized patients with AD.

Sleep and circadian function – AD: bi-directional relationship?

The role of AD-specific neurodegeneration in the genesis of circadian disruption has been well supported in animal and human studies. Emerging literature, however, points to likely bi-directional relationship between AD and circadian dysregulation.[132] Studies that employed animal models of AD including transgenic APP/PS1 mouse model and the PLB1 triple knock-in model have shed additional light onto these associations.[133–135] The sleep-wake states influence amyloid dynamics, and there is well-establish Aβ rhythmicity in CSF.[133,136] Sleep deprivation promotes Aβ deposition into insoluble amyloid plaques, and therefore likely has a negative impact on cognitive decline.[137] Further, poor sleep quality and specifically, reduced slow wave sleep results in neuronal hyperexcitability during sleep, which is yet another mechanism that promotes greater release of Aβ.[138] Similarly, sleep deprivation leads to increased Aβ levels in healthy individuals and to markedly increased Aβ accumulation in AD.[139] Cognitively intact individuals who have evidence of amyloid plaques have worse quality of sleep, sleep efficiency and overnight awakenings compared with healthy controls.[140]

Several circadian-based interventions have been attempted to improve sleep-wake cycles and circadian function in AD. Melatonin seems not be effective at restoring rest-activity cycles in AD, as measured by actigraphy.[135,141] Light therapy may be effective in restoring circadian rest-activity behaviors but also in improving sleep quality in the AD population.[142–144]

Conclusions

Numerous studies have demonstrated the importance of healthy circadian rhythmicity in maintaining neurological homeostasis. Future research on chronobiology of neurologic diseases will involve greater understanding of the role that circadian phenomena play at the cellular and molecular level in the pathogenesis of brain disorders. This will form the foundation for the development of new circadian-based interventions to improve clinical management of brain disorders. For example, with increasing understanding of the importance of circadian rhythmicity for brain health, one important direction will be to focus on the importance of chronopharmacology in neurological disorders. Already considered in

other medical disciplines, time of day needs to be accounted for when considering side effects but also efficacy of pharmacological therapies for neurological disorders. Circadian system has therefore become a novel diagnostics and therapeutic target for neurological disorders.

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Key Points

- Numerous brain diseases demonstrate a clear rhythmicity of symptoms and its outcomes appear to be influenced by the time of day.
- Circadian rhythm dysfunction is common in neurodegenerative disorders such and Alzheimer's, Parkinson's and Huntington's diseases.
- Circadian disruption may be a significant risk factor for cerebrovascular and neurodegenerative disorders.
- The circadian system may be a novel diagnosis and therapeutic target for neurologic diseases.