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‘The clocks that time us’—circadian rhythms in neurodegenerative disorders

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Abstract

Circadian rhythms are physiological and behavioural cycles generated by an endogenous biological clock, the suprachiasmatic nucleus. The circadian system influences the majority of physiological processes, including sleep–wake homeostasis. Impaired sleep and alertness are common symptoms of neurodegenerative disorders, and circadian dysfunction might exacerbate the disease process. The pathophysiology of sleep–wake disturbances in these disorders remains largely unknown, and is presumably multifactorial. Circadian rhythm dysfunction is often observed in patients with Alzheimer disease, in whom it has a major impact on quality of life and represents one of the most important factors leading to institutionalization of patients. Similarly, sleep and circadian problems represent common nonmotor features of Parkinson disease and Huntington disease. Clinical studies and experiments in animal models of neurodegenerative disorders have revealed the progressive nature of circadian dysfunction throughout the course of neurodegeneration, and suggest strategies for the restoration of circadian rhythmicity involving behavioural and pharmacological interventions that target the sleep–wake cycle. In this Review, we discuss the role of the circadian system in the regulation of the sleep–wake cycle, and outline the implications of disrupted circadian timekeeping in neurodegenerative diseases.

Introduction

Circadian rhythms—physiological and behavioural cycles with a periodicity of approximately 24 h—are generated by an endogenous biological clock, the suprachiasmatic nucleus (SCN). In synchrony with the solar time, the circadian system dictates the 24 h rhythmicity in rest–activity behaviour, feeding, body temperature, hormonal levels and many other biological processes of the organism. Any disruption of this system can,

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therefore, negatively affect sleep quality, alertness, cognitive performance, motor control, mental health and metabolism.¹ Many of these functions become impaired in neurodegenerative disorders such as Alzheimer disease (AD), Parkinson disease (PD) and Huntington disease (HD), in which several brain areas—including the nuclei involved in circadian and sleep regulation—are affected by neurodegenerative processes. It is not surprising, therefore, that these disorders often entail progressive breakdown of the normal cycles of rest–activity, sleep and alertness; this disruption of circadian rhythms not only contributes to morbidity and poor quality of life, but could also be involved in driving the disease process itself.

In this Review, we provide a brief overview of the circadian system, and a comprehensive summary of the current understanding of the function of the circadian system in three common neurodegenerative disorders: AD, PD, and HD.

Human circadian system

Circadian timekeeping is orchestrated by sophisticated molecular loops. The circadian timing system has three distinct components: a pacemaker (SCN), afferent pathways for light and other stimuli that synchronize the pacemaker to the environment, and efferent output rhythms that are regulated by the SCN (Figure 1).

The SCN represents the core of the circadian system, and contains approximately 10,000 neurons in mice, and about 50,000 neurons in humans.^{2,3} The SCN is the main clock of the circadian system, and is composed of ‘core’ and ‘shell’ subnuclei. Both subnuclei have distinct neurochemical properties.⁴ γ -Aminobutyric acid (GABA) is the main neurotransmitter in nearly all neurons of the SCN; neurons that secrete vasoactive intestinal polypeptide are preferentially distributed in the SCN core, and neurons that secrete arginine vasopressin are located mostly in the SCN shell.

The main afferent pathways emerge from the melanopsin-containing retinal ganglion cells and reach the SCN directly via the retinohypothalamic tract, or indirectly via retinogeniculate pathways.⁵ The SCN also receives nonphotic information from the raphe nuclei, basal forebrain, pons, medulla and posterior hypothalamus. The main efferents project to the sub-paraventricular zone and paraventricular nucleus of the hypothalamus, as well as the dorsomedial hypothalamus, thalamus, preoptic and retrochiasmatic areas, stria terminalis, lateral septum, and intergeniculate nucleus. In addition, the SCN communicates using humoral signals such as transforming growth factor α , cardiotrophin-like cytokine factor 1, and prokineticin receptor 2.

Direct and indirect connections of the SCN with the autonomic nervous system regulate melatonin synthesis and corticosteroid secretion. These hormonal rhythms are well-accepted markers of endogenous rhythmicity. Circadian regulation of the autonomic nervous system has an important role in the regulation of peripheral tissues.⁶

Circadian rhythms are regulated by a core set of clock genes (Figure 2), including three *PER* genes (*PER1*, *PER2* and *PER3*), *CLOCK*, *ARNTL* (also known as *BMAL1*), and two plant cryptochrome gene homologues (*CRY1* and *CRY2*). These genes control a substantial

proportion of the genome: approximately 10% of all expressed genes estimated to be regulated by the clock genes. Furthermore, almost all peripheral tissues, as well as brain regions outside the SCN, contain autonomous circadian clocks. These clocks are influenced by their own distinct circadian synchronizers, but are probably synchronized by SCN-mediated messages, or by a direct input from the SCN.

Circadian dysfunction in AD

AD is clinically characterized by a slowly progressive cognitive decline, with predominant dysfunction in anterograde memory, along with aphasia, apraxia and executive dysfunction. The disease is pathologically defined by the accumulation of amyloid- β (A β) peptides in extracellular senile plaques, and of tau proteins in intracellular neurofibrillary tangles.^{7,8} These changes lead to neuronal death, spreading from the entorhinal cortex to the hippocampus and surrounding areas and eventually to the neocortex.⁹ Circadian rhythm dysfunction is common in patients with AD, and has a major impact on quality of life; it is also one of the most important factors leading to institutionalization of individuals with AD.^{10,11}

Functional indicators of circadian disruption

The circadian disturbances seen in AD are comparable to the ones seen with normal ageing, but are much more pronounced and severe. Sleep is often highly fragmented, with frequent awakenings. A phase delay of the nocturnal sleep period is a typical indicator of circadian rhythm disturbance in AD, and these changes increase with disease duration and progression,¹² often eventually leading to a virtual reversal of the day–night sleep pattern.

Alterations in the periodic changes in the core body temperature have also been described as an indicator of circadian dysfunction in AD.^{13,14} To some extent, these alterations, such as dampening of the amplitude in the 24 h body temperature rhythm, are also seen in normal ageing; however, phase delay, which can be observed in AD, is not seen in normal ageing.¹⁴ A recent study has shown an increase in distal skin temperature during the day in patients with AD, possibly as a result of altered circadian autonomic control.¹⁵

Important information on changes in circadian activity has been obtained by wrist-worn actigraphy devices that enable monitoring of rest–activity patterns.^{13,16,17} Patients with AD are more active during the night than are healthy controls, which is in line with the clinical picture of fragmented sleep. Changes in rest–activity patterns correlate with the severity of the dementia; in addition, the amplitude of the daily variation in the activity cycle was shown to be diminished in AD. A prospective study in over 1,200 participants demonstrated that these altered activity patterns could predict the development of mild cognitive impairment and/or AD,¹⁸ suggesting that impaired circadian rhythm is a preclinical finding, and might even contribute to the development of dementia. An actigraphy study in home-dwelling patients with early AD showed that whereas participants with mild dementia had activity patterns comparable to healthy controls, participants with moderate dementia showed a substantially disrupted rest–activity cycle.¹⁹ The most fragmented rhythms were found in institutionalized patients, and within this group, circadian rhythm fragmentation was associated with decreased levels of daytime activity.¹⁷

Activity patterns in humans display a temporal organization with so-called scale invariance, meaning that the statistical properties of fluctuations remain similar over different timescales. Such scale invariance was subsequently demonstrated in rats, and was shown to be critically dependent on the SCN.²⁰ In healthy older adults, scale-invariant correlations in activity rhythms decline with age.²¹ The greatest reduction in scale invariance—similar to that seen in experimental animal models with SCN lesions—has been found in patients with late-stage AD.

Neuroendocrine and neuropathological markers

The dynamics of melatonin secretion in AD have been studied extensively. Reductions in total melatonin levels are more profound in AD than in normally ageing individuals.^{22–24} In a postmortem study, a marked decrease in cerebrospinal fluid melatonin levels was found in patients with AD;²⁵ furthermore, the rhythmicity in melatonin secretion disappeared at the early—possibly already pre-clinical—stage of the illness,^{26,27} and the pattern became very irregular.²⁸

Postmortem studies have demonstrated a region-specific reduction in histidine decarboxylase mRNA levels in the tuberomammillary nucleus of patients with AD,²⁹ and diurnal expression of this histamine production rate-limiting enzyme was found to be reduced in neurodegenerative disease.³⁰

Several lines of research indicate the SCN is directly affected by the pathophysiological processes that underlie AD. Atrophy of the SCN, involving both volume reduction and decreased total cell count, has been demonstrated.² The number of neurons in the SCN that express melatonin receptor type MT1 decreases in late-stage AD, but not in the earlier disease stages.³¹ Besides loss of neurons, neurofibrillary tangles were observed in SCN neurons in patients with severe AD, even though amyloid plaques were scarce in this region.³² Within the SCN, neurons that express vasoactive intestinal polypeptide (VIP), arginine vasopressin (AVP) or neurotensin have been shown to be depleted in AD.^{32–35} Consequently, AVP levels are strikingly lower in AD, and vasopressin mRNA levels are already decreased in the preclinical stage of AD—these findings are thought to be related to the disappearance of the normal diurnal rhythm.³⁴ Importantly, progression of AD neuropathology correlates with increased circadian dysfunction, indicating a functional link between the two.¹²

Chronogenetics

The ‘chronogenetics’ of AD is complex, and our understanding of it is still in its infancy. The genetic underpinnings of circadian system disruption in AD are discussed in more detail elsewhere.³⁶ Although AD pathology seems to affect the pineal gland only to a limited degree,³⁷ melatonin secretion is disrupted and the diurnal pattern in the expression of the clock genes *ARNTL*, *PER1* and *CRY1* is lost in the pineal gland of patients with AD.³⁸ The periodic fluctuations in the expression of several clock genes are preserved in brain regions outside the SCN in patients with AD,³⁹ but abnormalities have been found in both the phase of the clock gene rhythms and the phase relationships between brain regions. These alterations reflect the disruption of the ‘master control’ by the SCN.

Circadian dysfunction in animal models

Precise assessment of circadian parameters (such as circadian period length) in patients with AD is virtually impossible due to difficulties in applying experimental designs such as constant routine studies in this population. Animal models of AD are useful, therefore, to disentangle the mechanisms responsible for circadian dysfunction.

The triple-transgenic (3xTg) mouse model contains three mutations that have been associated with AD in humans (*APP* LysMet670–671AspLeu, *MAPT* Pro301Leu and *PSEN1* Met146Val). In line with postmortem findings in patients with AD, the 3xTg mouse model exhibits decreased numbers of AVP and VIP neurons in the SCN.⁴⁰ In addition, circadian patterns of locomotor activity are altered: nocturnal activity is decreased and daytime activity is increased, and the mice have shorter free-running periods (circadian rhythms not entrained to external time cues). These alterations were observed even before the onset of AD pathology.⁴⁰ The 3xTg mice also showed age-dependent changes in core body temperature rhythms (phase advance and increased mean body temperatures) similar to those seen in healthy older adults.⁴¹ Mice that were transgenic only for human *APP* (Tg2576) showed no changes in circadian activity rhythms;⁴² however, marked extension of the free running period was seen, although normal entrainment by light remained possible.⁴³ A mouse model with gross overexpression of human *APP* (TgCRND8), considered to be a model for ‘aggressive amyloidosis’ with widespread plaque formation, exhibited disorganization of diurnal activity even before the emergence of AD pathology.⁴⁴

Circadian dysfunction and AD pathology

So far, we have discussed circadian disruption as a consequence of AD; however, increasing evidence suggests that circadian and/or sleep dysfunction can aggravate AD pathology, indicating a reciprocal relationship between the two. Evidence that the sleep–wake cycle influences amyloid dynamics,⁴⁵ and the possible neuroprotective effects of melatonin, one of the most important circadian regulators, support this hypothesis.⁴⁶

The bidirectional interaction between sleep and AD pathology has been discussed in detail elsewhere.⁴⁷ Mouse experiments showing that sleep deprivation resulted in a marked increase in A β accumulation led to the exciting hypothesis that disrupted sleep could be a causal contributor to the development of AD.⁴⁸ In 2013, sleep was shown to contribute to the clearance of metabolites such as A β from the brain in mice.⁴⁹ More recently, sleep deprivation has been shown to increase A β levels in healthy humans.⁵⁰ These experimental data are backed by several epidemiological studies showing that sleep restriction increases the risk of cognitive impairment.⁴⁷

Several *in vitro* and animal model studies have assessed the potential antioxidant, neuroprotective and anti-amyloidogenic effects of melatonin. These studies have been extensively reviewed recently.^{23,24} Melatonin inhibits the formation of β -sheets and amyloid fibrils,⁵¹ and analysis of mouse brain extracts revealed that treatment with melatonin leads to a modest reduction in cortical APP and A β levels.⁵² Treating Tg2576 mice with melatonin at an early age reduced the expected age-related increase in A β concentrations and, more importantly, increased survival.⁵³

Treatment of circadian dysfunction in AD

A number of double-blind controlled trials and several open-label studies have shown that melatonin can improve sleep quality and reduce sundowning.^{54–57} However, a large double-blind, randomized, placebo-controlled trial in 157 patients with AD failed to show a beneficial effect of melatonin on sleep patterns measured by actigraphy.⁵⁸ Another recent study also found no effects of melatonin on agitation, sleep or circadian rhythms in AD.⁵⁹ These negative findings are in line with an earlier meta-analysis, which found no significant effects of melatonin on cognitive impairment.⁶⁰

Several controlled trials have shown that bright light therapy can improve sleep quality and restore diurnal activity rhythms in patients with dementia.^{61–64} In two other studies, light therapy was found to stabilize diurnal activity rhythms without direct effects on sleep quality.^{65,66}

Circadian dysfunction in PD

PD is the second most common neurodegenerative disorder after AD.^{67,68} The cardinal features of PD result from degeneration of dopaminergic neurons within the substantia nigra, and include tremor, bradykinesia, rigidity, and gait impairment. Other neurotransmitter systems are also affected, and are responsible for numerous nonmotor manifestations of PD.

A growing body of evidence suggests alterations of the circadian system in PD.^{69,70} Dopamine is a neurotransmitter of major importance at several levels of the circadian system, and its metabolism and signalling activity are strongly influenced by the circadian clock, as reviewed elsewhere.⁷¹ Impaired circadian function in PD is implicated not only in dysregulation of the sleep–wake cycle, but also in autonomic, cognitive, psychiatric and motor manifestations of the disease.

Diurnal clinical fluctuations

Numerous studies have reported that the behaviours, symptoms and signs associated with PD, such as disruptions in motor activity,^{72–75} autonomic function,^{76–78} sleep–wake cycles^{79–81} and visual performance,⁸² as well as responsiveness to dopaminergic treatments,^{72,83} show diurnal fluctuation. These observations suggest circadian influences on the expression of clinical features of PD.

Fluctuations of motor symptoms in PD are very common. Actigraphy studies demonstrate lower peak activity level and lower amplitude of the rest–activity cycle in patients in PD than in healthy older adults.^{80,81} Increased physical activity and shorter periods of immobility during the night result in an almost flat diurnal pattern of motor activity in PD.⁸⁴ Patients with PD also have a more fragmented pattern of activity, with transitions from high-activity to low-activity periods, leading to less-predictable rest–activity rhythms than are seen in healthy older people.⁸⁵ In both stable patients with PD and those with ‘wearing off’ phenomena, motor symptoms tend to be more prominent in the afternoon and evening.^{72,83} This daily pattern seems to be independent of the timing of dopaminergic medications, and could be related to circadian regulation of dopaminergic systems. In support of this notion,

the responsiveness of PD motor symptoms to dopaminergic treatments declines throughout the day, despite the absence of significant changes in levodopa pharmacokinetics.⁷²

Alterations in the circadian regulation of the autonomic system have also been reported in PD. 24 h ambulatory blood pressure monitoring in patients with PD demonstrates reversal of the normal circadian rhythm of blood pressure, increased diurnal blood pressure variability, postprandial hypotension, and high nocturnal blood pressure;^{86,87} Holter electrocardiographic monitoring reveals a decrease in sympathetic activity during the day, combined with loss of circadian heart rate variability and disappearance of the sympathetic morning peak.⁸⁸ These abnormalities could arise within the peripheral autonomic ganglia, but the central networks, including the hypothalamus, might also be involved.^{89,90}

Circadian fluctuations in visual performance, as measured by contrast sensitivity, are altered in PD.⁸² Impaired regulation of retinal dopamine, which exhibits an endogenous circadian rhythm that is independent of light–dark cycles, is most likely to be responsible for these changes.⁹¹ Because circadian changes in contrast sensitivity can occur independently of circadian oscillations in motor symptoms, it is possible that the retina, striatum, cortex and other anatomical networks involved in visual processing can have differential threshold responses to the circadian signalling of dopamine.⁹²

Sleep disturbances are among the most common and disabling nonmotor symptoms of PD, and affect as many as 90% of patients.⁹³ The impact of circadian dysregulation on sleep and alertness in the PD population has not been systematically assessed. The aetiology of sleep disturbance is likely to be multifactorial, and to include the effects of PD-associated motor features on sleep, adverse effects of antiparkinsonian medications, and neurodegeneration of central areas that regulate sleep, such as the raphe nucleus and locus coeruleus; this degeneration is likely to underlie sleep impairment that emerges before the onset of the motor symptoms of PD.⁹⁴

Markers of circadian function

Only a few studies have attempted to identify markers of circadian function in PD. In a cohort of 26 individuals with PD, patients—with or without motor complications—who were treated with dopaminergic agents had a decreased amplitude of melatonin fluctuation, and the phase of secretion was advanced in comparison with recently diagnosed patients who were not yet receiving treatment.⁹⁵ These results suggest a trend toward a shift in the phase and a reduction in the amplitude of melatonin secretion during the evolution of PD, and emphasize a need to investigate the effects of dopaminergic medication on circadian function. Circadian fluctuation of body temperature and plasma cortisol did not differ between the groups in this study. In another study, melatonin secretion in nine patients with recently diagnosed PD was similar to healthy controls.⁹⁶ In a study of 12 patients with PD, 24 h mean cortisol production rate was higher and the mean secretory cortisol curve was flatter—indicating reduced diurnal variation—in the PD group than in the control group.⁹⁷ In a small study of eight recently diagnosed patients who were not receiving medication, no significant alterations were found in diurnal secretion profiles of growth hormone, thyrotropin and prolactin.⁹⁸

24 h rhythms of core body temperature are preserved in PD,⁹⁹ but basal body temperature is lowered in patients with parkinsonian symptoms.¹⁰⁰ Patients with PD and comorbid depression exhibit altered circadian rhythms of rectal temperature and decreased amplitudes of core body temperature.¹⁰¹

Although these investigations suggest altered circadian rhythmicity in PD, they should be interpreted with caution due to small sample sizes and study designs that reflect influences of both endogenous circadian and exogenous (light exposure, physical activity, meals, social schedules) rhythms on PD.

In a recent study that employed a modified constant routine experimental protocol in 20 patients with mild to moderate PD and 12 age-matched controls, significant blunting of the circadian rhythm of melatonin secretion and reduced amplitude of the melatonin rhythm was observed.¹⁰² Patients with excessive daytime somnolence had a particularly prominent reduction of the melatonin rhythm amplitude. In another study, notable reductions in the amplitude of melatonin secretion were also demonstrated in patients with *de novo* PD.¹⁰³ In contrast to these findings, an additional study reported a threefold increase in melatonin secretion in a cohort of medicated patients with PD.¹⁰⁴ Although further investigations are needed to confirm the role of neurodegenerative changes in disruption of circadian function, these observations support a role for circadian disruption in excessive daytime sleepiness associated with PD.

Several studies have demonstrated robust oscillatory patterns in the of core clock genes in human whole blood and peripheral blood mononuclear cells,^{105–107} demonstrating the feasibility of using clock gene expression as a marker of circadian function. In a study of 17 individuals with PD and 16 age-matched controls, the relative abundance of the clock gene *ARNTL* was notably lower during the night in patients with PD than in controls. Expression levels of *ARNTL* correlated with PD severity, as assessed by Unified PD Rating Scale scores (UPDRS).¹⁰⁸ The lack of diurnal variation in *ARNTL* expression was recently confirmed in another study.¹⁰³

Circadian entrainment

Numerous studies have demonstrated beneficial effects of supplemental wide-spectrum bright light therapy on sleep quality, daytime sleepiness, mood and quality of life in healthy elderly individuals and patients with dementia. Several lines of evidence provide a rationale for exploring supplemental light exposure in PD. For example, dopamine is a probable mediator of light signalling to the retinal circadian clock that provides direct input to the SCN.¹⁰⁹ Exposure to light facilitates the recovery of motor function in an experimental rat model of chronic PD.¹¹⁰

To date, only a few exploratory studies have examined the effects of bright light in patients with PD. In a case series of 12 patients, daily evening exposure to supplemental bright light of 1,000–1,500 lux improved sleep quality and mood, as well as bradykinesia and rigidity.¹¹¹ Similar beneficial effects of supplemental bright light on sleep, mood, anxiety and motor performance were reported in an open-label retrospective study of 129 levodopa-treated patients followed up for 8 years.¹¹² In another study, exposure to bright light of

7,500 lux was associated with improvements in UPDRS part I, II and IV scores, and alleviated daytime sleepiness.¹¹³ Although these studies demonstrated good feasibility and positive effects of bright light therapy on nonmotor and motor manifestations of PD, further validation studies involving larger cohorts and employing objective outcome measures are needed.

Circadian dysregulation in animal models

Animal models of PD provide an opportunity to further explore the functioning of the circadian system in PD and to address questions that cannot be investigated within the clinical research protocols in the PD population. Primates treated with the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine exhibit immediate disruption of the rest–activity rhythms, alterations in rapid eye movement (REM) sleep, and increased daytime sleepiness.^{114–116} In rats, dopaminergic depletion induced by bilateral striatal injection of 6-hydroxydopamine (6-OHDA) results in disturbances of circadian rhythms of heart rate, temperature and locomotor activity.^{117–119} In addition to disruption of behavioural rhythms, dopaminergic depletion induced by 6-OHDA has been demonstrated to be followed by blunting of diurnal fluctuation in the expression of the clock gene *PER2* in the striatum.¹²⁰ A mouse model overexpressing α -synuclein, a protein that has been implicated in the neuropathology of PD, exhibits altered circadian rest–activity rhythms and reduced daytime neuronal firing rate in the SCN.¹²¹ Animal models of circadian disruption in PD have been reviewed in more detail elsewhere.¹²²

Circadian dysfunction in HD

HD is a fatal autosomal dominant neurodegenerative condition that affects approximately 14–16 individuals per 100,000,¹²³ and typically becomes manifest in midlife.¹²⁴ The disease is caused by abnormal expansion of the trinucleotide CAG repeat¹²⁵ in exon 1 of the huntingtin gene (*HTT*),¹²⁶ leading to ubiquitous expression of mutant *HTT*.^{126–128} HD is characterized by progressively worsening motor and nonmotor deficits, including cognitive abnormalities that eventually lead to dementia,¹²⁹ neuropsychiatric disorders,¹³⁰ weight loss,¹³¹ and severe sleep^{132–137} and circadian disturbances.^{138,139}

Limitations and potential for research

Clinical experience and epidemiological and experimental data all indicate that the circadian system is affected in HD; however, patient data are limited. This lack of data could be attributable to the relatively low incidence of HD in the general population, and the methodological challenges of putting patients who exhibit complex combinations of motor, cognitive and psychiatric features through relatively intense protocols for circadian and sleep research. Furthermore, sleep problems in HD tend to go undiagnosed by physicians and underreported by patients, possibly due to a lack of insight or perceived relative unimportance of sleep problems when compared with the motor, cognitive and affective features that are recognized as key features of this disorder. In spite of these limitations, the study of patients with HD has great research potential by virtue of the genetic basis of the disease, which enables the identification and follow-up of premanifest individuals, and the ability to predict disease onset. These factors create a unique opportunity to investigate and

establish causality between the pre-morbid structural and functional degeneration of the brain and the clinical features, including circadian and sleep disruption. Such longitudinal studies could aid in elucidating the role of the circadian system and sleep behaviour in normal physiological processes, as well as in other neurodegenerative disorders.

Another important research opportunity in HD stems from the ability to make transgenic animal models of the disease. These models, especially mice, can recapitulate many of the main features of HD, and have been essential to our current understanding of the role of sleep and circadian disturbances in the condition. A need exists, however, for detailed prospective observational and interventional sleep and circadian studies in HD to confirm that the deficits reported in these animals are relevant for human disease.

Sleep–wake timing and sleep quality

Delayed sleep–wake timing and diurnal preference have been repeatedly linked to mental health problems, in particular depression.¹⁴⁰ Depression is a major problem in HD, along with apathy, anxiety and irritability.¹⁴¹ In a focused questionnaire-based sleep survey, wake-up time was markedly delayed in patients with manifest HD as compared with both premanifest mutation carriers and noncarrier controls, but no differences in bedtimes were observed.¹⁴² Self-reported sleep quality was also considerably reduced in the patients with manifest disease, whereas premanifest mutation carriers had intermediate sleep quality. These findings were confirmed in another cohort of manifest patients and premanifest mutation carriers; moreover, the later wake-up times were negatively associated with cognitive scores and total functional capacity, and positively associated with depressive symptoms. The degree of sleep phase delay in premanifest mutation carriers was intermediate between that of HD patients and controls.¹⁴³

In line with the self reports, a small polysomnography study involving nine patients with early-stage HD showed reduced sleep efficiency and increased time spent in bed, although the authors did not report whether this latter finding was due to an earlier bedtime or to a delayed get-up time.¹³² Another polysomnography study, however, reported that sleep onset before 9 pm was much more frequent in manifest and premanifest HD than in controls.¹³⁷ According to a large questionnaire-based community survey, sleep problems were highly prevalent (>87%) among the 292 individuals with HD, with early waking time being the most important sleep complaint.¹⁴⁴ Several other studies have shown that self-reported daytime sleepiness and sleep complaints are more prevalent in patients with HD than in controls.^{142,143,145} although it is not known how these subjective sleep reports relate to the objective measures of vigilance and sleep quality. The earliest objective sleep study using polysomnography was published in 1967¹⁴⁶ as a case report on a 25-year-old patient with HD who showed suppression of rapid eye movements during REM sleep as an early symptom. A later study, published in 1985, described increased sleep latency, worse sleep efficiency and interspersed wakefulness in a small cohort of patients with HD.¹³³ The few subsequent polysomnography studies have confirmed these findings;^{132,135–137,147} in addition, decreased slow-wave sleep,^{135,136,147} REM sleep disturbances^{132,135,137} and an increased number of sleep spindles have been documented.^{134,147}

Rest–activity rhythms

The initial continuous actigraphic assessments in patients with HD aimed to examine involuntary movements in the daytime, rather than the rest–activity cycle, as a core feature of HD. Despite the presence of chorea, these studies reported a decreased level in daytime activity^{148,149} that correlated with disease penetrance.¹⁴⁹ In another study, patients with mild to moderate disease exhibited a robust increase in total and maximal activity and spent longer times performing high-acceleration movements while they were awake compared with controls. These patients also showed more overnight activity than did the control individuals.¹⁵⁰

The first study that employed actigraphy specifically to assess circadian rest–activity rhythms in patients with HD found evidence of increased nocturnal activity, while daytime activity remained similar to controls. The increased activity during the night-time was primarily driven by having a sleep–rest period interspersed with activity bouts, and could not have been caused by the involuntary movement disorder, which subsides during sleep.¹³⁸ These results are reminiscent of the subjective and objective sleep reports in patients with HD, which show an increased number of awakenings and an overall decrease in sleep quality.^{132,133,135–137,142,143,147}

Rest–activity rhythms in animal models of HD

The genetic basis of HD enables the generation of transgenic models of disease that can recapitulate many of the main features of HD¹⁵¹ and, despite fundamental interspecies differences in sleep–wake behaviour, studies of circadian function in these animal models have helped us to understand the basis and progression of circadian rhythm disruption in HD. In the early stages of disease, the diurnal rest–activity cycle is fairly well conserved, and becomes increasingly disrupted as the disease progresses, with total disintegration in end-stage disease.^{138,139,152–158} This circadian disruption depends not only on age but also on gene dose:¹⁵⁹ the rest–activity disorganization becomes more prominent in animals that are homozygous for the mutation than in heterozygotes. The homozygotes also exhibited a more severely abnormal circadian behavioural response to light, and a steeper decline in locomotor rhythms.¹⁵⁹ Interestingly, in a transgenic sheep model of HD, the circadian abnormalities also depend on social factors: abnormalities of circadian behaviour emerged in sheep kept in an ‘HD-only’ flock, whereas the behaviour of HD sheep kept mixed with nontransgenic sheep remained relatively normal.¹⁵²

In most studies, the circadian disruption is associated with progressive impairment of sleep architecture and sleep EEG^{153,154,156,157} suggesting an interaction between disruption of circadian behaviour and fragmented sleep architecture, but with no exact indication on any causal relationship between the two. Restoration of circadian rhythmicity and sleep has been shown to alleviate the disease course in HD: reconsolidation of circadian entrainment by pharmacological agents or other interventions slows down cognitive decline and normalizes circadian gene expression.^{160–163} These effects are likely to be modulated by sex and genotype.¹⁶³

The central circadian pacemaker

Surprisingly few data are available on the integrity and function of the SCN in patients with HD. One study that measured blood melatonin reported that although patients with HD had similar overall melatonin concentrations to healthy controls, they displayed a delayed melatonin secretion rhythm, and the severity of the delay correlated with impairments in motor and other functions.¹⁶⁴ More recently, blood melatonin was shown to be already decreased in premanifest patients, with manifest patients having a more marked reduction. In both manifest and premanifest HD, timing of melatonin secretion onset was much more variable than in controls.¹⁶⁵

Several studies have found altered levels of cortisol in blood and urine in HD.^{152,160,166,167} Furthermore, changes in the pattern of pulsatile release of adrenocorticotrophic hormone, followed by increased pulsatile secretion of cortisol, correlated with CAG repeat size and could, thus, be caused directly by the central HD pathology rather than being secondary to any neuropsychiatric disease.¹⁶⁷ The VIP-containing cells of the SCN probably help to regulate cortisol secretion by inhibiting its release,¹⁶⁸ and postmortem studies in patients with HD have revealed loss of VIP and AVP expression within the SCN.¹⁶⁹ This decrease in VIP levels has also been associated with circadian disruption in transgenic animal models.¹⁵⁵

Besides the progressive circadian disruption of the rest–activity rhythm in transgenic animal models of HD, progressive disruption of circadian patterns of body temperature and heart rate has been found.¹³⁹ One study in a mouse model of HD reported abnormal cellular gene expression in the SCN and several other brain regions, indicative of dysfunction of the genetic underpinnings of the molecular clock,¹³⁸ but other studies reported no change in expression of the genes associated with this clock.^{139,159} The former study connected the impaired circadian rhythm to spontaneous electrical activity of SCN neurons, suggesting that the electrical activity within the central clock itself could be altered by the disease.¹³⁹ However, *in vitro* studies have described normal electrophysiological output and endogenous rhythms of circadian gene expression in the SCN, indicating that *in vivo* circadian disturbances in transgenic mice might be caused by abnormalities in the afferent pathways to the SCN.¹⁶¹ This idea is further supported by the normalization of circadian gene expression *in vivo* after re-entrainment of circadian rhythms by behavioural interventions in a transgenic mouse model of HD,¹⁶¹ although the study provided no direct evidence for normal electrophysiological activity of the SCN *in vivo*. Experimentally induced mitochondrial dysfunction leads to striatal lesions and can also contribute to sleep and/or circadian dysfunction, suggesting a mechanistic link that is relevant to HD.¹⁷⁰

In summary, although reports from patients and transgenic animal models are inconsistent, there is convincing evidence for major disruption of the circadian system in HD. This might be reversible, and could provide a strategy to slow down the disease process.

Conclusions

The circadian system controls a wide range of physiological and behavioural processes and coordinates their synchronicity. Increasing evidence shows suggests that the circadian

rhythms are dysregulated in neurodegenerative disorders. In this Review, we have highlighted the literature that spans clinical and animal studies of circadian function in three common neurodegenerative disorders: AD, PD and HD. While each of these disorders has its distinct phenotype–genotype signature, each also exhibits overlapping symptoms that could, at least in part, be based on circadian dysfunction. One of the best examples is disruption of the sleep–wake cycle, which represents one of the most robust output rhythms of the circadian system. Both human and animal studies have documented disruption of circadian timekeeping from physiological, molecular and behavioural perspectives in these three disorders. Impairments in circadian timekeeping are likely not only to influence regulation of sleep and alertness, but also affect mood, cognition, autonomic function and motor function in these disorders.

One of the key questions that remains unanswered is whether circadian disruption associated with neurodegeneration represents one of its consequences, or whether it could be one of the causative factors leading and/or contributing to the neurodegenerative cascade. In the future, longitudinal studies aimed at simultaneously examining circadian function and other disease manifestations throughout the course of these disorders will be critical in attempting to answer this question. These studies should include premanifest carriers of the HD mutant allele, individuals carrying mutations that increase the risk of AD, and individuals at high risk of development of PD, such as those with REM sleep behaviour disorder.

Regardless of whether circadian disruption represents a cause or a consequence of neurodegeneration, we argue that AD, PD and HD share ‘chronodegeneration’ as a common feature. This is an important notion, as interventions directed at normalizing circadian rhythmicity in these disorders might provide novel opportunities for much-needed therapies. These therapies could not only improve symptoms and quality of life, but also slow down disease progression. The circadian system, therefore, could be a new diagnostic and therapeutic target in neurodegenerative disorders.

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Review criteria

A search for original articles was performed in MEDLINE and PubMed. The search terms used were “circadian”, “suprachiasmatic nucleus”, “Parkinson’s”, “Alzheimer’s” and “Huntington’s”, alone and in combination. All articles identified were English-language, full-text papers. We also searched the reference lists of identified articles for further relevant papers.

Key points

- Sleep and circadian disruption are common in Alzheimer disease, Parkinson disease and Huntington disease
- Symptoms of circadian disruption range from subjective sleep complaints and alterations of sleep timing to severe disruptions in rest–activity cycles and sleep architecture
- Behavioural, physiological and molecular markers of circadian system function suggest progressive deterioration of circadian rhythmicity as the disease progresses
- The relationship between circadian dysfunction and neurodegenerative processes might be bidirectional: circadian dysfunction might exacerbate the disease processes
- Behavioural or pharmaceutical interventions that target sleep–wake cycles might reverse circadian disruption

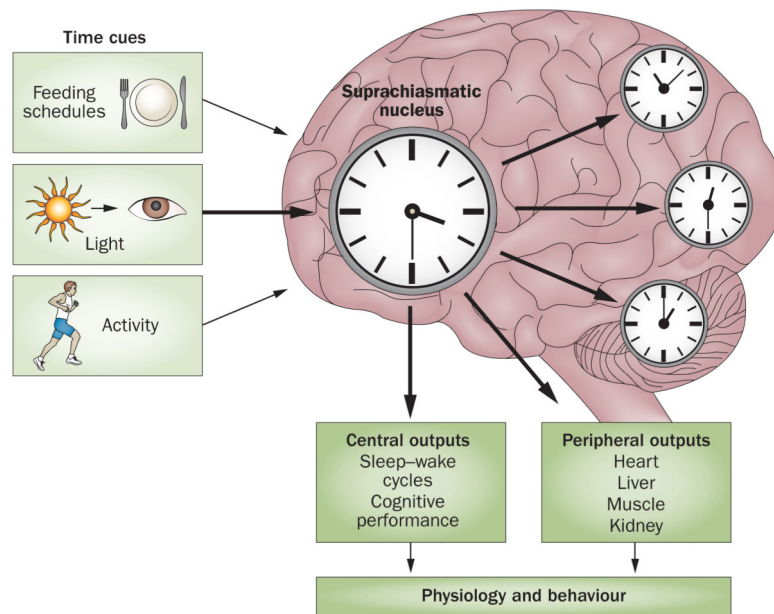


Figure 1.

A simplified scheme of the circadian system. The timing of human biological rhythms is synchronized to the rotation of the Earth, and is influenced by numerous external and internal time cues. These stimuli are known as 'zeitgebers' (German for 'time giver'). Light is the most important and potent zeitgeber. In addition to light, activity, feeding schedules, and the hormone melatonin also influence circadian timing. This synchronization can become disrupted, which eventually leads to misalignment or internal desynchronization. This loss of coordination of circadian rhythms can have negative consequences for sleep-wake cycles and numerous other biological functions.

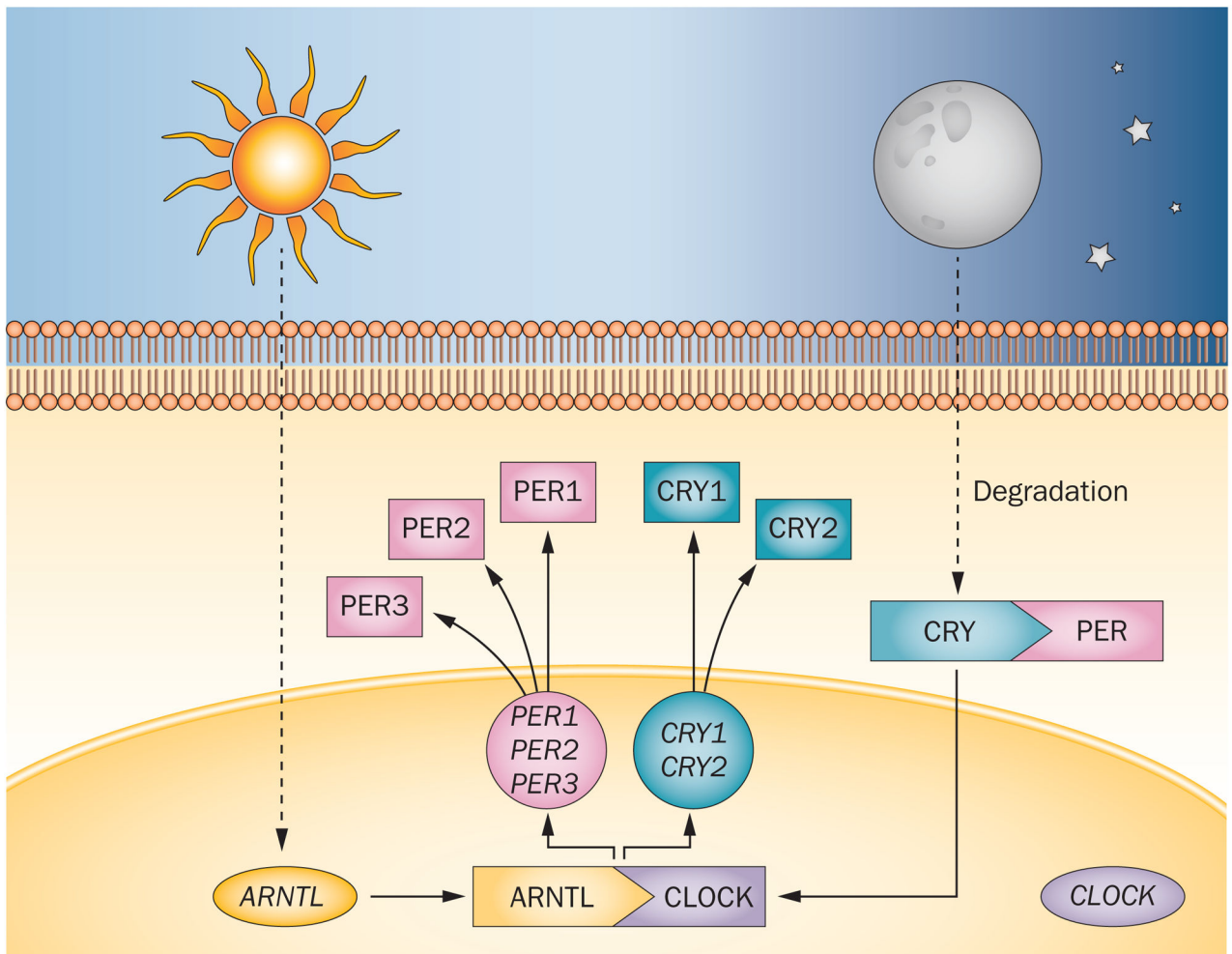


Figure 2.

Molecular organization of the circadian system. The proteins encoded by the core set of clock genes—*PER*, *CLOCK*, *ARNTL* (also known as *BMAL1*) and *CRY*—interact to create a self-sustaining negative transcription–translation feedback loop.¹⁷¹ The intracellular level of *CLOCK* remains steady throughout the 24 h period. The high level of *ARNTL* at the beginning of the day promotes the formation of *ARNTL*–*CLOCK* heterodimers, which in turn activate transcription of *PER* and *CRY*. As *PER* accumulates in the cytoplasm, it becomes phosphorylated and degraded by ubiquitylation. *CRY* accumulates in the cytoplasm late in the subjective day, and translocates to the nucleus to inhibit *ARNTL*–*CLOCK*-mediated transcription. At night, the *PER*–*CRY* complex is degraded, and the cycle starts again. This feedback loop ensures a high level of *ARNTL* and low levels of *PER* and *CRY* at the beginning of a new circadian day.