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Circadian clock and pathology of the ageing brain

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Abstract

Ageing leads to functional deterioration of many brain systems, including the circadian clock - an internal time-keeping system that generates 24 hr rhythms in physiology and behaviour. Numerous clinical studies have established a direct correlation between the severity of neurodegenerative disorders, sleep disturbances and weakening of circadian clock functions. The latest data from model organisms, gene expression studies and clinical trials imply that the dysfunction of the circadian clock may contribute to the progression of ageing and age-associated pathologies, suggesting a functional link between the circadian clock, and age-associated decline of brain functions. Potential molecular mechanisms underlying this link include the circadian control of brain metabolism, reactive oxygen species homeostasis, hormone secretion, autophagy and stem cell proliferation.

Introduction

The circadian system, or circadian clock, provides a wide range of organisms from archaeobacteria to humans with an adaptive advantage to the 24 hour periodicity in the Earth's rotation¹. The growing list of circadian-clock-controlled physiological processes includes metabolism, hormone secretion and cardiac function, all of which exhibit daily oscillations. The circadian system also maintains the internal coordination of multiple oscillators within and between various organ systems in order to increase the fitness of an organism and provide the most efficient response to the environment²⁻⁵. In humans, dysfunction of the circadian clock induced by shift work, for example, significantly increases the risk of developing metabolic syndromes, cardiovascular diseases and cancer, indicating that these circadian-clock-controlled processes play key roles in human physiology and pathology⁶. Although the molecular mechanisms are unknown, it has been suggested that shift work leads to the resynchronization of circadian oscillators, uncoupling different organ systems from each other and from the central pacemaker⁵.

A connection between the circadian clock and ageing has been recently proposed⁷. Whereas the effect of ageing on the performance of the circadian system has been known for many years⁸, recent data show that a dysfunctional circadian clock can in turn contribute to ageing and pathologies associated with old age⁹. Here we will discuss a potential role of the circadian clock in the age-associated decline of brain function, with specific emphasis on age-associated brain disorders and neurodegenerative diseases. While sometimes it is difficult to dissociate the effect of sleep abnormalities and circadian clock dysfunction, multiple lines of evidence suggest that the activity of the circadian clock in the regulation of cognition and mood is far beyond the circadian control of sleep and the rest/activity cycle.

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Here we will focus on the relationship between the circadian clock and brain ageing with an emphasis on sleep-independent mechanisms. The role of sleep in age-associated cognitive decline has been recently reviewed¹⁰ and is beyond the scope of this article.

The organization of the circadian clock

Virtually all tissues in an organism exhibit circadian oscillations in gene expression, underscoring the importance of the circadian clock throughout the body. Multiple reviews on the anatomical and physiological organization of the circadian clock have recently been published^{6, 7, 11}; therefore, here we provide only a short overview of the circadian clock system and the molecular components that form the circadian oscillator in the mammalian cell (Figure 1A). The central, or master, circadian clock is located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus¹². SCN neurons generate rhythmic electrical activity and produce synchronizing signals, which control the phases of the oscillations of so-called peripheral clocks operating in other tissues, such as the liver, heart and muscles. The rhythmic activity of the SCN is synchronized with the external light cues through signals from the retina. Peripheral tissues produce rhythmic physiological outputs which are orchestrated by the SCN and synchronized with the environment, thus providing optimal activity or response to an organism's needs at the specific time of the day¹³. Shift work-associated pathologies underscore the importance of such synchronization⁵.

The mechanisms underlying circadian rhythms involve circadian oscillations in gene expression, protein modifications and secretion. These oscillations are controlled by the products of the core circadian clock genes¹⁴. Experiments in model organisms, in which single or multiple clock genes have been deleted or mutated, have revealed a short list of genes that are critically important for circadian rhythms in locomotion, behaviour, physiology and gene expression. The current model connects these circadian clock genes and their products in transcriptional-translational feedback loops^{15, 16} (Figure 1B). Among clock gene products, there are positive regulators of transcription: BMAL1 (*Brain and Muscle Arnt Like protein 1*), its interacting partners CLOCK (*Circadian Locomotor Output Cycles Kaput*) or NPAS2 (*Neuronal PAS domain-containing protein 2*), and RORs (*Retinoid-related Orphan Receptors*), and negative regulators of transcription: CRYs (*Cryptochromes*), PERs (*Periods*) and Rev-Erb- α . The functions of CLOCK and NPAS2 proteins are partially redundant. The BMAL1:CLOCK or BMAL1:NPAS2 complexes specifically interact with and modify chromatin, which results in up regulation of the expression of a set of genes, including *Cry* and *Per* genes. Products of these genes, CRY and PER proteins form a complex that inhibits the activity of the BMAL1-containing complexes and thereby down regulate their own expression, thus forming a negative feedback loop. Rhythmic expression of *Per1* and *Per2* genes at the mRNA level can be detected in almost all tissues and serves as an indicator of circadian clock activity. Additional loops are formed with the help of Rev-Erb- α and RORs, which fine tune the oscillations generated by the main loop¹⁷. Post-translational modifications and degradation of circadian proteins provide additional levels of regulation¹⁸. It is also worth mentioning that although *Bmal1* is the only circadian clock gene with a non-redundant clock function¹⁹, it can be functionally substituted by *Bmal2*, if exogenous *Bmal2* is expressed in the SCN of *Bmal1* knockout mice²⁰. However, in contrast to *Clock* and *Npas2* which are redundant, endogenous *Bmal2* does not compensate for BMAL1 deficiency in *Bmal1* knock out mice¹⁹.

Circadian clock, sleep, mood and cognitive function

The expression of circadian clock genes rhythmically oscillates in different brain structures outside the SCN, suggesting the existence of multiple circadian clocks in the brain. It has been suggested that the synchronized activity of these clocks is critically important for a

number of mental processes and that loss of phase coherence between these clocks (under influence of shift work for example) can negatively affect cognitive function^{5, 21, 22}. The regulation of sleep by the circadian clock is well-established, however, recent work has shown that the clock is also involved in regulation of mood, memory and adaptation to novelty²³.

Sleep is controlled by an interaction between the homeostatic drive for sleep and circadian clock-generated signals. Local circadian clocks are present in the brain stem, thalamus and cortex - the brain structures associated with sleep control. Circadian control of neural activities in these centres is important for daily rhythms of wakefulness/sleep. Deficiency in the circadian clock induced by a targeted disruption of clock genes impairs sleep in mice⁵. The importance of the circadian clock in the sleep control in humans has also been demonstrated: a mutation in *Per2* gene was found to be responsible for Familial Advanced Sleep Phase Syndrome, while Delayed Sleep Phase Syndrome have been linked with polymorphisms in clock genes⁵.

Several lines of evidence link the circadian clock and regulation of mood²⁴. Linkage analysis studies in humans list circadian clock genes as candidates for the regulation of major depression, bipolar disorder and seasonal affective disorder²⁵. Another connection has been shown in a study in rodents: mice with mutation in the *Clock* gene demonstrate mania-like behaviour that has been attributed to increased dopaminergic activity in the ventral tegmental area²⁶. Interestingly, drugs used for treatments of mood-related disorders directly regulate the activity and expression of circadian clock genes²⁷. These results suggest that an impaired circadian clock significantly affects mood in experimental animals and most likely contributes to mood-related disorders in humans.

The role of the circadian clock in cognition and especially in memory formation and consolidation is currently an active area of research²⁸. The circadian clock probably regulates memory through several mechanisms. One potential mechanism involves the circadian control of sleep: indeed, consolidation of procedural and declarative memory is sleep-dependent, and quality and duration of sleep is critical for cognitive functions. However, a growing body of evidence indicates the involvement of the circadian clock in memory formation and/or consolidation that is independent from its role in the regulation of sleep. Recent studies in animals in which different components of the circadian clock have been disrupted demonstrated impairment of contextual, spatial and time-related memory, as well as impaired adaptation to a novel environment²⁹⁻³³. Targeted disruption of circadian genes leads to defects in particular types of memory task, but not others. For example, *Cry1,2-/-* mice exhibit a deficit in time-place learning but not in other types of associated learning³¹, *Per2-/-* mice demonstrate impairment in trace fear memory formation, but not in cued fear memory formation³⁴, *NPAS2-/-* mice have impaired cued and contextual fear memory formation³², and finally, *BMAL1-/-* and *CRY1-/-,CRY2-/-* deficient mice demonstrate opposite novelty-induced behaviours and habituation²⁹.

In humans, cognitive abilities are known to fluctuate throughout the day. To dissect the sleep and the circadian clock-dependent components of this fluctuation, the sleep/wake cycle and the circadian clock cycle were completely desynchronized through a forced non-24-hour day, in which subjects followed 20-hour or 28-hour rest/activity schedules. Under these extreme conditions the internal circadian clock cannot be adjusted to external cues and continues to run at its intrinsic period of about 24 hours. When performance in an addition/subtraction test and a psychomotor vigilance task were evaluated, the authors found that the subjects' abilities had a clear circadian profile, suggesting that the circadian clock has a sleep-independent effect on cognitive function in humans³⁵.

What molecular mechanisms could be engaged by the circadian system to control brain function? Long-term potentiation (LTP) requires activation of the transcriptional factor CREB through the MAP kinase and cyclic AMP-dependent pathways. In the mouse hippocampus, the level of cyclic AMP, phosphorylation of MAPK, which is a sign of activation, and CREB-dependent transcription exhibit circadian oscillations that peak during sleep time. Physiological and pharmacological interferences with circadian rhythms in MAPK phosphorylation significantly impair hippocampus-dependent memory formation³⁶. Thus, the circadian control of the AMP/MAPK/CREB signal transduction pathway provides a potential mechanistic explanation for the circadian control of memory³⁷.

Another potential mechanism is synchronization of local clocks throughout the brain. Temporal compartmentalization of metabolic and replication cycles in yeast was demonstrated to protect the cells' genome^{38,39}. A similar 'temporal partitioning' was suggested for the circadian-clock-dependent control of metabolic processes in peripheral tissues, specifically in the liver. According to this model, the phases of daily cycles of hepatic gene expression are locked by SCN signalling and, thus, local enzymatic activity is synchronized with the metabolic demands of activity and sleep^{13,40-44}. Likewise,⁵ if circadian clock genes are expressed in the hippocampus, cortex, amygdala and other structures with different phases, the internal synchronisation of these local brain clocks imposed by the SCN pacemaker⁴⁵ may affect cognition. Thus, during waking hours, the gene expression pattern must support brain functions such as acquisition, responsiveness and processing of stimuli⁵; whereas, during sleep, when the process of short-term memory consolidation occurs, the gene expression pattern must support synaptic rewiring⁵. However, at present there is no direct experimental support of this model.

Neurogenesis is an essential component of cognition⁴⁶ and may also be a mechanism through which the circadian clock regulates cognitive function. Circadian-clock-dependent regulation of neurogenesis has been proposed based on a few observations that neurogenesis among the olfactory projection neurons in lobsters⁴⁷ as well as cell proliferation in the dentate gyrus of the adult rat⁴⁸ fluctuates with the light-dark cycle. However, it is unclear if the observed rhythms in cell proliferation are due to true circadian control or they are coupled to daily patterns of activity or sleep.

Circadian clock and ageing

Ageing is a complex biological process affecting activity of many physiological systems including the circadian clock^{7,8}. Functional weakening of the circadian system with age has been known for many years. The effect of ageing on circadian clock activity has been reported in different model organisms including invertebrates^{49,50,51,52}, rodents⁵³ and primates⁵⁴, suggesting that the effect of ageing on the circadian system is highly conserved.

Phase advance and reduced amplitudes of circadian rhythms of temperature and hormone secretion (specifically melatonin and cortisol) have been detected in aged humans^{8,55}. However, there are discrepancies between studies on the effect of aging on melatonin and body temperature rhythms⁵⁶. A reduction of circadian amplitude was reported in several studies, but predominantly in old males⁵⁶. By contrast, no reduction in amplitude was observed in old females^{56,57}. The sensitivity of the circadian system to light is dramatically reduced with age as measured by the induction of c-fos expression in the SCN of hamsters⁵⁸, mice⁵⁹ and primates⁶⁰. This reduced response to light may contribute to the impaired entrainment of the circadian clock by light cues in aged rats⁶¹.

Ageing does not have an effect on the size or the number of neurons in the SCN⁶²; however, a decrease in the number of vasopressin expressing neurons has been found in the SCN of ageing rats⁶³. Aging brings about significant changes in electrophysiological and

neurochemical outputs of the SCN⁶⁴. The amplitude of the SCN cells' electrophysiological⁶⁵ and hormone secreting activity⁶⁶ and their gene expression levels^{67, 68} all decline in the ageing brain. These age-associated changes in the SCN have been proposed to be responsible for the impairment of circadian clock synchronization throughout the body⁸.

In mice, disruption of the circadian system by targeted deletions of clock genes significantly affects the rate of ageing. Deficiency of the transcriptional factor BMAL1 results in development of a premature ageing phenotype, characterised by multiple age-related pathologies and an almost three fold reduction in lifespan⁶⁹. Interestingly, flies with a mutation in the *cycle* gene (a drosophila homolog of *Bmal1*) have reduced longevity⁷⁰, although the effect is gender-specific as lifespan is reduced only in males. These findings suggest that the role of BMAL1 in ageing is conserved in evolution.

In mice, deficiency of CLOCK (*Clock*^{-/-}) results in an increased rate of inflammation, development of cataracts and a 15% reduction in longevity⁷¹. The lifespan of mice with mutations in both *Clock* and *Per2* genes have not been reported; however, after exposure to non-lethal doses of ionizing irradiation these mutants demonstrate a reduced lifespan and some ageing-associated phenotypes^{72, 73}. They do not develop the accelerated ageing phenotype that is characteristic for *Bmal1*^{-/-} mice so, although disruption of the circadian clock affects the rate of ageing regardless of the particular mechanism of disruption, the activity of some clock proteins, such as BMAL1, is much more important in the control of ageing than the activity of other proteins, such as CLOCK or PERs. This suggests that circadian clock proteins have non-circadian roles in ageing (see also^{53, 74}).

Circadian clock and cognitive impairment associated with brain ageing

Both healthy and pathological brain ageing are associated with multiple impairments in cognitive function. Sleep duration, quality and pattern together with phase of sleep and wakefulness are significantly different in elders^{75,10}. An ageing-related decline in spatial, declarative and other forms of memory is well-documented^{10, 76, 77}. Furthermore, changes in mood regulation: increased frequency of episodes of depression, mania and anxiety, are also observed with age⁷⁸⁻⁸⁰. How does the circadian clock contribute to these processes?

A potential role of the clock in brain ageing is illustrated in Figure 2. A decline in clock functions contributes to sleep impairment^{21, 22}, but as mentioned above, the effect of circadian system ageing on cognitive functions may be both sleep-dependent and sleep-independent. It is difficult to distinguish between these effects. For example, sleep is important for memory consolidation, thus, the disruption of normal sleep patterns as a result of circadian clock ageing can be one of the contributors to memory impairment^{5, 10}. In agreement with this, flattened amplitude of circadian activity in aged rats is associated with a deficit in long-term (sleep-dependent) spatial memory, whereas working memory is unaffected⁸¹. At the same time, sleep-independent mechanisms of clock-controlled memory and mood (discussed above) would also be impaired upon ageing of the circadian clock. Although ageing of the circadian system is not equivalent to the disruption of the circadian clock in circadian clock mutants, we may expect that the effects on cognition observed in circadian clock mutant models reflect to some extent the effects of circadian system impairment in the ageing brain. Further study of the role of specific circadian proteins in the control of cognition, sleep and ageing using circadian mutant animals may provide some clues about how ageing of the circadian clock contributes to age-related cognitive dysfunctions and might help to separate the effects of circadian rhythms and sleep on cognition.

Neurodegenerative diseases and the circadian clock

Ageing of the circadian system contributes to the decline in mental performance of aged brains, but the circadian clock may also be involved in specific age-associated neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's diseases (AD, PD and HD)²². Indeed, as it has been demonstrated through multiple clinical reports, while each of these three pathologies have their unique pathological signatures, the disruption of sleep and circadian rhythms is one of the common and earliest signs of Alzheimer's, Parkinson's and Huntington's diseases; abnormalities in the circadian clock and sleep worsen as the disease progresses^{22, 82} (see details on neurodegeneration associated circadian disruption in Box1). Degeneration of brain nuclei containing sleep circuits and circadian clock-regulating circuits in the SCN^{83, 84}, hypothalamus⁸⁵⁻⁸⁷, basal forebrain^{85, 88} and brain stem^{87, 89, 90} is one of the possible causes of sleep defects in patients with neurodegenerative diseases. These brain structures release different neurotransmitters; during wakefulness, excitatory neurotransmitters such as adrenaline, serotonin and histamine are released, whereas the release of inhibitory neurotransmitters such as GABA and galanin is suppressed. Disruption of this neurotransmitter release/suppression pattern with age or as a result of neurodegeneration may contribute to defects in sleep and circadian clock activity²². The negative effect of neurodegeneration on the circadian clock has been confirmed in animal models of AD⁹¹, PD⁹² and HD⁹³.

The correlation between neurodegeneration and circadian clock dysfunction raises important questions: first, whether or not the circadian system is involved in the pathophysiology of neurodegenerative diseases, and if it is, how does the circadian clock affect the development of neurodegenerative diseases? On the one hand, the intact circadian system may have neuroprotective functions; on the other hand, disruption of the circadian clock seems to promote neurodegeneration. Hypothetical connections between the circadian clock and neurodegeneration are illustrated in Figure 3 and are discussed in more detail.

One of the main features of the three above-mentioned neurodegenerative diseases is increased oxidative stress, which most likely plays a role in neurodegeneration⁹⁴. In AD, oxidative damage leads to an increased accumulation of DNA oxidation products in the nuclei of neurons and elevated levels of oxidized proteins and lipids, which can be found in plaques and neurofibrillary tangles. In PD, the products of protein oxidation and lipid peroxidation can be detected in Lewy bodies. Mitochondria dysfunctions are described in HD patients, and increased oxidative stress was reported in a mouse model of this disease. Increased oxidative damage results in the death of neurons, astrocytes and oligodendrocytes, as well as degeneration of normal brain structures. Possible mechanisms include dysfunction of damaged mitochondria, microglia overactivation, protein/lipid plaques formation and reduced antioxidant defence⁹⁴.

Weakened antioxidant defence in the ageing brain may contribute to increased oxidative stress; however, the mechanisms involved are unknown⁹⁵. The role of the circadian system in the regulation of reactive oxygen species homeostasis is well-established. ROS levels oscillate in different mouse tissues⁶⁹ and these rhythmic patterns are disrupted in mice with impaired circadian clocks. ROS misbalance was proposed as a potential mechanism of premature ageing of BMAL1-deficient mice; in agreement with this, treatment with the antioxidant NAC increased the longevity of these animals⁹⁶. Daily oscillations in the level of the products of lipid and protein oxidation have been observed⁹⁷. The circadian clock can orchestrate antioxidant defence by controlling the daily oscillation in the expression of antioxidant enzymes and low molecular weight antioxidants.

Potential mechanistic links between the circadian clock and ROS homeostasis have been studied in model organisms. In *Neurospora crassa*, the circadian clock may regulate ROS levels through the small membrane-anchored G-protein RAS-1⁹⁸ and through regulation of catalase expression and activity⁹⁹. In *Drosophila melanogaster*, the sensitivity to oxidative stress, protein carbonylation and hydrogen peroxide production changes throughout the day and these rhythms are disrupted in circadian mutants bearing a null mutation in the period gene. Reduced activity of catalase in circadian mutants may be responsible for their increased sensitivity to oxidative stress¹⁰⁰. It is possible that a similar mechanism regulates ROS homeostasis in mammals. In agreement with the importance of the circadian clock in redox state regulation, circadian rhythms of peroxiredoxin oxidation have been observed in nucleated and enucleated (red blood cells) cells¹⁰¹. Similar transcription independent circadian rhythms were observed in pico-eukaryotic alga *Ostreococcus tauri*¹⁰², but the underlying mechanisms are unknown in both cases.

Another possibility, although not demonstrated directly, is that the circadian clock regulates ROS production: multiple reports link the circadian clock with daily oscillations in metabolism and body temperature, and in turn, metabolic rhythms are intimately linked with the activity of the mitochondria and ROS generation as a side product of oxidative catabolism. Many metabolic enzymes and metabolism-regulating growth factors and hormones are under the direct control of the circadian clock¹³; disruption of the circadian clock leads to numerous defects in metabolism and to the development of metabolic syndromes, which are known to be associated with increased oxidative damage. If, similarly to the regulation of metabolism of the liver and other peripheral organs, the clock regulates metabolism in the brain, one can expect that disruption of this regulation will lead to oxidative damage. Death of brain cells, especially neurons and astrocytes, is a hallmark of neurodegeneration. Because differentiated neurons are unable to divide, mechanisms to repair damage are extremely important in the physiology of the neuron. Indeed, accumulation of damaged DNA may lead to activation of apoptotic programmes; damaged proteins and lipids may form aggregates, intra- and extracellular inclusions; damaged organelles, such as mitochondria, can directly induce cell death. Several mechanisms responsible for the elimination of damaged macromolecules may also be under the control of the circadian clock.

ROS are constantly produced in the brain as metabolic byproducts and probably as signal molecules; oxidative stress is one of the main reasons of brain cell death. Repair of oxidized DNA is critical for the survival of brain cells. Nucleotide excision repair systems remove two major products of DNA oxidation, 8-oxoguanine and thymine glycol. Nucleotide excision repair activity rhythmically oscillates during the day with a peak in the early evening¹⁰³. In agreement with this, one of the DNA damage recognition proteins, the core excision repair factor xeroderma pigmentosum A exhibits a circadian, time-dependent oscillation. Thus, it was proposed that circadian control of nucleotide excision repair plays an important role in neuroprotection¹⁰⁴. This role may be especially important in neurodegenerative diseases, which are associated with increased oxidative stress: disruption of the normal clock functions may result in reduced removal of DNA lesions and increased neuron death.

The three neurodegenerative diseases discussed are associated with the deposition of aggregates in the brain: B-amyloid plaques and neurofibrillary tangles in patients with AD, Lewy bodies in patients with PD and huntingtin-containing neuronal inclusion bodies in patients with HD, suggesting some failure in the systems responsible for the degradation of damaged proteins and other cytoplasmic components. The ubiquitin-proteasome dependent system and autophagy are the two major systems responsible for degradation of cellular proteins, including misfolded and damaged proteins^{105, 106}. Autophagy is also responsible

for the degradation of lipids and non-functional or damaged organelles such as mitochondria and peroxisomes. Although there is a significant difference between pathologies and causes of AD, PD and HD, defects in autophagy have been reported in all of these diseases¹⁰⁶. The mechanisms of autophagy deregulation in neurodegeneration are mostly unknown, but some insights have been provided by recent studies¹⁰⁶. In patients with AD the clearance of autophagic β -amyloid-containing vacuoles is defective. Increased autophagic degradation of mitochondria is another pathological change observed in AD¹⁰⁶. In patients with PD, autophagosomes accumulate, lysosome-dependent degradation of α -synuclein is impaired and targeting of damaged mitochondria for degradation through mitophagy is defective¹⁰⁶. Defective autophagy has also been implicated in the degradation of huntingtin aggregates and general protein turnover is reduced in patients with HD. The current model suggests that defects in cargo recognition result in autophagic vacuoles that contain minimal cargo¹⁰⁶. However, the relationship between autophagy and neurodegeneration is complex; autophagy must be tightly regulated as both suppression and over activation of autophagy can be dangerous¹⁰⁶.

The circadian clock is one of the potential systems for tuning autophagic activity¹⁰⁷. Daily rhythms of autophagy in rat hepatocytes and cardiomyocytes¹⁰⁸ (peaking near to resting phase and at a minimum at the time of feeding) have been reported. Similar oscillations have also been also reported in the kidney¹⁰⁹ and retina¹¹⁰. The physiological significance of these rhythms is unclear, as is whether the circadian clock is involved in the control of autophagy. The expression of several genes associated with autophagy rhythmically oscillate in the liver in a circadian manner suggesting a molecular connection between the circadian oscillator and autophagy¹⁰⁷. C/EBPbeta was identified as a key link between autophagy and the circadian clock; this transcriptional cofactor can activate autophagy *in vitro*, it is rhythmically expressed in the liver and the disruption of its circadian expression in mice lacking a functional liver clock correlates with disrupted rhythms in autophagy in the liver¹¹¹. If, like in the liver and the heart, autophagy has rhythmic variations in the brain, the disruption of circadian rhythms could lead to the accumulation of aggregates and damaged mitochondria, contributing to the development of neurodegenerative disease and other age-associated brain dysfunctions.

Another potential link connecting the circadian clock and neurodegeneration is the activity of melatonin¹¹². Melatonin is a peptide hormone produced by the pineal gland in a circadian manner. It has a myriad of activities, such as intracellular signal transduction and regulation of cell death and proliferation. Melatonin is also produced by other body tissues, but pineal gland production is the most relevant action of melatonin on brain function. The most studied melatonin function is its antioxidant activity. It was demonstrated that melatonin can be more efficient than many classical antioxidant scavengers such as vitamins E and C¹¹². Melatonin is a naturally synthesized compound, its high local concentration in the brain and cerebrospinal fluid makes it a highly attractive candidate to provide a molecular connection between the circadian clock and neuroprotection. Indeed, disrupted production of melatonin can significantly compromise the normal brain antioxidant defence. Additionally, melatonin production decreases with age, and could be a predisposing factor for neurodegeneration^{113, 114} and mood disorders¹¹⁵. The circadian production of melatonin is affected in Alzheimer's, Parkinson's and Huntington disease¹¹². Reduced amplitude, earlier timing of peak and diminished amount of total secretion in melatonin secretion rhythms have been reported for AD patients^{55, 116}. In HD patients, the timing of the evening peak in melatonin level is significantly delayed but total secretion is not different from control group¹¹⁷. Melatonin therapy (oral administration of the hormone) has recently been used for the treatment of AD and PD, but its efficacy is unclear (see next section).

Overactive glia and impaired immune functions have also been proposed to contribute to AD, PD and HD. It was recently demonstrated that disruption of circadian clock function affects the release of inflammatory cytokines in response to endotoxin¹¹⁸ or lipopolysaccharide challenge¹¹⁹. One of the potential mechanisms underlying this effect is the circadian-clock-dependent production of cortisol, which is a powerful regulator of the activity of the immune system. The daily oscillation of cortisol levels is significantly affected by ageing; thus, a defect in cortisol secretion may contribute to the misbalance of the immune system regulation and to the pathology of age-associated diseases.

Modulation of the circadian clock and brain ageing

Light therapy and melatonin treatments have been used for a long time as mechanisms to reset the circadian clock in humans. Several reports on the effects of light therapy and melatonin treatment on the progression of neuropsychiatric diseases in aged people or people suffering from specific disorders are promising¹²⁰. In patients with AD, treatment with melatonin has mixed results: no significant improvements in sleep between melatonin treated and control groups were reported in several double-blind randomised placebo controlled studies^{121–123}, but because the effects of melatonin are dependent on the phase of the circadian cycle, combinations of melatonin and bright light therapy significantly improve patients sleep and daytime activity according to other studies^{124, 125}. Mild cognitive impairment (MCI) is an etiologically heterogeneous syndrome, with about 12% of MCI cases being associated with AD. Melatonin alone or in combination with light therapy shows significant beneficial effects in patients with MCI¹¹². In mouse models of AD, treatment with melatonin inhibits oxidative and amyloid pathology, protects against cognitive deficits and neurodegeneration and increases survival^{126, 127}. Interestingly, *in vitro* melatonin interacts with amyloid β -protein and inhibits the formation of amyloid fibrils¹²⁸.

While melatonin demonstrates a significant neuroprotective role in animal model of PD¹²⁹, there is a controversy about its role in clinical treatment of PD. Use of melatonin in combination with bright light exposure improves sleep quality in PD patients, suggesting that the circadian clock can be used not only as early marker of the disease, but as a means of potential therapeutic intervention according to one study¹³⁰, according to other studies melatonin does not demonstrate any therapeutic effects^{131–133}, thus, more study on melatonin as a potential drug for PD is necessary.

Even more impressive are recent studies in experimental organisms, which suggest that it is possible to delay the development of neurodegenerative disease by treatment of sleep abnormalities and improvement of circadian clock functions. In a mouse model of HD, restoration of daily rest/activity cycle with the benzodiazepine alprazolam restored dysfunctional circadian clock gene expression, improved cognitive performance and significantly extended the lifespan of mice^{134, 135}. Scheduled feeding can also restore daily behavioural rhythms in this model, but the effect of this intervention on the development of pathology has not been reported¹³⁶.

It is also worth mentioning that many pharmacological drugs used for the treatment of neuropsychiatric disorders affect the function of the circadian clock leading to the possibility that they may, at least partially, act by restoring circadian clock function. Will the resetting of the circadian clock help to delay the decline in cognitive functions during normal ageing? To the best of our knowledge, no studies have been published on this subject.

Conclusions and future directions of research

During the last several decades human lifespan has dramatically increased, creating a new level of challenges for biomedical sciences. Chiefly, how to improve the quality of life of

the aged population and promote healthy ageing. Diseases of the ageing brain, specifically neurodegenerative diseases, attract significant attention because the incidence of these pathologies is on the rise. To develop rational strategies for the prevention and treatment of these diseases, it is necessary to identify the molecular pathways associated with these pathologies. The circadian clock is one of the body's physiological systems recently linked to the control of ageing. It is becoming clear that the physiological function of the circadian clock is relevant for multiple brain functions, including sleep, mood, and memory; therefore, ageing of the clock affects these functions and contributes to age-associated cognitive decline. Circadian clock-dependent control of several pathways known to be involved in the pathology of neurodegeneration, such as metabolism, ROS homeostasis and oxidative stress response, DNA damage repair and, potentially, autophagy suggests that defects in circadian clock functions may have causative roles in AD, PD and HD.

Many questions still remain to be answered. The hypothesis that the circadian clock is involved in the regulation of oxidative stress in the brain needs to be tested. Is the circadian clock involved in daily metabolic processes in the brain? How is this related to ROS generation? Is the circadian clock involved in brain antioxidant defence? What are the molecular mechanisms responsible? Is the beneficial effect of melatonin on the pathology of neurodegenerative diseases associated with restoration of circadian clock function, with the antioxidant properties of melatonin, or with some other melatonin function? The use of mouse strains that do not produce significant amounts of melatonin may shed some light on this issue. The therapeutic effect of melatonin was demonstrated in the mouse model of AD, therefore, it is possible to test if circadian clock functions are important for melatonin function by crossing AD transgenic mice with circadian clock mutant mice and investigating the effect of melatonin in the generated hybrids. Is the circadian clock involved in the control of autophagy in the brain? And if the clock is involved, does ageing-associated impairment of the circadian clock contribute to the deposition of extra- and intra-cellular aggregates in neurodegenerative diseases? Finally, recently several potential pharmacological modulators of the circadian clock *in vitro* have been reported. If the biological activity of these modulators is confirmed *in vivo*, they need to be tested in animal models of neurodegeneration. It will be important to see if they will improve the function of the clock under pathological conditions and even more important to see whether it will affect the development of the disease.

The evidence available so far warrants further research into the role of the circadian clock in the regulation of normal and pathological brain physiology. Targeting the circadian clock could be a novel direction for diagnosis and treatment of disorders of the ageing brain, including neurodegenerative conditions.

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Glossary

Circadian clock	A complex of genetically determined molecular, cellular and physiological processes, which result in the generation of near 24-hrs rhythms (known as circadian rhythms) in organism behaviour, metabolism etc.
Advanced Sleep Phase Syndrome (ASPS)	A circadian rhythm sleep disorder which causes a few hours advanced phase in circadian rhythms and the sleep/wake cycle. Familial ASPS is genetically determined syndrome associated with mutation in circadian clock gene <i>Per2</i> or Casein kinase 1 delta.
Delayed Sleep Phase Syndrome (DSPS)	Also known as Delayed Sleep Phase Disorder, is a circadian rhythm sleep disorder which causes a few hours delayed phase in circadian rhythms and the sleep/wake cycle. Light therapy, sleep phase chronotherapy and melatonin administration have been used for the treatment of DSPS.
Long-term potentiation (LTP)	LTP is an enhancement in synaptic strength and candidate cellular mechanism of learning and memory.
Synaptic rewiring	Synaptic rewiring, also known as a synaptic plasticity, is a process of formation and elimination of synapses in the nervous system.

Mitophagy

Mitophagy is a process of removal of mitochondria through macroautophagic pathways.

Light therapy

An experimental therapy that has been used to treat disorders associated with disrupted circadian rhythms. At a specific time of the day patients are exposed to light (daylight or artificial light) of defined intensity.

Box 1**Circadian disruption in ageing-associated neurodegenerative diseases**

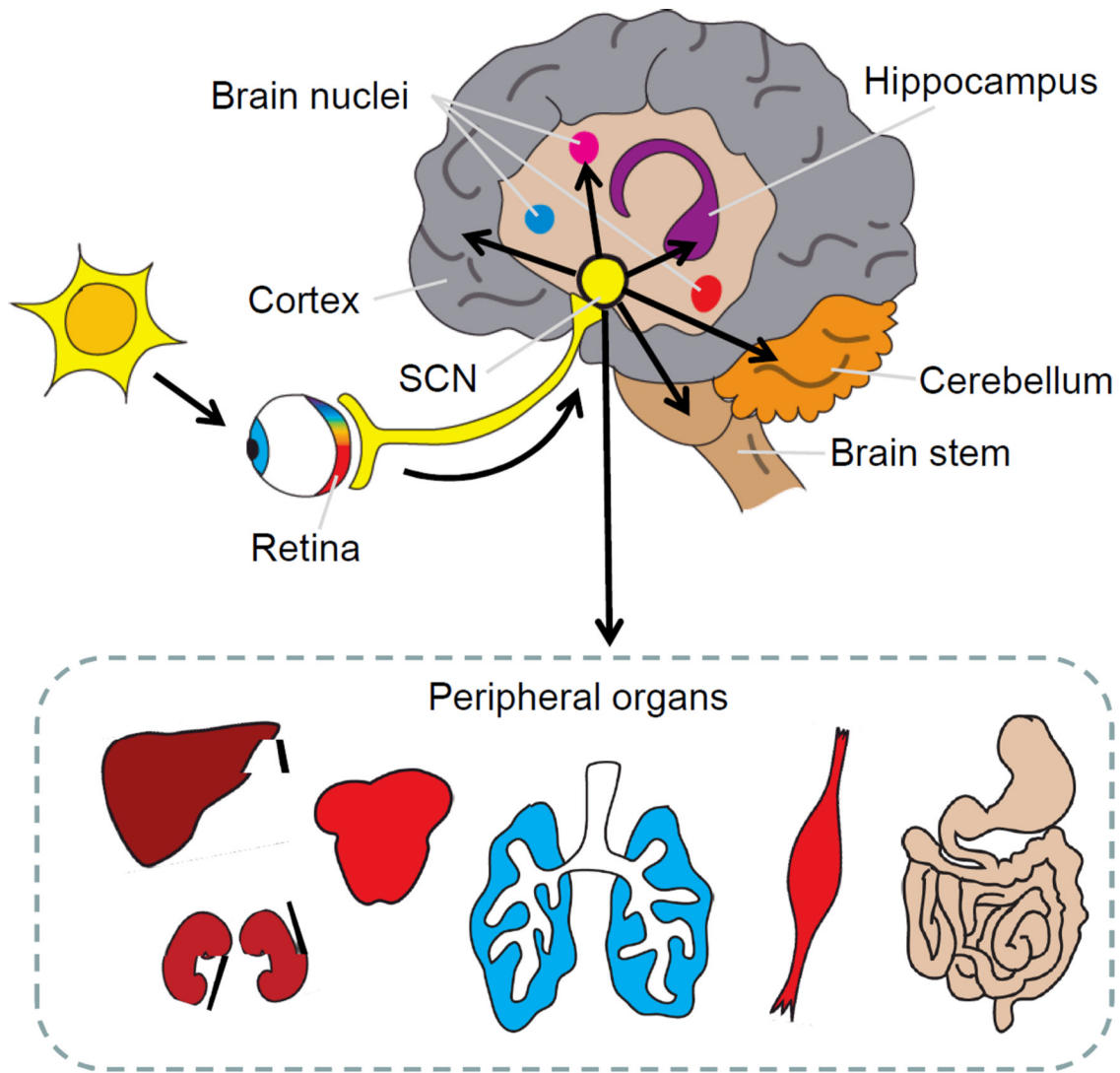
Alzheimer's disease (AD). AD is the most common neurodegenerative disease in aged humans. It is characterized by progressive dementia, memory impairment, mood change and disrupted circadian rhythms. The anatomical feature of AD is a degeneration of multiple regions of the brain.¹³⁷ Degeneration in the VLPO, SCN and basal forebrain is, almost certainly, responsible for problems with sleep and circadian rhythms¹³⁸. Nocturnal production of melatonin is also significantly reduced. Histological hallmarks of AD are extracellular protein deposits where β -amyloid peptide is a main component (senile amyloid plaques) and intraneuronal aggregates of hyperphosphorylated microtubule associated protein tau (neurofibrillary tangles)¹³⁷. Senile plaques and tangles play essential roles in generation of reactive oxygen species. Oxidative stress is, most likely, responsible for the death of neurons and astrocytes in the brain of AD patients⁹⁴.

Parkinson's disease (PD). PD is neurodegenerative disease that significantly affects a patient's motor functions. Typical pathological features are bradykinesia, tremor and rigidity¹³⁹. PD is associated with progressive loss of the substantia nigra dopaminergic neurons. Intracytoplasmic inclusions termed Lewy bodies formed by α -synuclein-containing aggregates and dystrophic neuritis are the most common anatomical abnormalities observed in the brain of PD patients¹⁴⁰. PD is associated with reduced mitochondria function and increased oxidative damage to lipids, proteins and DNA; protein and lipid aggregates found in Lewy bodies are generally oxidized. Evidence of circadian disruption in PD include: significant sleep disturbance, and problems with the ability to fall and/or stay asleep¹⁴¹. There are also indications for disrupted rhythms of melatonin release.

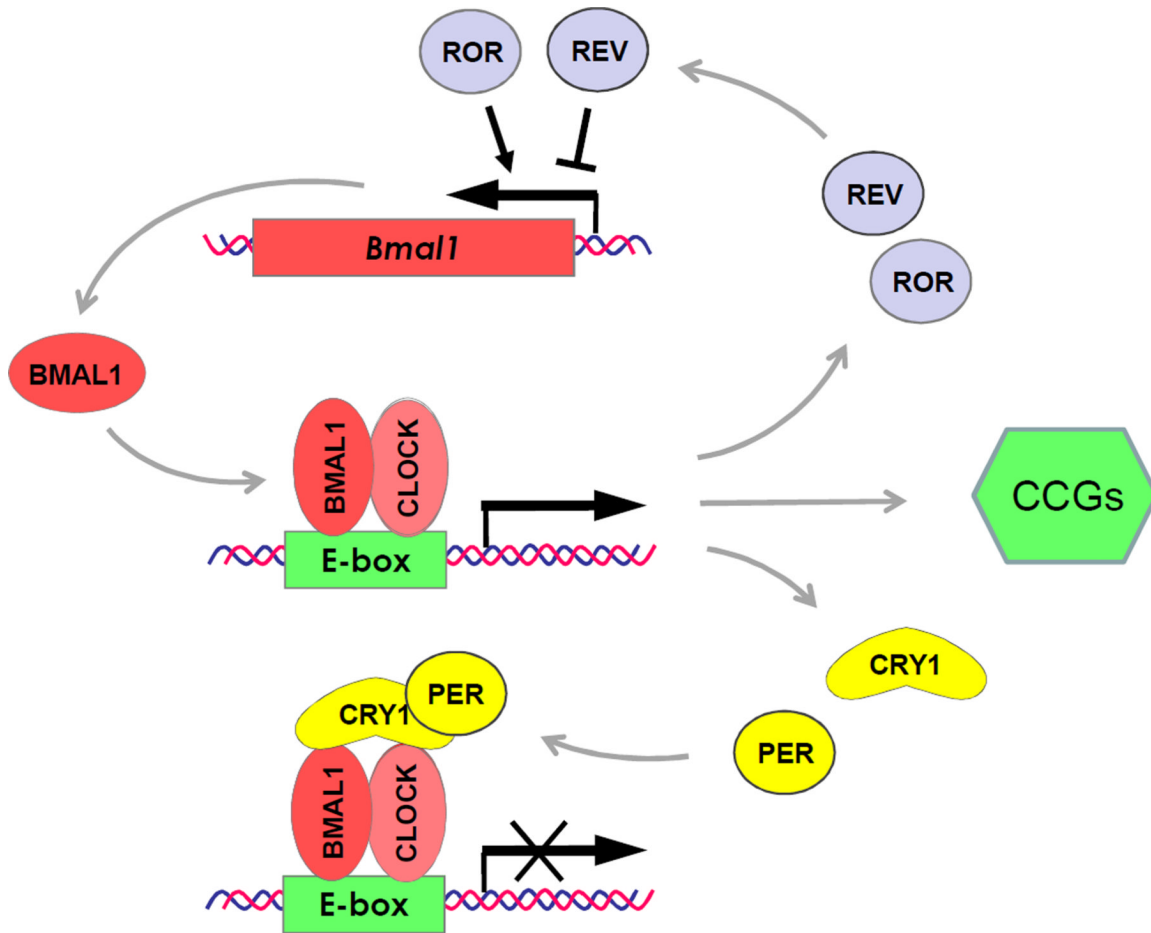
Huntington's disease (HD). HD is an autosomal dominant neurodegenerative disorder. Pathological features are cognitive impairment, motor skill impairment and premature death¹⁴². The disease is caused by expansion of trinucleotide repeat in the huntingtin gene, which leads to the formation of a polyglutamine tract at the N-terminus of the protein. The mutated protein cannot be efficiently degraded and forms aggregates leading to the accumulation of neuronal inclusion bodies. It was suggested that the inclusion bodies affect mitochondria and increase oxidative stress, which cause death of striatal neurons and astrocytes¹⁴². Atrophy of the lateral hypothalamus was suggested to contribute to the disruption circadian timing in HD patients¹⁴³.

Online 'at-a-glance' summary

- Recent data suggest that the circadian clock regulates cognitive functions such as memory and mood in sleep-dependent and sleep-independent manner.
- Some circadian clock proteins are important regulators of longevity.
- Circadian rhythms in sleep and behaviour are significantly affected by ageing; this impairment can contribute to the cognitive decline of ageing brain
- Circadian rhythms in sleep and behaviour are significantly disturbed in AD, PD and HD patients. Circadian clock disruption can serve as a biomarker of a neurodegenerative disease progression.
- Circadian clock dependent control of metabolism, oxidative stress response, DNA repair and autophagy can contribute to brain ageing and neurodegeneration.
- Restoration of circadian clock function in animal model of neurodegeneration improves a cognitive performance and increases the survival.
- Restoration of circadian rhythms with combined light and melatonin therapy improves sleep quality in humans.



A



B

Figure 1. Circadian clock in mammals

(A) A hierarchical organization of the circadian clock. The master pacemaker is located in the SCN of the hypothalamus and generates internal circadian rhythms in gene expression, electrophysiology and hormone secretion; direct projection from the retina transfers information about light/darkness to the SCN, which synchronizes a phase of SCN rhythms with the outside world. Local circadian clocks are found in different brain regions and throughout the body (peripheral oscillators). Electrical and humoral signals from the SCN synchronize phases of local circadian clocks oscillations. Local clocks generate rhythms in gene expression, metabolism and other physiological activities. (B) The molecular circadian oscillator. For the circadian clock transcriptional-translational negative feedback loop positive elements are shown in red, negative elements in yellow, and components that stabilize the loop in grey. Basic-HLH-PAS domain containing transcriptional factors BMAL1 and CLOCK (or NPAS2) regulate the transcription of genes with circadian E box elements in the promoter and represent positive elements of the transcriptional-translational feedback loop. The BMAL1:CLOCK complex activates the expression of *Per* and *Cry* genes. *PER* and *CRY* represent negative elements of the loop; they form complexes and inhibit the activity of BMAL1:CLOCK and hence their own expression. *Rev-Erb- α* and

RORs represent an additional loop, these transcriptional factors negatively (Rev-Erb- α) and positively (RORs) regulate the expression of BMAL1. Finally, the BMAL1:CLOCK complex regulates the expression of circadian clock controlled genes (CCGs), which provide a circadian output in physiology.

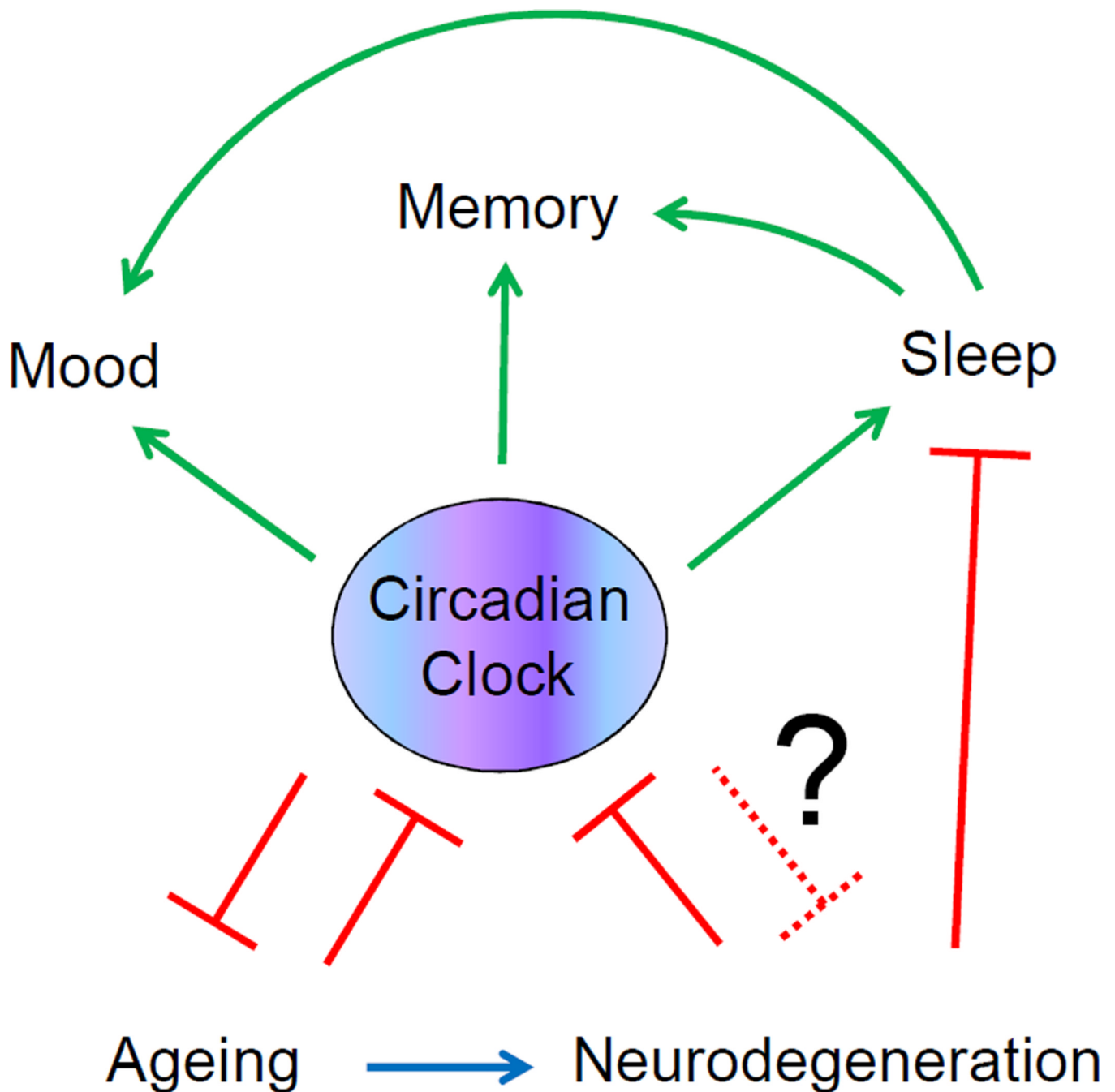


Figure 2. The circadian clock, ageing and cognitive functions

The circadian clock regulates sleep and other brain cognitive functions such as memory and mood in a sleep-dependent and sleep-independent manner. Ageing is associated with a decline in the activity of the circadian system; this decline in turn can contribute to ageing and to age-associated changes in sleep, memory and mood. Neurodegeneration is also associated with ageing and affects sleep and circadian clock functions, this disruption of sleep and circadian rhythms will affect cognitive functions. It is possible that the circadian clock is involved in control of neurodegeneration. Potential circadian clock independent effects of ageing and neurodegeneration on cognitive functions are omitted for simplicity.

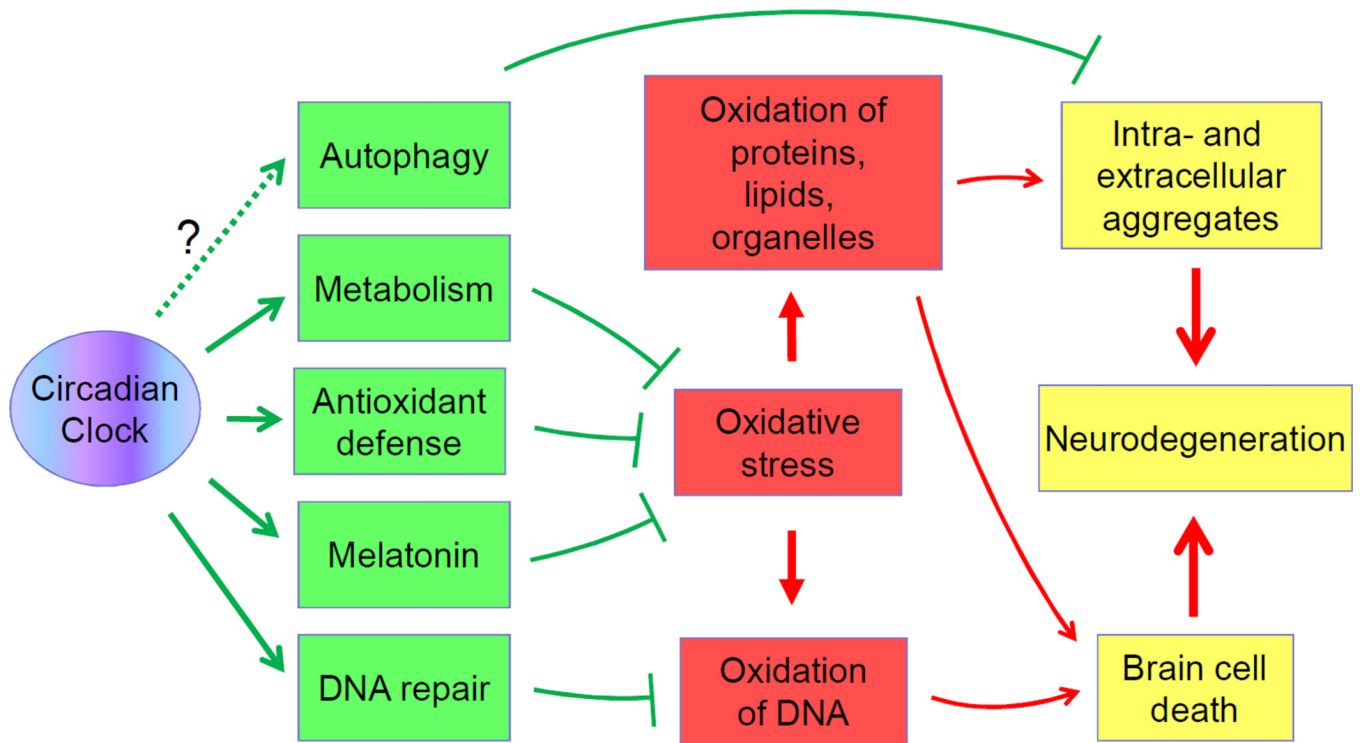


Figure 3. Potential mechanisms of circadian clock-dependent regulation of neurodegeneration

The circadian clock regulates metabolism, ROS homeostasis, DNA repair and, probably, autophagy (circadian clock controlled systems and pathways are shown in green). Disruption of circadian system function will compromise the activities of these systems, which will lead to oxidative stress (shown in red) and accumulation of intra- and extracellular aggregates in the brain. This in turn will lead to brain cell death and degeneration of brain structures (shown in yellow). Similar mechanisms can contribute to the changes in the brain during the normal ageing.