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Published Version:
Cunha Alves, T., Musilek, K., Monti, B. (2025). Interplay between circadian rhythms and epigenetics in neural stem cells and Alzheimer's disease. PROGRESS IN NEUROBIOLOGY, 252, 1-13 [10.1016/j.pneurobio.2025.102808].

Availability:
This version is available at: https://hdl.handle.net/11585/1022053 since: 2025-08-29

Published:
DOI: http://doi.org/10.1016/j.pneurobio.2025.102808

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PII: S0301-0082(25)00099-1

DOI: https://doi.org/10.1016/j.pneurobio.2025.102808

Reference: PRONEU102808

To appear in: *Progress in Neurobiology*

Received date: 10 April 2025
Revised date: 2 July 2025
Accepted date: 7 August 2025

Please cite this article as: Tânia Raquel Cunha Alves, Kamil Musílek and Barbara Monti, Interplay Between Circadian Rhythms and Epigenetics in Neural Stem Cells and Alzheimer's Disease, *Progress in Neurobiology,* (2025) doi:https://doi.org/10.1016/j.pneurobio.2025.102808

Interplay Between Circadian Rhythms and Epigenetics in Neural Stem Cells and Alzheimer’s Disease

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Abstract

The circadian clock, as a molecular timekeeper, influences most behavioural and physiological processes. Numerous symptoms associated with neurodegenerative diseases, such as sleep disorders, anxiety, and mood alteration, are linked to circadian clock dysregulation. Dysregulation of the circadian system is increasingly implicated in the onset and progression of Alzheimer's disease, and emerging evidence highlights a bidirectional relationship between Alzheimer’s disease and circadian clock disruption. A crucial point is that the circadian clock regulates adult neurogenesis, a process that is significantly impaired in Alzheimer’s disease. Recent advancements suggest that the dynamic epigenetic mechanisms—including DNA and histone modifications as well as regulation by non-coding RNA—act as a critical regulation for circadian rhythms and neurogenesis. Therefore, research on circadian disruption and, particularly, focus on harmonising the circadian clock with neurogenesis in neurodegenerative diseases may also speed up the creation of innovative, circadian-based treatments to counteract the progress of neurological disorders from a new perspective. In this review, we explore potential epigenetic mechanisms linking the circadian system to neurodegenerative diseases, with a focus on Alzheimer's Disease.

Keywords

Neurodegeneration, Circadian clock, Neurogenesis, Epigenetics, Melatonin

1. Introduction

The circadian system is a conserved biological cycle generated and regulated daily in a self-sustaining and oscillatory manner, responsible for coordinating a wide range of molecular, physiological, and behavioural processes (Nassan and Videnovic, 2022). Although the sleep-wake cycle is the most widely recognised output of the circadian system, the mammalian circadian clock affects many physiological processes, from hormonal secretion, metabolic homeostasis, and body temperature to complex processes, such as memory formation and cognition (Nassan and Videnovic, 2022). This intrinsic timing system incorporates a molecular loop that can be entertainable by external factors called *Zeitgebers*. Although *Zeitgebers,* such as body temperature, diet, gravity, and physical activity, have a role in setting the clock, light is the most potent cue to synchronise internal rhythm with the 24-hour solar day. Nonetheless, rhythms must be endogenously self-sustaining, at least for a few cycles, after the *Zeitgebers* are eliminated, in order to be classified as a circadian rhythm (Aschoff, 1981). The rhythm produced by the biological clock controls physiological functions to optimise them to a particular time of the day, keeping the harmony of physiological processes within the organism and with nature and environmental changes. Lack of internal synchrony can have long- or short-term health consequences, for instance, shift work is thought to be a carcinogenic factor and has been associated with an increased risk of dementia (Ling et al., 2023; Schernhammer et al., 2003). Epidemiological studies have revealed that the risk of all-cause dementia is associated with shift work, and particularly, an increased tendency is observed with a longer number of years working on night shifts (Ling et al., 2023; Wang et al., 2022c). Multiple lines of evidence have suggested that a disruption of the temporal synchronisation leading to internal circadian dysfunction plays a role in neurodegenerative diseases (Videnovic et al., 2014). Although the precise mechanisms by which circadian dysfunction instigates and exacerbates the disease progression still need to be defined, a growing body of evidence supports that a link exists (Nassan and Videnovic, 2022; Ruan et al., 2021). Therefore, the *circa 24-hour diurnal rhythms* could be considered a potential therapeutic target to counteract neurodegenerative diseases (Nassan and Videnovic, 2022; Ruan et al., 2021). The regulation of circadian rhythms may be largely determined by the epigenetic system as a noteworthy mediator of environmental influences. Neural stem cells, which are essential for brain plasticity and repair – and whose functions are impaired in AD – are increasingly recognised as being regulated by both circadian and epigenetic mechanisms, offering a promising link between clock disruption and impaired neurogenesis (Ali and von Gall, 2022). Altogether, understanding how circadian rhythms are regulated and how their disruption may contribute to neurodegenerative disease can open new avenues for therapeutic intervention, particularly through epigenetic mechanisms. Herein, we examine current evidence linking circadian and sleep disturbances to Alzheimer's disease, with a particular focus on how circadian regulation and epigenetic alterations affect neural stem cells and may contribute to disease progression.

2. The circadian pacemaker

The circadian system in animals is arranged hierarchically, with a central brain clock at the top of the hierarchy and peripheral clocks throughout the body (Hastings et al., 2018). Anatomically, in mammals, the master circadian clock is contained in the hypothalamus within the suprachiasmatic nucleus (SCN), a bilateral nerve cluster of about 20000 neurons in rodents and 10000 neurons in humans (Abrahamson and Moore, 2001; Hofman and Swaab, 2002). Each of the neurons has a self-sustained and cell-autonomous circadian oscillator with a broad range in circadian periodicity varying between 22 to 30 hours (Hastings et al., 2018). To be effective, the SCN neurons must be constantly entrained to the day-night cycle of 24 hours, and this is achieved by direct retinal innervation and transmitted to the SCN via the retinohypothalamic tract (RHT) (Lucas et al., 2012). A subset of ganglion cells in the inner layer of the retina that express the melanopsin photopigment are considered the main intrinsic circadian photoreceptors. The other extrinsic photoreceptors, such as the rods and cones, play an auxiliary role in maintaining the circadian environment (Lucas et al., 2012). The role and importance of the SCN in the circadian system have been extensively studied, and *in vitro*, SCN organotypic slice cultures sustained a remarkable circadian oscillation with stable, robust, and coherent molecular loops due to intact circuit communication (Patton et al., 2016). Additionally, *in vivo*, SCN disruption, either by an electrolytic lesion or by key genes knockdown, leads to a dramatically weakened circadian clock, disturbed resting state and appearance of anxiety-like behaviour in mice (Wang et al., 2023). Interestingly, SCN-specific *Bmal1*-knockdown mice have been proposed as a potential animal model of depression (Landgraf et al., 2016). Through gap-junction-mediated electrical coupling, the SCN neurons maintain communication and synchronisation and are coupled to each other in a network (Colwell, 2005). Consistent rhythm across the entire organism and strong circadian outputs are dependent on robust circadian rhythmicity due to the network between SCN neurons (Beaule et al., 2011).

2.1. Molecular components of the circadian system

The daily oscillations are known to be maintained by a complex transcriptional and translational feedback loop of a set of genes referred to as the core clock genes (Mohawk et al., 2012). At the core, CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL1 (Brain and Muscle Arnt-Like protein 1) proteins heterodimerise, translocate into the nucleus, and bind to E-box enhancer elements to activate the rhythmic transcription of their target genes, the clock-controlled genes (CCGs). Amongst these are the remaining components of this feedback network, such as *PER* (Period)1, 2, and 3 and *CRY* (Cryptochrome)1 and 2 (Figure 1) (Mohawk et al., 2012). Once translated and upon reaching the threshold, these proteins interact and function as repressors of CLOCK:BMAL1 activity. Consequently, the transcription of *Per* and *Cry* is reduced, leading to the closing of this central negative feedback loop. Additionally, an auxiliary feedback loop is present, and its components, such as REV-ERB nuclear receptors and nuclear receptor ROR (RAR-related orphan receptor), are under the regulation of CLOCK:BMAL1. REV-ERBs can inhibit *Bmal1* expression, whereas RORs compete with REV-ERBs for shared DNA binding sites, ROREs (ROR response elements) and promote *Bmal1* expression (Mohawk et al., 2012). Nonetheless, a reductionist approach to simplify the molecular clock's fundamental mechanics is not feasible, and a multitude of different signals and different levels of regulations are in place to produce an integrated output over the 24-

hour cycle. For instance, even though PER proteins' timely accumulation was thought to be the stoichiometrically limiting step with phosphorylation by CK1 (Casein kinase 1) having a key role in PER stability (Lee et al., 2001), experiments with *Per2* mutant mice suggest that PER2 degradation can be a noncrucial (An et al., 2022). Additionally, compensatory mechanisms are settled, for example, with NPAS2 (Neuronal PAS Domain Protein 2) showing an overlapping role with CLOCK and shown to be able to compensate for the loss of CLOCK (DeBruyne et al., 2007). In mice with mutant PER2 unable to interact with CK1 steadily, although the loss of PER phosphorylation and subsequently lower CLOCK-BMAL1 expression rhythm amplitude was observed, the locomotor activity rhythms were maintained (An et al., 2022). Even though some level of circadian oscillations and locomotor activity may persist without PER phosphorylation, the circadian system presents several layers of complex regulation to orchestrate durable, fine-tuned circadian clock oscillations. Based on data collected from both small-scale and high-throughput experiments in mammals, 43% of all protein-coding genes have been shown to present oscillatory transcripts in a least one organ, indicating to be under-regulation of the core network. However, the proportion of rhythmic genes is highly tissue-specific, typically ranging from 2% to 20% in a given tissue (Zhang et al., 2014). In particular, one study analysed gene expression from post-mortem brain samples following time-of-death analysis, and among the healthy controls, a minimum of 417 genes were reported to show rhythmic oscillation across different brain regions, with, for example, 922 rhythmic transcripts in the dorsolateral prefrontal cortex (Li et al., 2013). Therefore, the ongoing exploration of the connections between molecular processes and the circadian clock reveals substantial interplay. The most well-recognized output of the circadian clock is the sleep/wake cycle (Franken and Dijk, 2024), but the CC governs diverse metabolic processes, while metabolic factors such as glucose, oxygen, ATP, NAD+, and glucocorticoids levels influence circadian function through AMPK (AMP-activated protein kinase) and SIRT1 (Sirtuin 1) activity (Marcheva et al., 2013). Among the physiological systems influenced by the circadian rhythm, metabolism remains the most extensively studied. Notably, insulin has a direct impact on circadian clock by regulating *Clock* expression in the liver. FOXO3 (Forkhead box O3), via the insulin-PI3K signalling, is crucial for circadian rhythmicity as it binds to the *Clock* promoter, forming a direct link between metabolism and the circadian clock (Chaves et al., 2014).

2.2. Impact of epigenetics on the circadian clock

The circadian feedback loops are intricately regulated by epigenetic mechanisms as important regulators, as well as mediators of the environment. In addition to the endogenous mechanisms, the *Zeitgebers*, the exogenous cues, can modulate the genetic code through epigenetic mechanisms, thus regulating *Clock* gene expression flexibly and dynamically over the day-night cycle (Koike et al., 2012). Several lines of evidence show that chromatin remodelling is an integral modulator of circadian gene transcription (Koike et al., 2012; Ripperger and Schibler, 2006). In particular, CLOCK has been shown to function as a histone acetyltransferase (HAT) (Doi et al., 2006), and SIRT1, a class III histone deacetylase (HDAC), counteracts the CLOCK activity (Belden and Dunlap, 2008). CLOCK protein was reported to act primarily at H3 and H4 and H3 Lys-14 was reported to be a major site. Due to the role of acetylation at H3 Lys-14 on transcriptional activation, the HAT function of CLOCK is considered a crucial player for the rhythmic input to the circadian clock (Doi et al., 2006). On the other hand, SIRT1 targets *Bmal1* and *Per2* and is suggested to regulate specifically the amplitude of Clock-regulated gene expression, although SIRT1 activity is not imperative for the clock rhythm (Belden and Dunlap, 2008). A key example of histone modifications (Figure 2A) in circadian control involves the core repressor protein, REV-ERBα (Kim et al., 2018). REV-ERBα rhythmically recruits the NCoR-HDAC3 corepressor complex to specific genomic regions, leading to histone deacetylation and transcriptional repression of target genes (Kim et al., 2018). Additionally, DNA methylation patterns exhibit circadian oscillations, which are crucial for the rhythmic expression of clock genes. For instance, the promoter regions of core clock genes, such as *BMAL1* and *PER2*, show dynamic methylation changes that correlate with their transcriptional activity (Cronin et al., 2017). Remarkably, Cronin and collaborators showed that rhythmic methylation of *BMAL1* was altered in samples from Alzheimer's patients' postmortem brains and fibroblasts and is associated with alteration in *BMAL1* rhythmic expression (Cronin et al., 2017). Beyond DNA methylation and histone modifications, non-coding RNA (Figure 2B) represents other critical layer of circadian regulation. The miRNA miR-132, induced via a MAPK/CREB-dependent mechanism, exhibits circadian oscillations in expression and has been shown to target the *Clock* gene (Cheng et al., 2007) and play a role in cognitive capacity (Aten et al., 2018). Several miRNAs (Figure 2B) have been suggested to regulate the circadian clock as deeply analysed in a comprehensive review (Kinoshita et al., 2020). Interestingly, DNA methylation-derived epigenetic clock (Figure 2C), biomarkers based on DNA methylation, is highly correlated to chronological age (Bell et al., 2019; Horvath and Raj, 2018). One of the earliest models and extensively used in age and cancer research is Horvath's clock, which is based on CpGs sites (Wang et al., 2022a). Curiously, a sizable part of the 353 CpGs sites of Horvath's clock are found close to promoters of genes related to development and differentiation (Horvath, 2013). Notably, in neuronal cell cultures, these CpGs sites closely correspond with the differentiation status distinguishing between neural precursors to mature neurons (Horvath, 2013).

2.3. Circadian Clock in Diseases

Circadian disruptions have been linked to mental and physical health problems, and evidence points to a bidirectional connection between disease and the circadian rhythms in immunologic, cardiometabolic, allergic, neurodegenerative and psychiatric disorders (Xie et al., 2019). Assessing circadian disruption involves measures such as phase (timing), period and amplitude of circadian rhythms and alignment between environmental and endogenous rhythms (Fishbein et al., 2021). To monitor circadian rhythms and sleep, melatonin and its metabolite 6-sulfatoxymelatonin are currently considered the standard biomarkers in clinical trials and practice. However, due to the limitations of these metabolites, there is a continuous effort to find a more suitable biomarker and greater potential for chronotherapy (Mirick and Davis, 2008; Tomita et al., 2019; Uberos et al., 2011). Clinically, the circadian influences can be determined to have a significant role in symptoms or disease onset, often showing a clear circadian preference, as seen in the early morning peaks of myocardial infarction and stroke, along with night-time exacerbation of asthma and inflammatory diseases (Muller et al., 1985; Scheer et al., 2021). Genetically, diseases resulting from mutations in clock genes are rare in humans. Nevertheless, mutations in core clock genes cannot be overlooked, and genome-wide association studies have identified clock gene SNPs linked to increased risk for tumour development, sleep disorders and metabolic and neurodegenerative diseases (Gršković and Korać, 2023). Genetic variants in clock genes lead to sleep deprivation, which, in turn, has been linked to increased amyloid-beta accumulation, contributing to Alzheimer’s disease (AD) susceptibility and progression. Associations between variants of different circadian genes have been observed together with potential risk factors for AD and other neurodegenerative diseases (Table 1). For illustration, preference for morning or evening activity, sleep quality, and duration have been suggested to be, to some extent, genetically inherited traits (Gršković and Korać, 2023; Liu et al., 2022). Interestingly, approximately 45% of the variability in sleep duration and quality has been assigned to genetic variations (Kocevska et al., 2021). An example of such mutation is a missense mutation (S662G) in the core gene *PER2*, causing familial advanced sleep phase syndrome (Gu et al., 2012). Advanced sleep phase syndrome is a circadian disruption triggering sleep onset in the early evening (18:00–20:00hours) and sleeplessness in the early morning (01:00– 03:00h) (Gršković and Korać, 2023; Liu et al., 2022). On the other hand, mutation of the core clock genes is often used to study clock-related dysfunction. In animal studies, disruptions in the intrinsic clocks of animals relative to external timing cues can lead to various phenotypes and diseases such as obesity, metabolic dysfunction that impacts cognition and mood, anxiety, sleep alterations, and depression-like behaviour (Birky and Bray, 2014; Karatsoreos et al., 2011). Although sleep and circadian rhythms are modified with ageing, sleep-wake disruption is found to be more severe in AD patients than typical age-related disruption. In particular, the type of disruption seems to be distinct between ageing and AD, with AD patients presenting increased sleep fragmentation with longer night-time awakening periods, excessive daytime naps and decreased daytime activity (Weissová et al., 2016). An indirect role of the molecular circadian clock in AD is already well established. Poor sleep adversely affects behaviour and cognitive processes (Lv et al., 2022). Furthermore, there is mounting evidence that sleep deprivation increases the amount of soluble amyloid in the brain and causes insoluble amyloid to accumulate even in the preclinical stage of AD (Ju et al., 2014; Ju et al., 2013; Roh et al., 2012). Recent studies have also demonstrated that Aβ can directly disrupt the molecular circadian clock by promoting the degradation of core clock components such as BMAL1 and CBP, leading to impaired *Per2* transcription and altered circadian rhythms (Song et al., 2015). In addition to molecular changes, APP(β-amyloid precursor protein)-overexpressing TgCRND8 mice, a well-characterized Aβ model, exhibit age-dependent alterations in activity rhythms and increased stereotypic behaviors, resembling circadian and behavioral symptoms observed in AD patients (e.g. restlessness and sleep disruption) (Ambrée et al., 2006). In addition to Aβ mouse models, hyperphosphorylated tau has been suggested to be negatively affecting sleep quality and duration. Mice with pure tauopathies have been shown to have sleep disturbance, suggesting that tau is a major contributor to sleep disturbance in AD (Lew et al., 2021). Lack of sleep raised tau protein concentration in human CSF (cerebrospinal fluid) and accelerated the spread of tau aggregates (Wang and Holtzman, 2020). Both Aβ and tau mouse models demonstrate altered sleep and circadian phenotypes, further supporting a link between AD pathology and circadian dysfunction.

3. Circadian Clock Dysregulation in Alzheimer's Disease

Many neurobiological processes are regulated over the 24-hour cycle, such as neurogenesis, neurotransmission, inflammation, and neuronal metabolism. Neurodegenerative disorders frequently involve a progressive breakdown of the circadian rhythms that govern rest, activity, sleep, alertness, psychological processes, motor control, and metabolism (Hastings and Goedert, 2013). One common feature of many neurodegenerative diseases is the acceleration of disturbances in the sleep/wake rhythm (Hastings and Goedert, 2013). AD is the most common chronic age-dependent neurodegenerative disorder that is characterised by an accumulation of Aβ (amyloid beta) plaques and hyperphosphorylated tau (Association, 2023). In this irreversible disorder, characterised by progressive cognitive decline, the symptoms evolve gradually over several years. The initial signs of the disease include forgetting recent events or conversations. However, as the disease progresses, severe memory problems develop, along with the loss of the ability to perform everyday tasks (Abubakar et al., 2022). Importantly, disturbances in sleep and circadian rhythms frequently emerge in the preclinical phases of AD, often preceding noticeable cognitive symptoms. These include fragmented sleep, excessive daytime sleepiness with reduced daytime activity levels and increased nighttime awakenings (Rigat et al., 2023). One particularly phenomenon observed in AD patients is “sundowning,” a syndrome marked by increased confusion, agitation, and behavioral disturbances occurring in the late afternoon or evening (Volicer et al., 2001). As AD progresses, additional symptoms may manifest, such as increasing confusion and disorientation, obsessive, repetitive or impulsive behaviour, delusions, problems with speech or language, disturbed sleep, changes in mood, and difficulty performing spatial tasks (Abubakar et al., 2022). The exact mechanisms underlying the pathogenesis of AD remain elusive, and molecular mechanisms are complex and multifactorial, involving genetic, biochemical, and environmental factors. Central to the neuropathological hallmarks of AD are Aβ plaques, neurofibrillary tangles, gliosis, and neuronal loss (Zheng and Wang, 2024). APP is a transmembrane protein that, upon proteolytic cleavage by β-secretase and γ-secretase produces Aβ peptides. These peptides can aggregate to form amyloid plaques, a hallmark of AD pathology (Guo et al., 2020). Mutations in the *APP* gene can increase the production of Aβ, leading to early-onset familial Alzheimer’s disease (FAD) (Lanoiselée et al., 2017). Relatedly, mutations in the *PSEN1* (Presenilin 1) gene are the most common cause of FAD (Lanoiselée et al., 2017). *PSEN1*, a component of the γ-secretase complex, plays a crucial role in the cleavage of APP, and therefore, *PSEN1* mutations result in altered γ-secretase activity, leading to increased production of the pathogenic Aβ42 isoform (Borchelt et al., 1996). This isoform is more prone to aggregation and is a major component of amyloid plaques (Guo et al., 2020). The accumulation of Aβ peptides in the brain triggers a cascade of events, including tau hyperphosphorylation, neurofibrillary tangle formation, synaptic dysfunction, and neuronal death (Guo et al., 2020), and are accompanied by neuroinflammation (Leng and Edison, 2021). Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA regulation, play significant roles in the pathogenesis of AD, as deeply reviewed elsewhere (De Plano et al., 2024; Migliore and Coppedè, 2022; Nikolac Perkovic et al., 2021). In AD, the disease progression is accompanied by the circadian disturbance severity, but surprisingly, circadian disturbance is an early symptom of the disease and, therefore may be a useful tool for prediction and early diagnostic marker (Van Someren, 2000). Nonetheless, it is now widely appreciated that circadian clock abnormalities are not only a symptom of AD but, conceivably, circadian disruptions feed into the onset and progression of AD, while a proper circadian system provides greater resilience to AD pathogenesis. It is still widely debated whether a bidirectional link or something more complex is afoot between AD and circadian abnormalities (Hastings and Goedert, 2013). Interestingly, mechanisms linking AD-associated genes and circadian abnormalities have been implied. One study in microglia and bone marrow-derived macrophages has implicated that the AD-associated gene *Psen2* has potential roles in immune systems through the DNA hypermethylation-mediated repression of REV-ERBa (Nam et al., 2022). Additionally, circadian disturbances appear to correlate with the degree of amyloid plaque burden (Kang et al., 2009; Wang et al., 2016). One study using *in vivo* microdialysis in mice showed that Aβ levels secreted into the brain interstitial fluid in the hippocampus of mice fluctuate during the day (Kang et al., 2009). Addedly, Aβ levels were found to be negatively correlated with the amount of time asleep indicating a role of the circadian rhythm in supporting the clearance of Aβ (Kang et al., 2009). Moreover, Aβ has been shown to disturb molecular clock homeostasis and cause changes to metabolic circadian rhythmicity in human fibroblasts and primary mouse neurons in the presence of pre-aggregated Aβ (Schmitt et al., 2017). Neurodegeneration within SCN, evaluated by measurements of the glia/neuron ratio, has been observed in AD patients. Interestingly, the loss of neurotensin cells and arginine vasopressin cells, within the SCN is linked to different effects, circadian amplitude, and activity fragmentation (Harper et al., 2008). The undisputed key signature of neurodegeneration is protein aggregation and Aβ plaques, and tau neurofibrillary tangles in AD. This raises the question of how the circadian clock and clock-control processes intervene in protein aggregation: the highest direct impact comes from circadian regulation on preserving a healthy proteome, critical to preventing toxic aggregation and neurodegeneration. Circadian control over pro-neurodegenerative factors has been reported. One study shows that CLOCK/BMAL1 modulates *Psen2 (Presenilin 2)* gene expression and that *Psen2* exhibits a strong circadian rhythm. PSEN2, associated with early-onset AD, regulates the levels of Aβ, and its rhythmic expression has been suggested both in SCN and in peripheral tissues (Bélanger et al., 2006; Panda et al., 2002). Additionally, a recent study linked the core clock gene, *Bmal1*, to the astrocyte proteostasis (McKee et al., 2023). Both *in vitro* and *in vivo*, deletion of *Bmal1* in astrocytes leads to an activation state that increases extracellular protein degradation while impairing astrocytes' ability to support neurons and disturbing circadian rhythms (McKee et al., 2023). And *Bmal1*-deficient astrocytes exhibit enhanced endocytosis and lysosome-dependent protein cleavage *in vitro* (McKee et al., 2023). Additionally, behaviour studies in *Bmal1*-KO mice previously showed changes related to locomotion and cognitive capacity (Castro-Zavala et al., 2022), with reports of reduced lifespan and age-related pathologies (Kondratov et al., 2006). This potential role of clock proteins in the control of degradation pathways supports the hypothesis that circadian disruptions feed into the onset and progression of AD. Previously, circadian genes were also found enriched among genes linked to illness with substantially greater frequencies than would be predicted (Zhang et al., 2014). And AD risk genes are associated with circadian genes. Based on GWAS meta-analysis, 41 AD-risk genes have been identified (Jansen et al., 2019; Kunkle et al., 2019). From these 41 AD-risk genes, 13 genes are suggested to be under the regulation of the circadian clock in the SCN (Figure 3A) (Pembroke et al., 2015). Early-onset AD has been strongly associated with three dominantly inherited mutations in *App*, *Psen1*, and *Psen2* (Karch and Goate, 2015) and *Psen2* and *App* show significant fluctuating gene expression (Figure 3B-D).

4. Neural stem cells and neurogenesis

Neural stem cells (NSCs) are a unique population of cells essential for brain development and repair. NSCs are primarily located in two neurogenic regions of the adult mammalian brain: the subventricular zone (SVZ) of the lateral ventricles and the sub granular zone (SGZ) of the dentate gyrus in the hippocampus (Bond et al., 2015). NSCs possess the ability to self-renew by symmetric divisions and differentiate into various neural lineages via asymmetric divisions, including neurons, astrocytes, and oligodendrocytes. Neurogenesis in the hippocampus is defined by the ability to produce new neurons from precursor cells involving cell division, migration, and differentiation of NSCs in the hippocampus and, therefore, plays an important role in learning and memory (Moradi et al., 2021). During embryonic development, NSCs are highly proliferative, contributing to the formation of the complex architecture of the brain. In adults, NSCs maintain a more quiescent state, but they can be activated in response to specific stimuli, such as injury or learning experiences (Shi et al., 2024). The regulation of NSCs is a complex process and epigenetic mechanisms have emerged as key regulators of the sequential stages of neurogenesis. A previous study identifies that the selective translation of epigenetic modifiers, such as histone methyltransferases and demethylases, is crucial for the temporal progression and differentiation of NSCs (Wu et al., 2022). In particular, fibrillarin (FBL) is suggested to be a key driver by enhancing translationally the H3K27me3 modifiers (Wu et al., 2022). Moreover, extensive research has established that chromodomain helicase DNA-binding domain 5 (CHD5) is specifically expressed in neural tissues and has a role in promoting neuronal differentiation by enhancing the activation of neuronal genes, such as *NeuN* and *Ncam* (Egan et al., 2013). Peptide pull-down assays using nuclear lysates from mouse cortices and human SH-SY5Y neuroblastoma cells indicated that the endogenous CHD5 protein was significantly enriched on H3K27me3, which contributes to the silencing of non-neuronal genes. This suggests that the direct binding of CHD5's chromosomal domain to H3K27me3 is essential for neuronal differentiation (Egan et al., 2013). A recent study demonstrated the role of CHD5 in promoting neuronal differentiation via the regulation of Six3 to repress *Wnt5a* (Shrestha et al., 2023). Recent developments in cerebellar granule cells showed that H3K4me3/H3K27me3 bivalency is required to regulate the precise timing of this differentiation (Mätlik et al., 2023). Within the analysis of gene ontology of all genes that were bivalent at two different time points of differentiation, genes associated with neurogenesis were frequent. Additionally, neuron projection morphogenesis and synaptic signalling also showed a strong association (Mätlik et al., 2023). Bivalency is a notable feature of the epigenetic regulation of neurogenesis. Bivalence is thought to be a steady-state mechanism or transcriptionally inactive prepared for rapid expression when stimulated, and hence, following differentiation, these epigenetic markers exhibit monovalent characteristics of suppression or activation (Albert and Huttner, 2018).

5. Adult neurogenesis' interplay with the circadian clock and Alzheimer's Disease

The links between the circadian clock, AD, and the specific involvement of each cell type in the disease course are puzzling and poorly understood. AD itself is a challenging enigma, with over 34 canonical and intricately linked pathways (Mizuno et al., 2012). Additionally, the clock-controlled genes are rhythmically transcribed in an organ-specific manner (Zhang et al., 2014). Adding an extra level of complexity, the effects of a protein rhythm are not straightforwardly correlated with the tissue gene expression. A good example could be insulin-like growth factor (IGF1). The expression of *Igf1* fluctuates highly in the liver, however, considering that liver-derived IGF1 is the major source of circulating IGF1, IGF1 signalling in other tissues is most likely under clock influence (Zhang et al., 2014). Besides, IGF1 is able to cross the blood-brain barrier and exert critical functions within the CNS, including promoting neurogenesis and providing neuroprotection (Mir et al., 2017; Zeng et al., 2024). Thus, deciphering the genetic effects and underlying molecular mechanisms for shared pathways between AD and tissue-specific clock-controlled genes may shed more insights, although it requires careful deliberations. The hippocampus, the adult neurogenesis centre, is one of the most affected regions in AD (Babcock et al., 2021). Within the complex nature of AD, neuronal loss is a major pathological hallmark of AD, and one common feature, reported as well in other neurodegenerative diseases, is impairment in the proliferation of progenitor cells (Moreno-Jiménez et al., 2019). Numerous studies have addressed the interplay between the circadian clock and NSCs proliferation and differentiation (Ali and von Gall, 2022; Bouchard-Cannon et al., 2013; Malik et al., 2015). The reduction of neurogenesis function, due to its crucial role in maintaining brain plasticity and function throughout life, increases the rate of neurodegeneration (Polis and Samson, 2021). Cognitive reserve, as the brain's ability to withstand neuropathological damage and maintain cognitive function despite brain ageing or injury, is highly dependent on neurogenesis and synaptogenesis (Vockert et al., 2024). The idea that CCs may regulate adult neurogenesis was first supported by a study using *Bmal1* and *Per2* knockout mouse models (Bouchard-Cannon et al., 2013). Thymidine Analog Injections revealed that timely cellular proliferation in the SGZ is desynchronised with the absence of *Per2* or *Bmal1*, leading to quiescent neural progenitor cells losing their ability to enter the cell cycle at the right time. In particular, the authors suggest that PER2 is involved in gating the cell-cycle entrance of quiescent neural progenitor cells, while BMAL1 affects the cell-cycle exit timing (Bouchard-Cannon et al., 2013). Interestingly, a follow-up *in vitro* study found that differentiation of neurosphere cultures is affected by the abolishment of circadian proteins, resulting in unusually high differentiation into glial cells rather than neurons and overall higher cell death (Malik et al., 2015). Together, these data suggest that clock genes regulate adult NSCs via *Per2* and *Bmal1*, with potential implications for treating impaired brain functions. More recent studies have additionally highlighted the timing importance of neurogenesis through the influence of circadian rhythms (Ali and von Gall, 2022). Further work is needed to determine how circadian clock proteins influence the NSCs differentiation and proliferation and, whether such proteins are accountable for the NSC's pathogenesis of AD. A conceivable connection can be found in the molecular pathways' dysfunction in NSCs. AlzPathway is an AD signalling pathway map that gives mechanistic cues in intra-, inter- and extra-cellular processes to untangle the AD mechanism (Mizuno et al., 2012). When looking at the AD pathway in NSCs, molecules associated with the WNT signalling pathway appear as key involvement in dysregulated pathways (Figure 4A). Several lines of evidence have confirmed the link between dysregulated WNT signalling and the pathogenesis of AD (Abubakar et al., 2022; Inestrosa et al., 2002; Inestrosa and Toledo, 2008; Nagu et al., 2022; Palomer et al., 2019). WNT signalling is an essential signal transduction pathway that controls the balance between self-renewal and induction of neuronal differentiation (Aghaizu et al., 2020), and studies using adult rat hippocampal neural progenitor cells showed that WNT signalling preserves the multipotency of NSCs and controls their differentiation (Wexler et al., 2009). Several genes in WNT signalling are under circadian regulation (Matsu-Ura et al., 2018). As per expression profiles of genes, data from microarrays of different tissues, from WNT signalling 126 genes in SCN, 32 in the brain stem and 28 in the cerebellum were found to be rhythmically expressed (Soták et al., 2014). ChIP-Seq analysis and shRNA knockdown of *Bmal1* demonstrated a direct link between WNT and circadian clock with rhythmic occupancy of BMAL1 on promoters of components of the WNT pathway, such as *Wnt10a, β-catenin, Dishevelled Segment Polarity Protein 2, and Transcription Factor 3* (Guo et al., 2012). In contrast, over-expression of *Bmal1* increased *β-catenin* expression and cell proliferation (Lin et al., 2013).

6. Melatonin as a potential bridge between the circadian clock and adult neurogenesis

The production and release of several hormones follow a daily pattern, and among these are melatonin, cortisol, prolactin, thyroid hormone, and growth hormone (Dijk et al., 2012; Gnocchi and Bruscalupi, 2017; Posadzki et al., 2018; Vakili et al., 2016; Yuzhen and Zheng, 2021). Melatonin, or *N*-acetyl-5-methoxytryptamine, often referred to as the “sleep hormone”, plays a critical role in regulating the circadian clock. Melatonin is an indole amine mainly produced and best known to be secreted by the pineal gland (Posadzki et al., 2018). It should be noted that additional sources of melatonin are observed, and melatonin production by peripheral cells is indicated to act by autocrine or paracrine mechanisms (Reiter et al., 2024; Slominski et al., 2012). From the pineal gland, melatonin is secreted into the bloodstream, and beyond its role in sleep onset, duration, and quality, melatonin exhibits antioxidant properties and regulates glucose homeostasis and energy balance. Synthesised from tryptophan through serotonin, melatonin levels typically rise in the evening, promoting sleep, and levels drop in the morning, aiding wakefulness (Lee et al., 2021). Interestingly, longer sleep duration was positively associated with its longer secretion (Duffy et al., 2022). Numerous clinical studies are ongoing for a variety of diseases (Boutin et al., 2023). Nevertheless, the specific direct or indirect mechanisms of melatonin action in such pathologies are still sparsely elucidated. Therefore, scepticism persists with reasonable questioning of the direct role of melatonin in such a wide range of diseases, and further experimental evidence with clarification of the impact of confounding factors, such as sleep, and a critical assessment is required. Notwithstanding, melatonin’s role in sleep regulation and circadian rhythms has been addressed in numerous studies (Yao et al., 2023). Research has firmly established that melatonin primarily exerts its effects through two G protein-coupled receptors, melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2) (Liu et al., 2016), which are widely expressed in various mammalian organs and in neurogenic niches (Ahmad et al., 2023). Furthermore, some antidepressants, such as agomelatine, specifically target MT receptors, highlighting their potential therapeutic roles in mood regulation (Liu et al., 2016). It is suggested that MT1 is primarily involved in controlling the rapid eye movement (REM) stages of the alertness state during sleep, while MT2 preferentially promotes non-REM (NREM) sleep (Wang et al., 2022b). Studies suggest that activation of the MT1 receptor may stimulate the proliferation of NSCs and progenitor cells, ultimately leading to increased neurogenesis (Boiko et al., 2022). The MT2 receptor, on the other hand, might be more involved in neuronal differentiation and survival (Chern et al., 2012). Activation of these receptors triggers a cascade of downstream signalling events, including key pathways such as the ERK/MAPK pathway, the PI3K/Akt pathway, and the cAMP/PKA pathway (Figure 4C). The ERK/MAPK pathway plays a crucial role in cell proliferation and survival, making it a likely target for melatonin's neurogenic effects (Tiong et al., 2020). Involved in cell growth, survival, and neuroprotection, the PI3K/Akt pathway represents another potential mechanism through which melatonin might promote neurogenesis (Yu et al., 2019). The cAMP/PKA pathway regulates gene expression and neuronal differentiation. It's important to note that these pathways are interconnected and may act synergistically to promote neurogenesis. Melatonin appears to influence the expression and release of neurotrophic factors, which are essential for neuronal survival, growth, and differentiation (Armstrong and Niles, 2002; Tiong et al., 2020). Two key neurotrophic factors implicated in melatonin's neurogenic effects are brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor. Brain-derived neurotrophic factor (BDNF) is a key regulator of neurogenesis, neuronal survival, and synaptic plasticity, and melatonin upregulates BDNF via SIRT1 (Caruso et al., 2021), while Glial cell line-derived neurotrophic factor (GDNF) supports the survival and differentiation of dopaminergic neurons (Bourque and Trudeau, 2000). By increasing the levels of these neurotrophic factors, melatonin could indirectly promote the proliferation, differentiation, and survival of newly generated neurons. Beyond its receptor-mediated effects and influence on neurotrophic factors, melatonin also exhibits potent antioxidant and anti-inflammatory properties, which could contribute to its neurogenic potential by protecting NSCs and progenitor cells from oxidative stress (Bocheva et al., 2024). Additionally, melatonin can activate Wnt/β-catenin signalling (Shen et al., 2017).

7. Melatonin as an epigenetic circadian regulator for neurogenesis in Alzheimer’s Disease

Emerging evidence suggests that melatonin might influence neurogenesis through epigenetic mechanisms (Figure 4B), particularly by modulating DNA methylation patterns (Linowiecka et al., 2023). Melatonin appears to impact the activity of DNMTs, suggesting another layer of complexity in melatonin's regulatory role (Linowiecka et al., 2023). Specifically, it has been suggested to regulate DNMT1, which plays a crucial role in maintaining methylation patterns during cell division and differentiation (Linowiecka et al., 2023). In particular, 6-methyladenosine (m6A) modification has been suggested to be shaped by melatonin (Yang et al., 2020), to be involved in neurogenesis (Yoon et al., 2017), and to associate with neurodegenerative pathways (Du et al., 2021), consequently contributing to Alzheimer’s pathogenesis (Zhao et al., 2021). Additionally, the effects of melatonin may be linked to its regulation of nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 plays a crucial role in managing oxidative stress and inflammation and provides a neuroprotection role by modulating microglia activation (Saha et al., 2022). Moreover, Nrf2 promotes the proliferation and differentiation of NSCs (Kärkkäinen et al., 2014). Melatonin has been suggested to facilitate the activation of the Nrf2 gene’s promoter by recruiting CREB-binding protein (CBP)/p300 (Korkmaz et al., 2012; Sun et al., 2009). In NSCs, melatonin administration elicits a significant increase in histone H3 acetylation, accompanied by an upregulation of histone deacetylase isoforms, potentially as a compensatory response to melatonin-induced histone hyperacetylation (Sharma et al., 2008). This finding is consistent with a different study analysing the role of melatonin in neurogenesis (Li et al., 2017). Melatonin rescued the differentiation potential of NSCs by increasing the acetylation of histone H3 lysine 14 (H3K14). This process involves enhancing the histone acetyltransferase activity of CRB/p300 via ERK signalling pathways. The increased H3K14 acetylation alters the chromatin state of the promoters of bHLH factors Neurogenin1 and *NeuroD1*, activating their transcription and initiating neuronal differentiation (Li et al., 2017). One study using human hippocampal RNA samples and murine primary hippocampal cultures has implicated that in AD, WNT dysregulation is due to epigenetic mechanisms via SIRT2 (Palomer et al., 2022). The study found reduced levels of WNT receptors, *Frizzled1* and Frizzled7 mRNA in the hippocampus of early AD stages and this reduction was associated with decreased H4K16ac and increased SIRT2 activity at the promoters of these genes (Palomer et al., 2022).

8. Future perspectives

Circadian clock and neurogenesis are areas of interest in AD, both pathologically and therapeutically. Despite the critical role of epigenetic regulation in the CC and neurogenesis, these fields have often been studied separately in connection to AD. Aberrant DNA methylation, histone modifications, and non-coding RNA expression patterns have been implicated in the pathogenesis of AD (De Plano et al., 2024), affecting not only neuronal function but also the regenerative capacity of NSCs. Disease development is often accompanied by changes in histone modifications, and intervention in histone modifications can also activate endogenous repair mechanisms in the nervous system. Therefore, it is necessary to understand the regulatory functions of different types of histone modifications since, targeting epigenetic mechanisms within NSCs holds promise for novel therapeutic strategies against AD. By restoring the rhythm of the circadian clock and its epigenetic regulators, we may be able to enhance neurogenesis, promote neuronal survival, and ultimately slow down or even reverse the cognitive decline associated with this devastating disease. Further research is needed to fully elucidate the intricate interplay between circadian rhythms, epigenetic modifications, and neural stem cell function in the context of AD.

Abbreviations

AD: Alzheimer’s disease; AMPK: AMP-activated protein kinase; APP: Amyloid-beta precursor; Aβ: β-amyloid; BDNF: Brain-derived neurotrophic factor; BMAL1: Brain and Muscle Arnt-Like protein 1; CBP: CREB-binding protein; CCGs: Clock-controlled genes ; CK1: Casein kinase 1; CLOCK : Circadian Locomotor Output Cycles Kaput; CREB: cAMP-response element binding protein; CRY 1 : Cryptochrome ; CSF:

Cerebrospinal fluid; ERK: Extracellular signal-regulated kinases; FAD: Familial Alzheimer’s disease ; FOXO3: Forkhead box O3; GDNF: Glial cell line-derived neurotrophic factor; HAT: Histone acetyltransferase; HDAC: Histone deacetylase; MAPK: Mitogen-activated protein kinases; NPAS2 : Neuronal PAS domain-containing protein 2; Nrf2: Nuclear factor erythroid 2-related factor 2; NSC: Neural Stem Cell; PER: Period; PSEN1: Presenilin 1; PSEN2: Presenilin 2; RHT: Retinohypothalamic tract ; ROR: RAR-related orphan receptor; ROREs:ROR response elements; SCN: Suprachiasmatic nucleus; SGZ: Sub granular zone; SIRT: Sirtuin; SVZ: Subventricular zone

Acknowledgements

The figures 1, 2 and 4 were developed partly using Biorender.com.

Funding

This study was funded by the European Union within Marie Skłodowska-Curie Actions under grant agreement no. 101072895 – TClock4AD - Targeting Circadian Clock Dysfunction in Alzheimer's Disease – and supported by #NEXTGENERATIONEU (NGEU) and funded by the Ministry of University and Research (MUR), National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022).

CRediT authorship contribution statement

TCA wrote the manuscript. BM conceptualized the general manuscript. Both KM and BM revised the manuscript. All authors have read and agreed to the final version of the manuscript.

Declaration of Competing interests

The authors declare that they have no competing interests.

References

Abrahamson, E.E., Moore, R.Y., 2001. Suprachiasmatic nucleus in the mouse: retinal innervation, intrinsic organization and efferent projections. Brain Res 916, 172-191.https://doi.org/10.1016/s0006-8993(01)02890-6.

Abubakar, M.B., Sanusi, K.O., Ugusman, A., Mohamed, W., Kamal, H., Ibrahim, N.H., . . . Kumar, J., 2022. Alzheimer's Disease: An Update and Insights Into Pathophysiology. Frontiers in Aging Neuroscience 14.https://doi.org/10.3389/fnagi.2022.742408.

Aghaizu, N.D., Jin, H., Whiting, P.J., 2020. Dysregulated Wnt Signalling in the Alzheimer's Brain. Brain Sci 10.https://doi.org/10.3390/brainsci10120902.

Ahmad, S.B., Ali, A., Bilal, M., Rashid, S.M., Wani, A.B., Bhat, R.R., Rehman, M.U., 2023. Melatonin and Health: Insights of Melatonin Action, Biological Functions, and Associated Disorders. Cellular and Molecular Neurobiology 43, 2437-2458.https://doi.org/10.1007/s10571-023-01324-w.

Albert, M., Huttner, W.B., 2018. Epigenetic and Transcriptional Pre-patterning—An Emerging Theme in Cortical Neurogenesis. Frontiers in Neuroscience 12.https://doi.org/10.3389/fnins.2018.00359.

Ali, A.A.H., von Gall, C., 2022. Adult Neurogenesis under Control of the Circadian System. Cells 11.https://doi.org/10.3390/cells11050764.

Allebrandt, K.V., Teder-Laving, M., Akyol, M., Pichler, I., Müller-Myhsok, B., Pramstaller, P., . . . Roenneberg, T., 2010. CLOCK gene variants associate with sleep duration in two independent populations. Biol Psychiatry 67, 1040-1047.https://doi.org/10.1016/j.biopsych.2009.12.026.

Ambrée, O., Touma, C., Görtz, N., Keyvani, K., Paulus, W., Palme, R., Sachser, N., 2006. Activity changes and marked stereotypic behavior precede Abeta pathology in TgCRND8 Alzheimer mice. Neurobiol Aging 27, 955-964.https://doi.org/10.1016/j.neurobiolaging.2005.05.009.

An, Y., Yuan, B., Xie, P., Gu, Y., Liu, Z., Wang, T., . . . Liu, Y., 2022. Decoupling PER phosphorylation, stability and rhythmic expression from circadian clock function by abolishing PER-CK1 interaction. Nat Commun 13, 3991.https://doi.org/10.1038/s41467-022-31715-4.

Armstrong, K.J., Niles, L.P., 2002. Induction of GDNF mRNA expression by melatonin in rat C6 glioma cells. Neuroreport 13, 473-475.https://doi.org/10.1097/00001756-200203250-00023.

Aschoff, J. 1981. Freerunning and Entrained Circadian Rhythms. In: *Biological Rhythms*. pp. 81-93. Ed. J. Aschoff. Springer US: Boston, MA.

Association, A., 2023. 2023 Alzheimer's disease facts and figures. Alzheimers Dement 19, 1598-1695.https://doi.org/10.1002/alz.13016.

Aten, S., Hansen, K.F., Price, K.H., Wheaton, K., Kalidindi, A., Garcia, A., . . . Obrietan, K., 2018. miR-132 couples the circadian clock to daily rhythms of neuronal plasticity and cognition. Learn Mem 25, 214-229.https://doi.org/10.1101/lm.047191.117.

Babcock, K.R., Page, J.S., Fallon, J.R., Webb, A.E., 2021. Adult Hippocampal Neurogenesis in Aging and Alzheimer's Disease. Stem Cell Reports 16, 681-693.https://doi.org/10.1016/j.stemcr.2021.01.019.

Bacalini, M.G., Palombo, F., Garagnani, P., Giuliani, C., Fiorini, C., Caporali, L., . . . Italian Multicentric Group on clock genes, a.i.A.D., 2022. Association of rs3027178 polymorphism in the circadian clock gene PER1 with susceptibility to Alzheimer’s disease and longevity in an Italian population. GeroScience 44, 881-896.https://doi.org/10.1007/s11357-021-00477-0.

Beaule, C., Granados-Fuentes, D., Marpegan, L., Herzog, E.D., 2011. In vitro circadian rhythms: imaging and electrophysiology. Essays Biochem 49, 103-117.https://doi.org/10.1042/bse0490103.

Bélanger, V., Picard, N., Cermakian, N., 2006. The Circadian Regulation of Presenilin-2 Gene Expression. Chronobiology International 23, 747-766.https://doi.org/10.1080/07420520600827087.

Belden, W.J., Dunlap, J.C., 2008. SIRT1 is a circadian deacetylase for core clock components. Cell 134, 212-214.https://doi.org/10.1016/j.cell.2008.07.010.

Bell, C.G., Lowe, R., Adams, P.D., Baccarelli, A.A., Beck, S., Bell, J.T., . . . Rakyan, V.K., 2019. DNA methylation aging clocks: challenges and recommendations. Genome Biol 20, 249.https://doi.org/10.1186/s13059-019-1824-y.

Benedetti, F., Dallaspezia, S., Colombo, C., Pirovano, A., Marino, E., Smeraldi, E., 2008. A length polymorphism in the circadian clock gene Per3 influences age at onset of bipolar disorder. Neuroscience Letters 445, 184-187.https://doi.org/10.1016/j.neulet.2008.09.002.

Birky, T.L., Bray, M.S., 2014. Understanding circadian gene function: Animal models of tissue-specific circadian disruption. IUBMB Life 66, 34-41.https://doi.org/10.1002/iub.1241.

Bocheva, G., Bakalov, D., Iliev, P., Tafradjiiska-Hadjiolova, R., 2024. The Vital Role of Melatonin and Its Metabolites in the Neuroprotection and Retardation of Brain Aging. International Journal of Molecular Sciences 25, 5122

Boiko, D.I., Shkodina, A.D., Hasan, M.M., Bardhan, M., Kazmi, S.K., Chopra, H., . . . Skrypnikov, A.M., 2022. Melatonergic Receptors (Mt1/Mt2) as a Potential Additional Target of Novel Drugs for Depression. Neurochemical Research 47, 2909-2924.https://doi.org/10.1007/s11064-022-03646-5.

Bond, A.M., Ming, G.L., Song, H., 2015. Adult Mammalian Neural Stem Cells and Neurogenesis: Five Decades Later. Cell Stem Cell 17, 385-395.https://doi.org/10.1016/j.stem.2015.09.003.

Borchelt, D.R., Thinakaran, G., Eckman, C.B., Lee, M.K., Davenport, F., Ratovitsky, T., . . . Sisodia, S.S., 1996. Familial Alzheimer's disease-linked presenilin 1 variants elevate Abeta1-42/1-40 ratio in vitro and in vivo. Neuron 17, 1005-1013.https://doi.org/10.1016/s0896-6273(00)80230-5.

Bouchard-Cannon, P., Mendoza-Viveros, L., Yuen, A., Kærn, M., Cheng, H.-Ying M., 2013. The Circadian Molecular Clock Regulates Adult Hippocampal Neurogenesis by Controlling the Timing of Cell-Cycle Entry and Exit. Cell Reports 5, 961-973.https://doi.org/10.1016/j.celrep.2013.10.037.

Bourque, M.J., Trudeau, L.E., 2000. GDNF enhances the synaptic efficacy of dopaminergic neurons in culture. Eur J Neurosci 12, 3172-3180.https://doi.org/10.1046/j.1460-9568.2000.00219.x.

Boutin, J.A., Kennaway, D.J., Jockers, R., 2023. Melatonin: Facts, Extrapolations and Clinical Trials. Biomolecules 13.https://doi.org/10.3390/biom13060943.

Caruso, G.I., Spampinato, S.F., Costantino, G., Merlo, S., Sortino, M.A., 2021. SIRT1-Dependent Upregulation of BDNF in Human Microglia Challenged with Aβ: An Early but Transient Response Rescued by Melatonin. Biomedicines 9, 466

Castro-Zavala, A., Alegre-Zurano, L., Cantacorps, L., Gallego-Landin, I., Welz, P.-S., Benitah, S.A., Valverde, O., 2022. Bmal1-knockout mice exhibit reduced cocaine-seeking behaviour and cognitive impairments. Biomedicine & Pharmacotherapy 153, 113333.https://doi.org/10.1016/j.biopha.2022.113333.

Chaves, I., van der Horst, Gijsbertus T.J., Schellevis, R., Nijman, Romana M., Koerkamp, Marian G., Holstege, Frank C.P., . . . Hoekman, Marco F.M., 2014. Insulin-FOXO3 Signaling Modulates Circadian Rhythms via Regulation of Clock Transcription. Current Biology 24, 1248-1255.https://doi.org/10.1016/j.cub.2014.04.018.

Chen, Q., Huang, C.Q., Hu, X.Y., Li, S.B., Zhang, X.M., 2013. Functional CLOCK gene rs1554483 G/C polymorphism is associated with susceptibility to Alzheimer's disease in the Chinese population. J Int Med Res 41, 340-346.https://doi.org/10.1177/0300060513476430.

Cheng, H.-Y.M., Papp, J.W., Varlamova, O., Dziema, H., Russell, B., Curfman, J.P., . . . Obrietan, K., 2007. microRNA Modulation of Circadian-Clock Period and Entrainment. Neuron 54, 813-829.https://doi.org/10.1016/j.neuron.2007.05.017.

Chern, C.M., Liao, J.F., Wang, Y.H., Shen, Y.C., 2012. Melatonin ameliorates neural function by promoting endogenous neurogenesis through the MT2 melatonin receptor in ischemic-stroke mice. Free Radic Biol Med 52, 1634-1647.https://doi.org/10.1016/j.freeradbiomed.2012.01.030.

Colwell, C.S., 2005. Bridging the gap: coupling single-cell oscillators in the suprachiasmatic nucleus. Nat Neurosci 8, 10-12.https://doi.org/10.1038/nn0105-10.

Cronin, P., McCarthy, M.J., Lim, A.S.P., Salmon, D.P., Galasko, D., Masliah, E., . . . Desplats, P., 2017. Circadian alterations during early stages of Alzheimer's disease are associated with aberrant cycles of DNA methylation in BMAL1. Alzheimers Dement 13, 689-700.https://doi.org/10.1016/j.jalz.2016.10.003.

De Plano, L.M., Saitta, A., Oddo, S., Caccamo, A., 2024. Epigenetic Changes in Alzheimer's Disease: DNA Methylation and Histone Modification. Cells 13.https://doi.org/10.3390/cells13080719.

DeBruyne, J.P., Weaver, D.R., Reppert, S.M., 2007. CLOCK and NPAS2 have overlapping roles in the suprachiasmatic circadian clock. Nature Neuroscience 10, 543-545.https://doi.org/10.1038/nn1884.

Dijk, D.J., Duffy, J.F., Silva, E.J., Shanahan, T.L., Boivin, D.B., Czeisler, C.A., 2012. Amplitude reduction and phase shifts of melatonin, cortisol and other circadian rhythms after a gradual advance of sleep and light exposure in humans. PLoS One 7, e30037.https://doi.org/10.1371/journal.pone.0030037.

Doi, M., Hirayama, J., Sassone-Corsi, P., 2006. Circadian regulator CLOCK is a histone acetyltransferase. Cell 125, 497-508.https://doi.org/10.1016/j.cell.2006.03.033.

Du, B., Zhang, Y., Liang, M., Du, Z., Li, H., Fan, C., . . . Bi, X., 2021. N6-methyladenosine (m6A) modification and its clinical relevance in cognitive dysfunctions. Aging (Albany NY) 13, 20716-20737.https://doi.org/10.18632/aging.203457.

Duffy, J.F., Wang, W., Ronda, J.M., Czeisler, C.A., 2022. High dose melatonin increases sleep duration during nighttime and daytime sleep episodes in older adults. J Pineal Res 73, e12801.https://doi.org/10.1111/jpi.12801.

Egan, Chris M., Nyman, U., Skotte, J., Streubel, G., Turner, S., O'Connell, David J., . . . Bracken, Adrian P., 2013. CHD5 Is Required for Neurogenesis and Has a Dual Role in Facilitating Gene Expression and Polycomb Gene Repression. Developmental Cell 26, 223-236.https://doi.org/10.1016/j.devcel.2013.07.008.

Fishbein, A.B., Knutson, K.L., Zee, P.C., 2021. Circadian disruption and human health. The Journal of Clinical Investigation 131.https://doi.org/10.1172/JCI148286.

Forbes, E.E., Dahl, R.E., Almeida, J.R., Ferrell, R.E., Nimgaonkar, V.L., Mansour, H., . . . Phillips, M.L., 2012. PER2 rs2304672 polymorphism moderates circadian-relevant reward circuitry activity in adolescents. Biol Psychiatry 71, 451-457.https://doi.org/10.1016/j.biopsych.2011.10.012.

Franken, P., Dijk, D.J., 2024. Sleep and circadian rhythmicity as entangled processes serving homeostasis. Nat Rev Neurosci 25, 43-59.https://doi.org/10.1038/s41583-023-00764-z.

Gnocchi, D., Bruscalupi, G., 2017. Circadian Rhythms and Hormonal Homeostasis: Pathophysiological Implications. Biology (Basel) 6.https://doi.org/10.3390/biology6010010.

Gršković, P., Korać, P., 2023. Circadian Gene Variants in Diseases. Genes 14, 1703

Gu, X., Xing, L., Shi, G., Liu, Z., Wang, X., Qu, Z., . . . Xu, Y., 2012. The circadian mutation PER2S662G is linked to cell cycle progression and tumorigenesis. Cell Death & Differentiation 19, 397-405.https://doi.org/10.1038/cdd.2011.103.

Guo, B., Chatterjee, S., Li, L., Kim, J.M., Lee, J., Yechoor, V.K., . . . Ma, K., 2012. The clock gene, brain and muscle Arnt-like 1, regulates adipogenesis via Wnt signaling pathway. Faseb j 26, 3453-3463.https://doi.org/10.1096/fj.12-205781.

Guo, T., Zhang, D., Zeng, Y., Huang, T.Y., Xu, H., Zhao, Y., 2020. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer’s disease. Molecular Neurodegeneration 15, 40.https://doi.org/10.1186/s13024-020-00391-7.

Harper, D.G., Stopa, E.G., Kuo-Leblanc, V., McKee, A.C., Asayama, K., Volicer, L., . . . Satlin, A., 2008. Dorsomedial SCN neuronal subpopulations subserve different functions in human dementia. Brain 131, 1609-1617.https://doi.org/10.1093/brain/awn049.

Hastings, M.H., Goedert, M., 2013. Circadian clocks and neurodegenerative diseases: time to aggregate? Curr Opin Neurobiol 23, 880-887.https://doi.org/10.1016/j.conb.2013.05.004.

Hastings, M.H., Maywood, E.S., Brancaccio, M., 2018. Generation of circadian rhythms in the suprachiasmatic nucleus. Nature Reviews Neuroscience 19, 453-469.https://doi.org/10.1038/s41583-018-0026-z.

Hida, A., Kitamura, S., Katayose, Y., Kato, M., Ono, H., Kadotani, H., . . . Mishima, K., 2014. Screening of clock gene polymorphisms demonstrates association of a PER3 polymorphism with morningness-eveningness preference and circadian rhythm sleep disorder. Sci Rep 4, 6309.https://doi.org/10.1038/srep06309.

Hofman, M.A., Swaab, D.F. 2002. A brain for all seasons: cellular and molecular mechanisms of photoperiodic plasticity. In: *Progress in Brain Research*. pp. 255-280. Elsevier.

Horvath, S., 2013. DNA methylation age of human tissues and cell types. Genome Biology 14, 3156.https://doi.org/10.1186/gb-2013-14-10-r115.

Horvath, S., Raj, K., 2018. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat Rev Genet 19, 371-384.https://doi.org/10.1038/s41576-018-0004-3.

Hua, P., Liu, W., Chen, D., Zhao, Y., Chen, L., Zhang, N., . . . Kuo, S.H., 2014. Cry1 and Tef gene polymorphisms are associated with major depressive disorder in the Chinese population. J Affect Disord 157, 100-103.https://doi.org/10.1016/j.jad.2013.11.019.

Inestrosa, N., De Ferrari, G.V., Garrido, J.L., Alvarez, A., Olivares, G.H., Barría, M.I., . . . Chacón, M.A., 2002. Wnt signaling involvement in beta-amyloid-dependent neurodegeneration. Neurochem Int 41, 341-344.https://doi.org/10.1016/s0197-0186(02)00056-6.

Inestrosa, N.C., Toledo, E.M., 2008. The role of Wnt signaling in neuronal dysfunction in Alzheimer's Disease. Molecular Neurodegeneration 3, 9.https://doi.org/10.1186/1750-1326-3-9.

Jansen, I.E., Savage, J.E., Watanabe, K., Bryois, J., Williams, D.M., Steinberg, S., . . . Posthuma, D., 2019. Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. Nat Genet 51, 404-413.https://doi.org/10.1038/s41588-018-0311-9.

Jones, C.R., Campbell, S.S., Zone, S.E., Cooper, F., DeSano, A., Murphy, P.J., . . . Ptácek, L.J., 1999. Familial advanced sleep-phase syndrome: A short-period circadian rhythm variant in humans. Nat Med 5, 1062-1065.https://doi.org/10.1038/12502.

Ju, Y.E., Lucey, B.P., Holtzman, D.M., 2014. Sleep and Alzheimer disease pathology--a bidirectional relationship. Nat Rev Neurol 10, 115-119.https://doi.org/10.1038/nrneurol.2013.269.

Ju, Y.E., McLeland, J.S., Toedebusch, C.D., Xiong, C., Fagan, A.M., Duntley, S.P., . . . Holtzman, D.M., 2013. Sleep quality and preclinical Alzheimer disease. JAMA Neurol 70, 587-593.https://doi.org/10.1001/jamaneurol.2013.2334.

Kang, J.E., Lim, M.M., Bateman, R.J., Lee, J.J., Smyth, L.P., Cirrito, J.R., . . . Holtzman, D.M., 2009. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 326, 1005-1007.https://doi.org/10.1126/science.1180962.

Karatsoreos, I.N., Bhagat, S., Bloss, E.B., Morrison, J.H., McEwen, B.S., 2011. Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. Proceedings of the National Academy of Sciences 108, 1657-1662.https://doi.org/doi:10.1073/pnas.1018375108.

Karch, C.M., Goate, A.M., 2015. Alzheimer's disease risk genes and mechanisms of disease pathogenesis. Biol Psychiatry 77, 43-51.https://doi.org/10.1016/j.biopsych.2014.05.006.

Kärkkäinen, V., Pomeshchik, Y., Savchenko, E., Dhungana, H., Kurronen, A., Lehtonen, S., . . . Koistinaho, J., 2014. Nrf2 regulates neurogenesis and protects neural progenitor cells against Aβ toxicity. Stem Cells 32, 1904-1916.https://doi.org/10.1002/stem.1666.

Kim, S.E., Kim, S., Kim, H.J., Kim, R.E., Kim, S.A., Shin, C., Lee, H.W., 2022. CLOCK Genetic Variations Are Associated With Age-Related Changes in Sleep Duration and Brain Volume. J Gerontol A Biol Sci Med Sci 77, 1907-1914.https://doi.org/10.1093/gerona/glab365.

Kim, Y.H., Marhon, S.A., Zhang, Y., Steger, D.J., Won, K.-J., Lazar, M.A., 2018. Rev-erbα dynamically modulates chromatin looping to control circadian gene transcription. Science 359, 1274-1277.https://doi.org/doi:10.1126/science.aao6891.

Kinoshita, C., Okamoto, Y., Aoyama, K., Nakaki, T., 2020. MicroRNA: A Key Player for the Interplay of Circadian Rhythm Abnormalities, Sleep Disorders and Neurodegenerative Diseases. Clocks & Sleep 2, 282-307

Kocevska, D., Barclay, N.L., Bramer, W.M., Gehrman, P.R., Van Someren, E.J.W., 2021. Heritability of sleep duration and quality: A systematic review and meta-analysis. Sleep Medicine Reviews 59, 101448.https://doi.org/10.1016/j.smrv.2021.101448.

Koike, N., Yoo, S.-H., Huang, H.-C., Kumar, V., Lee, C., Kim, T.-K., Takahashi, J.S., 2012. Transcriptional Architecture and Chromatin Landscape of the Core Circadian Clock in Mammals. Science 338, 349-354.https://doi.org/doi:10.1126/science.1226339.

Kondratov, R.V., Kondratova, A.A., Gorbacheva, V.Y., Vykhovanets, O.V., Antoch, M.P., 2006. Early aging and age-related pathologies in mice deficient in BMAL1, the core componentof the circadian clock. Genes Dev 20, 1868-1873.https://doi.org/10.1101/gad.1432206.

Korkmaz, A., Rosales-Corral, S., Reiter, R.J., 2012. Gene regulation by melatonin linked to epigenetic phenomena. Gene 503, 1-11.https://doi.org/10.1016/j.gene.2012.04.040.

Kovanen, L., Donner, K., Kaunisto, M., Partonen, T., 2017. PRKCDBP (CAVIN3) and CRY2 associate with major depressive disorder. Journal of Affective Disorders 207, 136-140.https://doi.org/10.1016/j.jad.2016.09.034.

Kovanen, L., Kaunisto, M., Donner, K., Saarikoski, S.T., Partonen, T., 2013. CRY2 genetic variants associate with dysthymia. PLoS One 8, e71450.https://doi.org/10.1371/journal.pone.0071450.

Kunkle, B.W., Grenier-Boley, B., Sims, R., Bis, J.C., Damotte, V., Naj, A.C., . . . Pericak-Vance, M.A., 2019. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates Aβ, tau, immunity and lipid processing. Nat Genet 51, 414-430.https://doi.org/10.1038/s41588-019-0358-2.

Landgraf, D., Long, J.E., Proulx, C.D., Barandas, R., Malinow, R., Welsh, D.K., 2016. Genetic Disruption of Circadian Rhythms in the Suprachiasmatic Nucleus Causes Helplessness, Behavioral Despair, and Anxiety-like Behavior in Mice. Biol Psychiatry 80, 827-835.https://doi.org/10.1016/j.biopsych.2016.03.1050.

Lanoiselée, H.M., Nicolas, G., Wallon, D., Rovelet-Lecrux, A., Lacour, M., Rousseau, S., . . . Campion, D., 2017. APP, PSEN1, and PSEN2 mutations in early-onset Alzheimer disease: A genetic screening study of familial and sporadic cases. PLoS Med 14, e1002270.https://doi.org/10.1371/journal.pmed.1002270.

Lavebratt, C., Sjöholm, L.K., Soronen, P., Paunio, T., Vawter, M.P., Bunney, W.E., . . . Schalling, M., 2010. CRY2 is associated with depression. PLoS One 5, e9407.https://doi.org/10.1371/journal.pone.0009407.

Lee, B.H., Hille, B., Koh, D.-S., 2021. Serotonin modulates melatonin synthesis as an autocrine neurotransmitter in the pineal gland. Proceedings of the National Academy of Sciences 118, e2113852118.https://doi.org/doi:10.1073/pnas.2113852118.

Lee, C., Etchegaray, J.P., Cagampang, F.R., Loudon, A.S., Reppert, S.M., 2001. Posttranslational mechanisms regulate the mammalian circadian clock. Cell 107, 855-867.https://doi.org/10.1016/s0092-8674(01)00610-9.

Lee, H.J., Kim, L., Kang, S.G., Yoon, H.K., Choi, J.E., Park, Y.M., . . . Kripke, D.F., 2011. PER2 variation is associated with diurnal preference in a Korean young population. Behav Genet 41, 273-277.https://doi.org/10.1007/s10519-010-9396-3.

Leng, F., Edison, P., 2021. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nature Reviews Neurology 17, 157-172.https://doi.org/10.1038/s41582-020-00435-y.

Lew, C.H., Petersen, C., Neylan, T.C., Grinberg, L.T., 2021. Tau-driven degeneration of sleep- and wake-regulating neurons in Alzheimer's disease. Sleep Med Rev 60, 101541.https://doi.org/10.1016/j.smrv.2021.101541.

Li, J.Z., Bunney, B.G., Meng, F., Hagenauer, M.H., Walsh, D.M., Vawter, M.P., . . . Bunney, W.E., 2013. Circadian patterns of gene expression in the human brain and disruption in major depressive disorder. Proceedings of the National

Academy of Sciences 110, 9950-9955.https://doi.org/doi:10.1073/pnas.1305814110.

Li, X., Chen, X., Zhou, W., Ji, S., Li, X., Li, G., . . . Hao, A., 2017. Effect of melatonin on neuronal differentiation requires CBP/p300-mediated acetylation of histone H3 lysine 14. Neuroscience 364, 45-59.https://doi.org/10.1016/j.neuroscience.2017.07.064.

Li, Y., Cao, Z., Wu, S., Wang, C., Dong, Y., Zhao, N.O., . . . Zhang, X., 2022. Association between the CLOCK gene polymorphism and depressive symptom mediated by sleep quality among non-clinical Chinese Han population. J Affect Disord 298, 217-223.https://doi.org/10.1016/j.jad.2021.10.070.

Li, Y., Cao, Z., Wu, S., Wang, C., He, S., Dong, Y., Zhang, X., 2021. Association of job stress, CLOCK gene polymorphism and their interaction with poor sleep quality. J Sleep Res 30, e13133.https://doi.org/10.1111/jsr.13133.

Liberman, A.R., Kwon, S.B., Vu, H.T., Filipowicz, A., Ay, A., Ingram, K.K., 2017. Circadian Clock Model Supports Molecular Link Between PER3 and Human Anxiety. Scientific Reports 7, 9893.https://doi.org/10.1038/s41598-017-07957-4.

Lin, E., Kuo, P.H., Liu, Y.L., Yang, A.C., Kao, C.F., Tsai, S.J., 2017. Effects of circadian clock genes and environmental factors on cognitive aging in old adults in a Taiwanese population. Oncotarget 8, 24088-24098.https://doi.org/10.18632/oncotarget.15493.

Lin, F., Chen, Y., Li, X., Zhao, Q., Tan, Z., 2013. Over-expression of circadian clock gene Bmal1 affects proliferation and the canonical Wnt pathway in NIH-3T3 cells. Cell Biochem Funct 31, 166-172.https://doi.org/10.1002/cbf.2871.

Ling, Y., Yuan, S., Huang, X., Tan, S., Huang, T., Xu, A., Lyu, J., 2023. The association of night shift work with the risk of all-cause dementia and Alzheimer's disease: a longitudinal study of 245,570 UK Biobank participants. Journal of Neurology 270, 3499-3510.https://doi.org/10.1007/s00415-023-11672-8.

Linowiecka, K., Slominski, A.T., Reiter, R.J., Böhm, M., Steinbrink, K., Paus, R., Kleszczyński, K., 2023. Melatonin: A Potential Regulator of DNA Methylation. Antioxidants (Basel) 12.https://doi.org/10.3390/antiox12061155.

Liu, C., Tang, X., Gong, Z., Zeng, W., Hou, Q., Lu, R., 2022. Circadian Rhythm Sleep Disorders: Genetics, Mechanisms, and Adverse Effects on Health. Front Genet 13, 875342.https://doi.org/10.3389/fgene.2022.875342.

Liu, J., Clough, S.J., Hutchinson, A.J., Adamah-Biassi, E.B., Popovska-Gorevski, M., Dubocovich, M.L., 2016. MT1 and MT2 Melatonin Receptors: A Therapeutic Perspective. Annu Rev Pharmacol Toxicol 56, 361-383.https://doi.org/10.1146/annurev-pharmtox-010814-124742.

Liu, J.J., Sudic Hukic, D., Forsell, Y., Schalling, M., Ösby, U., Lavebratt, C., 2015. Depression-associated ARNTL and PER2 genetic variants in psychotic disorders. Chronobiol Int 32, 579-584.https://doi.org/10.3109/07420528.2015.1012588.

Lou, F., Li, M., Ren, Y., Luo, X.G., Liu, N., Li, X., 2017. CLOCK rs1801260 Polymorphism is Associated with Susceptibility to Parkinson's Disease in a Chinese Population. Neurosci Bull 33, 734-736.https://doi.org/10.1007/s12264-017-0167-5.

Lucas, R.J., Lall, G.S., Allen, A.E., Brown, T.M., 2012. How rod, cone, and melanopsin photoreceptors come together to enlighten the mammalian circadian clock. Prog Brain Res 199, 1-18.https://doi.org/10.1016/b978-0-444-59427-3.00001-0.

Lv, Y.-N., Cui, Y., Zhang, B., Huang, S.-M., 2022. Sleep deficiency promotes Alzheimer's disease development and progression. Frontiers in Neurology 13.https://doi.org/10.3389/fneur.2022.1053942.

Malik, A., Kondratov, R.V., Jamasbi, R.J., Geusz, M.E., 2015. Circadian Clock Genes Are Essential for Normal Adult Neurogenesis, Differentiation, and Fate Determination. PLOS ONE 10, e0139655.https://doi.org/10.1371/journal.pone.0139655.

Marcheva, B., Ramsey, K.M., Peek, C.B., Affinati, A., Maury, E., Bass, J., 2013. Circadian clocks and metabolism. Handb Exp Pharmacol, 127-155.https://doi.org/10.1007/978-3-642-25950-0_6.

Mätlik, K., Govek, E.E., Paul, M.R., Allis, C.D., Hatten, M.E., 2023. Histone bivalency regulates the timing of cerebellar granule cell development. Genes Dev 37, 570-589.https://doi.org/10.1101/gad.350594.123.

Matsu-Ura, T., Moore, S.R., Hong, C.I., 2018. WNT Takes Two to Tango: Molecular Links between the Circadian Clock and the Cell Cycle in Adult Stem Cells. J Biol Rhythms 33, 5-14.https://doi.org/10.1177/0748730417745913.

McKee, C.A., Polino, A.J., King, M.W., Musiek, E.S., 2023. Circadian clock protein BMAL1 broadly influences autophagy and endolysosomal function in astrocytes. Proc Natl Acad Sci U S A 120, e2220551120.https://doi.org/10.1073/pnas.2220551120.

Migliore, L., Coppedè, F., 2022. Gene–environment interactions in Alzheimer disease: the emerging role of epigenetics. Nature Reviews Neurology 18, 643-660.https://doi.org/10.1038/s41582-022-00714-w.

Mir, S., Cai, W., Carlson, S.W., Saatman, K.E., Andres, D.A., 2017. IGF-1 mediated Neurogenesis Involves a Novel RIT1/Akt/Sox2 Cascade. Scientific Reports 7, 3283.https://doi.org/10.1038/s41598-017-03641-9.

Mirick, D.K., Davis, S., 2008. Melatonin as a biomarker of circadian dysregulation. Cancer Epidemiol Biomarkers Prev 17, 3306-3313.https://doi.org/10.1158/1055-9965.Epi-08-0605.

Mizuno, S., Iijima, R., Ogishima, S., Kikuchi, M., Matsuoka, Y., Ghosh, S., . . . Tanaka, H., 2012. AlzPathway: a comprehensive map of signaling pathways of Alzheimer's disease. BMC Syst Biol 6, 52.https://doi.org/10.1186/1752-0509-6-52.

Mohawk, J.A., Green, C.B., Takahashi, J.S., 2012. Central and peripheral circadian clocks in mammals. Annu Rev Neurosci 35, 445-462.https://doi.org/10.1146/annurev-neuro-060909-153128.

Moradi, H.R., Hajali, V., Khaksar, Z., Vafaee, F., Forouzanfar, F., Negah, S.S., 2021. The next step of neurogenesis in the context of Alzheimer's disease. Mol Biol Rep 48, 5647-5660.https://doi.org/10.1007/s11033-021-06520-9.

Moreno-Jiménez, E.P., Flor-García, M., Terreros-Roncal, J., Rábano, A., Cafini, F., Pallas-Bazarra, N., . . . Llorens-Martín, M., 2019. Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. Nat Med 25, 554-560.https://doi.org/10.1038/s41591-019-0375-9.

Muller, J.E., Stone, P.H., Turi, Z.G., Rutherford, J.D., Czeisler, C.A., Parker, C., . . . et al., 1985. Circadian variation in the frequency of onset of acute myocardial infarction. N Engl J Med 313, 1315-1322.https://doi.org/10.1056/nejm198511213132103.

Nagu, P., Sharma, V., Behl, T., Pathan, A.K.A., Mehta, V., 2022. Molecular Insights to the Wnt Signaling During Alzheimer's Disorder: a Potential Target for Therapeutic Interventions. J Mol Neurosci 72, 679-690.https://doi.org/10.1007/s12031-021-01940-5.

Nam, H., Lee, Y., Kim, B., Lee, J.-W., Hwang, S., An, H.-K., . . . Yu, S.-W., 2022. Presenilin 2 N141I mutation induces hyperactive immune response through the epigenetic repression of REV-ERBα. Nature Communications 13, 1972.https://doi.org/10.1038/s41467-022-29653-2.

Nassan, M., Videnovic, A., 2022. Circadian rhythms in neurodegenerative disorders. Nature Reviews Neurology 18, 7-24.https://doi.org/10.1038/s41582-021-00577-7.

Nikolac Perkovic, M., Videtic Paska, A., Konjevod, M., Kouter, K., Svob Strac, D., Nedic Erjavec, G., Pivac, N., 2021. Epigenetics of Alzheimer’s Disease. Biomolecules 11, 195

Palomer, E., Buechler, J., Salinas, P.C., 2019. Wnt Signaling Deregulation in the Aging and Alzheimer's Brain. Front Cell Neurosci 13, 227.https://doi.org/10.3389/fncel.2019.00227.

Palomer, E., Martín-Flores, N., Jolly, S., Pascual-Vargas, P., Benvegnù, S., Podpolny, M., . . . Salinas, P.C., 2022. Epigenetic repression of Wnt receptors in AD: a role for Sirtuin2-induced H4K16ac deacetylation of Frizzled1 and Frizzled7 promoters. Molecular Psychiatry 27, 3024-3033.https://doi.org/10.1038/s41380-022-01492-z.

Panda, S., Antoch, M.P., Miller, B.H., Su, A.I., Schook, A.B., Straume, M., . . . Hogenesch, J.B., 2002. Coordinated Transcription of Key Pathways in the Mouse by the Circadian Clock. Cell 109, 307-320.https://doi.org/10.1016/S0092-8674(02)00722-5.

Patton, A.P., Chesham, J.E., Hastings, M.H., 2016. Combined Pharmacological and Genetic Manipulations Unlock Unprecedented Temporal Elasticity and Reveal Phase-Specific Modulation of the Molecular Circadian Clock of the Mouse Suprachiasmatic Nucleus. J Neurosci 36, 9326-9341.https://doi.org/10.1523/jneurosci.0958-16.2016.

Pembroke, W.G., Babbs, A., Davies, K.E., Ponting, C.P., Oliver, P.L., 2015. Temporal transcriptomics suggest that twin-peaking genes reset the clock. Elife 4.https://doi.org/10.7554/eLife.10518.

Polis, B., Samson, A.O., 2021. Neurogenesis versus neurodegeneration: the broken balance in Alzheimer's disease. Neural Regen Res 16, 496-497.https://doi.org/10.4103/1673-5374.293138.

Posadzki, P.P., Bajpai, R., Kyaw, B.M., Roberts, N.J., Brzezinski, A., Christopoulos, G.I., . . . Car, J., 2018. Melatonin and health: an umbrella review of health outcomes and biological mechanisms of action. BMC Medicine 16, 18.https://doi.org/10.1186/s12916-017-1000-8.

Reiter, R.J., Sharma, R., Tan, D.X., Chuffa, L.G.A., da Silva, D.G.H., Slominski, A.T., . . . Kleszczynski, K., 2024. Dual sources of melatonin and evidence for different primary functions. Front Endocrinol (Lausanne) 15, 1414463.https://doi.org/10.3389/fendo.2024.1414463.

Rigat, L., Ouk, K., Kramer, A., Priller, J., 2023. Dysfunction of circadian and sleep rhythms in the early stages of Alzheimer's disease. Acta Physiologica 238, e13970.https://doi.org/https://doi.org/10.1111/apha.13970.

Ripperger, J.A., Schibler, U., 2006. Rhythmic CLOCK-BMAL1 binding to multiple E-box motifs drives circadian Dbp transcription and chromatin transitions. Nat Genet 38, 369-374.https://doi.org/10.1038/ng1738.

Roh, J.H., Huang, Y., Bero, A.W., Kasten, T., Stewart, F.R., Bateman, R.J., Holtzman, D.M., 2012. Disruption of the sleep-wake cycle and diurnal fluctuation of β-amyloid in mice with Alzheimer's disease pathology. Sci Transl Med 4, 150ra122.https://doi.org/10.1126/scitranslmed.3004291.

Ruan, W., Yuan, X., Eltzschig, H.K., 2021. Circadian rhythm as a therapeutic target. Nat Rev Drug Discov 20, 287-307.https://doi.org/10.1038/s41573-020-00109-w.

Saha, S., Buttari, B., Profumo, E., Tucci, P., Saso, L., 2022. A Perspective on Nrf2 Signaling Pathway for Neuroinflammation: A Potential Therapeutic Target in Alzheimer's and Parkinson's Diseases. Frontiers in Cellular Neuroscience 15.https://doi.org/10.3389/fncel.2021.787258.

Sakurada, K., Konta, T., Takahashi, S., Murakami, N., Sato, H., Murakami, R., . . . Kayama, T., 2021. Circadian Clock Gene Polymorphisms and Sleep-Onset Problems in a Population-Based Cohort Study: The Yamagata Study. Tohoku J Exp Med 255, 325-331.https://doi.org/10.1620/tjem.255.325.

Scheer, F., Hilton, M.F., Evoniuk, H.L., Shiels, S.A., Malhotra, A., Sugarbaker, R., . . . Shea, S.A., 2021. The endogenous circadian system worsens asthma at night independent of sleep and other daily behavioral or environmental cycles. Proc Natl Acad Sci U S A 118.https://doi.org/10.1073/pnas.2018486118.

Schernhammer, E.S., Laden, F., Speizer, F.E., Willett, W.C., Hunter, D.J., Kawachi, I., . . . Colditz, G.A., 2003. Night-Shift Work and Risk of Colorectal Cancer in the Nurses' Health Study. JNCI: Journal of the National Cancer Institute 95, 825-828.https://doi.org/10.1093/jnci/95.11.825.

Schmitt, K., Grimm, A., Eckert, A., 2017. Amyloid-β–Induced Changes in Molecular Clock Properties and Cellular Bioenergetics. Frontiers in Neuroscience 11.https://doi.org/10.3389/fnins.2017.00124.

Sharma, R., Ottenhof, T., Rzeczkowska, P.A., Niles, L.P., 2008. Epigenetic targets for melatonin: induction of histone H3 hyperacetylation and gene expression in C17.2 neural stem cells. J Pineal Res 45, 277-284.https://doi.org/10.1111/j.1600-079X.2008.00587.x.

Shen, Z., Zhou, Z., Gao, S., Guo, Y., Gao, K., Wang, H., Dang, X., 2017. Melatonin Inhibits Neural Cell Apoptosis and Promotes Locomotor Recovery via Activation of the Wnt/β-Catenin Signaling Pathway After Spinal Cord Injury. Neurochem Res 42, 2336-2343.https://doi.org/10.1007/s11064-017-2251-7.

Shi, J., Wang, Z., Wang, Z., Shao, G., Li, X., 2024. Epigenetic regulation in adult neural stem cells. Frontiers in Cell and Developmental Biology 12.https://doi.org/10.3389/fcell.2024.1331074.

Shrestha, P., Jaganathan, A., Huilgol, D., Ballon, C., Hwangbo, Y., Mills, A.A., 2023. Chd5 Regulates the Transcription Factor Six3 to Promote Neuronal Differentiation. Stem Cells 41, 242-251.https://doi.org/10.1093/stmcls/sxad002.

Slominski, R.M., Reiter, R.J., Schlabritz-Loutsevitch, N., Ostrom, R.S., Slominski, A.T., 2012. Melatonin membrane receptors in peripheral tissues: distribution and functions. Mol Cell Endocrinol 351, 152-166.https://doi.org/10.1016/j.mce.2012.01.004.

Song, H., Moon, M., Choe, H.K., Han, D.-H., Jang, C., Kim, A., . . . Mook-Jung, I., 2015. Aβ-induced degradation of BMAL1 and CBP leads to circadian rhythm disruption in Alzheimer's disease. Molecular Neurodegeneration 10, 13.https://doi.org/10.1186/s13024-015-0007-x.

Soták, M., Sumová, A., Pácha, J., 2014. Cross-talk between the circadian clock and the cell cycle in cancer. Ann Med 46, 221-232.https://doi.org/10.3109/07853890.2014.892296.

Sun, Z., Chin, Y.E., Zhang, D.D., 2009. Acetylation of Nrf2 by p300/CBP augments promoter-specific DNA binding of Nrf2 during the antioxidant response. Mol Cell Biol 29, 2658-2672.https://doi.org/10.1128/mcb.01639-08.

Tiong, Y.L., Ng, K.Y., Koh, R.Y., Ponnudurai, G., Chye, S.M., 2020. Melatonin promotes Schwann cell dedifferentiation and proliferation through the Ras/Raf/ERK and MAPK pathways, and glial cell-derived neurotrophic factor expression. Exp Ther Med 20, 16.https://doi.org/10.3892/etm.2020.9143.

Tomita, T., Mori, T., Onishi, Y., 2019. β-Arrestin 1 (ARRB1) serves as a molecular marker of the peripheral circadian rhythm. International Journal of Oral Science 11, 32.https://doi.org/10.1038/s41368-019-0065-y.

Uberos, J., Augustin-Morales, M.C., Molina Carballo, A., Florido, J., Narbona, E., Muñoz-Hoyos, A., 2011. Normalization of the sleep-wake pattern and melatonin and 6-sulphatoxy-melatonin levels after a therapeutic trial with melatonin in children with severe epilepsy. J Pineal Res 50, 192-196.https://doi.org/10.1111/j.1600-079X.2010.00828.x.

Vakili, H., Jin, Y., Cattini, P.A., 2016. Evidence for a Circadian Effect on the Reduction of Human Growth Hormone Gene Expression in Response to Excess Caloric Intake. J Biol Chem 291, 13823-13833.https://doi.org/10.1074/jbc.M116.722744.

Van Someren, E.J., 2000. Circadian and sleep disturbances in the elderly. Exp Gerontol 35, 1229-1237.https://doi.org/10.1016/s0531-5565(00)00191-1.

Videnovic, A., Lazar, A.S., Barker, R.A., Overeem, S., 2014. 'The clocks that time us'--circadian rhythms in neurodegenerative disorders. Nat Rev Neurol 10, 683-693.https://doi.org/10.1038/nrneurol.2014.206.

Vockert, N., Machts, J., Kleineidam, L., Nemali, A., Incesoy, E.I., Bernal, J., . . . the, D.s.g., 2024. Cognitive reserve against Alzheimer’s pathology is linked to brain activity during memory formation. Nature Communications 15, 9815.https://doi.org/10.1038/s41467-024-53360-9.

Volicer, L., Harper, D.G., Manning, B.C., Goldstein, R., Satlin, A., 2001. Sundowning and circadian rhythms in Alzheimer's disease. Am J Psychiatry 158, 704-711.https://doi.org/10.1176/appi.ajp.158.5.704.

Wang, C., Holtzman, D.M., 2020. Bidirectional relationship between sleep and Alzheimer’s disease: role of amyloid, tau, and other factors.

Neuropsychopharmacology 45, 104-120.https://doi.org/10.1038/s41386-019-0478-5.

Wang, K., Liu, H., Hu, Q., Wang, L., Liu, J., Zheng, Z., . . . Liu, G.-H., 2022a. Epigenetic regulation of aging: implications for interventions of aging and diseases. Signal Transduction and Targeted Therapy 7, 374.https://doi.org/10.1038/s41392-022-01211-8.

Wang, Q., Lu, Q., Guo, Q., Teng, M., Gong, Q., Li, X., . . . Tao, Y., 2022b. Structural basis of the ligand binding and signaling mechanism of melatonin receptors. Nat Commun 13, 454.https://doi.org/10.1038/s41467-022-28111-3.

Wang, X., Wang, L., Yu, Q., Xu, Y., Zhang, L., Zhao, X., . . . Li, L., 2016. Alterations in the expression of Per1 and Per2 induced by Aβ31-35 in the suprachiasmatic nucleus, hippocampus, and heart of C57BL/6 mouse. Brain Res 1642, 51-58.https://doi.org/10.1016/j.brainres.2016.03.026.

Wang, Y., Guo, H., He, F., 2023. Circadian disruption: from mouse models to molecular mechanisms and cancer therapeutic targets. Cancer and Metastasis Reviews 42, 297-322.https://doi.org/10.1007/s10555-022-10072-0.

Wang, Z.Z., Sun, Z., Zhang, M.L., Xiong, K., Zhou, F., 2022c. Relationship between shift work, night work, and subsequent dementia: A systematic evaluation and meta-analysis. Front Neurol 13, 997181.https://doi.org/10.3389/fneur.2022.997181.

Weissová, K., Bartoš, A., Sládek, M., Nováková, M., Sumová, A., 2016. Moderate Changes in the Circadian System of Alzheimer's Disease Patients Detected in Their Home Environment. PLoS One 11, e0146200.https://doi.org/10.1371/journal.pone.0146200.

Wexler, E.M., Paucer, A., Kornblum, H.I., Palmer, T.D., Geschwind, D.H., 2009. Endogenous Wnt signaling maintains neural progenitor cell potency. Stem Cells 27, 1130-1141.https://doi.org/10.1002/stem.36.

Wu, Q., Shichino, Y., Abe, T., Suetsugu, T., Omori, A., Kiyonari, H., . . . Matsuzaki, F., 2022. Selective translation of epigenetic modifiers affects the temporal pattern and differentiation of neural stem cells. Nature Communications 13, 470.https://doi.org/10.1038/s41467-022-28097-y.

Xie, Y., Tang, Q., Chen, G., Xie, M., Yu, S., Zhao, J., Chen, L., 2019. New Insights Into the Circadian Rhythm and Its Related Diseases. Front Physiol 10, 682.https://doi.org/10.3389/fphys.2019.00682.

Xu, Y., Ma, H., Zhao, T., Wen, D., Wen, Y., Qiao, D., Liu, Z., 2019. Association Between Period 3 Gene Polymorphisms and Adverse Effects of Antidepressants for Major Depressive Disorder. Genet Test Mol Biomarkers 23, 843-849.https://doi.org/10.1089/gtmb.2019.0065.

Yang, L., Liu, X., Song, L., Su, G., Di, A., Bai, C., . . . Li, G., 2020. Melatonin restores the pluripotency of long-term-cultured embryonic stem cells through melatonin receptor-dependent m6A RNA regulation. J Pineal Res 69, e12669.https://doi.org/10.1111/jpi.12669.

Yao, D., Li, R., Hao, J., Huang, H., Wang, X., Ran, L., . . . Wang, M., 2023. Melatonin alleviates depression-like behaviors and cognitive dysfunction in mice by regulating the circadian rhythm of AQP4 polarization. Translational Psychiatry 13, 310.https://doi.org/10.1038/s41398-023-02614-z.

Yoon, K.J., Ringeling, F.R., Vissers, C., Jacob, F., Pokrass, M., Jimenez-Cyrus, D., . . . Song, H., 2017. Temporal Control of Mammalian Cortical Neurogenesis by m(6)A Methylation. Cell 171, 877-889.e817.https://doi.org/10.1016/j.cell.2017.09.003.

Yu, S., Zhang, X., Xu, Z., Hu, C., 2019. Melatonin promotes proliferation of neural stem cells from adult mouse spinal cord via the PI3K/AKT signaling pathway. FEBS Letters 593, 1751-1762.https://doi.org/10.1002/1873-3468.13458.

Yuzhen, C., Zheng, F., 2021. The effect of circadian rhythm on prolactin/PRLR-mediated intracellular signaling profiles in vivo and in vitro. Tissue and Cell 73, 101570.https://doi.org/10.1016/j.tice.2021.101570.

Zeng, L., Yu, T., Liu, H., Li, M., Wang, J., Wang, C., Xu, P., 2024. IGF-1’s protective effect on OSAS rats’ learning and memory. Sleep and Breathing 28, 1919-1928.https://doi.org/10.1007/s11325-024-03047-8.

Zhang, R., Lahens, N.F., Ballance, H.I., Hughes, M.E., Hogenesch, J.B., 2014. A circadian gene expression atlas in mammals: Implications for biology and medicine. Proceedings of the National Academy of Sciences 111, 16219-16224.https://doi.org/doi:10.1073/pnas.1408886111.

Zhao, F., Xu, Y., Gao, S., Qin, L., Austria, Q., Siedlak, S.L., . . . Zhu, X., 2021. METTL3-dependent RNA m(6)A dysregulation contributes to neurodegeneration in Alzheimer's disease through aberrant cell cycle events. Mol Neurodegener 16, 70.https://doi.org/10.1186/s13024-021-00484-x.

Zhao, R., Sun, J.B., Deng, H., Cheng, C., Li, X., Wang, F.M., . . . Qin, W., 2022. Per1 gene polymorphisms influence the relationship between brain white matter microstructure and depression risk. Front Psychiatry 13, 1022442.https://doi.org/10.3389/fpsyt.2022.1022442.

Zheng, Q., Wang, X., 2024. Alzheimer's disease: insights into pathology, molecular mechanisms, and therapy. Protein & Cell.https://doi.org/10.1093/procel/pwae026.

Tables

Table 1. Association of clock genetic variants with disease and traits related to ageing, Alzheimer's, and other neurodegenerative disorders.

Gene	SNP	Population	Genotype	Disease/ Associated phenotype	Ref.
BMAL1	rs1026071	Japanese	A>G	Insomnia, early awakening	(Sakurada et al., 2021)
BMAL1	rs1562438	Japanese	C>T	Insomnia	(Sakurada et al., 2021)
CLOCK	rs3805151	Korean	T>A, C	Abnormal sleep duration	(Kim et al., 2022)
CLOCK	rs6850524	Korean	C>A, G, T	Abnormal sleep duration	(Kim et al., 2022)
CLOCK	rs4580704	Korean	A>C, G	Sleep duration	(Kim et al., 2022)
CLOCK	rs10002541	Korean	T>C	Age-related changes in sleep duration, poor sleep	(Kim et al., 2022)
CLOCK	rs11932595	Caucasian	A>G, T	Sleep duration and quality	(Li et al., 2021)
CLOCK	rs12649507	Chinese & Caucasian	G>A, T	Sleep duration	(Allebrandt et al., 2010; Li et al., 2022)
CLOCK	rs1801260	Chinese	A>G	Parkinson's Disease	(Lou et al., 2017)

CLOCK	rs3749473	Taiwanese	T>C	Cognitive aging	(Lin et al., 2017)
CLOCK	rs1554483	Chinese	C>G	Alzheimer’s disease	(Chen et al., 2013)
CRY1	rs2287161	Chinese	C>G, A, T	Depression	(Hua et al., 2014)
CRY2	rs2292910	Finnish	A>C	Depression	(Kovanen et al., 2017)
CRY2	rs10838524, rs7121611, rs7945565, rs1401419	Finnish & Swedish	A>G	Dysthymia	(Kovanen et al., 2013)
CRY2	rs1401419	Finnish	T>C	Dysthymia, Depression	(Kovanen et al., 2013)
CRY2	rs7945565	Finnish	A>G	Dysthythmia	(Kovanen et al., 2013)
CRY2	rs10838527	Swedish & Finnish	A>G	Depression	(Lavebratt et al., 2010)
NPAS2	rs17655330	Taiwanese	A>C	Cognitive aging	(Lin et al., 2017)
PER1	rs7221412	European	A>G	Depression	(Zhao et al., 2022)
PER1	rs3027178	Italian	T>G	Alzheimer's disease[1]	(Bacalini et al., 2022)
PER2	rs2304672	Italian	G>C	Cognitive function	(Forbes et al., 2012)
PER2	rs10462023	Swedish	G>A, T	Depression	(Liu et al., 2015)
PER2	rs121908635		T>C	Familial advanced sleep phase disorder	(Jones et al., 1999)
PER2	rs934945	Korean	C>T	Diurnal preference	(Lee et al., 2011)
PER3	rs228697	Chinese, Japanese	C>G	Agitation, Diurnal sleep preference, Anxiety	(Hida et al., 2014; Liberman et al., 2017)
PER3	rs228729	Chinese	T>C	Agitation	(Xu et al., 2019)

PER3	rs57875989	Various	Deletion/insertion	Depression, Anxiety, Diurnal preference	(Benedetti et al., 2008; Liberman et al., 2017)
RORA	rs13329238	Taiwanese	C>A	Cognitive aging	(Lin et al., 2017)
RORB	rs10781247	Taiwanese	G>A	Cognitive aging	(Lin et al., 2017)

[1] G allele protective effect

Declaration of Competing Interest

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Figure legends

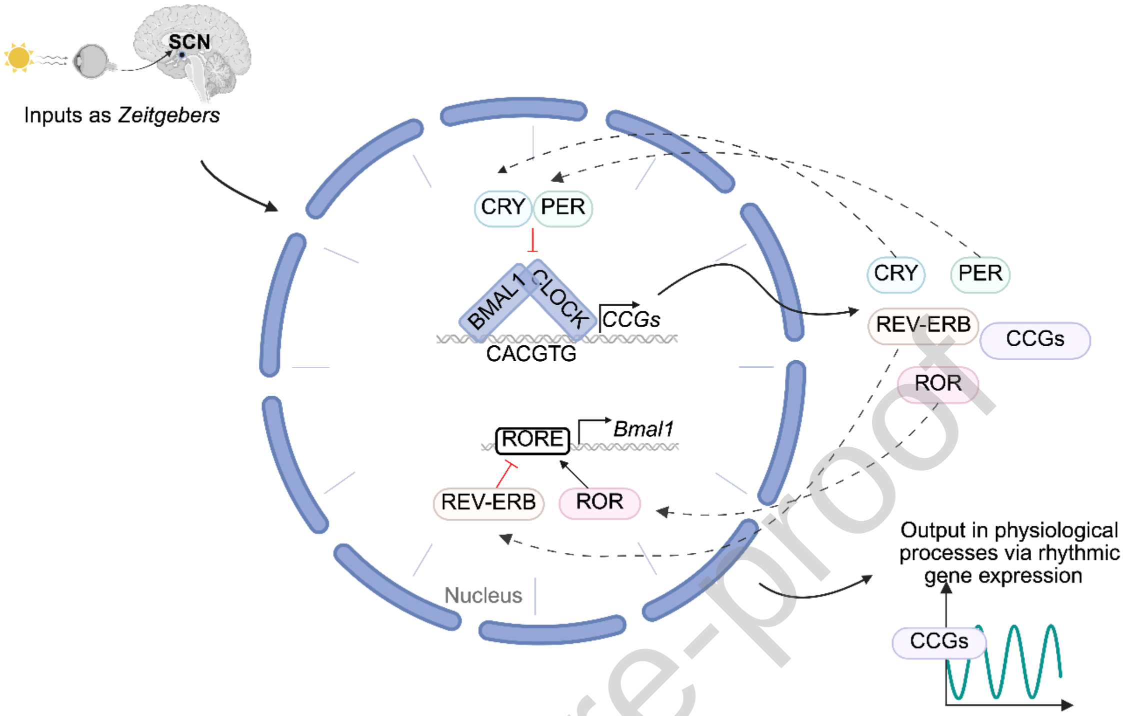

Figure 1

Molecular basis of the circadian clock

Schematic representation of the molecular circadian oscillator that consists of feedback loops. The primary negative feedback loop of the circadian oscillator involves Clock, Bmal1, Per1, Per2, Cry1 and Cry2 genes. In the core loop, CLOCK and BMAL1 heterodimerise to drive the expression of clock-regulated genes via E-box transcription. Subsequently, PER and CRY proteins heterodimerise and translocate to the nucleus to inhibit CLOCK/BMAL1-driven transcription. A secondary feedback loop is composed of an antagonistic regulation of BMAL1, with two nuclear receptors, REV-ERBα and REV-ERBb, as repressors and RORs as activators.

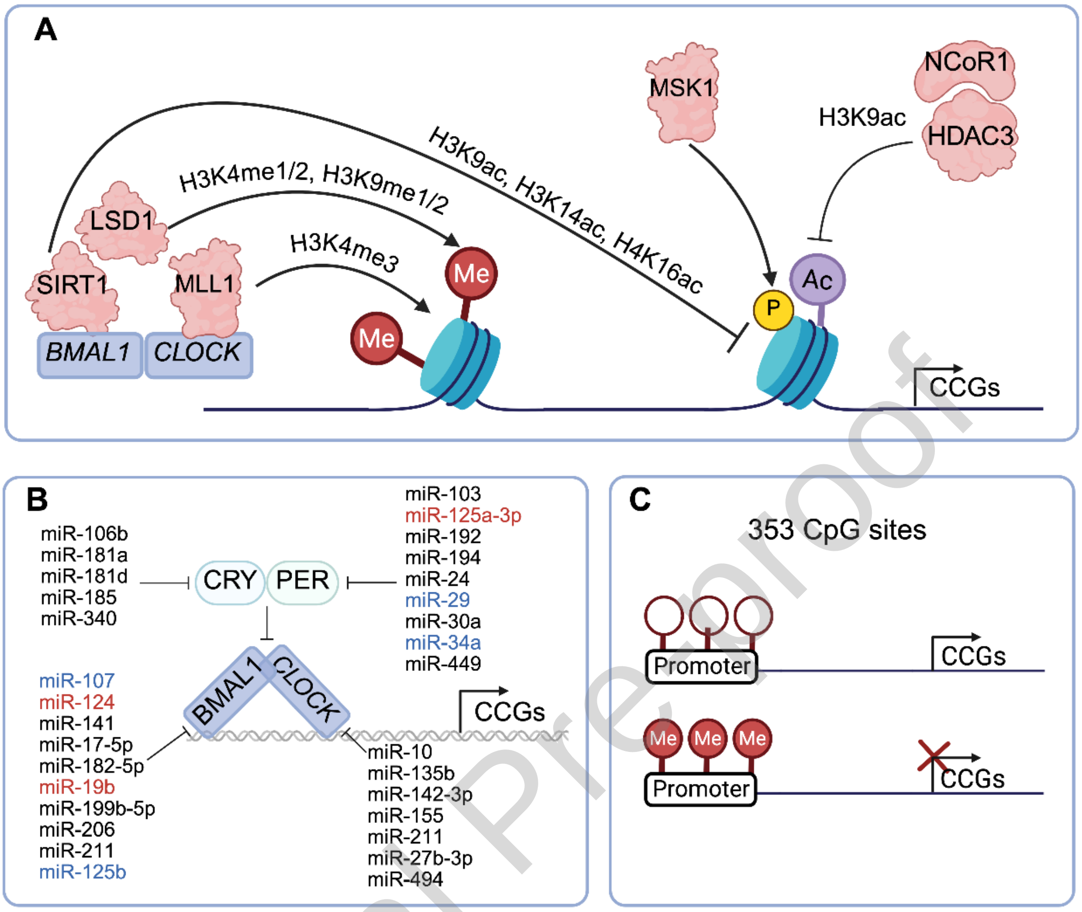

Figure 2

Epigenetic regulation of the circadian clock

(A) Histone modifications, (B) DNA methylation and (C) non-coding RNA regulation of the circadian clock. Several miRNAs directly regulate the central components of the CC. miRNA involved additionally in Alzheimer’s Disease and neurogenesis are marked in blue and red, respectively.

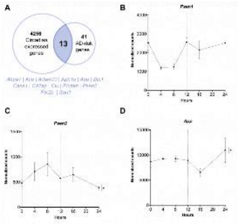

Figure 3

Circadian rhythmicity of AD-risk genes in SCN

(A) Venn diagram showing the overlapping between SCN circadian-expressed genes and AD-risk genes. The 13 AD-risk genes suggested to be under the regulation of the circadian clock in the SCN are listed below. (B-D) Gene expression of PSEN1, PSEN2 and APP, genes related to early onset AD. Gene information, including the expression levels of each mentioned gene, was found through the SCNseq database. Fluctuating genes, whose expression significantly altered over time with a sinusoidal oscillatory pattern were counted as circadian expressed genes and in PSEN1, PSEN2 and APP expression are denoted with an asterisk (*q < 0.05).

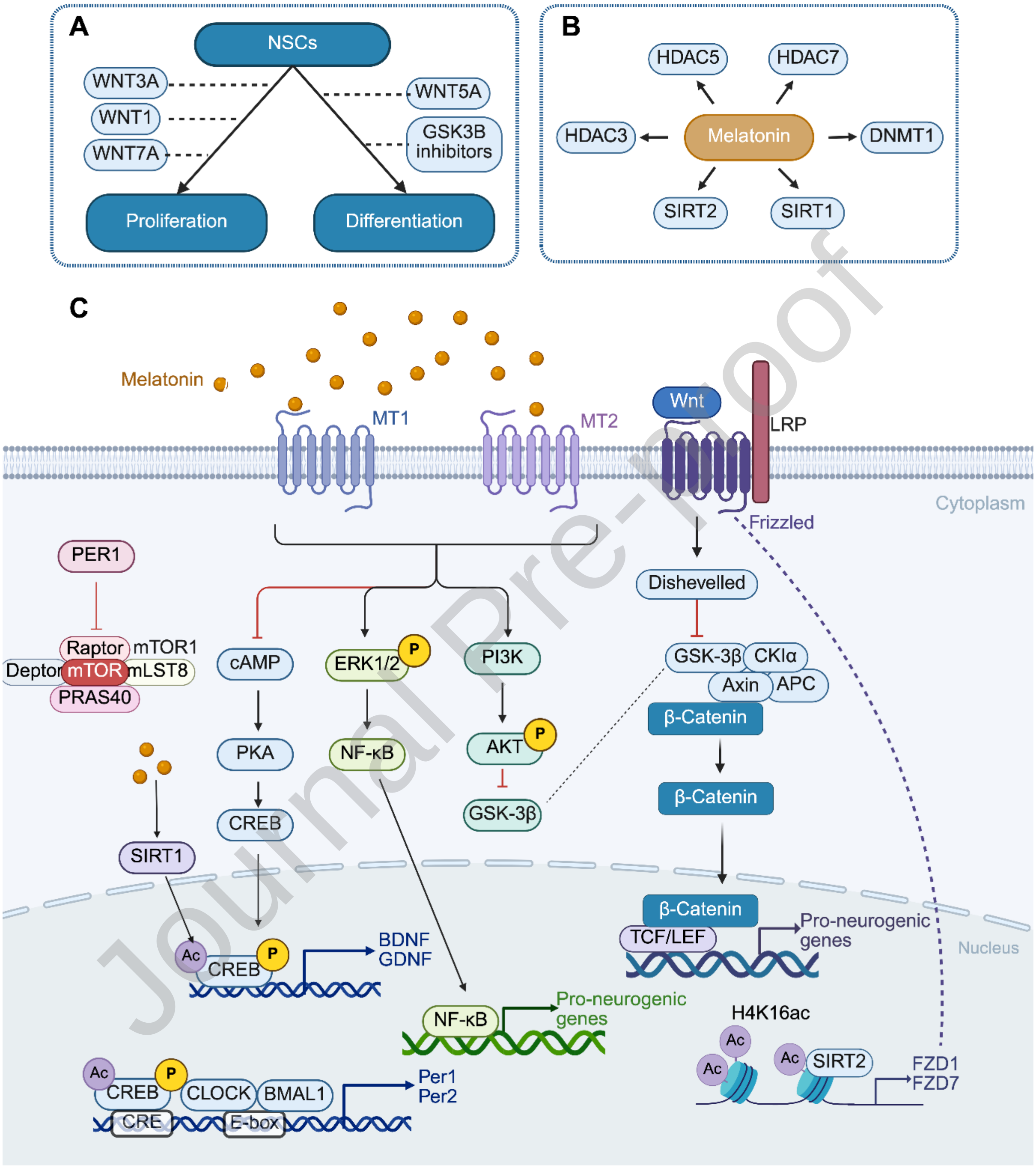

Figure 4

Neurogenesis interplay with circadian clock and AD

(A) WNT pathway-associated molecules dysregulated in AD neural stem cells. Obtained from AlzPathway. (B) Melatonin-inducted expression of epigenetic regulatory enzymes. (C) Model of involved signalling pathways of melatonin mechanism and CC regulating proliferation and differentiation of NSCs in AD.

Highlights

- The circadian clock regulates behavioural and physiological processes and is disrupted in neurodegenerative diseases, contributing to the onset and progression of Alzheimer's disease.
- Adult neurogenesis, crucial for brain function, is regulated by the circadian clock and is significantly impaired in Alzheimer's disease.
- Epigenetic mechanisms play a key role in circadian rhythm and neurogenesis regulation.
- Circadian-epigenetic mechanisms offer a novel therapeutic approach for Alzheimer's disease and other neurodegenerative diseases.