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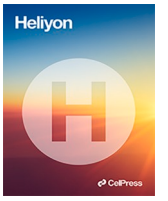

Review article

Epigenetic events influencing the biological clock: Panacea for neurodegeneration

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ABSTRACT

The human biological clock is the 24-h internal molecular network of circadian genes in synchronization with other cells in response to external stimuli. The rhythmicity of the clock genes is maintained by positive and negative transcriptional feedback loops coordinating the 24-h oscillation in different tissues. The superchiasmatic nucleus, the central pacemaker of the biological clock diminishes with aging causing alterations in the clock rhythmicity leading to the onset of neurodegenerative diseases mainly Alzheimer's disease, Parkinson's disease, and Huntington's disease. Studies have shown that brain and muscle Arnt -like 1 (Bmal1) and Circadian Locomotor Output Cycles Kaput (Clock) gene expression is altered in the onset of neurodegeneration. One of the major symptoms of neurodegeneration is changes in the sleep/wake cycle. Moreover, variations in circadian clock oscillations can happen due to lifestyle changes, addiction to alcohol, cocaine, drugs, smoking, food habits and most importantly eating and sleep/awake cycle patterns which can significantly impact the expression of circadian genes. Recent studies have focused on the molecular function of clock genes affected due to environmental cues. Epigenetic modifications are influenced by the external environmental factors. This review aims to focus on the principal mechanism of epigenetics influencing circadian rhythm disruption leading to neurodegeneration and as well as targeting the epigenetic modulators could be a novel therapeutic approach to combat neurodegenerative disorders.

1. Introduction

In biological processes, 24-h circadian rhythmic oscillations are maintained in all organisms in response to environmental fluctuations and play a vital role in maintaining metabolic as well as physiological homeostasis [1]. Moreover, the biological/circadian clock can also function autonomously producing oscillations in the absence of external cues known as the free-running period [2]. The suprachiasmatic nucleus (SCN) is the master circadian clock located in the brain which synchronizes with the peripheral clock genes expressed in other tissues and organs in the human body [3]. The circadian clock modulates the physiological and behavioural functions involving the sleep/awake cycle, cognitive functions, alertness and metabolic actions [4]. The cyclic expression of genes is controlled by the circadian clock and its disruption can lead to alterations in physiological and metabolic activity [5]. Remodelling of the circadian clock like histone modifications, nuclear receptor activity, and energy homeostasis depends on different environmental factors influencing the epigenetics mechanisms [6]. Disruption of the sleep/awake cycle is a common symptom in neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, and Huntington's disease which occurs in the initial stages of the disease

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Abbreviations

AD	Alzheimer's disease
APP/PS1	Amyloid precursor protein/presenilin 1
AVP	arginine vasopressin
BMAL1	Brain and muscle Arnt -like 1
CAG	cytosine, adenine, and guanine;
CBP	CREB binding protein
CCGs	clock-controlled genes
CLOCK	Circadian Locomotor Output Cycles Kaput
CRY	cryptochrome
Cry1	cryptochrome 1
Cry2	cryptochrome 2
CSD	Chronic sleep disorder
CSF	cerebrospinal fluid
CpG	5′C-phosphate-G3
DNMTs	DNA methyltransferases
HD	Huntington's disease
HDAC3	histone deacetylase 3
IL-1β	interleukin-1 β
MT1	melatonin receptor 1
MT2	melatonin receptor 2
Nf-κB	nuclear factor-κB
NPAS2	neural PAS domain protein 2
NAMPT	nicotinamide phosphoribosyl transferase
PD	Parkinson's disease
Per 1	period 1
Per 2	period 2
PER	period
PP1	phosphatases 1
PP5	phosphatases 5
PPAR	Peroxisome proliferator-activated receptor
ROR	receptor-related orphan receptor
SCN	suprachiasmatic nucleus
SIRT1	silent mating type information regulation 2 homolog
SIN3	paired amphipathic helix protein Sin3a
,	ten-eleven translocation
TTFL,	Transcription/translation feedback loops
TIM	Timeless
WT	wild-type

progression [7]. The concept that proteins and DNA can impact 24-h circadian rhythmic oscillations in all organisms is an over-simplified action. The key metabolites of disrupted metabolic pathways could also impact epigenetics which eventually causes changes in the gene expression pattern contributing to alterations in the biological clock [8]. Epigenetic processes involve methylation, acetylation and several RNA-mediated changes affecting gene expression [9]. In circadian rhythmicity, the epigenetic changes influence specific transcription factors like brain and muscle Arnt -like 1 (BMAL1) and Circadian Locomotor Output Cycles Kaput (CLOCK) [10]. Alterations in the BMAL1 and CLOCK impact the rhythmic expression of clock genes which is associated with the onset of neurodegenerative diseases [11]. The epigenetic pattern shows variability that could indicate each cell type lasting stable over the life span and is associated with early modification for adult-onset neurodegenerative diseases [12]. However, the mechanism underlying the disruption of circadian clock machinery leads to neurodegeneration has not been fully explored. This review focuses on the epigenetic link to the biological clock gene disruption under various environmental cues leading to neurodegenerative disorders.

2. Biological clock machinery: the 24-hour cycle

The biological clock is a 24-h cycle that is regulated by external signals like the light-dark cycle, temperature, food and sunlight. The hypothalamic suprachiasmatic nucleus (SCN) is the master circadian pacemaker in mammals that coordinate with the tissue-specific oscillators to generate rhythmicity. Generally, in mammals, the light/dark signals enter through the retina and are transmitted to the central pacemaker of the hypothalamus: SCN which further synchronizes every cellular clock in the periphery tissues. All the organs and tissues synchronize within the 24-h rhythmicity through the coordination between peripheral tissues and the central

nervous system [13,14].

The identification and cloning of first clock genes in *Drosophila melanogaster* were vital in understanding the molecular evidence of core circadian rhythm and the discovery mainly attributed to understanding the major regulators of the circadian clock [15]. The distinct transcription factors of circadian rhythm are brain and muscle Arnt-like 1 (BMAL1) and Circadian Locomotor Output Cycles Kaput (CLOCK). Circadian rhythm is mainly modulated by Period genes (Per 1, Per 2) and cryptochrome genes (Cry1, Cry2). All of these gene expressions are regulated by the master molecular clock transcription factor (BMAL1)/CLOCK as well as the period/-cryptochrome complex. Briefly, in the clock machinery, the gene expression of 24-h rhythmicity occurs by the formation of interlocking transcription/translation feedback loops (TTFL). The TTFL is driven by clock proteins: CLOCK and BMAL1 (activators) and PER and CRY (repressors). The CLOCK: BMAL1 activates the transcription of Per and Cry genes and other clock-controlled genes. In the cytoplasm, the PER and CRY proteins heterodimerize and translocate to CLOCK: BMAL1 in the nucleus to restrict its transcription. Degradation of PER and CRY proteins relieves CLOCK: BMAL1 and the cycle starts over with 24-h rhythmicity [16]. The intrinsic period of the clock is controlled by casein kinases CKId, and CKIe and regulated by phosphatases PP1 and PP5 respectively which determine the degradation and the rate of PER: CRY complex entry into the nucleus [17]. The amplitude of circadian oscillation is maintained by a cyclic proteolytic degradation of the repressor complex. Degradation takes place upon the recruitment of F-box protein FBXL3 and when the casein kinase Iε (CKIε) phosphorylates the PER proteins [17–19]. The CLOCK-BMAL1 activator complex initiates a new transcriptional cycle within 24 h based on these events [20]. Multiple genes such as vasopressin D site albumin promoter binding protein get regulated via the E-boxes present in the promoters of CLOCK-BMAL1. The cyclic expression of additional CCGs (clock-controlled genes) gets regulated by the other genes encoding transcription factors. Apart from E-boxes, the D-boxes or receptor-related orphan receptor (ROR) response elements get modulated by the binding of transcription factors to regulatory consensus sequences. There are additional transcriptional-translation regulatory loops that also contribute to the function of circadian machinery. Nuclear receptors: retinoic acid receptor-related orphan receptor-α (RORα) and erythroblastosis virus-α (REV-ERBα) are reversed which comprise an additional loop playing an important role in Bmal1 expression. In the Bmal1 promoter, the binding of transcription factors to ROR response elements (ROREs) initiates either the activation of Bmal1 transcription on ROR alpha or repression by binding of Rev-erbα [21,22]. The feedback loop is completed by the transcription of the gene: Rev-erbα inducing the activation and expression with robust rhythmicity by CLOCK-BMAL1 (Fig. 1) [23].

Mutations in CKId or loss of a single phosphor-acceptor site on PER2 reduce the intrinsic period of the clock in mice, whereas in humans it could lead to sleep phase disorders [24,25]. The second TTFL occurs by the activation of ROR a,b,c and repression by REV-ERB alpha/REV-ERB beta. TTFL causes changes in the transcription of Bmal1 and slows down the mRNA expression of Cry1 which is important for proper circadian timing [26]. Fascinatingly, recent evidence shows a bidirectional relationship linking circadian balance and neurodegeneration, indicating that circadian machinery could have a significant role in the prognosis of neurodegenerative diseases [27]. Hence, any disruption or alterations in the core clock machinery can cause an imbalance in circadian homeostasis

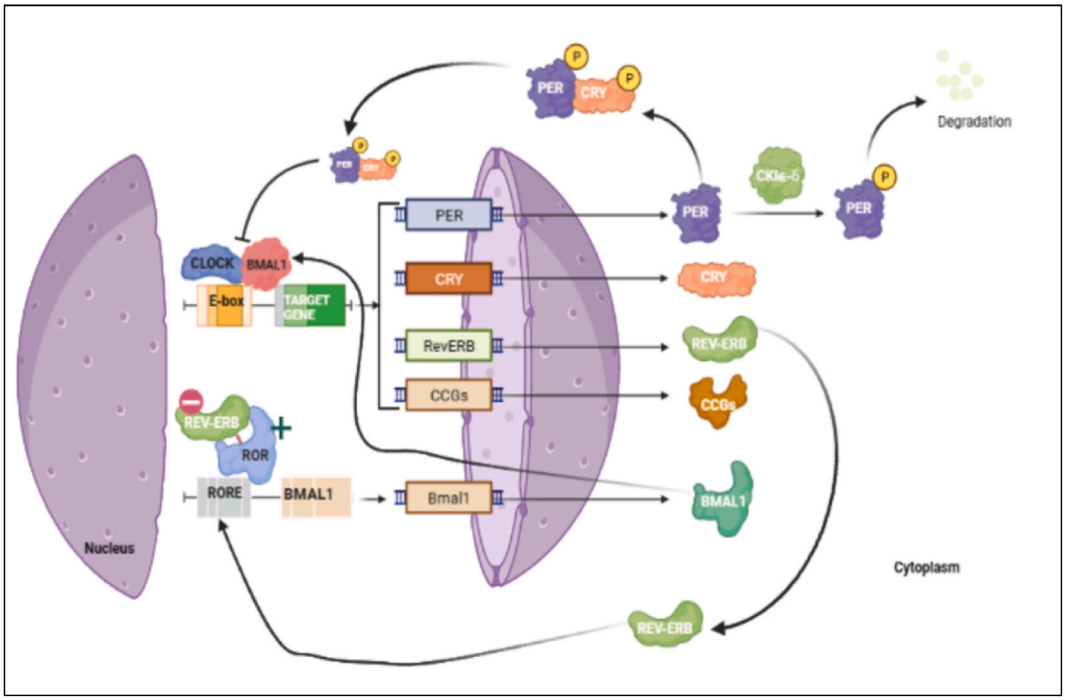

Fig. 1. Transcriptional-Translation loop of circadian clock machinery. In the positive arm, Clock and Bmal1 heterodimerize activate the transcription of circadian genes: Per, Cry, ROR, Nr1d1. In the negative arm, Per and Cry repress the action of Clock/Bmal1 to repress their transcription. REV-ERBα and ROR mediate arbitrate action on Bmal1 gene expression.

affecting human health.

3. Disrupted Clock stems to neurodegenerative diseases

The synchronized whole organism's circadian clock function could be impacted due to suprachiasmatic alteration and light/dark cycle changes. Natural oscillation of the cellular clock in different regions of the brain, cognition, and hippocampus-dependent learning including cellular rhythms in peripheral organs like the liver and heart are also modulated by the circadian clock which could be impacted when the core clock machinery is altered. A study conducted by Zhang et al., 2014 highlighted more than 100 genes showing circadian oscillations from the cerebellar and brain samples through transcriptomic studies. Merely changing the sleep/awake timing and feeding pattern in mice led to variations in the oscillation of the hippocampus specifically in SCN, thus developing the disability in learning and memory function [28].

Specific neurodegenerative diseases like Alzheimer's disease, Parkinson's disease and Huntington's disease have a common symptom of disturbance in sleep/wake cycles which shows that there are changes in the circadian rhythm, a decrease in hormone release and biochemical changes like antioxidant production. Research evidence shows that alterations in circadian rhythmicity precede the occurrence of cognitive and motor symptoms in neurodegenerative diseases and lead to the onset of the disease [29–32]. Circadian rhythm oscillates for approximately 24-h periods entrained by external factors controlling the cellular metabolism, hormone secretions, sleep pattern and cardiac function. Additionally, the cross-linking of the circadian clock with the regulation of brain health is a major focus element in the process of neurodegeneration. Recent research studies in mice are performed through the deletion of clock genes to unwind the cellular function and neuro-pathological changes in the brain. Acute astrogliosis, oxidative damage, learning, memory impairment, synaptic deterioration, and hippocampus neurogenesis are the prominent neuronal disorders observed in mice with Bmal1 deletion [33]. Irregularity in the bmal1 and per2 rhythmicity expressions was observed in the patients with AD, PD and HD and also in the animal study of the mentioned disease model. A complex pattern of alterations was observed in bmal1 mRNA expression in Alzheimer's disease. In different brain regions and peripheral tissues, the bmal1 mRNA expressions were rhythmic but there was a difference in the temporal phase of the tissues when compared with healthy control [34]. The pineal clock gene oscillations of bmal1, per1 and cry1 mRNA were lost in individuals with AD [35]. Decreasing rhythmicity of per2mRNA and PER2 protein expression in different brain regions of SCN and peripheral tissues was observed in the rodent model of Parkinson's disease [36,37]. Likewise, in the rodent model of Huntington's disease, the expression of per2mRNA was disrupted in both central and peripheral tissues [38,39].

In neurodegenerative diseases, researchers also aim to study the effect of rhythm-related environmental factors, day-to-day activities, sleep deprivation and genetic factors and further evaluate if the disturbance in the circadian clock influences the progression of the disease. Interestingly, Niu et al., 2021 examined expression levels of circadian genes and chronic sleep deprivation in transgenic mice. The results revealed chronic sleep deprivation reduced learning and memory and further increased the progression of AD disease in mice. Bmal1, Clock, and Cry1 expression levels were abnormal in the chronic sleep disorder (CSD) in circadian-related experimental mice and changes were more compelling in the mice with AD pathology [40]. Amyloid precursor protein/presenilin 1 (APP/PS1) mutations affected the expression of clock genes [41]. Additionally, the study focusing on BMAL1 protein level and tau phosphorylation was found to be abnormal in the retro spinal cortex of the AD mice model compared with wild-type (WT) mice. The CSD caused a significant increase in the level of tyrosine hydroxylase. The BMAL1 alternations weaken the blood-brain barrier by pericyte dysfunction and directly participate in the cellular antioxidant responses [42]. Therefore, changes in Bmal1 expression are interlinked with the chronic sleep disorder. The continuous alteration of natural circadian rhythms influences health due to extensive effects on pro-inflammatory and gene transcription processes. The possibility of Parkinson's disease (PD) is higher in individuals with single nucleotide polymorphisms of per1 and bmal1 [43]. In addition, even single nucleotide polymorphisms in CLOCK and BMAL1 genes could be a reason for susceptivity to AD. Notably, an association was found between rs3027178 polymorphism in the per1 circadian gene of AD patients and healthy controls of the Italian population. These studies signify the potential effect of circadian disturbances involving the role of genetic mechanisms in age-related disorders and the longevity of life [44]. Other genes which are regulated by the clock genes, such as the presenilin-2 are also associated with the neurocognitive disorder [45]. Beta-amyloid peptide levels are modulated by the presenilin-2 gene. Also, presenilin-2 is regulated through the transcriptional, post-transcriptional process by CLOCK: BMAL dimers in the peripheral tissues [46]. A recent research study by Nam Hyeri et al., 2022, explored how presenilin 2 N141I mutation abrogates the expression of the circadian gene. In the innate immune system, presenilin 2 N141I gene mutation leads to the excessive production of clock gene-controlled cytokines through the DNA hypermethylation-arbitrated repression of REV-ERBα [47]. Hence, an association between circadian clock genes and molecular components could also be a major reason leading to the onset of neurodegenerative diseases.

Generally, changes in the melatonin secretion levels and the suprachiasmatic nucleus are presumed to be one of the main bases of alteration in circadian rhythm in Alzheimer's disease. Gamma-aminobutyric acid and arginine vasopressin neurons are present in the suprachiasmatic nucleus which sends a direct hindrance projection to the paraventricular nucleus of the hypothalamus. Further, it activates the secretion of melatonin by the pineal glands. The circulating melatonin is enacted by melatonin receptors (MT1 and MT2) and restricts the firing of SCN. The melatonin secretion increases 2 h before a normal bedtime and remains raised during the night hours. The deficit expression of MT1 receptors and arginine vasopressin (AVP) in the SCN could lead to changes in normal melatonin rhythm and its production [48–50]. During the onset of AD, the levels of amyloid beta are controlled by the sleep-wake cycle and the circadian rhythm. An experimental study performed by Kang et al., 2009 witnessed that transgenic and wild-type mice had higher concentrations of amyloid beta during the wakefulness studied by in vivo microdialysis and diurnal variations were observed in the human cerebrospinal fluid (CSF) samples [51]. A preclinical study of Alzheimer's disease reported that circadian rhythm changes

appeared very early in the preclinical phase of Alzheimer's disease patients when compared to healthy controls. This was also correlated with the pathology of Alzheimer's disease and amyloid beta ratio to CSF phosphorylated tau [52]. Studies reveal the relationship between increased levels of Alzheimer's disease-associated biomarkers to sleep-wake cycle disruption. Further to understand if there is a link between the circadian rhythm phenotypic deterioration to the clock gene's molecular function, Hyundong Song et al., 2015 identified the role of amyloid-β protein expression, transcriptional control, and post-translational impairment of molecular circadian clock proteins including BMAL1, PER2, CREB binding protein (CBP) [53]. The study indicated disturbed expression of per2 at mRNA, and protein levels due to BMAL1 and CREB binding protein (CBP) degradation caused by Aβ. BMAL1 degradation is correlated with the sumoylation and related functional changes of BMAL1 [54]. N-cadherin cleavage by amyloid beta elevated the CBP degradation, contributing to the circadian impairment of AD patients.

The second most common neurodegenerative disease is Parkinson's disease (PD) and about one million individuals are affected by PD worldwide. Progressive depletion of dopaminergic neurons and imbalance in other neurotransmitters lead to Parkinson's disease [55]. Increasing evidence shows that the circadian rhythm is disturbed in patients with PD. Dopamine metabolism is influenced by the circadian system and dopamine plays a significant role in circadian regulation [56]. Along with dopamine, the iron metabolism induces circadian changes for instance in symptoms linked with restless legs syndrome which is a movement dysfunction associated with Parkinson's disease [57]. The symptoms of neurodegenerative diseases are more prevalent during the early onset of ageing. In studies related to neurodegeneration and ageing in the *Drosophila melanogaster*, mutant phenotypes had an increase in oxidative stress but loss of dopaminergic neurons was more significant. Additionally, constant levodopa (I DOPA) treatment in an animal model study of Parkinson's disease pathology with 6-hydroxydopamine resulted in a decrease in BMAL1, RORα leading to cognitive dysfunction, and circadian function impairment [58]. Studies show that cortisol levels are higher in the initial stages of PD and the somatropic, lactotrophic, and thyrotropic axes remain undamaged at the onset of disease progression. The fat cells release endocrine factors like adipokines, which have an essential role in body mass regulation and metabolism. A study focusing on melatonin and adipokines in PD subjects revealed twice the reduced concentration of melatonin in early-stage PD subjects when compared to healthy individuals. Moreover, no difference in adiponectin and lectin was found in PD patients compared to controls. There is a possible involvement of both melatonin and hormones released by adipose tissue in the pathogenicity of Parkinson's disease [59].

Another disorder causing progressive neurodegenerative disorders in the central nervous system is Huntington's disease. This genetic disorder is caused due to an autosomal dominant mutation. The CAG triplet repeats in the gene encoding Huntington's protein lead to this deadly genetic neurodegenerative disease [60]. VIPergic (vasoactive intestinal polypeptide) signalling has an important role in maintaining circadian rhythmicity and neuropeptide vasoactive intestinal polypeptide (VIP) and its receptor VPAC2 are expressed in the SCN of the hypothalamus. Interestingly, Fahrenkrug et al., 2007 found reduced VIP mRNA, VPAC2 receptor mRNA levels, decrease in VIP immunostaining in the suprachiasmatic nucleus. The changes were associated with alterations in circadian rhythm [61]. Therefore, a decrease in VIPergic signalling could be a major mechanism associated with the alteration of the circadian clock. In the transgenic R2/6 Huntington disease model, circadian changes with an increase in activity during daytime and reduced activity during night-time was been observed [62,63]. The disturbance in day-night time activity of the R6/2 mice aggravated with the development of the disease-causing behaviour disturbances. The main reason for the circadian sleep-wake cycle could be due to an alteration in circadian expression by the SCN. Disturbances in the expression of mPer2 and bmal1, clock genes in the motor cortex and striatum were observed in the R6/2 mice. The effect of the circadian mechanism leading to HD pathogenicity has not been much recognized. However, it is known that there is damage to the hypothalamus during the HD disease progression [64,65]. In HD animal models, the stabilization of circadian rhythmicity reduces cognitive impairments and can be an important target to suppress the development of HD and improve the life quality of HD patients [66].

4. Inciting the inflammatory cytokines in response to the circadian rhythm

Disease-associated action and ageing could increase neuronal loss due to pro-inflammatory signalling. Different cellular and molecular events like mitochondrial dysfunction, oxidative stress, alpha-synuclein oligomerization, and increased iron concentration activate microglial cells causing neuroinflammation and neurodegeneration. Eventually, these events engage in neuronal apoptosis over time triggering astrocytes population and microglia in specific regions of the brain. Environmental and cellular stresses like neurotoxins, stress, hypoxic, oxidative stress, and osmotic lead to the activation of neuronal immune responses [67]. In the case of neurodegenerative disorders, we see that the majority of existing Parkinson's disease studies both with animal models and human clinical samples have linked neuroinflammation with environmental stress that leads to progressive deterioration of the brain neurons. Thus, anti-inflammatory therapy could give essentially neuroprotective effects to patients having neurodegenerative disorders. Interestingly, it is found that the effects of circadian disruption on health may also be mediated by alterations in the gut microbiome, which has been shown to exhibit circadian rhythmicity and play a critical role in maintaining metabolic homeostasis [68]. One of the major functions of the circadian clock is to arbitrate the timing of distinct activities of the immune system involving the recruitment of leukocytes, production of cytokines and cell proliferation [69]. Clock gene expression could be disrupted by the immune mediators, various cytokines, chemokines, and hormones associated with the pro-inflammatory responses are also influenced by the circadian clock. Protein complexes important for the production of chemokines and cytokines are activated by CLOCK and CRY, and as discussed before the CLOCK activation of these complexes is inhibited by BMAL1. Periodic levels of cytokines and chemokines are produced by the interdiction of CLOCK's activation due to the binding of BMAL1 to e-boxes of immune mediator genes. These changes result in increased chemokines and cytokines production levels during the active phase of inflammatory responses [70]. The association between molecular interactions between the circadian clock and the immune system is explored to some extent. For instance, pulmonary inflammatory responses were focused more during COVID-19 and were under circadian control. Recently, in the mesenchymal cells, it

has been found that REV-ERB alpha has a critical control of fibrosis [71].

Evidence shows that the expression or repression of the immune system is controlled by the molecular circadian clock [72]. Additionally, the transcription of inflammatory genes is regulated by the rhythmic acetylation or methylation of histones. There is also proof that circadian clock proteins are directly involved in key inflammatory pathways like the NF-kB protein family. NF-kB-mediated transcription is downregulated by BMAL1 and REV-ERBα during inflammatory-mediated response. ROS production is inhibited via NRF2-dependent suppression by BMAL1-regulated IL-1b response. Eventually, b-cell clocks are disturbed by changes in the expression of NAD + -dependent deacetylase SIRT1 by the pro-inflammatory cytokine IL-1b [73] (Fig. 2). The innate link between the immune system and circadian rhythmicity is likely to provide more protection during the daytime whereas reduced stimulation during the night. Chronic activation of astrocytes and microglia leading to neuroinflammation is the main contributor to neurodegenerative disease [74–76]. Astrocytes express potent circadian functions like the neurons [77]. Knockout of brain-specific BMAL1 depreciates the blood-brain barrier leading to loss of activation of pericytes, microglia, astrogliosis and inflammatory gene expression [78,79]. Likewise, microglia and their inflammatory response function exhibit circadian clock function and show circadian variation [80,81]. One of the major discoveries in this area is that activation of microglia and synapse degradation occurs during the knockout of brain-specific BMAL1. Recently studies show that the component of the circadian clock: REV-ERBα is the main regulator of microglia activation and neuroinflammation. Reverb deletion in mice immediately leads to the activation of microglial cells in the hippocampus, higher expression of secondary astrogliosis and proinflammatory cytokines. Higher NF-κB activation and proinflammatory phenotypes were observed in primary Reverb$^{-/-}$ microglia. The daily rhythmicity of microglial synaptic phagocytosis is directed by the expression of Rev-erbα. Thus, neurodegeneration diseases caused by a disturbance in astrocytes and microglia provide the process by which disruption of circadian rhythmicity leads to inflammation in the brain [82].

In the inflammatory cells, circadian clock proteins: BMAL1 and REV-ERBα control the molecular mechanism of cytokines, chemokines and oxidant response.

5. Circadian rhythmicity to neurodegenerative disease: from an epigenetics viewpoint

A study by Hulme et al., 2020 investigated the epigenetic regulation of BMAL1 with sleep disturbances and Alzheimer's disease. It was found methylation across CpG (5′C-phosphate-G3') was strongly related to each other. CpG2 methylation was higher concluding that BMAL1 methylation is linked with sleep and depressive symptoms, alterations in cognitive measures and tau pathology [83]. There is a compelling involvement of circadian genes in neurodegenerative disorders. The daily function of the circadian molecular system depends on epigenetic mechanisms. The transcription feedback loop among CLOCK/BMAL and PER/CRY requires a periodic cycle of histone acetylation/deacetylation. It is observed that CLOCK has histone acetyltransferase activity [84]. The promoter sequence of Per1, Per2, and Cry1 has acetylated histone H3. SIN3 (paired amphipathic helix protein Sin3a) protein complex contains the histone deacetylase protein (HDAC) which is recruited by the PER protein complex when Per1 and Per2 get translated. The repression of Per genes happens when the protein complex deacetylates the histone which was acetylated by CLOCK. Additional regulation happens by this rhythmic histone acetylation/deacetylation corresponding to the transcription feedback loop of CLOCK/BMAL and PER/CRY [85,86]. In the case of epilepsy, the circadian regulation and metabolism of the brain are functioned by

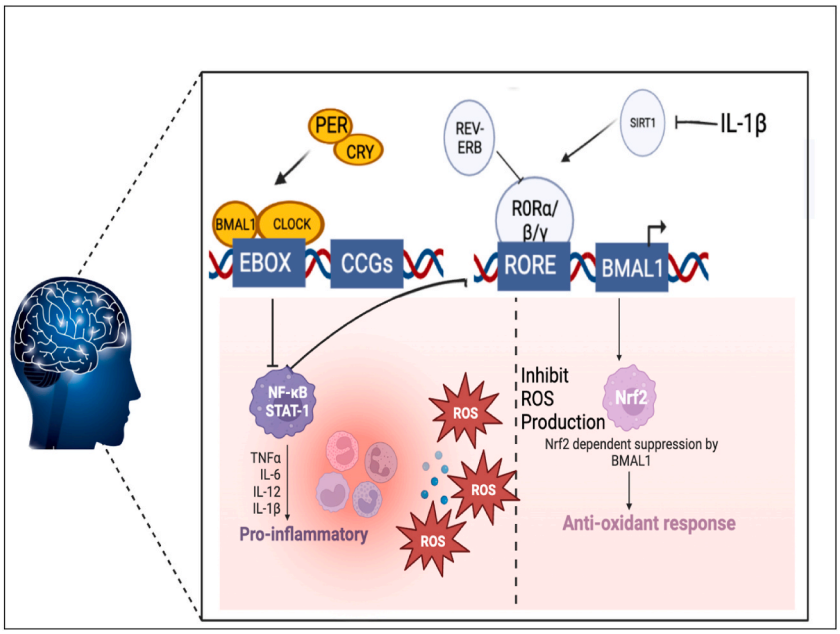

Fig. 2. Pro-inflammatory response due to circadian clock genes.

the epigenetic mechanism of sirtuin. These proteins are associated with histone deacetylase which needs NAD + for its enzymatic activity. Interestingly, because of this special feature, the cellular metabolism and redox state are regulated by the sirtuin deacetylase activity [87]. It has been reported that disturbances in the circadian mechanism lead to oxidative stress (Fig. 3). Deletion of Bmal1 in mice caused neurodegeneration in mice due to neuronal damage and oxidative stress [27]. Even mutations of the circadian genes in cells affected the response to oxidative stress revealing that circadian genes have a role in the survival of cells and death signalling [88, 89]. Henceforth, we find that the circadian molecular mechanism functions by the protein-protein interaction and the epigenetics regulation for the periodic rhythmicity. The molecular mechanisms of circadian rhythms imply extensive post-translational regulation, including phosphorylation, ubiquitination, and acetylation of clock proteins such as PER and CRY [90].

The activation of SIRT3 is restricted during decreased levels of NAD + which causes the release of ROS and pro-inflammatory cytokines leading to the onset of neurodegeneration.

The discovery of non-coding RNA molecules, such as microRNAs, that are involved in regulating circadian rhythms has led to further insight into the molecular mechanisms that underlie these processes [91]. Disruption of circadian rhythms, either by environmental factors such as shift work or by genetic mutations can have profound effects on health and disease, including increased risk of metabolic disorders, cardiovascular disease, and cancer. Histone modifications and methylation changes might be taking part in regulating circadian gene transcription and regulation of clock genes [92,93]. It was found in brain samples of Alzheimer's disease that the circadian methylation rhythms and methylation are disturbed but the pathways mediating circadian changes and epigenetic regulation of circadian genes are not fully investigated [94] (Table 1).

Remarkably, Cermakian and team examined the post-mortem sample of Alzheimer's patients and healthy control. It was found that there were significant changes in the mRNA expression of PER1, PER2 and BMAL1 genes. The samples included the pineal gland, cingulate cortex and bed nucleus of stria terminalis of AD patients and controls [95]. Studies involved in understanding the role of abnormal epigenetic mechanisms indicated that BMAL1 expression in brain and fibroblast samples from control and AD patients is controlled by the regulation of DNA methylation. This reveals the interlink between epigenetic dysregulation causing the changes in clock genes in AD [94]. Astonishingly, targeting the circadian repression of REV-ERBα/β increased the expression of BMAL1, and increased phagocytosis activity of microglial Ab. It is a unique strategy by marks the inhibition of REV-ERBs for controlling the neuroinflammation and clearance of amyloid-beta in AD [96]. Even though it is evident that sleep disturbances and circadian changes are seen in AD patients the molecular mechanism of Ab is still less understood. A study performed by Janine L et al. suggested that histone deacetylase HDAC3 reduces Per1 expression in the ageing hippocampus causing impairment in long-term memory. Thus, epigenetic repression of Per1 is an important factor interwinding age-related disorder in both circadian rhythmicity and the formation of long-term memory [97].

The epigenetic link between circadian clock genes and PD is very few. A significant role of promoter methylation of clock genes contributed to the onset of PD pathogenicity. A study performed on 206 PD patients and 181 healthy controls revealed that

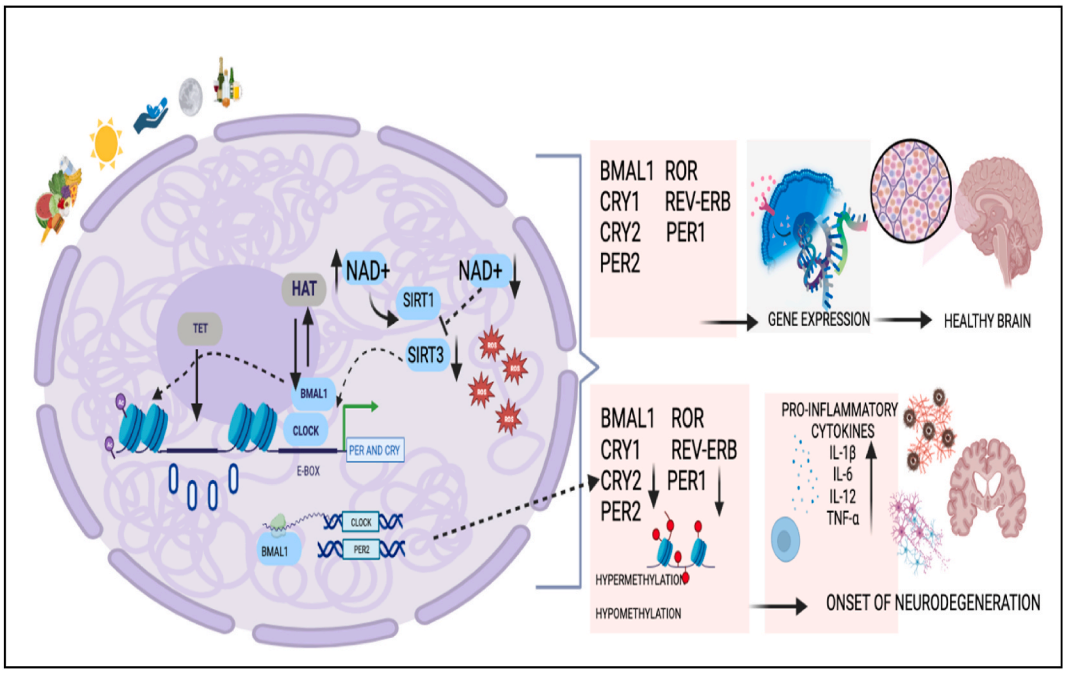

Fig. 3. The circadian genes regulation by epigenetic mechanism. External cues (food, water, alcohol, drugs, morning, night, temperature) influence the expression of circadian genes. By intrinsic activity of CLOCK, the CLOCK-BMAL1 binds to the promoter of clock genes and TET demethylates at CpG islands. Interaction of CLOCK-BMAL1 with HDACs influences gene expression. Circadian genes are influenced by mitochondria through the production of NAD+ and activation of SIRT1 AND SIRT3.

Table 1
Changes in circadian gene expression in the pathogenicity of neurodegenerative diseases.

DISEASE	MODEL	OBJECTIVE	FINDINGS	REFERENCE
AD	Human brain sample, cultured fibroblasts	To explore the association of DNA methylation and circadian rhythm in AD pathogenicity	Varied rhythmic methylation of *BMAL1* in AD brains and fibroblasts. Abnormal epigenetic modulations is linked to circadian changes in AD.	[94]
AD	AD post mortem tissues: brain samples	To demonstrate acetylation-associated pathway disruption in AD patients	Histone deacetylase 1 & 2 (HDAC1, HDAC2), CREB-Binding protein (CBP), P300/CBD associated protein (PCAF) levels reduced in AD in the frontal cortex, a substantial increase in histones (H3, H2B) in the frontal cortex. Acetylation dysfunction observed in AD samples.	[117]
PD	Clinical sample of PD patients	To explore the DNA methylation of CpG sites in neuronal PAS domain protein 2 (NPAS2) and cryptochrome circadian clock 1 (CRY1) and its association with PD	Hypomethylation of NPAS2 at early PD and no significant changes of CRY1	[118]
PD	Clinical sample of PD patients	The find if abnormality in expression altered clock genes is due to changes in CpG methylation	Methylation was observed in only CRY1 and NPAS2 promoters. Hypomethylation of NSAP2 promoter in PD patients	[98]
Dementia	Clinical sample of dementia patients	To study the CpG island methylation on circadian genes (PER1, PER2, PER3, CRY1, CRY2, CLOCK, BMAL1, TIM, CK1ε) promoters	Rev-erbα agonist SR9009 decreased the microglial polarization and NLRP3 inflammasome activation. Rev-erbα to be a possible therapeutic target for PD.	[119]
HD	Mice model: R6/1 transgenic HD mice	Correlation of altered BDNF gene expression and DNA methylation profile in HD	Decreased BDNF mRNA in hippocampus which is independent of increased methylation in gene sequence, changes sex-specific methylation levels at CpG sites in male and female brains	[120]

methylation occurred only in Cry1 and NPAS2 (neural PAS domain protein 2, a paralog of CLOCK) promoters. Nevertheless, other circadian genes like bmal1, per1, per2, cry2 and clock were not regulated by DNA methylation in both control and PD patients [98]. Regardless, there was another study that found the epigenetic regulation involving the occurrence of DNA methylation in the CpG island of nine circadian genes: bmal1, cry1, cry2, clock, per1, per2, ckIe and tim (Timeless) in 7 out of 80 dementia patients. The incidence of DNA methylation in healthy control individuals was observed [99]. On top of that in the circadian genes, more frequency (35.7 %) of methylation in CpG island was found in dementia patients with Lewy bodies [100]. Considering this observation we understand that DNA methylation could be a significant reason in the event of PD and dementia pathogenicity. The synchronization of target genes and the miRNAs are mostly tissue-specific and currently miRNAs are also observed to be epigenetic modulators that form a miRNA-epigenetic feedback loop influencing the gene expression proliferation. The epigenetic changes in an individual and epigenome profiles are depicted in phenotypes. A recent study by Larsen et al., 2023 studied the objective and subjective sleep patterns among youngsters. The team identified that the genes: PRR7, SDK1, and FAM172A which are involved in neuropsychiatric disorders could be a potential link to epigenetic modulations (DNA methylation) in genes regulating the circadian oscillation [101]. Additionally, Bolouki and team reported hypermethylation at TSS500 CpGs S_shores and upregulation of CLOCK genes [102]. Thus, epigenetic modulations are also an important reason for the pathological condition and therefore knowledge of epigenetic changes helps in the development of treatments for neurodegenerative diseases [103].

6. The circadian regulation linking cellular metabolism and epigenetics

Ageing of the brain is linked with metabolic, neurophysiologic and morphological alterations linked with learning and memory loss [104]. The control over circadian expression occurs through post-translational modifications and by chromatin remodelers. Circadian transcription is modulated by phosphorylation, methylation and acetylation. Chromatin remodelers are also viewed as metabolic sensors which use metabolites for enzymatic activity. NAD + - dependent deacetylase sirtuin 1 (SIRT1) is one of the metabolites that is associated with the control of the circadian clock through physical interaction with CLOCK and cellular metabolism [105]. The levels of NAD + oscillate with the circadian cycle and enzymatic HDAC action of SIRT1 oscillation is further associated with the metabolic state of the cell and epigenetic mechanism depending on the clock genes [106,107]. Desynchronization of peripheral clocks potentially entreats by changes in the metabolism-clock interface, has been associated with chronic and metabolic disorders with circadian-controlled genes being enhanced between non-circadian-controlled genes versus disease-associated genes [108].

SIRT1 functions as a feedback signal of systemic nutrients through the neurons of the ventromedial hypothalamus [109]. An intrinsic acetyl-transferase activity is observed through the main circadian regulator CLOCK which is involved in acetylating histones and non-histone proteins through circadian-dependent chromatin remodelling. Depending on the NAD + levels, deacetylase SIRT1 counteracts the CLOCK acetyl-transferase activity [110]. At the molecular level, AMPK is a key regulator for the uptake of glucose, and fatty acid oxidation and essential for intracellular metabolism. In the hypothalamus, sleep distress causes increased phosphorylated AMPK [111]. In the peripheral clocks, AMPK increases the SIRT1 activity through both NAMPT (nicotinamide phosphoribosyl transferase)-dependent and independent pathways [112]. It is hypothesized that the AMPK-clock connection is only involved in metabolic tissue or can also be involved in the central SCN. There is a possibility of regulation connecting epigenetic modulation with sleep and metabolism (Fig. 3). Likewise, the modulation of mitochondria manages the diurnal rhythms of acetylation of mitochondrial

proteins to control oxidative phosphorylation. Therefore, circadian mitochondrial regulation is important and further alteration or loss of clock genes could cause higher oxidative damage and morphological changes. The association between SIRT1 and circadian clock genes is important for the regulation of metabolism function, circadian rhythmicity and the ageing process [113]. A study by Schmutz and team found that PER2 combined with PPAR caused alteration in its activity at target genes involved in metabolism like glucose 6-phosphatase explicitly with the activities of Peroxisome proliferator-activated receptor gamma to control lipid metabolism [114, 115]. Cedernaes and team investigated the peripheral human tissue samples to check the effect of clock genes at epigenetic and transcription levels because of sleep deprivation. It was found that higher methylation in the promoter and promoter interacting enhancer regions of CRY1 and PER1 under the acute sleep deprivation condition whereas the gene expression of BMAL1 and CRY1 was decreased in the skeletal muscle when comparing acute total sleep deprivation when compared to sleep conditions [116]. As a result, we observe that in the metabolic tissues, being awake during the night can cause changes in the epigenetic and transcriptional profile of circadian genes. Overall, the epigenetic modifications controlling the circadian genes influence cellular function and metabolism. Therefore, extensive studies focusing on circadian metabolomics will elucidate the association of epigenetic regulation of clock genes regulating different metabolites during 24-h oscillation. Together, it can be a novel therapeutic strategy to combat both neurological and metabolic diseases.

7. Concluding remarks

Currently, the involvement of epigenetic mechanisms in the synchronization of circadian rhythmicity is more evident. To understand their importance in the onset and progression of neurodegenerative disorder and neuroinflammation, we completely reviewed the circadian mechanism and the role of epigenetics in their regulation. Remarkably, different epigenetic mechanisms regulate the circadian genes and majorly DNA methylation of these genes causes changes in their expression. Mostly Bmal1, Cry1, and Clock genes were altered in mice models with Alzheimer's and Parkinson's disease pathology. The circadian clock machinery controls the cellular metabolism and further understanding the complexity of its connection through cellular, metabolomic methods intertwined with genetics will highlight the potential target to combat disease conditions. Research in circadian rhythms will favour finding novel therapeutic interventions that target clock proteins and their associated molecular pathways to improve health outcomes for individuals with circadian rhythm disorders.

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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.

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