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REVIEW ARTICLE

Circadian Rhythm Disruption and Alzheimer's Disease: The Dynamics of a Vicious Cycle

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Abstract: All mammalian cells exhibit circadian rhythm in cellular metabolism and energetics. Autonomous cellular clocks are modulated by various pathways that are essential for robust time keeping. In addition to the canonical transcriptional translational feedback loop, several new pathways of circadian timekeeping - non-transcriptional oscillations, post-translational modifications, epigenetics and cellular signaling in the circadian clock - have been identified. The physiology of circadian rhythm is expansive, and its link to the neurodegeneration is multifactorial. Circadian rhythm disruption is prevelant in contamporary society where light-noise, shift-work, and transmeridian travel are commonplace, and is also reported from the early stages of Alzheimer's disease (AD). Circadian alignment by bright light therapy in conjunction with chronobiotics is beneficial for treating sundowning syndrome and other cognitive symptoms in advanced AD patients. We performed a comprehensive analysis of the clinical and translational reports to review the physiology of the circadian clock, delineate its dysfunction in AD, and unravel the dynamics of the vicious cycle between two pathologies. The review delineates the role of putative targets like clock proteins PER, CLOCK, BMAL1, ROR, and clock-controlled proteins like AVP, SIRT1, FOXO, and PK2 towards future approaches for management of AD. Furthermore, the role of circadian rhythm disruption in aging is delineated.

Keywords: Circadian rhythm coupling, redox, suprachiasmatic nuclei, sleep-wake cycle, post-translational modifications, aging.

1. INTRODUCTION

Life on earth has evolved with endogenous mechanisms of periodicity that allow organisms to adapt to the environment through anticipation [1]. Some simpler archaic oscillators are conserved across kingdoms and have integrated with complex timekeeping systems in multicellular organisms [2]. These biological rhythms account not only for subtle biochemical changes but govern our daily behavior, including the sleep-wake cycle, mood, and attention. Circadian (Latin: about a day) rhythms are the most widely studied form of biological rhythms that oscillate every 24 hr. Humans have a free-running circadian period of 24.18 hr. [3], which is entrained and synchronized to the geophysical time exogenously through photic zeitgebers (German: time giver) [4]. Photic entrainment mitigates slight aberrations in the circadian clock. However, the ramifications of chronic disruptions are severe. Circadian rhythms may be disrupted endogenously by genetic mutations or exogenously through mistimed environmental cues.

Alzheimer's disease (AD) is characterized by progressive loss of memory and other cognitive functions that severely impact the patients' social skills and ability to perform a rou-

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tine task. Presence of amyloid plaques, hyperphosphorylated tau protein in the patients' brains are the hallmarks of AD. More than 50 million people globally are living with dementia, and AD accounts for 70 % of the cases. This figure is predicted to double every twenty years [5]. The rising numbers stem from a dire lack of effective treatment. Therefore, it is crucial to identify and understand contributing factors to the AD pathology, which may be modified to manage and slow its progression at the early stages. Circadian rhythm disruption (CRd) is observed in Alzheimer's patients from the early stages of the disease [6-8]. Moreover, postmortem analysis of the brains confirms morphological changes in the core machinery of the central circadian clock [9]. The clinical evidence of CRd and AD association is overwhelming. However, whether CRd is a cause or the consequence of AD is not fully understood.

Here, we review the published literature from clinical and translational studies and discuss in succession all features of the clock machinery and their dysfunction in AD.

2. CIRCADIAN CLOCK

2.1. Circuitry of the Master-clock in Health and AD

All mammalian cells in brain and periphery contain an autonomous circadian clock that is modulated by various pathways for robust time keeping. Autonomous circadian clocks are coupled and entrained by the suprachiasmatic nuclei (SCN) located bilaterally in the ventromedial hypothalamus, also known as the master-clock [10]. A human SCN contains ca. 50,000 neurons constituting the core and the shell sub-nuclei. A light stimulus (photic cue) is transmitted to the core of SCN *via* glutamate signaling through the retinohypothalamic tract (RHT). In contrast, serotonergic signaling occurs through the raphe nuclei and cholinergic signaling through the basal forebrain and pons transmit non-photic cues [11, 12]. Melanopsin-containing retinal ganglion cells (mRGCs) are a class of retinal photoreceptors that regulate the circadian photoentrainment of the master clock [13]. Six types of mRGCs have been identified, depending on the location of their dendritic arborization in the inner plexiform layer. mRGCs are an essential component for the SCN photoentrainment, and its deterioration has been directly associated with circadian rhythm disruption [14]. mRGCs signaling not only entrains the circadian system, but also modulate mood and memory through the SCN and other pathways independent of the circadian system [15, 16]. The mRGCs activate glutamatergic neurons in the RHT, that further entrain and induce a robust expression of immediate early genes (IEG) in the SCN (described in Section 3.2). Subsequently, SCN entrains other brain structures and peripheral clocks through humoral signaling and thus maintains an adaptive phase control over all autonomous clocks [17].

A network of efferent circuits extends from the SCN to sub-paraventricular zone (sPVZ), dorsomedial hypothalamus (DMH), thalamus, lateral septum, stria-terminalis, and intergeniculate nuclei. The human SCN is connected to thirty-five brain regions through direct neuronal projection and eighty-five regions through multisynaptic connections [18]. The resting potential of the SCN is high (-50mV) in the daytime, and it vigorously activates other brain areas. In contrast, the neural activity is relatively low (-60mV) at night [19]. SCN ablation in the hamsters and its subsequent transplantation efficaciously recapitulates their circadian rhythm of locomotor activity. Since this effect is achieved regardless of the SCN orientation, it implies a primary role of the diffusible signaling molecules like prokineticin 2 (PK2), arginine vasopressin (AVP) and vasoactive intestinal polypeptide (VIP) in the entrainment [20]. VIP cells are abundant in the ventrolateral core and AVP cells in the dorsomedial shell of the SCN, and these molecules play an inextricable role in the communication within and outward from the SCN. Retinorecipient neurons in the SCN express VIP and play a crucial role in resetting the circadian clock [21]. Furthermore, PK2 receptor 2 (Prokr2) is essential for SCN mediated neuronal activation in the cortex and hippocampus, although it is not required for the intracellular timekeeping [22]. SCN organizes circadian rhythms in a scale-invariant manner. This essential factor allows organisms to smoothly transition through the seasonal changes in light-dark cycles [23]. A clock gene period 2 (*Per2*) also acts as an IEG and responds to photic zeitgeber (described in Section 3.2), which adds a calendar role to the circadian clock by daily photic remodeling [24].

AD patients exhibit dampened and delayed rhythms of the locomotor activity and core body temperature [7]. Circadian rhythm in the SCN of rats shows shortening of free-running period which leads to amplitude dampening and phase advances of some peripheral tissues relative to light/dark cycle [25]. However, the amplitude decrease is highly significant, and the circadian phase is commonly delayed in AD patients [8]. These physiological changes can be explained by examining the morphology and mediators of the circadian system, which are severely affected in AD brains. There is a significant reduction of retinal nerve fiber layer, loss of optic nerve axons and the mRGCs are severely affected by Aβ aggregation in the flat-mounted AD retinas [26]. The authors of the study concluded that mRGC degeneration is a contributor to circadian misalignment in AD patients. Furthermore, there is a significant decrease in the neuronal density and volume of the SCN in AD patients compared to the age-matched controls [9]. AD patients also exhibit diminished expression of neuroprotective peptides (AVP and neurotensin) in the SCN that is supplemented by an increased astrocyte-to-neuron ratio [27]. The decrease in protein levels of the AVP is paralleled by a decrease in its mRNA expression in the SCN of AD patients [28]. In addition, the pre-AD pathologic triple-transgenic AD mice (*3xTg-AD*) express a significantly reduced number of AVP and VIP secreting neurons in the SCN [29]. It implies that the dysfunction in the AVP and VIP signaling precedes AD pathology, though the responsible molecular pathways remain elusive.

Another SCN output molecule PK2 acts as an endangering mediator for cerebral damage and plays a critical role in neuronal autoimmunity [30]. Exogenous administration of $A\beta_{42}$ increases the mRNA levels of *Pk2* and its receptor *Prokr2* in the hippocampus of mice in a time-dependent manner. Furthermore, PC1 (a Prokr2 antagonist) ameliorates long term potentiation impairments in *Tg2576* AD mice and suppresses the $A\beta_{42}$ induced toxicity in cultured neurons of

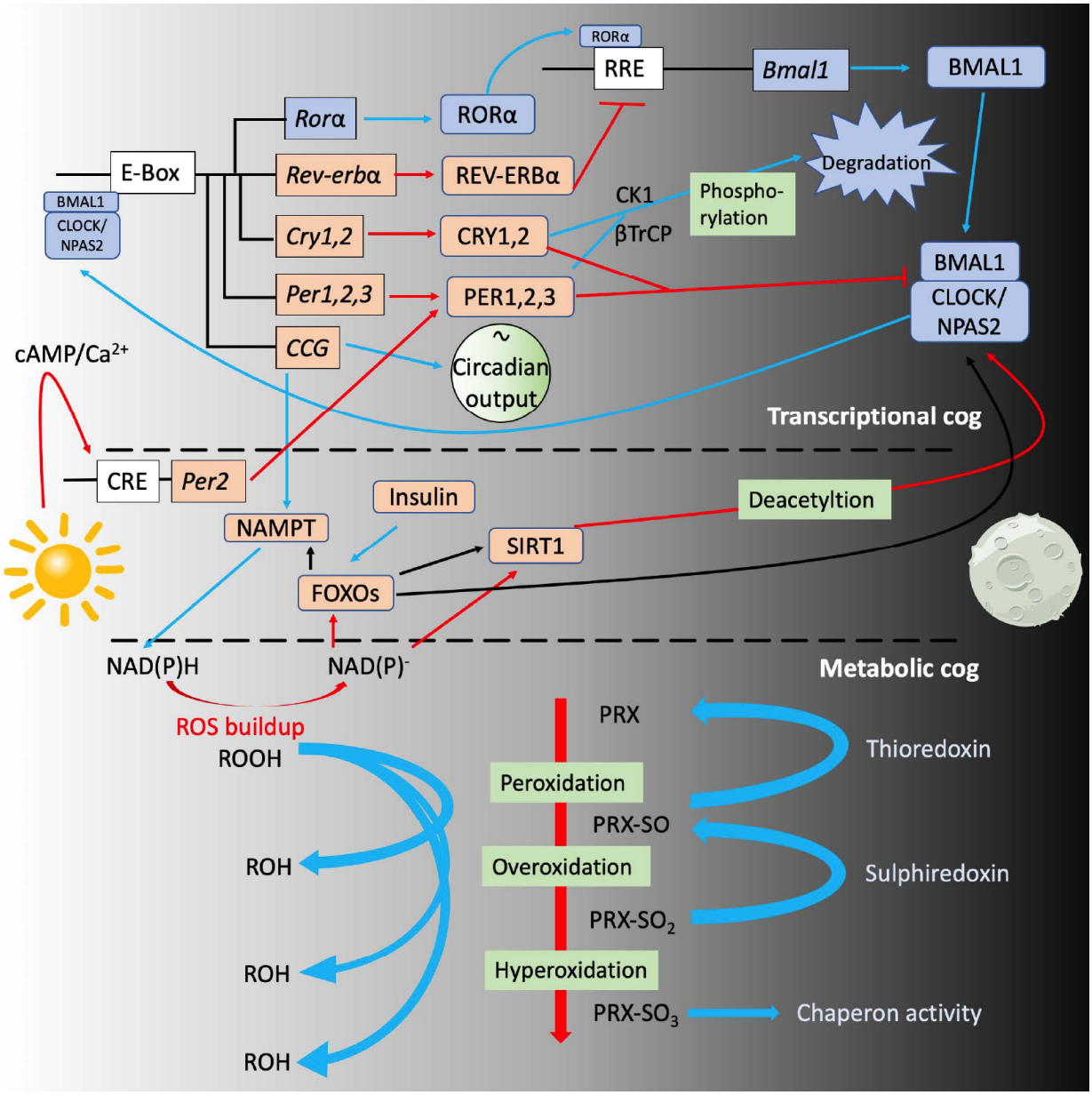

Fig. (1). Transcriptional cog and metabolic cogs of the circadian clock. The schematic shows the cycles of TTFL and metabolic cog in the duration of a 24 hr day (left, daytime; right, nighttime). Both TTFL and metabolic cog cross-talk through mediators such as NAMPT, SIRT1, FOXO *etc* shown in space within the depiction of cogs. Note that transcription Per2 gene is also driven by CRE promoter. Solid black lines, transcription; blue arrows, the forward limb of the TTFL; red arrows, the negative limb of the TTFL; orange boxes, forward loop components; blue boxes, repressor components; red block arrows, oxidation; and blue block arrows, resolution. Abbreviations: BMAL1, brain and muscle ARNT-like protein; cAMP, cyclic adenosine monophosphate; CCG, clock-controlled genes; CK1, casein kinase 1; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; FOXO, forkhead box-O; NAD(P)H, nicotinamide adenine dinucleotide phosphate; NAMPT, nicotinamide phosphoribosyltransferase; NPAS2, neuronal PAS domain protein 2; PER, period; PRX, peroxiredoxins; ROR, retinoic acid-related orphan receptor; SIRT1, sirtuin 1; TTFL, transcription-translation feedback loop; βTrCP, the ubiquitin ligase scf complex. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

mice [31]. PK2 acts as an interface and mediates $A\beta_{42}$ induced toxicity through the glutamatergic system by activating the AMPA receptors [32]. Although this group shows a piece of compelling evidence for the relationship of PK2 system and Aβ toxicity in AD, the chosen model is relevant to the post-amyloid-pathologic stages of AD. There is a lack of evidence for the role of PK2 signaling in AD preceding the amyloid pathology.

2.2. Transcriptional Cog in Health and AD

Nucleated cells display a transcription-translation feedback loop (TTFL) among the clock genes, the first cog in the circadian clock. Core clock genes *viz.* circadian locomotor output cycles kaput (*Clock*), brain and muscle ARNT-like 1 (*Bmal1*), period (*Per 1, 2* & *3*) and cryptochrome (*Cry 1* & *2*) form the TTFL (Fig. **1**), however, there are 14 representa-

tive clock genes [33]. *Npas2* (a *Clock* paralog) dominates extra-SCN areas of the mammalian brain [34]. Briefly, *Clock* and *Bmal1* genes constitute the positive limb, and *Per* and *Cry* genes constitute the negative limb of the TTFL. CLOCK: BMAL1 dimer acts as a transcription factor that promotes the E-box dependent transcription of *Per* and *Cry* genes, which are later translated into repressor proteins, PER and CRY [35]. Three isoforms of PER (1, 2 & 3); and two isoforms of CRY (1 & 2) differentially regulate the positive limb by influencing the CLOCK and BMAL1 associations [36, 37]. Finally, the repressor proteins are degraded by post-translational modifications that disinhibit the positive limb.

The post-translational modifications of the repressor proteins are an essential step in maintaining the circadian period (detailed in Section 3.1) [38, 39]. CLOCK: BMAL1 dimer also induces the transcription of retinoic acid-related orphan receptor alpha (*Rorα*) and *Rev-erbα* genes. Subsequently, RORs activate, and REV-ERBs repress the transcription of *Bmal1* gene [35]. Additionally, core clock genes transcribe up to 10% of the total genes expressed in mammals, known as the clock-controlled genes (CCG) [33] (Fig. **1**). CCGs are translated into various proteins, intracellular enzymes and hormones that impart the influence of circadian clock over other biological systems and overall physiology of the organism. RNAseq and DNA-array of mice reveal that 43% of the coding-RNA genes, as well as more than a thousand of the conserved non-coding-RNA genes, exhibit oscillatory transcriptions in an organ-specific manner [40].

AD patients display an out-of-phase expression of *Bmal1* and *Per2* mRNAs (compared to the age-matched controls) in the cingulate cortex and other brain areas implicated in motivated behavior and decision making [41]. Additionally, single-nucleotide polymorphism of the *Clock* and *Bmal1* genes have been associated with a high risk of AD in the Chinese population [42-45], although more studies are required to corroborate these findings. *APP*x*PS1* transgenic mice show diminished expression of *Per2* in the hypothalamus and hippocampus [46], which is a sign of disrupted autonomous clocks. Furthermore, PER2 regulates the cellular response to oxidative stress by influencing the *Bcl-2* gene transcription. Embryonic fibroblasts from *Per2* mutant mice are more resistant to oxidative stress-induced cell death compared to the wild-type [47]. In contrast, deletion of *Per* gene in neurodegeneration-prone, carbonyl-reductase mutant Drosophila accelerates the symptoms of neurodegeneration and symptoms of aging [48]. This suggests that the optimal oscillatory expression of *Per2* at the tissue level is requisite for normal neurophysiology.

Furthermore, the deletion of *Bmal1*, the primary driving force of the TTFL, disrupts the sleep-wake cycles and renders the central TTFL arrhythmic in mice [49]. Contrarily, the sleep deprivation and mistimed light exposure can also repress the expression of BMAL1 in mice leading to ineffective binding of CLOCK: BMAL1 dimer to the chromatin [50, 51]. Furthermore, *Bmal1* deletion in mice results in the development of AD-like pathology, marked by the cortical and hippocampal astrogliosis [52], and memory impairment [53]. Conversely, a pathological concentration of $A\beta_{42}$ facilitates BMAL1 degradation [54] resulting in circadian dysfunction. The literature suggest that the associations between the circadian rhythms disruption (CRd) and AD pathology is bilateral, and a vicious loop is formed between the two pathologies, Fig. **3**; however, what sets the loop into action is not yet known. A possible solution is examining the autonomous clocks by single-cell analyses. Interestingly, recent research found that $A\beta_{42}$ expression in glia, but not neurons of the SCN disrupts the central circadian clock in Drosophila, which may provide some clarity to the mechanism of AD-induced-CRd [55]. However, a clear picture of CRd-induced-AD is still a work in progress.

2.3. Non-transcriptional or Metabolic Cog in Health and AD

Rhythmic processes of intracellular reactive oxygen species (ROS) production manifest as redox oscillations, the second cog in the circadian clock. The marker of redox oscillations, peroxiredoxin 1 (PRX1), a thiol-dependent peroxidase is conserved through archaea which is speculated to have evolved after the Great Oxidation Event, 2.5 billion years ago [2]. These oscillators are conserved across kingdoms and are also present in the primitive anucleated cells, and therefore do not require much-advanced transcription mechanisms [56, 57]. Six isoforms of peroxiredoxins are reported in mammals that localize in the cytosol (PRX 1, 2, 5 & 6), the mitochondria (PRX 3 & 5) and the endoplasmic reticulum (PRX4) [58]. Oxidation of PRX (1 - 6) at the peroxidatic cysteine residue yields disulphide-PRX that is recycled by thioredoxins known as the fast loop. Alternatively, PRX may enter an over- or hyper-oxidized ($PRX\text{-}SO_{2/3}$) state. Sulfiredoxin sluggishly recycles the $PRX\text{-}SO_2$, known as the slow loop. However, its transition to hyper-oxidized $PRX\text{-}SO_3$ is non-reversible, and it serves as a non-peroxidatic chaperon (Fig. **1**) [59].

Selective deletion of 2-Cysteine-PRX dampens the amplitude of the PRX1 expression. However, the rhythms persist, possibly through compensation by the TTFL mechanism [2]. Furthermore, other antioxidant biomolecules such as glutathione and mRNA levels of catalase, superoxide dismutase, heme oxygenase-1, and cyclooxygenase-2 also display a circadian rhythm [60, 61]. The rhythmic expression of these antioxidant proteins is abolished in *Clock* mutant Drosophila and mice [62, 63]. It represents a bidirectional interaction between redox oscillations and the TTFL (described in Section 4). Pentose phosphate pathway (PPP) has been recently implicated in the remodeling of both TTFL and the non-transcriptional oscillations. PPP is a critical source of NAD(P)H that impels the redox oscillation by regulating the oxidative states on PRX. Additionally, PPP remodels the TTFL by recruiting archetypal histone acetyltransferase P300 that inhibits the binding of BMAL1: CLOCK dimer to the DNA [64].

The association of PRX system with AD has been long registered; however, its role as a marker of the redox oscillations has recently become evident. Post-mortem analysis of AD brains shows an elevation in levels of cytosolic PRX (1 & 2) and a reduction in levels of mitochondrial PRX3 [65]. The reduced levels of PRX3 signify a compensatory response to oxidative damage. Furthermore, total levels of oxidatively-modified PRX are altered in the erythrocytes of AD patients in a way that is distinguishable from vascular de-

mentia patients [66]. The authors explored the credibility of oxidatively modified PRX(PRX-$SO_{2/3}$) in the diagnosis of AD. The PRX proteins serve as a reliable indicator of oxidative stress in the cell. The oscillating levels of oxidized PRX imply an oscillation in metabolic activity and energy expenditure in the cell. It is widely accepted that oxidative stress plays a decisive role in the early stages of AD [66-69]. However, it may also have a crucial role in the onset of AD in healthy subjects. There is plenty evidence for the role of oxidative stress in the instigation of AD-specific pathological mechanism, for instance, processing/activity of APP and BACE1 and γ-secretase are profoundly influenced by the redox status of the cell [67-69]. Exogenous administration of $A\beta_{42}$ in *Prx6* knock-in mice accelerates memory loss; induces oxidative damage; induces astrogliosis; and upregulates APP, C99, BACE1 [70]. The role and involvement of rhythmic nature of redox states in AD is still an area of active research. However, these studies suggest that the PRX dyshomeostasis acts an accelerant of AD pathology, whether this impairment also contributes to the initiation of the disease remains to be ascertained.

3. REGULATION OF THE CIRCADIAN CLOCK

3.1. Post-Translational Regulation of the Clock in Health and AD

Enzymatic modifications of the proteins by ubiquitination, phosphorylation or acetylation are essential for regulation of the clock proteins. Post-translational modifications of the clock proteins are a requisite for robust timekeeping in eukaryotes [71]. In mammals, two closely related isoforms of casein kinase 1 (CK1 δ and ε) are implicated in the modulation of circadian rhythms [72]. CK1 ε/δ phosphorylates and degrades the repressive clock protein PER [73]. Ralph and Menaker [74], in their pioneering work, reported that a mutation at the autosomal locus (tau) is associated with the shorter circadian period in tau hamsters. Subsequently, the responsible gene was identified to be *Ck1*, which whether expressed homo- or heterozygous abnormally shortens the circadian period due to differential degradation patterns of the PER proteins [75]. Another nuclear protein βTrCP also degrades PER2 by ubiquitination [76]. Furthermore, the circadian clock is stable across a range of temperature fluctuations, known as the 'temperature compensation' [77]. Temperature compensation is a phylogenetically conserved trait that is attributable to post-translational modifications of the clock proteins. Initially, it was proposed that CK1(ε and δ) are temperature insensitive kinases, and thus may be responsible for temperature compensation by its action on the phosphoswitch [78]. Finally, a more comprehensive representation of temperature sensitive phosphoswitch was proposed, based on two competing phosphorylation sites on PER2. The authors also report that phosphorylation of PER2 by CK1ε can be "switched off" by ubiquitination by βTrCP [79]. Furthermore, the post-translational phosphorylation of CRY1 may also regulate the circadian clock. The ratio of active to phosphorylated CRY1 in a cell modifies its repressive activity on BMAL1: CLOCK and determines the circadian period [80].

Chromatin remodeling by histone modifications also alters the expression of clock controlled genes (CCG) [81]. Moreover, the mechanisms of histone modifications such as methylation, acetylation, and phosphorylation also exhibit a circadian rhythm [82]. Initial work indicated that the binding of CLOCK: BMAL1 dimer to E-box promoter regions on chromatin is associated with histone acetylation [83]. Subsequent studies revealed that CLOCK protein posseses acetyltransferase properties and: rhythmically acetylates histone H3 to expose promoter regions of the CCG; acetylates its partner BMAL1; and facilitates CRY dependent inhibition of the positive limb of TTFL [84, 85]. Conversely, Sirtuin 1 (SIRT1) is a class III histone deacetylase that counterbalances acetyltransferase activity of the CLOCK, and thereby indirectly regulates the circadian clock by regulating the the acetylation rates of H3 and BMAL1, and functions as an "enzymatic rheostat of circadian function" [86]. Biosynthesis of SIRT1, in turn, is controlled by the CLOCK: BMAL1 dimer. The dimer promotes the transcription nicotinamide phosphoribosyltransferase (*Nampt*) gene, that is translated to a crucial enzyme in the regulation of SIRT1 expression [87]. Furthermore, the expression of SIRT1 is regulated by both external and internal factors, such as diet, exercise, and intracellular oxidative stress [88]. While deeply integrated within the transcriptional and non-transcriptional cogs of the clock, SIRT1 also regulates the neuroimmunity by inhibiting the microglial activation of the transcription factor, NF-κB [89]. Furthermore, the clock protein REV-ERBα recruits SIRT1, and collectively modulate the transcription of lipid biosynthetic genes in the mammalian liver [90].

*Ck1*δ mRNA levels show a 24-fold increase in the hippocampus of AD brains, and its protein expression parallels the mRNA expression and colocalizes with senile plaques and tau deposits [91]. CK1δ targets more than fifteen sites on tau protein that are hyperphosphorylated in the insoluble paired-helical-filament tau extracted from AD brains [92]. Furthermore, there is a significant reduction in *Sirt1* mRNA levels that negatively correlates with the duration of symptoms and the accumulation of tau in AD brains [93]. Acetylation of tau proteins by histone acetyltransferase p300 inhibits the proteasomal degradation of hyperphosphorylated tau. In contrast, deacetylation by *Sirt1* promotes degradation of hyperphosphorylated tau. Therefore, deletion of *Sirt1* upregulates the levels of acetylated tau, and hence contributes to tauopathy [94]. Calorie restriction is also beneficial in preventing Aβ pathology. A 30% calorie restriction significantly reduces cortical $A\beta_{42}$ concentration that negatively correlates with SIRT1 protein concentration in a primate model of AD [95]. The implication of these proteins in AD pathology further supports the conception that the association between CRd and AD is multifactorial and bi-directional.

3.2. Cellular Signaling in the Clock in Health and AD

Cellular signaling in the circadian clock is a fast-growing area of basic research, primarily because these pharmacologically modifiable pathways and targets are relevant to the drug discovery prospects. Cellular signaling is at the core of circadian rhythm entrainment. Visual phototransduction (described in Section 2.1) through RHT stimulates post-synaptic n-methyl-d-aspartate receptors (NMDAr) in the SCN and activates the transcription factor cAMP response element-binding that induces the transcription of IEGs *c-fos* and *Per2*

[96]. SCN-specific deletion of NMDAr abolishes light-induced phase shifts in hamsters [97]. Since the clock gene *Per2* is also an IEG, its transcription is driven by the E-box as well as the CRE promoter (Fig. **1**). Therefore, the rhythmic expression of *Per2* under normal light/dark conditions is unaffected by the SCN-specific deletion of *Bmal1* or *Cry* (*1 & 2*). This indicates an essential role of cAMP/Ca^{2+} signaling in the circadian rhythms [98]. cAMP/Ca^{2+} signaling plays a fundamental role in maintaining the amplitude, phase, and period of the circadian rhythm. Pharmacological inhibition of cAMP signaling results in dampened peaks, phase resetting, and increased circadian period (>31 hr.) [99]. cAMP/Ca^{2+} signaling is modulated bilaterally by light-driven glutamate bouts and TTFL-driven protein dynamics [98]. Circadian resetting of post-synaptic SCN neurons through phototransduction relies on Ca^{2+} signaling, which opens a possibility that chronic or mistimed light may be capable of disrupting Ca^{2+} homeostasis within the cells.

A family of transcription factors - forkhead box-O class of transcription factors (FOXO) - is attracting a widespread interest as they may bridge the gap between the cellular signaling and the TTFL. FOXO proteins are regulated by ROS and insulin *via* JNK and PI3K pathways respectively and stimulate the transcription of various genes (including *Clock*) [100, 101]. Furthermore, FOXO3 stimulates the transcription of *Sirt1* through a protein-53-dependent, nutrient sensing pathway [102]. Other transcriptional targets of FOXO proteins are *Nampt* and autophagy-related gene 14 (*Atg14*), which are essential for the lipid metabolism and autophagy. Additionally, *Nampt* and *Atg14* mRNA exhibit a circadian rhythm, and their genes contain promoter regions for both FOXO proteins and CLOCK: BMAL1 [103, 104]. The fact that these redox responsive genes are integrally regulated by FOXO proteins and CLOCK: BMAL1, shows an association between cellular signaling and the circadian clock, although the exact mechanism of this integration is still an area of active research.

Two-photon Ca^{2+} analysis of *APP* mice cortex reveals a significant calcium overload in the neurons proximal to the amyloid plaques, which results in distorted neuritic morphologies and a loss of spinodendritic calcium compartmentalization [105]. The hyperactive neurons in the proximity of plaques show an abnormal increase in the Ca^{2+} transients as a result of synaptic disinhibition [106]. Thus, it follows that plaque-surrounding-neurons of the SCN may exhibit hyperactivity due to the calcium currents. Since Ca^{2+} signaling plays essential role in circadian entrainment, we propose that Ca^{2+} dyshomeostasis caused by $A\beta_{42}$ species may contribute to the circadian dysfunction observed in AD. The above discussed studies emphasize how Ca^{2+} dyshomeostasis progresses after the onset of AD. However, Ca^{2+} dyshomeostasis may also play a role in the progression of AD. High levels of cytosolic Ca^{2+} favors the amyloidogenic microprocessing of APP and thereby results in Aβ production in pathological proportions [107]. Additionally, the nuclear factor of activated T cells 1 (NFAT1), a transcription factor that binds the *Bace1* promoter region is activated by high levels of intracellular Ca^{2+} concentrations [108]. Ca^{2+} also regulates the proteolytic activity of BACE1 by modifying the acidity of the cytosolic medium [109]. The above reviewed literature suggests that calcium dyshomeostasis and Aβ production characterizes a bi-directional relationship, and further demonstrates the existence of a vicious loop between AD pathology and CRd, Fig. **3**.

$A\beta_{42}$ peptides are found to induce dephosphorylation and mitochondrial translocation of the FOXO3a, which promotes its association with the mitochondrial DNA [110]. Further, the study reports that FOXO3a induces mitochondrial damage as a downstream effect of cytochrome C oxidase subunit-1 gene downregulation. The authors of the study also report that $A\beta_{42}$ associated mitochondrial damage can be suppressed by knocking out *FOXO3a* gene, implicating the role of FOXO in AD. However, this only represents one facet of the complex relationship between FOXO and AD, more studies are required to ascertain this relationship.

4. COUPLING OF RHYTHMS IN HEALTH AND AD

A plethora of physiological rhythms are coupled to maintain homeostasis. For example, a coordination between natural light-dark cycles, activity-rest periods, and feeding cycles is crucial for optimal orchestration of the circadian rhythms (Fig. **2**). At the molecular level in smaller organisms like Neurospora, a temporal relationship between the intracellular redox state and circadian system is indispensable for a robust circadian clock [111]. Light induced entrainment is fundamental to TTFL in the SCN as opposed to the food availability dependent entrainment of TTFL in the peripheral clocks. Therefore, forced feeding in mice uncouples their activity- and metabolic rhythms and has a deleterious effect on the molecular clock [112]. Furthermore, abrupt shifts in the light-dark cycle impede the SCN's adaptive phase control on peripheral clocks [17]. Insulin resistance, hypertension, and inverted cortisol rhythms are the consequences of such uncoupling that leads to stress, metabolic- and cardiovascular disorders [113].

The synchronicity between TTFL and redox rhythms is essential for a robust circadian clock [114]. There is a cyclic relationship between TTFL and redox oscillations (Fig. **2**). The binding of CLOCK: BMAL1 to the E-box promoter region is pH sensitive and regulated by the ratio of oxidized to reduced NAD cofactors [115, 116]. Furthermore, redox rhythms expressed by the SCN influence its entrainment by modulating the neuronal excitability through membrane-bound K^+ channels [117]. Redox system also imparts influence over the TTFL through its other elements. Redox cofactor flavin adenine dinucleotide plays a decisive role in stabilizing the repressor protein CRY [118]. Nuclear factor erythroid-derived 2-like 2 (NRF2) upregulates the transcription of *Rev-erbα* gene in oxidatively stressed conditions [119, 120]. TTFL, in turn, regulates the cellular redox status through the expression of CCG [121]. The transcription of the redox-sensing genes such as NAD(P)H dehydrogenase-quinone 1, aldehyde dehydrogenase 2, and *Nrf2* is influenced by the activity of CLOCK and BMAL1 [52, 63]. Other feedback loops also exist within the circadian clock. The association between CLOCK: SIRT1 dimer and NAMPT controls the NAD+ salvage pathway through a transcriptional-enzymatic feedback loop [122]. A similar feedback loop is present within the interactions of CLOCK-SIRT1 and acetyl-

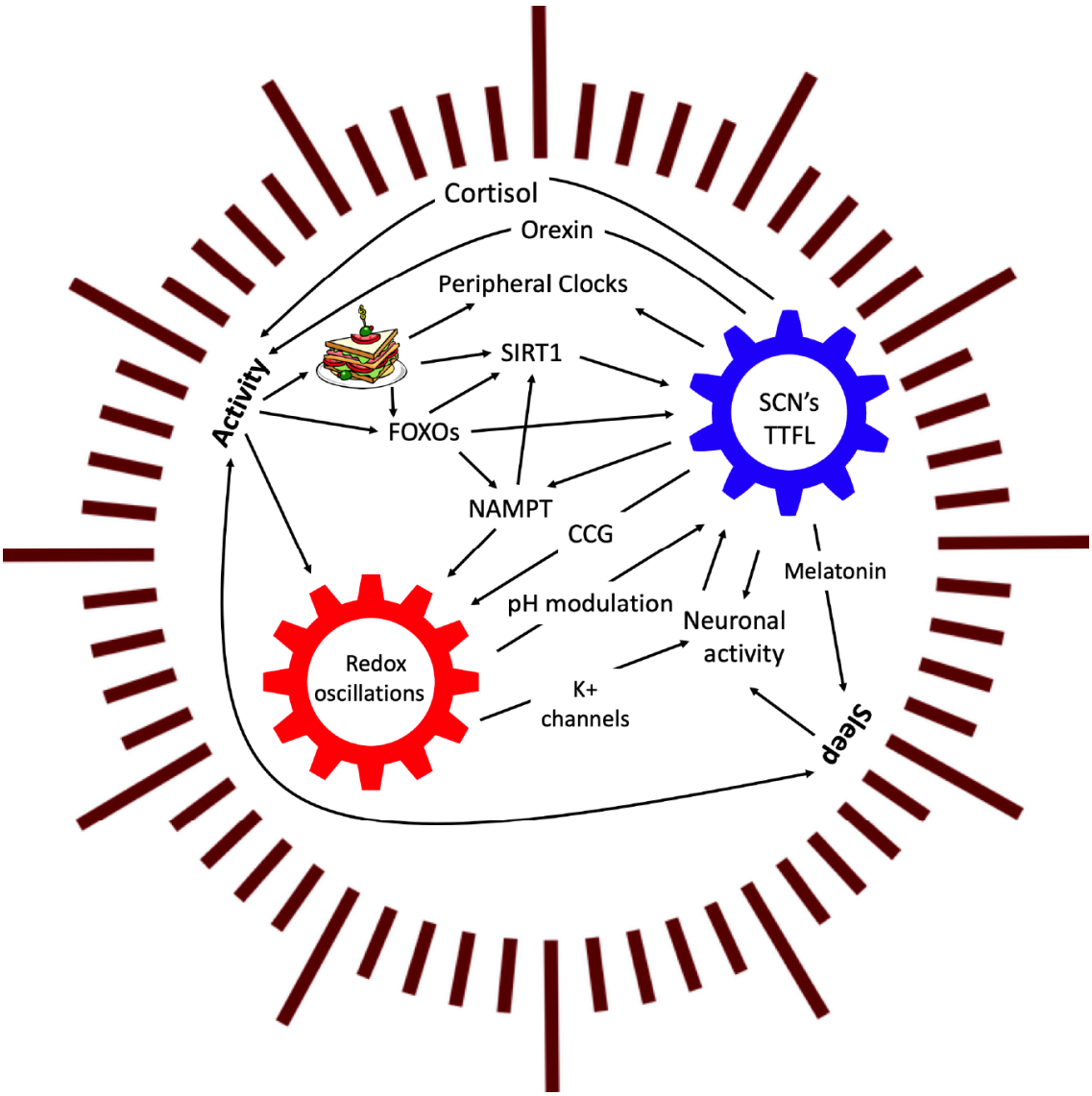

Fig. (2). Organization of circadian rhythms, the coupling of TTFL, metabolic cog, and sleep-wake cycle. The coupling of various cyclic processes is necessary for robust circadian clock. TTFL and redox cog cross-talk through various mediators which is also modulated by individual activities such as feeding, sleep and physical exercise. Abbreviations: CCG, clock-controlled genes; FOXO, forkhead box-O; NAMPT, nicotinamide phosphoribosyltransferase; SIRT1, sirtuin 1; TTFL, transcription-translation feedback loop. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

CoA synthetase-1, a key regulator of post-translational modifications in histones [123].

CRd is the primary reason for the institutionalization of AD patients [6]. Circadian rhythms are uncoupled by mistimed light or feeding cycles, a common occurrence in chronic shift-work or repetitive transmeridian travel, which might have serious implications in AD pathogenesis. Oscillations in the clock gene expression are detectable in the post-mortem AD brains. However, their phases are desynchronized [41], thus highlighting the insufficiency of the SCN to synchronize the autonomous clocks. Cho and colleagues [124] found that levels of circulating cortisol were chronically elevated in the cabin-crew of transatlantic flights accompanied by spatial memory deficits and a significant reduction in hippocampal volume. As discussed before, the disrupted hormonal cycles could result from the loss of SCN's adaptive phase control on peripheral clocks. A follow-up on 1,282 earlier cognitively-normal elderly women revealed that dampened and delayed circadian rhythms significantly increases the odds of developing dementia compared to the age-matched controls [125].

In line with the clinical findings, mimicking jet-lag in mice shows memory impairment and faulty adult neurogenesis in the hippocampus, a key area involved in AD [126]. Cognition and memory are a result of coordinated activity within a network of neuronal pathways. The desynchronized circadian oscillations in the neurons may affect memory processing. The significance of circadian system in memory formation and processing is well reported. GABA output from the SCN influences hippocampus-dependent memory

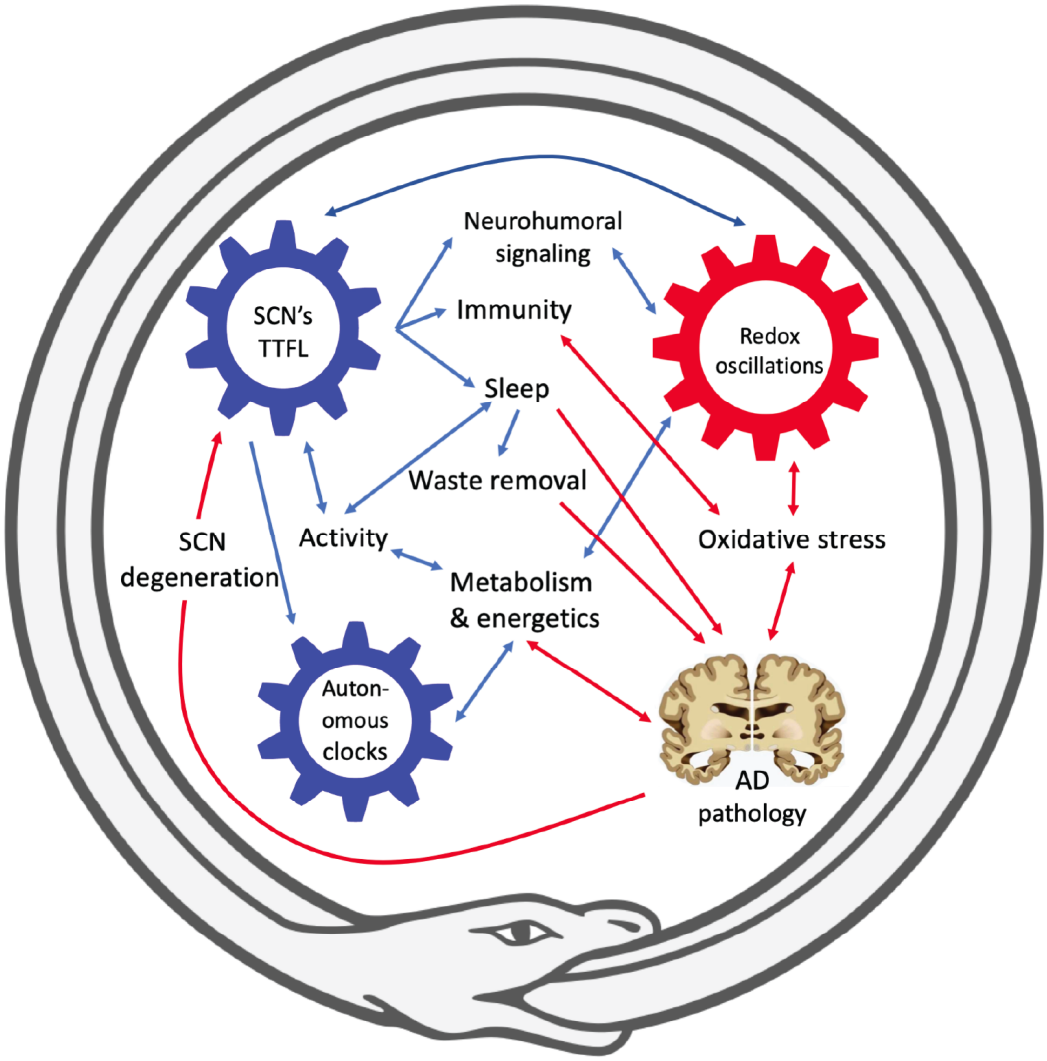

Fig. (3). A schematic of the putative pathways of AD onset by circadian rhythms dysfunction (CRd) and the intricate feedback loop between AD pathology and CRd depicted by the ouroboros symbol. The schematic shows a variety of physiological pathways that harmonize the circadian system, and pathological pathways that may contribute to AD pathology in the event of CRd and *vice versa*, forming a feedback loop. Blue lines represent the physiological pathways, and red lines represent the pathological pathways. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

[127]. Furthermore, CRd due to exogenous factors such as mistimed light [126-129], and feeding time [130]; or endogenous factors such as genetic mutations [53], have been shown to significantly impair the memory performance of experimental animal. The memory loss and oxidative stress appear early and are more pronounced in the jetlagged transgenic AD mice (*APPSwDI NOS2-/-*) [131]. The presented elements of circadian clock and its regulatory mechanisms are found dysregulated and thereby reinforce the AD pathology, Table **1**. Further studies aiming to modify functioning of the targets of circadian clock and its links to mediators like NADPH, SIRT1, NRF2, acetyl co-A and GABA could be a better way to investigate novel therapeutic strategies for ameliorating circadian misalignment in AD.

5. SLEEP-WAKE CYCLES IN HEALTH AND AD

Sleep is a physiological requirement throughout the animal kingdom. However, the type and duration of sleep may vary among species. Pioneering research to understand the nature of sleep-wake cycles revealed a thalamocortical switch between arousal and inhibitory signals. Recent developments in the field reveal a prominent role of fast acting neurotransmitters glutamate and gamma-aminobutyric acid (GABA). The primary glutamatergic inputs from the parabrachial nucleus and pedunculopontine tegmental nucleus propagate the arousal, and GABAergic inputs from ventrolateral preoptic nucleus (VLPO), median preoptic, and parafacial zone promote sleep by inhibition of the arousal system [132]. The complex circuits of sleep are extensively reviewed elsewhere [133]. Interestingly, SCN plays a pivotal role in the sleep circuitry and determines "when" and "how much" of the sleep is required. Both the VLPO and lateral hypothalamus receive SCN inputs through sPVZ to DMH, and a lesion to any unit of the circuit abolishes the circadian nature of the sleep-wake cycle [134]. The opponent-process model of sleep [135] states that the SCN driven arousal sys-

Table 1. List of various components and regulators of the circadian clock, and their dysfunction in AD.

Component	Role in Circadian Rhythm	Variation/affect Relevant to AD	AD Model	Refs.*
AVP, VIP	Neurohumoral signaling from the SCN	Decreased protein and mRNA expression	Human	[27, 28]
		Decreased neuronal secretion	Mice	[29]
BMAL1	TTFL component	Out of phase mRNA expression	Human	[41]
		Deletion causes astrogliosis and cognitive impairments, $A\beta_{42}$ decreases protein expression	Mice	[52, 53, 54]
Ca^{2+}	Cellular signaling in circadian clock/entrainment	Overload and increased transients in neurons proximal to the plaques	Mice	[105, 106]
		Cytosolic load increases $A\beta_{42}$ levels	Rat	[107]
CK1	TTFL component and post-translational regulation	Increased protein and mRNA expression	Human	[91]
FOXO3a	Cellular signaling in circadian clock	Induce $A\beta_{42}$ dependent mitochondrial damage	Rat	[110]
Melatonin and its receptor MT1	Sleep-wake cycle	Decrease	Human	[152, 153]
Orexin	Propagates wakefulness	Detrimental	Mice	[157]
PER2	TTFL component	Out of phase mRNA expression	Human	[41]
		Deletion accelerates neurodegeneration and aging	Drosophila	[48]
		Diminished rhythms	Mice	[46]
PK2 and its receptor Prokr2	Neurohumoral signaling from the SCN	Increased protein and mRNA expression, detrimental	Rat	[31]
PRX	Marker of non-transcriptional rhythms	Increased expression of PRX (1 & 2), decreased expression of PRX6	Human	[65, 66]
PRX6		Overexpression accelerates Aβ induced memory loss, *Bace1* activation and oxidative stress	Mice	[70]
SCN	Master clock	Decreased volume and neuronal density, astrogliosis	Human	[9, 27]
SIRT1	Histone modifications and post-translational regulation	Decreased mRNA expression	Human	[93]
		Overexpression decreases $A\beta_{42}$ levels	Mice	[89]
		Overexpression decreased the hyperphosphorylated tau levels	Primates	[95]

*References are also cited in the text and numbered here according to its appearance in the text.

tem opposes the homeostatic sleep load during the day. Then, the rising sleep load meets with a declining wakefulness drive (inhibition of arousal system) at the end of the subjective day, and the sleep gate is unlocked. This model holds SCN to be pivotal in the regulation of the sleep-wake cycle. To illustrate, the SCN-targeted deletion of the *Clock* or *Cry* gene causes a significant decline or increase in total sleep time, respectively [134]. Furthermore, a global deletion of clock genes causes fragmented sleep and aberrant switching between rapid eye movement (REM) and non-REM states. Additionally, a significantly large REM rebound is observed after sleep deprivation in canonical loss-of-function clock mutant Drosophila [136].

SCN also regulates the release of melatonin from pineal gland, and it, in turn, promotes sleep by suppressing the SCN's neuronal activity through forming a positive feedback loop by activation of melatonin receptor 1 (MT1) [137]. A cluster of neurons in the lateral hypothalamus secrete orexin facilitated by multi-synaptic inputs from the SCN during the day time and propagate wakefulness [138]. Sleep-wake cycles also regulate the neuronal activity of the SCN [139], and thereby establishes a bilateral relationship between the circadian clock and sleep physiology (Fig. **2**). This relationship is apparent in the dramatic changes observed in clock gene expressions and electroencephalographic changes observed in the cerebral cortex of the sleep-deprived mice [140]. Sleep deprivation results in deleterious effects on chromatin remodeling mechanisms, which, in turn, modifies the binding of BMAL1: CLOCK dimer to its specific genes on the DNA and renders the TTFL arrhythmic [50]. Twenty-seven metabolites including serotonin, tryptophan, and taurine, as well as the markers of inflammation and neuronal injury, are significantly increased in blood plasma after sleep deprivation

in humans [141, 142]. Mistimed and insufficient sleep also decreases the number of rhythmic genes in the human blood transcriptome [143, 144]**.** It is evident that the temporal alignment between the circadian phases and the sleep-wake cycle affects the individuals' quality of sleep as well as their health [145]. Misalignment of feeding cycles and sleep-wake cycles leads to uncoupling of TTFL in the SCN from that of hippocampus of mice leading to spatial memory deficits [130].

Furthermore, *in vivo,* two-photon imaging of awake and asleep mice revealed that sleep drives the clearance of neurotoxic metabolites from the brain by enhancing the convective exchange between the extracellular fluid and cerebrospinal fluid (CSF) [146]. The authors reported that the extracellular space is increased by 60% in asleep and anesthetized mice by promoting the convective flux. The glymphatic system promotes waste removal from the brain during sleep [147]. However the evidence of its relation with the circadian system is lacking. Briefly, the glymphatic system is a glial-based perivascular clearing system or a "pseudo" lymphatic system in the brain, and it transports soluble waste proteins and metabolites to the bonafide lymphatic system in the dural meninges and cranial nerves which are further drained into the deep cervical lymph nodes [148]. Furthermore, direct observations of the glymphatic system in humans have not been made, and considering the physiological differences between rodents and humans like brain mass, metabolic- and heart-rate, this research is still in its infancy.

Clinical evidence shows that nurses working the night shift routinely exhibit a disrupted REM/nREM sleep equilibrium, reduced total time spent in bed, and abrupt awakenings [149]. Sleep disturbances strongly correlate with the severity of cognitive symptoms in AD [6]. Piromelatine, a multimodal sleep drug is in phase II of clinical trials for AD therapy. Interestingly, AD patients experience protracted disruptions in their sleep-wake cycles that precede the onset of clinical symptoms. Chronic sleep disturbance - for four years - is associated with an increased risk of developing AD (OR = 1.23) and mortality (OR = 1.18) [150]. Sundowning syndrome in AD, is characterized by the worsening of cognitive and motor symptoms through the evening and night time, and it can be effectively treated by the circadian rhythm realignment with bright light therapy [151].

Furthermore, levels of circulating melatonin in the CSF and expression of its receptor MT1 in the SCN is also diminished in AD patients [152, 153]. Furthermore, chronotherapy with melatonin reduces total Aβ load by improving sleep quality in adjunction to its antioxidant effects [154, 155]. The release of melatonin from pineal gland is influenced by the SCN, and as discussed before, melatonin acts on MT1 receptors in the SCN to promote sleep. It may be possible that AD related SCN degeneration may contribute to melatonin dysregulation and potentiate sleep disturbances in AD patients. More studies are required to understand these dynamics. The concentrations of Aβ species in the CSF of the mice varies with the rest-activity cycle [156]. Sleep deprivation or infusion of orexin (wakefulness promoter) exacerbate the aggregation of Aβ peptides, which can be reversed by sleep-promoting orexin antagonists [157]. Collectively, these studies show a bilateral relationship between sleep deprivation and AD pathology, Fig. **3**.

Insufficient sleep also affects the convective fluxes mentioned earlier in this section, and hinders the removal of neurotoxic waste products including $A\beta_{42}$ from the mice brain [146], and thus promotes its aggregation. Significant suppression of waste removal by the glymphatic system has been observed in normally aged and *APP/PS1* mice [158, 159]. Although a complete understanding of mechanisms of the glymphatic system such as physical forces propelling the solute transport is still in progress, it harbors the excellent potential for therapy of neurodegenerative disorders [160, 161]. In addition, histidine decarboxylase catalyzes the production of histamine in locus coereleus of the brain and regulates sleep-wake cycles. A significant reduction in the expression of histidine decarboxylase mRNA is observed in AD patients [162]. These reports highlight the association between AD pathology and sleep-wake homeostasis which is directly controlled by the circadian clock.

6. CIRCADIAN RHYTHM IN AGING

More than 50% of the nuclear receptors that regulate metabolism (28 of 49) exhibit circadian oscillations in their mRNA expression [163]. The ROS load in a cell profoundly influences metabolism by restricting the redox reactions in a particular direction [164]. As emphasized before, redox states and the TTFL have a bilateral relationship, indicating that the dysfunction in one can adversely impact the other. Epigenetic-oxidized-redox-shift theory of aging implies that a sedentary lifestyle causes a shift in redox balance towards an oxidized state that contributes to the mitochondrial damage and senility [165]. The levels of oxidized- cysteine and glutathione in human plasma were found to increase with aging [166].

Furthermore, *Bmal1* deficient mice display a host of symptoms in their significantly short lifespan. The symptoms of *Bmal1* KO mice involve premature cataracts, reduced subcutaneous adipose tissue, organ shrinkage, aberrant metabolism, and oxidative damage in various tissues [167]. These symptoms also depend on the timing of expression (or lack thereof) of *Bmal1*. *Bmal1* deletion in adulthood results in brain astrogliosis and ocular abnormalities, however, it does not significantly affect life span, body weight, blood glucose levels, fertility, and age-dependent arthropathy [168]. Age-related suppression of *Bmal1* expression also disrupts redox homeostasis in the cerebral cortex leading to oxidative damage facilitated neurodegeneration, as observed in *Bmal1* KO mice [52]. Rhythmic expression of *Clock* and *Bmal1* genes dampens and becomes desynchronized in the old mice brains [169]. Furthermore, *Clock* mutant mice are obese, hyperlipidemic, hyper-insulinemic, hyperglycemic, and steatotic [170]. Multi-unit neural activity in the SCN and sPVZ (primary output of the SCN) gradually declines with age [171]. Transplantation of fetal SCN in aged rats remarkably restores their circadian rhythms of body temperature, feeding, and activity [172].

CRd by forced phase shift induced by exposure to mistimed light increases mortality of the aged mice [173]. These pieces of evidence imply that CRd due to exogenous factors

like mistimed feeding or light, and endogenous factors like redox dyshomeostasis or molecular dysfunction may contribute to aging. Specific molecules deeply embedded in circadian clock such as FOXO proteins, SIRT1, and melatonin are known for their critical roles in longevity [174, 175]. The mean levels of melatonin and cortisol decrease with age but their circadian patterns are altered differently with aging. Whereas the acrophase of melatonin shows a delay with increasing age, the acrophase of cortisol shows an advance. This indicates a weakened responsiveness of the circadian system in the elderly, and altered relationship between SCN and tissue-specific clocks driving these hormonal rhythms (pineal gland for melatonin and adrenal gland for cortisol) [176]. Since melatonin and cortisol are deeply rooted in the clock machinery, future investigations for their precise roles in aging are required to address these caveats.

CONCLUSION

Circadian rhythms are fundamental to all mammalian cells and are coupled by the SCN. CRd is typical in contemporary societies where light-noise, shift-work, and transmeridian travel are common. The scientific evidence suggests that the physiology of circadian clock - TTFL and nontranscriptional oscillations - and its modulation by cellular signaling is adversely affected in AD. The dysregulation of these elements also contribute to the AD progression, and the result is a self-reinforcing vicious cycle. The present review presents a strong correlation between dysregulated elements of CR like Per, CLOCK, Bmal1, AVP with the cellular factors like SIRT1, FOXO, PRX, PK2 and ROR, which may serve as putative pharmacological targets to restore circadian alignment for AD. Bright light therapy, in conjunction with chronobiotics is beneficial for treating sundowning syndrome and other cognitive symptoms in advanced AD patients. Future investigations dissecting the role of circadian misalignment in the early stages of AD may provide key insights to design future preventive measures and therapeutics.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
APP	=	Amyloid precursor protein
ATP	=	Adenosine triphosphate
AVP	=	Arginine vasopressin
Aβ	=	Beta-amyloid
BACE1	=	Beta-site amyloid precursor protein cleaving enzyme 1
BMAL1	=	Brain and muscle ARNT-like protein
cAMP	=	Cyclic adenosine monophosphate
CCG	=	Clock-controlled genes
CK1	=	Casein kinase 1
CLOCK	=	Circadian locomotor output cycles kaput
CRd	=	Circadian rhythm disruption
CRY	=	Cryptochrome
DMH	=	Dorsomedial hypothalamus
FOXO	=	Forkhead box-O
IEG	=	Immediate early gene
mRGCs	=	Melanopsin-containing retinal ganglion cells
NAD(P)H	=	Nicotinamide adenine dinucleotide phosphate
NAMPT	=	Nicotinamide phosphoribosyltransferase
NFAT1	=	Nuclear factor of activated T cells-1
NF-κB	=	Nuclear factor kappa B
NMDAr	=	N-methyl-d-aspartate receptor
NPAS2	=	Neuronal PAS-domain protein 2
PER	=	Period
PK2	=	Prokineticin 2
PRX	=	Peroxiredoxins
REM	=	Rapid eye movement
RHT	=	Retinohypothalamic tract
ROR	=	Retinoic acid-related orphan receptor
SCN	=	Suprachiasmatic nucleus
SIRT1	=	Sirtuin 1
sPVZ	=	Sub-paraventricular zone
TTFL	=	Transcription-translation feedback loop
VIP	=	Vasoactive intestinal peptide
VLPO	=	Ventrolateral preoptic nucleus
βTrCP	=	The ubiquitin ligase scf complex

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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