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Research Article

The Influence of Sleep on Brain Health

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Abstract

Sleep plays a crucial role in maintaining brain health and cognitive function. It is well-known that disrupted sleep is a common symptom of Alzheimer's disease (AD). However, emerging evidence suggests that even suboptimal sleep can increase the risk of developing AD. The deacetylase Sirtuin 1 (Sirt 1), which is encoded by the SIRT1 gene, has been found to influence sleep by affecting wake-sleep neurotransmitters and somnogens. Both animal and human studies have provided support for a complex relationship between sleep, Sirt 1/SIRT1, and AD. Various hypotheses have been proposed to explain the significant impact of Sirt 1/SIRT1 on neurons involved in promoting wakefulness and sleep, as well as their associated mechanisms and neurotransmitters. However, there is a lack of research investigating the interaction between sleep and Sirt 1/SIRT1 as a key component of sleep regulation in relation to AD pathology. In this review, we aim to explore the potential association between Sirt 1/SIRT1, sleep, and the development of AD. Considering that sleep is a modifiable risk factor for AD and recent studies suggest that the activation of Sirt 1/SIRT1 can be influenced by lifestyle and dietary interventions, further research in this area is necessary to investigate its potential as a target for the prevention and treatment of AD.

Keywords: Brain Health; Slow Wave Sleep; NREM Sleep

Introduction

Insufficient sleep or poor sleep quality has been linked to a wide range of negative health outcomes and subsequent economic burdens [1]. Research has shown that sleep plays a crucial role in brain health and the maintenance of cognitive abilities by regulating neuroplasticity, information processing, and memory consolidation [2]. Older adults often experience suboptimal sleep, characterized by difficulties in falling and staying asleep, frequent awakenings, and a decrease in restorative slow-wave sleep and rapid eye movement (REM) sleep [3]. The prevalence of these sleep disturbances tends to increase with age and can be attributed to various factors such as changes in sleep behavior due to aging, stress, anxiety, medication use, underlying diseases, or a combination of these factors [4].

A growing body of literature has focused on the relationship between sleep disturbances and neurodegenerative diseases. Patients with Alzheimer's disease (AD) often exhibit clinical symptoms of sleep abnormalities, with increased fragmentation being one of the earliest reported symptoms or complaints [5]. Electroencephalogram (EEG) recordings in AD patients have shown a significant reduction in slow-wave sleep and REM sleep, as well as disruptions in arousal in response to external stimuli [6]. Additionally, the sleep-wake cycle in AD patients is frequently disrupted by nocturnal awakenings and reduced daytime wakefulness following naps [7-9].

The alterations in sleep architecture are believed to worsen the pathology of cerebral AD. Specifically, during deep sleep, there is a reduced clearance of Ab-amyloid in the brain, leading to enhanced deposition and ultimately contributing to the worsening of cognitive symptoms [10]. However, accumulating evidence suggests that there is a bidirectional relationship between sleep and AD. It is not just a symptom of AD, but poor-quality sleep, insufficient sleep, and excessive daytime napping are also proposed

to increase the risk of developing AD in the future [11]. A meta-analysis conducted in 2017 supports this notion, indicating that individuals with sleep disturbances have a 1.55 times higher risk of developing AD compared to those without sleep disturbances. Additionally, poor sleep accounts for up to 15% of the population attributable risk for AD [12]. It is important to note that this estimate may underestimate the true extent of the problem, as many of the studies included in the analysis relied on self-reported sleep measures rather than objective assessments.

Sleep is regulated by two processes: the homeostatic process and the circadian process. These processes control various aspects of sleep behavior and associated variables. The protein Sirtuin 1 (Sirt 1) is involved in both the circadian rhythm and the homeostatic process of sleep. It is associated with wake-sleep neurotransmitters and somnogens, further highlighting its role in regulating sleep [13,14]. Accordingly, the role of Sirt 1 in cell survival is of great significance, as it is believed to provide protection against the deposition of Ab-amyloid and the development of AD-related tau pathology [15,16]. In this review, we aim to explore the potential connections between Sirt 1, its encoding gene SIRT1, sleep regulation, and AD. Additionally, we will discuss various activators of Sirt 1 in the context of AD prevention, and propose recommendations for future research that may contribute to a deeper understanding of the intricate and multifaceted relationship between Sirt 1/SIRT1, sleep, and the etiology of AD (Figure 1).

Sirtuin	Functions in Aging
Sirt1	Lifespan extension, DNA repair, Cell cycle arrest, Cellular senescence
Sirt2	Cell cycle regulation
Sirt3	Mitochondrial function, Oxidative stress, Centenarian-linked SNPs
Sirt4	Fatty acid oxidation, Apoptosis
Sirt5	Fatty acid oxidation, Oxidative stress
Sirt6	Lifespan extension, DNA repair, Genome stability, Telomere maintenance
Sirt7	Epigenetic regulation, Stress resistance, Apoptosis

Figure 1:

Sirtuins, also referred to as Silent information regulator 2 (Sir2) proteins, were initially discovered in yeast (Saccharomyces cerevisiae). They belong to a conserved family of nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylases and are classified as class III histone deacetylases (HDACs). Sirtuins play a crucial role in the removal of acetyl groups from both histones and non-histone proteins, including transcription factors and enzymes. Among the seven sirtuins found in humans and other mammals, Sirt 1 is the most extensively studied and will be the main focus of this review [17]. The SIRT1 gene, responsible for encoding Sirt 1, is located on chromosome 10 (Chr10q21.3) in humans. These enzymes, known for their potential anti-aging effects, tend to decrease in levels as individuals age [18]. Consequently, they are considered promising candidates for the investigation of age-related diseases such as Alzheimer's disease (AD) [18,19]. Sirt 1 has been associated with various biological processes in mammals, including aging, calorie restriction, metabolism, cancer, stress responses, chromosomal stability, cell differentiation, and the regulation of the circadian clock [20,21]. The exact mechanisms underlying the decline of Sirt 1 with age remain unknown. However, its reduction has been observed in both human and animal models during midlife, a period when age-related changes in sleep disorders and wakefulness commonly occur [22,23].

Methods and Materials

The following databases were searched for this review article: To find the most significant comparative research on the relationship between sleep and brain health, its therapeutic options, search engines like Google Scholar, PubMed, and Directory Open Access Journal databases. Keywords like sleep, brain health, slow wave

sleep, NREM sleep, amyloid precursor protein, Sirtuin, Alzheimer's disease, sleep disorders, retinoic acid, amyloid production, and drugs are also used. After assessing the quality and strength of the findings, meta-analyses, systematic reviews, large epidemiological studies, and randomized control trials were used as the main sources of information where they were available (Figure 2).

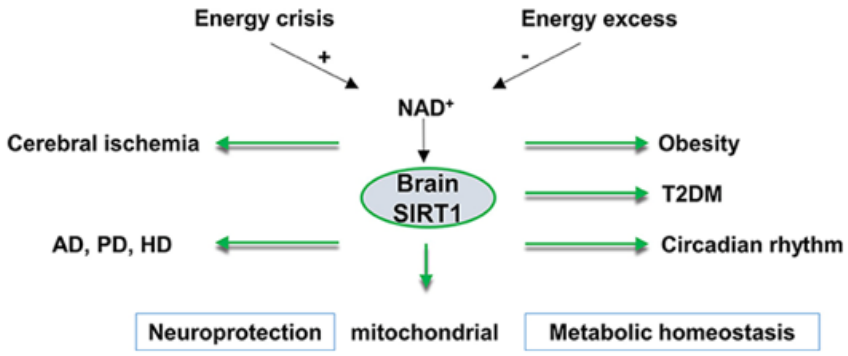

Figure 2:

Results

Alzheimer

Regarding Alzheimer's disease, Sirt 1 has been proposed to have a potential protective effect by modulating the acetylation homeostasis of proteins and enzymes associated with the disease [19,24]. One of the hallmarks of AD is the accumulation of Ab-amyloid peptides in the brain, resulting from the sequential cleavage of the amyloid precursor protein (APP) by the enzyme beta-secretase. Conversely, activation of alpha-secretase suppresses Ab-amyloid production [16]. Sirt 1, deacetylation of transcriptional factors related to alpha-secretase and beta-secretase enzymes, may reduce the burden of Ab-amyloid in the brain [15,16]. For instance, Sirt 1 directly promotes the transcription of the gene encoding alpha-secretase. This is achieved by removing acetyl groups from the retinoic acid receptor beta, a key regulator of alpha-secretase transcription. Additionally, the induction of alpha-secretase by Sirt 1 activates the Notch pathway, which plays a role in the repair of damaged neurons [15].

Sirt 1 has been found to play a role in the deacetylation of tau, which leads to the ubiquitination of hyperphosphorylated tau. This process facilitates the proteasomal degradation of tau and prevents the formation of tau tangles, a hallmark of Alzheimer's disease (AD) [25]. Studies have shown that Sirt 1 is expressed in neurons of the hippocampus, a brain region critical for memory and learning functions that are impaired in AD [21,26]. In AD, there is a reduction in Sirt 1 expression in the brain, which correlates with the accumulation of AD pathology and disease progression [27,28]. Additionally, cognitive disorders have been observed in SIRT1 knockout mice [20], and dysregulation of the Sirt 1 pathway has been implicated as a critical mediator of AD pathogenesis in animal models [29]. Importantly, animal studies have demonstrated that SIRT1 gene expression in the hippocampus and other brain regions can be increased through interventions such as dietary restriction or physical exercise, suggesting potential approaches for enhancing Sirt 1-mediated neuroprotection [18,30].

Sirt 1 and Sleep

The relationship between Sirt 1 and sleep will be discussed in more detail later. Sleep in mammals is categorized into different stages based on cortical electroencephalography (EEG) activity, including REM sleep and non-REM (NREM) sleep, which consists of three sub-stages: N1, N2, and N3 (also known as slow-wave sleep). According to conventional sleep models, wake-promoting neurons (WPNs) and sleep-promoting neurons (SPNs) create a "switch" system in which they compete for network dominance. In the human brain, WPNs and SPNs are primarily located in the brainstem and diencephalon, accounting for less than 1% of neurons. These neurons are associated with different neurotransmitters and have opposing modulatory effects [31].

SPNs are believed to play a role in controlling sleep by inhibiting wake-promoting centers, such as GABAergic neurons in the ventrolateral preoptic nuclei and melanin-concentrating hormone (MCH)-producing neurons in the diencephalon [33,34]. This suggests that the regulation of sleep involves multiple molecular mechanisms and genes, rather than a singular one. Sleep physiology can be examined from two different perspectives: 1) the timing of sleep, which is regulated by the circadian process (process C) in the brain and is independent of sleep itself, and 2) the duration of sleep, which is influenced by the homeostatic, sleep-dependent process (process S) [35,36]. There is a potential interaction between process C and process S in the regulation of sleep [37]. In humans, process C is demonstrated by REM sleep and exhibits a circadian rhythm that closely correlates with body temperature. These processes are minimally affected by sleep and wakefulness within the past 24 hours [38]. In contrast, external factors such as prior wake or sleep

can impact process S, which determines N3, and slow-wave activity in EEG [35].

The Circadian System

The circadian system plays a crucial role in regulating sleep timing. Circadian clock regulators are divided into positive and negative categories. Brain and Muscle ARNT-Like 1 (BMAL1; also known as Aryl hydrocarbon receptor nuclear translocator-like protein 1, ARNTL) and Circadian Locomotor Output Cycles Kaput (CLOCK, and its paralogue Neuronal Per-Arnt-Sim domain protein 2, NPAS2) are positive regulators in mammals. These 'master genes' drive rhythmic gene expression and control biological functions under circadian regulation. BMAL1: CLOCK protein heterodimers initiate the transcription of target genes, including those encoding periods (Pers) and cryptochromes (Crys), which are negative circadian clock regulators. The resulting proteins form dimers that inhibit further transcription of BMAL1 and CLOCK (Figure 3). This negative transcriptional feedback loop allows the cycle to repeat through a low level of transcriptional activity, thereby creating a 24-hour rhythm in mammals [39]. CLOCK protein exhibits histone acetyltransferase (HAT) activity. Studies on animals have demonstrated that Sirt 1, with its deacetylase function, counteracts the HAT activity of CLOCK, subsequently influencing the expression of Cry1, Per1, and Per2 in mice [40-42]. Deletion of Sirt1 in mouse models results in disruption of circadian rhythm and an inability to adapt to a new light-dark cycle. The decrease in both SIRT1 expression and NAD+ levels with aging could be a potential mechanism for the weakening of circadian control in older adults [13].

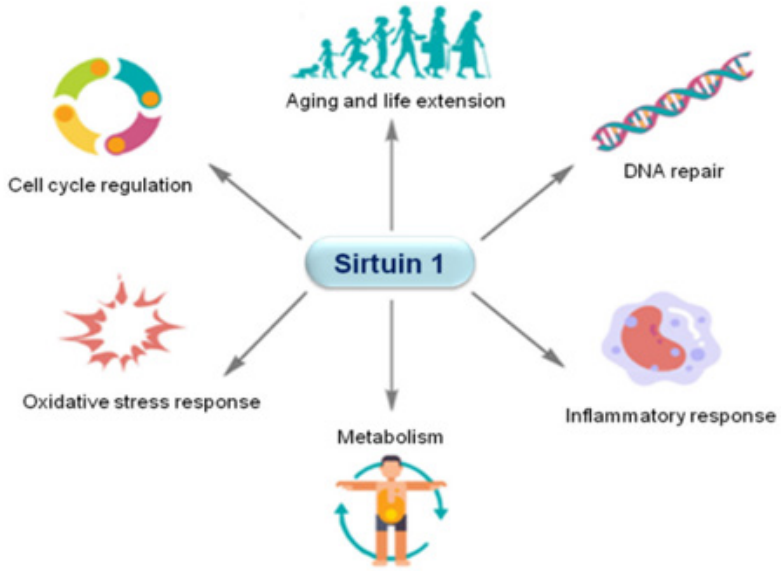

Figure 3:

The Circadian System

The circadian system plays a crucial role in regulating the timing of sleep, while the homeostatic process is responsible for controlling the duration of sleep. The homeostatic sleep drive, which is the pressure to sleep, increases as the time spent awake increases, and decreases during sleep, returning to a 'baseline' level after a night of good quality sleep. In cases of sleep deprivation, lost sleep can be compensated for by increasing the amount of sleep. Conversely, excessive sleep leads to a decrease in the inclination to sleep. The homeostatic process is considered a fundamental regulatory mechanism for sleep. Delta waves, with a frequency of 0.5-4 Hz recorded through EEG, are typically linked to N3 (slow wave) sleep, defining deep sleep, and are controlled by the homeostatic process [43].

Animal studies have suggested that Sirt 1 may play a role in maintaining delta waves during NREM sleep [23,44]. Consistent with this idea, research on humans has shown that delta power in EEG decreases with age, which is in line with the reduced levels of Sirt 1 in aging individuals. It is worth noting that delta power is not only associated with sleep quality but also with longevity and metabolic complications [45,46]. Therefore, it is plausible to suggest that Sirt 1 contributes to sleep homeostasis, although the exact mechanism behind this relationship requires further investigation.

Satoh et al. conducted a study on transgenic mice that overexpressed Sirt 1 specifically in the brain (BRASTO mice) and found that these aged mice had higher delta power during NREM sleep compared to control mice. Interestingly, there was no difference in delta power during wakefulness, indicating that the aged BRASTO mice experienced higher quality or deeper sleep

[44]. Similarly, another study on mice with knockdown of SIRT1 in specific brain regions (dorsomedial and lateral hypothalamic nuclei) showed a decrease in sleep quality [23]. A recent study in mice proposed that Sirt 1 may mediate sleep quality through the Sirt 1/Nk2 homeobox 1 (Nkx2-1)/orexin type 2 receptor (Ox2r) pathway, which is a major pathway involved in maintaining delta power during NREM sleep [44].

Sleep Disturbances

Sleep disturbances are well-established in individuals with dementia due to Alzheimer's disease (AD) [47]. Importantly, evidence suggests that these sleep disturbances not only coexist with AD but also increase the risk of cognitive decline and dementia [11,48,49]. This is believed to occur through the modulation of neurobiological changes in the brain, including increased atrophy, accumulation of brain Ab-amyloid and tau pathology (hallmarks of AD), as well as reduced brain glucose metabolism [50-54]. Recent research indicates the significance of sleep quality in relation to the functioning of the glymphatic system in the brain [10]. Studies have shown that an increase in delta power and a decrease in heart rate during sleep are associated with improved glymphatic flow [55]. Similar to the lymphatic system in other organs, the glymphatic system acts as a "housekeeping" system for the brain [56], removing waste products such as tau oligomers and Ab-amyloid protein, which are linked to Alzheimer's disease and cognitive function [57]. Additionally, findings from studies conducted on mice suggest that an increase in delta power during recovery sleep specifically enhances cognitive performance that relies on the prefrontal brain regions [58].

Changes in circadian rhythms have been observed in both healthy aging and age-related diseases like Alzheimer's disease. A recent review has summarized evidence of age-related alterations in various aspects of the circadian system, including: 1) reduced expression of circadian-related genes like CLOCK and BMAL1, 2) changes in structures responsible for light transmission and processing, such as the pupil and retina, and 3) decreased amplitude of rhythmic behaviors, disturbances in circadian timing, and an increased prevalence of sleep disorders [59]. Even in healthy older adults without clinical symptoms of sleep disorders, the aging process is associated with a decline in sleep quality and quantity, reduced sleep depth and intensity, compromised sleep integrity, and a higher frequency of daytime napping [60].

Accumulating evidence suggests that circadian rhythm disruption in age-related diseases, such as Alzheimer's disease, is even more pronounced. This disruption has been proposed as a biomarker for the presence and severity of Alzheimer's pathology [61]. Indeed, several key processes implicated in the development of Alzheimer's disease are believed to follow a circadian rhythm, including cerebral blood flow, glymphatic system function, Ab-amyloid clearance, melatonin production, and metabolism [61].

Orexin

Orexin, a substance that affects both WPNs and SPNs in the brain, plays a crucial role in maintaining stable sleep and wake cycles [66]. However, its main function seems to be in generating a signal that promotes wakefulness. Research suggests that orexin and its receptors also contribute to the development and progression of neurodegenerative diseases like Alzheimer's disease (AD) [67]. There have been reports of dysregulation in the orexin system in the presence of AD pathology, leading to changes in sleep patterns [68,69]. In individuals with mild cognitive impairment, which often precedes AD, increased levels of orexin in the cerebrospinal fluid have been associated with impaired REM sleep [70,71]. However, the exact mechanism by which alterations in the orexin system worsen sleep in AD still needs to be clarified. It is worth noting that orexin also plays a critical role in regulating stress. Since stress and stress hormones are linked to both AD and reduced sleep quality, this additional function of orexin should be taken into account when considering its relationship with sleep and AD.

The gene encoding the orexin type 2 receptor (OX2R) is a key target of Sirt 1 in the hypothalamus. Sirt 1 has been observed to increase the expression of OX2R, particularly in the dorso-medial and lateral regions of the hypothalamus. The OX2R pathway, which also involves the orexin type 1 receptor, plays a crucial role in arousal, physical activity motivation, and metabolism. Studies have shown that transgenic mice with increased Sirt 1 levels in the brain exhibit enhanced longevity and delayed aging due to the dose-dependent upregulation of OX2R. These findings suggest a potential mechanism by which Sirt 1 influences sleep and Alzheimer's disease through the orexin system [72].

Acetylcholine (ACh)

Acetylcholine (ACh) is an essential component of the arousal system, playing a critical role in wakefulness and REM sleep. However, direct analysis of ACh has been challenging, leading some to believe that ACh does not directly regulate sleep, but rather sleep stages regulate ACh levels. In Alzheimer's disease, the cholinergic nuclei in the basal forebrain degenerate, resulting in decreased activity of choline acetyltransferase and acetylcholinesterase, which contributes to cholinergic dysregulation in AD patients. The decline in cholinergic tone may be responsible for cognitive and arousal impairments [73].

Sirt 1 has been found to influence the expression of ACh receptors and choline levels in the brain, suggesting another potential mechanism through which Sirt 1 may impact sleep and Alzheimer's disease. Cytidine-50-diphosphate-choline (CDP-choline) is a naturally occurring compound that serves as a source of choline in metabolic pathways for ACh biosynthesis. CDP-choline has neuroprotective properties and has been shown to have significant positive effects on memory and behavior [5,14,74]. A recent investigation demonstrated that CDP-choline has the ability to enhance the expression of Sirt1 protein in the rat brain, providing neuroprotection [75]. Additionally, it has been proposed that alpha 7 nicotinic acetylcholine (ACh) receptors can enhance the activity of Sirt1 by increasing the levels of its cofactor NAD+ within the cells [76]. Furthermore, the anti-aging properties associated with these receptors seem to be mediated by Sirt1 [76]. Notably, in an animal model of Alzheimer's disease (AD), treatment with an agonist of the

alpha 7 nicotinic ACh receptor resulted in neuroprotective effects and improved learning and memory abilities [77]. It is plausible to suggest that these beneficial effects were mediated by Sirt1.

The role of monoaminergic neurotransmitter systems in the sleep-wake cycle has been extensively studied [5,31,32]. These systems are most active during wakefulness, exhibit reduced activity during non-rapid eye movement (NREM) sleep, cease functioning before and after rapid eye movement (REM) sleep, and resume firing before the onset of wakefulness [78]. Impairment of the monoaminergic system is commonly observed in AD. Due to the relatively low number of monoaminergic fibers in the brain and the fact that these neurons have long, unmyelinated axons, they are more susceptible to neurological abnormalities associated with AD pathology. Specifically, monoaminergic neurons project into the hippocampus and cortical regions that are significantly affected by the accumulation of hyperphosphorylated tau and Ab-amyloid [79].

Sirt1 is expressed in monoaminergic neurons, where its presence is crucial for normal wakefulness and the proper functioning of wake-active neurons. Studies involving transgenic animals and the conditional loss of brain Sirt1 in adult mice have shown that the absence of Sirt1 leads to significant disturbances in wakefulness and a reduction in wake time, without affecting sleep consolidation [23]. Furthermore, this research also revealed an age-related decline in Sirt1 levels specifically in wake-active neurons, excluding serotoninergic wake-active neurons [23].

Another study conducted on mice found that SIRT1, a protein, can regulate the levels of monoamines by deacetylating NHLH2, a transcription factor for the gene MAO-A. MAO-A encodes an enzyme called monoamine oxidase A, which is involved in the breakdown of monoamine neurotransmitters [80]. Additionally, research conducted in a laboratory setting demonstrated that overexpression of a specific microRNA called miR-142 led to a decrease in neuronal expression and enzymatic activity of MAO-A through the downregulation of SIRT1 [81]. Abnormal expression of microRNAs has been linked to the development of various neurodegenerative disorders, potentially through the influence of SIRT1 on neurotransmission. Therefore, the modulation of monoaminergic neurotransmitter systems represents another possible mechanism through which SIRT1 can impact sleep and Alzheimer's disease.

MCH

Melanin-concentrating hormone (MCH), a neuropeptide, plays a role in reducing locomotor activity, conserving energy, and promoting sleep when there is a surplus of energy [82]. It is also believed to be involved in negative energy balance by reducing activity and REM sleep [83]. Depletion of MCH, either through genetic knockout or the use of an antagonist, is thought to decrease both NREM and REM sleep, increase sleep fragmentation, and heighten alertness [84]. Animal studies have indicated that increased levels of MCH can lead to improved memory, learning, and performance [85].

There is emerging evidence indicating that the function of MCH (melanin-concentrating hormone) is disrupted in Alzheimer's disease (AD), and this disruption is associated with AD-related characteristics such as the presence of neurofibrillary tangles composed of hyperphosphorylated tau proteins. MCH receptors are widely distributed in the hippocampus and cortex, which are regions particularly susceptible to AD-related neuropathology and neurodegeneration. Consequently, the disturbed function of MCH in AD and its potential effects on learning and memory performance may be attributed to a decrease in MCH receptors.

A recent study has provided evidence that Sirtuin 1 (Sirt 1), a protein involved in various cellular processes, including sleep regulation, plays a role in the regulation of MCH in neurons that express pro-opiomelanocortin (POMC), which promote sleep. Therefore, inhibiting Sirt 1 in these regions could potentially impair MCH functions. Additionally, the Sirt 1/Forkhead Box O1 (FoxO1)/POMC signaling pathway has been proposed as a potential regulatory mechanism for MCH activity. This pathway is believed to contribute to the regulation of energy balance, food intake, and the sleep-wake cycle. Taken together, these findings suggest that MCH could be another target through which Sirt 1 may influence sleep and AD [86,87].

Adenosine

Adenosine, along with its receptors, plays a crucial role in regulating both circadian rhythm and the sleep drive. Adenosine itself possesses sleep-inducing properties and is considered a "sleep substance" that modulates the sleep-wake cycle through its A1 and A2A receptor subtypes, which are the most prevalent receptor subtypes in the mammalian brain. Studies have demonstrated that a decrease in its derivative adenosine triphosphate (ATP) and an increase in extracellular adenosine levels are positively associated with sleep patterns [88,89]. Activation of A1 receptors enhances slow-wave activity [90], which is the primary indicator of homeostatic sleep regulation. Additionally, caffeine has been suggested to influence the sleep-wake pattern through A2A receptors [91]. The signaling molecule cyclic AMP, derived from adenosine, is itself a component of the circadian clock and indirectly triggers the transcription of numerous circadian genes while also influencing cell cycle timing. AMP kinase, a cellular energy sensor that relies on AMP, can phosphorylate multiple clock proteins, including Sirt 1, thereby upregulating this enzyme and affecting downstream pathways. As mentioned earlier, the function of Sirt 1 is also influenced by NAD+ cofactor levels, which are regulated by both circadian and metabolic processes [92]. The neuromodulatory role of adenosine and its receptors has been observed in various neurodegenerative conditions, including Alzheimer's disease (AD) [93]. Epilepsy is reported in 10% to 22% of AD patients, often occurring during the early stages of the disease or even before the formation of cerebral Ab-amyloid plaques [94]. It is believed that global DNA hypermethylation is associated with chronic epilepsy [95], and disruption of adenosine homeostasis is implicated in this mechanism. Consequently, therapeutic administration of adenosine may improve DNA methylation profiles and potentially alleviate the progression of epilepsy [94].

A recent investigation revealed that Sirt 1 in the brain plays a crucial role in managing epilepsy, while adenosine enhances

epigenetic modifications, neuron survival, and synaptic plasticity [93]. However, the impact of adenosine impairment on AD pathophysiology is intricate. In the short term, increased adenosine levels could potentially have therapeutic benefits by suppressing methyltransferase and subsequently reducing DNA methylation changes, which are commonly observed in the brains of AD patients [96]. Additionally, elevated adenosine levels and the resulting increased A1 receptor activity improve the hyperexcitability and excitotoxicity network in AD parenchyma. Conversely, heightened A2 receptor activity due to increased adenosine levels leads to memory deficits and AD pathology. Overall, these findings suggest that the positive effects of elevated adenosine levels are likely dependent on the specific receptor subtype [96].

Melatonin

Melatonin, a metabolite of the amino acid tryptophan, is produced in the pineal gland. In humans, melatonin contributes to various physiological processes, including the regulation of circadian rhythm and sleep physiology. Following two hours of endogenous melatonin secretion at night, sleep propensity significantly increases [97]. In diurnal species, melatonin reduces the wake-promoting signal of the circadian clock, thereby promoting sleep [98]. However, nocturnal melatonin secretion is disrupted with advancing age and in neurodegenerative disorders such as AD, leading to abnormal sleep patterns [99]. Melatonin secretion decreases in individuals with mild cognitive impairment, which is often the earliest manifestation of AD neuropathology [100,101] and continues to decline as the disease progresses [100]. A recent study indicated that mild cognitive impairment patients with alterations in melatonin production experience disturbances in the circadian clock, resulting in increased wakefulness at night and prolonged REM latency [102].

Figure 4:

One possible explanation for these effects could be the excessive regulation of monoamine oxidase in AD, which leads to a decrease in serotonin, the precursor of melatonin [103]. Studies conducted on animals and in vitro also indicate that administering melatonin can improve AD pathology by potentially reducing the production of Ab-amyloid through increased secretase activity and decreased b-and c-secretases [104-106]. Additionally, melatonin has been found to up-regulate ADAM10 (A Disintegrin and Metalloproteinase 10) in vitro by activating the SIRT1 pathway [104]. ADAM10 is the primary a-secretase in neurons and is responsible for cleaving APP in a way that suppresses Ab-amyloid production. These in vitro findings are supported by an animal study where long-term melatonin administration to aged mice resulted in positive changes to secretase activity in the hippocampus, accompanied by a decrease in phosphorylated NF-jB and an increase in Sirt 1 [106]. The mice also showed improved spatial memory following melatonin treatment. Based on these findings, the authors suggest that dietary supplementation to counteract age-related melatonin loss could be a potential therapeutic approach for preventing and managing AD [106]. The effects of melatonin treatment have also been studied in rats subjected to total sleep deprivation [107]. After total sleep deprivation, the rats exhibited significant impairment in spatial memory and reduced Sirt 1 levels in the hippocampus. However, when the sleep-deprived rats were given melatonin

doses of 5, 25, 50, or 100 mg/kg/day, the expression of Sirt 1 in the hippocampus was preserved. These neurobiological benefits of melatonin treatment were accompanied by improved performance in behavioral tests. As a result, the authors propose melatonin as a potential therapeutic strategy for preventing memory deficits caused by total sleep deprivation and suggest that Sirt 1 may play a role in mediating these beneficial effects [107]. Numerous studies have also emphasized the significant involvement of Sirt 1 in regulating melatonin function to enhance insulin resistance, aging, and anti-inflammatory properties; [108-110] all of which have implications for Alzheimer's disease (AD) risk and development. The cumulative findings in this section propose melatonin as an additional target by which Sirt 1 could potentially influence sleep and AD (Figure 4).

Retinal

The function of the retinal in mammals involves the localization of the functional photopigment melanopsin within intrinsically photosensitive retinal ganglion cells (ipRGCs), which plays a role in non-visual photoreceptive functions. The functions of melanopsin illustrate that light not only communicates with the circadian clock but also interacts intricately with various neurological and pathological processes [111,112]. The response to light by the body is crucial for the regulation of rhythmic physiological functions, such as hormonal cycles, and the expression of negative circadian clock regulator genes Per and Cry. Consequently, ipRGCs play a significant role in the adjustment of the circadian clock. The depletion of ipRGCs, whether acquired or inherited in neurodegenerative diseases, results in the impairment of dopaminergic neurons in the retina. Similarly, disruptions in light detection or transmission to the retina due to aging or conditions like cataracts, lead to the dysregulation of circadian synchrony and subsequent impairment of various physiological processes, including sleep. In line with these discoveries, the decrease in melanopsin levels seems to be associated with insomnia, depression, and cognitive decline [112,113].

Blue light at 460 nm has been suggested to enhance cognitive functions both during the day and at night [114]. However, the disruption of the circadian clock may impact the effects of exposure to the blue light spectrum, particularly in older individuals leading to decreased melatonin levels and reduced alertness [115,116]. Studies have shown retinal thinning and vascular disturbances in the retina of individuals with Alzheimer's disease (AD). Additionally, AD-related markers such as Ab-amyloid plaques, hyperphosphorylated tau, and neurodegeneration have been identified in the retinas of individuals with early signs of AD. Recent research indicates that retinal scans could potentially aid in the early diagnosis of AD [117-119]. Sirt 1, found in various parts of the eye, plays a crucial role in maintaining retinal health and function. In mice lacking SIRT1, abnormalities in retinal cell layers and increased apoptosis of retinal progenitor cells have been observed. Sirt 1 influences aging, inflammation, oxidative stress, angiogenesis, and neuroprotection in the retina and ocular systems. The expression of SIRT1 in retinal tissue is influenced by light, with levels increasing at night, suggesting a tissue-specific regulation of SIRT1 in the eye [120-125].

Discussion

The presence and severity of Alzheimer's retinopathy are likely to have a negative impact on the transmission of light to the retina, which in turn affects various physiological functions such as sleep and the expression of SIRT1 [126]. Activators of Sirt 1, including dietary factors and other modifying strategies, have been proposed to counteract these effects. Several approaches, such as intermittent fasting, calorie restriction, and exercise combined with calorie restriction, have been shown to increase the levels of Sirt 1 mRNA in human muscle tissue. Animal studies have also demonstrated that calorie restriction can elevate Sirt 1 levels in the brain, particularly in the vulnerable hypothalamus region affected by AD neuropathology [127,128]. Additionally, compounds like Rhein derived from rhubarb and DOPET found in olive oil, grape juice, and wine have shown potential therapeutic effects in animal models of AD by activating the Sirt 1 pathway and improving mitochondrial biogenesis. However, further research is needed to determine the efficacy of these treatments in humans [129].

The increase in SIRT1 activity observed in this study was accompanied by enhanced clearance of neurotoxic Ab-amyloid through a-secretase-mediated mechanisms, resulting in neuroprotection. Resveratrol, a polyphenol found in grapes and grape products like red wine, has been well-established as an activator of Sirt 1 both in laboratory settings and in living organisms [130-133]. Furthermore, studies conducted on patients with Alzheimer's disease (AD) have shown that high doses of resveratrol can reduce AD biomarker levels in cerebrospinal fluid, provide neuroprotection in brain regions affected by early AD, and slow cognitive decline while maintaining function in individuals with mild to moderate AD. It is important to note, however, that the beneficial effects of resveratrol are not solely dependent on Sirt 1 activation, as this compound has been found to modulate various intracellular signaling pathways. The impact of Sirt 1/SIRT1-activating strategies, such as those mentioned above, on AD risk and sleep-related factors, remains to be determined, as does their potential therapeutic role in AD treatment.

In terms of future research directions, accumulating evidence from both animal and human studies suggests a complex and multifaceted relationship between Sirt 1/SIRT1, sleep, and the development of AD. However, further research is needed to fully understand this relationship. One recommendation for future studies is to simultaneously measure Sirt 1 levels and sleep parameters in well-characterized longitudinal cohorts of aging individuals and those with AD. By assessing Sirt 1 levels in plasma, serum, or cerebrospinal fluid, along with sleep efficiency, duration, and stages, across the continuum of AD progression (from preclinical to prodromal and dementia stages), we can gain a better understanding of the relationship between Sirt 1, sleep, and the progression of AD.

Furthermore, by including individuals who maintain their cognitive abilities over time (both with and without AD biomarkers), the study can also consider the impact of healthy aging compared to pathological aging. This analysis is crucial for understanding how age influences the relationship between Sirt 1/SIRT1, sleep, and AD.

Age is the greatest risk factor for AD, and both sleep patterns and Sirt 1 are associated with the aging process. Once the relationship between Sirt 1/SIRT1, sleep, and AD etiology is well understood, the next logical step would be to investigate the effects of Sirt 1 activators (such as resveratrol, intermittent fasting, and calorie restriction) on sleep patterns and AD biomarkers simultaneously. This research could provide insights into how these approaches could potentially be used to delay or prevent the onset of AD-related dementia.

Conclusion

A growing body of evidence from animal and human studies supports a significant and complex relationship between Sirt 1/SIRT1, sleep, and AD. Various hypotheses have been proposed to explain the critical role of Sirt 1/SIRT1 in the mechanisms and neurotransmitters related to wake-promoting neurons (WPNs) and sleep-promoting neurons (SPNs). However, there is a lack of studies investigating the interaction between sleep and Sirt 1/SIRT1, a key component of the circadian clock, in relation to AD pathology. This review has explored the potential association between Sirt 1/SIRT1, sleep, and AD etiology. Considering that sleep is a modifiable risk factor for AD and recent studies suggest that Sirt 1/SIRT1 activation can be influenced by lifestyle and dietary approaches, further research is needed to explore its potential as a target for AD prevention and treatment.

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Conflict of Interest

No Conflict of Interest.

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