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Circadian and Sleep-Wake Dysfunctions of the Hypothalamus in Alzheimer's Disease Progression

Angelina Kovalchuk[1] and Joanna Eckhardt[#]

[1]Vanguard High School, USA
[#]Advisor

ABSTRACT

Alzheimer's disease (AD) is a disorder that causes degeneration of brain cells, cognitive decline, and memory loss. AD is characterized by both the accumulation of tau proteins and the amyloid plaques, which inhibit cell function. Cognitive symptoms are considered manifestations of late-stage AD, though other manifestations such as sleep alterations occur long before these symptoms. Moreover, specific subcortical areas of the brain are affected very early on in AD progression, even before cognitive structures such as the hippocampus. One notable region is the hypothalamus, which regulates circadian rhythms, sleep-wake structure, and other metabolic signals. The hypothalamus is significant in AD progression due to its protective qualities and influence on disease development. This paper investigates the regulation of circadian and sleep-wake cycles within the hypothalamus and how desynchronization may contribute to AD pathogenesis in preclinical and early stages of the disease. Because the hypothalamus is a complex and varied structure, other processes of the hypothalamus are also discussed due to their influence on the sleep-wake cycle. Circadian rhythms also vary among different populations, potentially affecting AD onset. Understanding the influence of circadian and sleep-wake cycles on early AD pathology can provide insight into new interventions and therapeutics preceding later stages of the disease.

Introduction

Alzheimer's disease (AD) is a slowly progressing neurological disease characterized by a degeneration of brain cells and is the most common form and cause of dementia.[1] Several pathological hallmarks indicate AD pathology, specifically the presence of neuritic plaques and neurofibrillary tangles in brain tissue.[2]

About 50 million people live with dementia worldwide, and this number is expected to reach 152 million by 2050. Dementia not only affects individuals, but their families and the economy, with global costs estimated at about 1 trillion USD annually.[3] No cure for AD currently exists, but treatments attempting to target symptoms of AD have been developed.[4]

The most pronounced cognitive manifestation of AD is short and long-term memory loss, although there are several other indicators, including alterations in behavior.[5] However, some manifestations of AD, such as weight loss, sleep, and circadian dysfunction, can precede cognitive decline.[6] This suggests an early effect on structures involved in these mechanisms in AD pathogenesis, most notably the hypothalamus.

The purpose of this paper is to discuss the role of sleep and circadian dysfunctions in the hypothalamus in the progression of early AD. This paper will discuss how the hypothalamus is affected early in AD, the extent of its role in modulating circadian rhythms, and how dysfunction of these rhythms contributes to the progression of AD. Due to the hypothalamus being a complex and varied structure, the focus of this paper is specifically the regulation of circadian rhythms within the sleep-wake cycle, but other circadian mechanisms will also be discussed due to their communication with this cycle and their influence on AD progression. This paper will

also highlight the variability in circadian dysfunction among different populations and how they influence the development of AD, as well as potential therapeutics that target circadian rhythms.

Alzheimer's Disease Overview

Some of the effects of AD include the degeneration of brain cells, cognitive decline, and memory loss. Several neuropathological changes indicate AD progression, including the accumulation of lesions, atrophy of brain tissue, and other factors such as neuroinflammation and oxidative stress. The two main accumulative lesions in AD pathology are amyloid plaques and neurofibrillary tangles. Amyloid plaques are the excess aggregation of beta-amyloid protein (Aβ), which disrupts normal neuronal function.[1] Dense accumulation of these plaques can overstimulate neurons, damage axons and dendrites, and cause loss of synapses, which results in cognitive impairment.[7] Eventually, the buildup of Aβ is theorized to result in an "amyloid cascade," which consists of inflammation, oxidation, and excess of excitatory neurotransmitters, all contributing to neurotoxicity. Neurofibrillary tangles (NFT) are abnormal filaments of tau proteins, which are found in microtubules of neurons and are essential in providing structure to the cell. Abnormal aggregation of these proteins results in twisting of filaments, which causes disconnection from microtubules, transport inhibition, and neuronal loss. Tau and amyloid aggregation are thought to act in parallel pathways, enhancing each other's effects.[4] The neuronal loss from both leads to a shortage and imbalance between various neurotransmitters, and to the cognitive deficiencies apparent in AD such as memory loss.[1]

The exact cause of AD is unknown but appears to be multifactorial with a myriad of potential risk factors, including age, genetics, head injury, smoking, diabetes, and low physical and mental activity.[2, 5] However, the underlying cause of pathological changes such as Aβ and NFT accumulation are still unknown. Proposed hypotheses include the reduced clearance of Aβ deposits with age and the deficit of acetylcholine (ACh), a neurotransmitter essential in cognitive function. Aβ plaques are thought to reduce the release of ACh, causing synaptic loss and thus impacting cognitive function.[1]

There are three proposed clinical phases of AD. The first stage, preclinical AD, may last for several years until accumulation of Aβ reaches a critical level.[2] During this stage, early pathological changes may be present, but there is no functional impairment of daily activities.[1] Following this is the pre-dementia phase, in which early-stage clinical pathology is present but functional impairment has not reached extreme levels. Lastly there is a clinically defined dementia phase, in which cognitive and functional impairment is severe and there is a significant accumulation of Aβ and NFT.[2]

The Hypothalamus

EEG readings show that brain regions involved in sleep and circadian control are affected very early in AD pathogenesis.[8] This is supported by the density of Aβ plaques in this area, which correlates strongly with the progression of the disease.[9] Among these regions is an interconnected subcortical system consisting of the locus coeruleus, mammillary nucleus, and the hypothalamus.[10]

The hypothalamus is a region of the brain that helps coordinate the endocrine system by releasing hormones that affect several different glands and body systems. It is located in the center of the brain above the pituitary gland and inferior to the thalamus. This region orchestrates signals from the central nervous system and regulates basic body functions such as growth, reproduction, metabolism, and homeostasis.[11, 12] Aside from regulating the endocrine and nervous systems, the hypothalamus is essential in the regulation of sleep and the sleep-wake cycle.[6]

Circadian Rhythms

The hypothalamus contains the suprachiasmatic nucleus (SCN), which synchronizes circadian rhythms throughout the body. Circadian rhythms are cyclical patterns and signals within the body that regulate the timing of physiological functions. These rhythms are intrinsic, follow the 24-hour day-night cycle, and are entrained by external cues known as "zeitgebers." This internal clock allows organisms to sense and anticipate daily fluctuations in the environment.[13]

The most powerful zeitgeber for the circadian clock is light, though other cues include temperature, food, and various environmental changes.[13] The SCN regulates these signals through the peripheral nervous system and various hormonal axes, constituting a web of interlinked feedback loops.[14] While most notably involved in regulating sleep, the circadian clock is also observed in body temperature, heart rate, hormone secretion, red blood cell production, and various other physiological characteristics of the body.[15]

The releases of certain hormones are found to be circadian in nature, the most characteristic of these being melatonin,[16] which is involved in the timing of the sleep-wake cycle. The degree to which an individual is entrained to circadian rhythms can partly be determined by melatonin release, described by dim-light melatonin onset (DLMO). In this process, dim light hitting specialized retinal cells called intrinsically photoreceptive retinal ganglion cells (ipRGCs) sends signals to the SCN to release melatonin.[13, 17] Alternatively, increased light suppresses melatonin secretion.[18] Control of melatonin release occurs with glutamatergic inputs from the SCN through a specific signaling pathway involving the paraventricular nucleus, intermediolateral cell column in the spinal cord, and nervous system ganglia.[19] The signal is sent to the pineal gland, which is responsible for secretion (Figure 1).

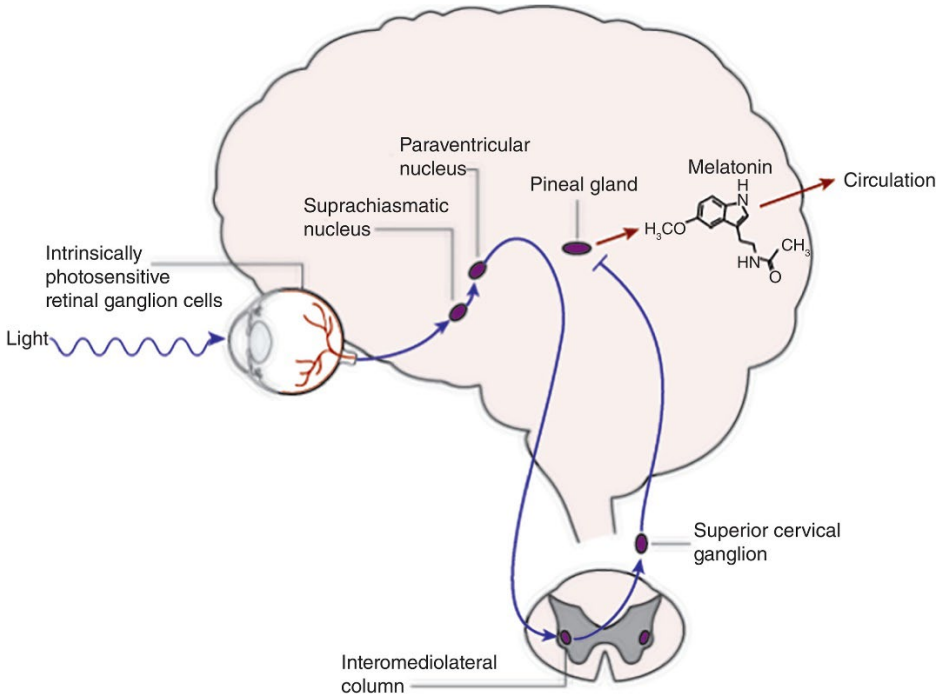

Figure 1. The pathway of melatonin onset from exposure to light. Light hitting ipRGCs sends signals to the SCN to release melatonin through the signaling pathway as shown. The signal travels from the SCN through a nervous system pathway to the pineal gland, which secretes melatonin for circulation. (Adapted from Ostrin, L.)

When melatonin synthesis is impaired, circadian rhythmicity of certain functions such as blood glucose regulation is lost.[13] DLMO is believed to accurately represent the timing of the SCN. In addition, melatonin rhythms are easier to observe than other circadian manifestations, such as body temperature rhythms. Under normal conditions, melatonin levels begin to increase 2-3 hours before the usual onset of nocturnal sleep. These levels reach their peak in the early morning hours and decrease around usual waking time.[20] Changes to this pattern could imply circadian alterations.

Hypothalamic Defects in Alzheimer's Disease

Dysfunction within the hypothalamus is correlated with sleep dysfunction in AD,[6] as suggested by its central role in regulating sleep systems. Hypothalamic atrophy has been observed using neuroimaging in AD patients in preclinical stages.[11, 14] Consistent with this observation, AD pathology such as Aβ plaques and NFTs are regularly observed in the hypothalamus of early-stage AD patients.[12]

In addition to structural and pathological abnormalities, the function of the hypothalamus appears to be commonly dysregulated in AD in early stages. The hypothalamus is responsible for the release of the neuropeptide orexin, a hormone critical in maintaining sleep-wake structure and promoting wakefulness. Orexin levels appear to be altered in individuals with AD, with abnormal levels being associated with REM sleep disruption and sleep fragmentation.[6]

Circadian and Sleep-Wake Dysfunctions in Alzheimer's Disease

Sleep-Specific Alterations in Alzheimer's Disease

A bidirectional relationship between circadian dysfunction, sleep, and AD has been proposed.[8] This is due to the essential role of sleep in clearing extracellular metabolites such as Aβ.[21] It is hypothesized that sleep disturbances increase Aβ deposition, which in turn cause hypothalamic atrophy and sleep disruption.

The five stages of sleep include wakefulness, N1, N2, N3, and Rapid Eye Movement (REM). These cycles repeat over the course of the sleep period approximately 4 to 6 times. N3, also known as slow-wave sleep (SWS) and considered to be the deepest stage of sleep, is characterized by low frequencies and high amplitudes (delta waves).[22] The structure of the sleep cycle is affected by circadian rhythms, particularly in the duration of the sleep phases. SCN degeneration has been identified in AD, consistent with sleep alterations observed in patients.[11, 14] Specific alterations include the loss of SWS and REM sleep. SWS has been shown to potentiate Aβ clearance via the glymphatic system, emphasizing the essential role of sleep in reducing AD progression. SWS is also especially significant in memory retention and preserving synaptic plasticity. SWS is shown to decrease with age, which is exacerbated in AD and contributes to memory problems.[14, 17, 21] Similarly, reduced sleep was associated with an increased risk of developing dementia and AD. Animal studies found that transgenic mice with increased amyloid deposition exhibit sleep disturbances.[12]

Chronic sleep deprivation is implicated in neurodegenerative diseases such as AD, but the overall contribution of this cause is still unknown. Total and continuous sleep deprivation leads to deleterious effects, increasing Aβ plaques in transgenic mice. Conversely, appropriate levels of sleep, particularly SWS, decrease the production of Aβ and aid in its clearance from the brain.[17] Diminished SWS in AD means that neurons spend more time in excited states, producing more Aβ protein. Overproduction leads to further overexcitement, perpetuating Aβ progression in a vicious cycle.[9, 17]

Additionally, sleep and circadian dysfunction may be a factor in dysfunctional tau metabolism. Many tau-related changes appear in areas involved in sleep regulation in early stages, indicating potential involvement

of tau proteins in sleep disturbance in AD. Certain transgenic animal models suggest that tau pathology may also induce sleep disruption.[17]

Circadian-Specific Alterations in Alzheimer's Disease

Impairment to any hypothalamic nuclei can cause a deficit in its function, and therefore impairment to the SCN causes desynchronization of circadian rhythms.[23] Circadian rhythms communicate with nearly all systems and risk factors involved in the progression of AD. Failure to synchronize circadian rhythms drastically reduces the amount of stress that can be tolerated by the body, and thus increases susceptibility to develop disease.[14, 17]

Decreased circadian activity and delayed rhythms may result in an increased risk of dementia. Sleep disorders such as fragmented and reduced sleep, which are associated with circadian rhythms, are described in all stages of AD. Shorter sleep duration and poor sleep quality were reported in older adults with AD and were associated with greater Aβ burden.[12] Other sleep-wake changes observed in AD patients include sleep fragmentation, increased wakefulness, and decreased levels of daytime activity due to sleeping during the day. Studies have also shown that Aβ plaques disturb the molecular clock, which leads to changes in circadian rhythmicity.[17]

Alterations in sleep-wake hormones regulated by the hypothalamus may also potentiate AD progression. Transgenic mice without the orexin gene, which helps maintain sleep-wake structure, show decreases in Aβ pathology, while increased wakefulness increases Aβ pathology.[12] Moreover, certain evidence suggests circadian rhythms and the sleep-wake cycle have a role in regulating Aβ levels. Both animal and human models have a pronounced diurnal rhythm of Aβ, with peak concentrations occurring during wakefulness.[17]

Also, production of the sleep-wake hormone melatonin is shown to decrease with aging, which is also considered a critical factor in AD onset. As an essential modulator of circadian rhythms, melatonin impairment may have a role in AD progression. The circadian rhythm of melatonin release is also dysregulated in patients with AD. Loss of melatonin is correlated with oxidative damage in AD, and patients with AD demonstrate a lower level of melatonin compared with healthy patients. Aside from its core function, melatonin has anti-inflammatory, cytoprotective, and antioxidant properties. Melatonin is important for immune cell function, cell protection, mitochondrial function, and energy homeostasis. This suggests the decreased function of these factors as an additional consequence of circadian disruption. Melatonin additionally inhibits the secretion process of amyloid proteins, suggesting a potential role of melatonin in decreasing the aggregation of AD pathology. Additionally, neurodegeneration attributed to tau aggregation may be attenuated by melatonin due to inhibiting the expression of genes involved in neuronal death.[14, 17]

Correlations between circadian dysfunction and AD pathology highlight a bidirectional relationship, with circadian dysfunction discussed as both a cause and pathological agitator for AD. Circadian disruption manifesting in the sleep-wake cycle leads to neuroinflammation and disease susceptibility, which then influences melatonin and other hormone levels, Aβ accumulation, and dysregulation of other body systems, therefore perpetuating AD pathology. Conversely, AD results in Aβ and tau accumulation, which then affects neuroinflammation and degeneration of circadian neurons.[17] Several pathological factors in the relationship between circadian dysfunction and AD are highlighted in Figure 2.

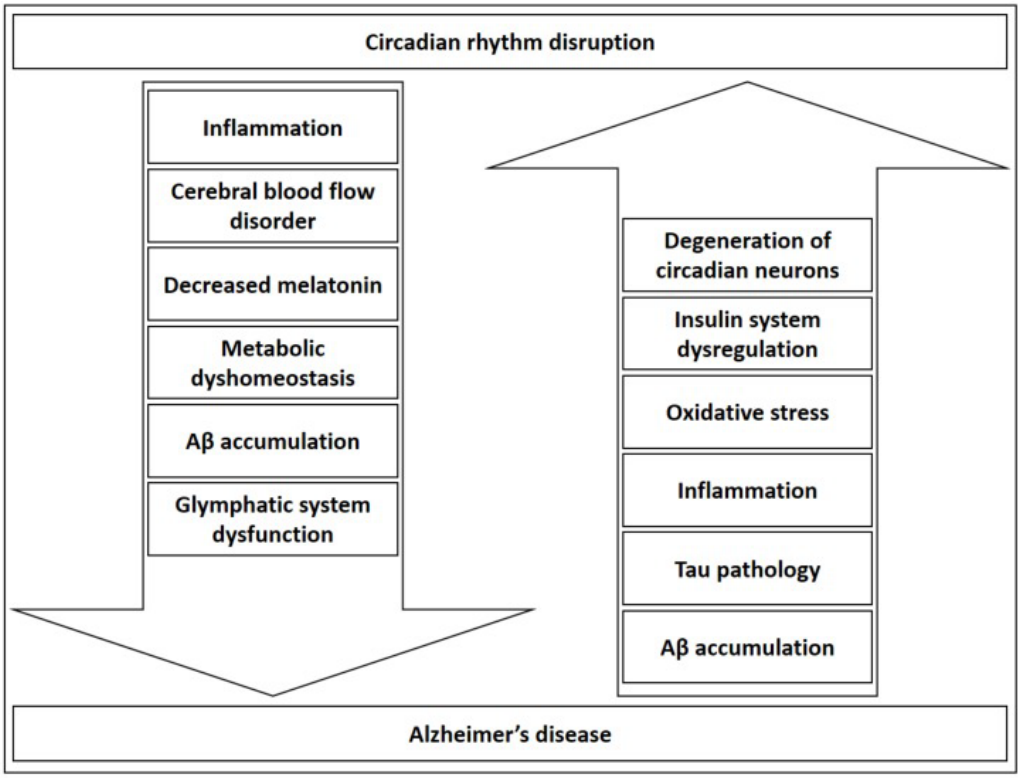

Figure 2. Several pathological factors in the bidirectional relationship between circadian dysfunction and AD. Circadian disruption leads to neuroinflammation and disease susceptibility, which then influences melatonin levels, Aβ accumulation, and dysregulation of other body systems, worsening AD pathology. AD results in Aβ and tau accumulation, which affects neuroinflammation, physiological dysregulation, and degeneration of circadian neurons, therefore disrupting circadian rhythms. (Adapted from Homolak, J. *et al.*)

Circadian abnormalities also progress together with cognitive and functional deterioration. When modeling circadian behavior, AD patients show changes in the fitted models of cosine curves. In one study, patients demonstrated a lower amplitude of activity within a 1-day cycle, reduced goodness of fit of the circadian rhythm, and later acrophases, or the time at which the peak of the rhythm occurs, of activity. One sample of patients had a large mean time difference between their activity acrophases, which was associated with greater activity during the night. AD patients also experienced less motor activity during the day and a lower interdaily stability (synchronization of rhythms to the light-dark cycle), of activity,[15] indicating a lower consistency of activity patterns. These findings implicate circadian rhythms in behavioral symptoms of AD.

Higher levels of regular nocturnal motor activity correlate with aggressive behavior and agitation in the early morning and evening, a phenomenon known as "sundowning".[17] Varying observations have been reported for AD patients, with some being more agitated in the morning, some in the afternoon, and some showing agitation within no specific time frame. Sundowning has been ascribed to environmental influences.[15] This suggests the possibility of certain zeitgebers implicated in circadian changes also playing a role in sundowning behavior.

The Influence of Other Hypothalamic Processes on Circadian Rhythms

Although a main function of circadian rhythms is regulating sleep, the other functions of the hypothalamus in circadian expression may also contribute to the progression of AD. Among these functions are the insulin and metabolic system, the immune system, and the regulation of stress responses. Impairment to any of these systems may contribute to circadian dysfunction and, as a result, AD progression.

Metabolism and Circadian Rhythms

Circadian system failure is theorized to be a result of degeneration of neurons regulating the SCN clock and dysfunction in the insulin system.[17] Disruption can also occur due to degeneration of cells of the basal cholinergic forebrain, which project to the SCN. This suggests a relationship between AD neurodegeneration and the circadian clock's ability to entrain rhythms.[14]

Metabolic changes may be involved in circadian and sleep disruption. Insulin resistance has been linked to an increased risk of AD due to regulating brain metabolism. Homeostatic processes involved in the insulin system include synaptic plasticity and neuronal growth and survival.[14, 17] Additionally, sleep-wake misalignment causes an unscheduled secretion of insulin and increased markers of insulin resistance and inflammation.[16] Insulin signaling, therefore, may be a key process in its development.

Apolipoprotein E (APOE) is a gene responsible for lipid metabolism, and presence of the APOE ε4 allele can lead to mitochondrial dysfunction and in turn insulin and metabolic defects. The circadian clock regulates a majority of metabolic activity and therefore circadian dysfunction due to metabolic changes can serve as a major risk factor for AD.[14]

Metabolic disorders such as type 2 diabetes cause damage to the hypothalamus by similar mechanisms as those observed in AD. Physiological effects of these disorders have been shown to lead to insulin and leptin resistance, stress, and inflammatory cascades within the hypothalamus. This provides further evidence that hypothalamic and circadian dysfunction can influence the progression of AD. Additionally, type 2 diabetes contributes to deposition of neurotoxic hormones and decreases Aβ clearance, further worsening AD pathology.[17]

Clinical studies suggest a correlation between sleep disruption and metabolic balance, which includes the relationship between sleep time and body mass index. Shortened sleep durations have been connected to reduced energy expenditure, which also affects thermogenesis and temperature homeostasis. Metabolic function may also disrupt certain phases of the sleep cycle, including SWS.[13]

Metabolic abnormalities seem to occur very early in AD, indicating that processes affecting energy systems could be important in the initial pathogenesis of AD. However, circadian variation within the metabolic system is very pronounced due to both internal and external mechanisms.[17] Highlighting metabolic dysfunction as an important risk factor of AD and identifying causes may improve understanding of the disease and potential therapeutic approaches.

The Immune System and Circadian Rhythms

It is proposed that Aβ plaques stimulate cells in the nervous system to secrete proinflammatory substances such as cytokines and chemokines that dysregulate the immune system and its ability to respond to external influences. These nervous system cells, microglia and astrocytes, contain intrinsic clocks that are regulated by circadian rhythms. The internal processes of these cells contribute to the regulation of the sleep-wake cycle.[13] In addition, significant alterations in sleep patterns resulted in an altered immune response in mouse models.[16]

Disruption of the circadian clock leads to a desynchronized response in the peripheral nervous system, and ultimately a higher immunological vulnerability. Immune and metabolic features are found to interact with

each other. Insulin, as well as melatonin, modulates neuroinflammation in AD pathology. Melatonin is vital for immune system function, regarded as an immunological buffer due to its specific anti-inflammatory and protective properties. Melatonin can also suppress immune response and inflammation when this reaction is excessive. It may also improve insulin resistance, decreasing the risk of AD.[17]

Stress and Circadian Rhythms

In addition to metabolic and immunologic changes, circadian stress responses as regulated by the hypothalamic-pituitary-adrenal (HPA) axis may also influence AD progression. This is due to the rhythmic regulation of glucocorticoids, steroid hormones involved in reducing inflammation and influencing metabolism. Glucocorticoids follow a circadian rhythm and levels peak slightly before the onset of the active phase, which occurs during the day for humans. Due to glucocorticoids being anti-inflammatory, production and release is important for normal cell activity and function. Decreased function of these factors is another example of circadian disruption. Glucocorticoid loss may lead to inflammation in brain areas and exacerbation of AD.[24]

Circadian influence from the SCN also includes regulation of the adrenal gland, which is responsible for production of several essential hormones. The adrenal clock is important for regulating circadian rhythms of the HPA axis[24] and thus implicates it as a potential factor in circadian dysfunction.

There is a level of communication between the HPA axis and the immune system, in which immune cells activate the HPA axis and glucocorticoids affect the viability and function of many different immune cell types. Glucocorticoids also have a stimulatory role on immune processes, but chronic stress is found to suppress the peripheral immune response. Stress-induced alterations in the rhythmicity of the HPA axis can alter immune responses and increase the risk of certain diseases.[24]

Discussion

Circadian Differences Among Populations

Most knowledge about the human circadian system is based on research in men, though certain characteristics are shown to differ between men and women. Women demonstrate an earlier timing of clock gene rhythms and a shorter average intrinsic circadian period.[25, 26]

Particularly with the sleep-wake cycle, women have an earlier timing of the melatonin rhythm, an earlier timing and longer duration of sleep, and an increased presence of SWS. This suggests nighttime impairment is greater in women than in men, since the accuracy of circadian rhythms deteriorates more in a longer period of wakefulness. Women are more affected by abnormal sleep schedules, demonstrating delayed biological sleep times, and seem to be at an increased risk of injury due to abnormal sleep patterns. [25, 26]

Because women are shown to need more sleep and sleep regulation, this may imply a difference in susceptibility to neurological diseases such as AD. This is in line with the fact that almost two-thirds of Americans with AD are women.[27] However, sleep and circadian differences may not fully account for this number, and a multitude of different factors may contribute to the larger proportion. Regardless, this disparity in circadian rhythms indicates that circadian and sleep treatments should reflect differences in gender.

The Vulnerability of the Hypothalamus in Alzheimer's Disease

The influential role of hypothalamic dysfunction in AD progression may be due to the nature of the hypothalamus as well as its function. Many hypothalamic signaling pathways affected in AD have been shown to improve synaptic function, protect against neuronal death, and inhibit Aβ and tau accumulation. Therefore, hypothalamic

dysfunction suppresses hormones and brain signaling mechanisms important for protecting against AD and maintaining cognitive function.[28] This highlights a bidirectional relationship between hypothalamic dysfunction and AD progression.

Additionally, hypothalamic vulnerability may be due to the involved and diverse function of the hypothalamus in virtually all body systems, such as metabolism, hormone signaling, and immune function. Any negative change in physiological functions may be reflected in the hypothalamus and thus potentially affect hypothalamic dysfunction.

Treatments and Interventions

Treatments and interventions aimed at regulating the circadian clock and sleep may show beneficial results due to the influence of these systems on AD progression, specifically in early stages. For example, physiological fluctuations triggered by changes in blood pressure and glucose levels can influence SCN neuronal behavior, and as a result circadian behavior.[13] Managing certain disorders interfering with circadian rhythms and sleep would allow affected systems to function properly, significantly reducing neuroinflammation as well as perpetuating amyloid clearance.[17, 21] Also, treating circadian dysfunction early in disease progression may be an appropriate course for preventing dysfunction in later stages. One way of doing this is leveraging certain zeitgebers and stimuli affecting the circadian clock that may significantly slow AD progression by reducing the influence of circadian dysfunction.

One such stimuli is scheduled exercise, which is proposed to prevent circadian disruption as well as stimulate circadian resynchronization. Meal timing and content also stimulates circadian rhythms, with poor meal timing and quality desynchronizing circadian rhythms and negatively affecting metabolic processes, both of which worsen AD pathology. Conversely, appropriate meal timing and quality can resynchronize circadian rhythms and therefore regulate metabolism.[17]

Bright-light therapy is a known treatment for circadian dysfunction and consequently AD. Consistent bright-light exposure has been shown to decrease daytime sleep and increase nighttime sleep, resulting in significantly improved sleep-wake cycles and even improvements in cognition for individuals in early stages of AD.[17]

Melatonin also proves to be a promising therapeutic target for AD due to its multiple beneficial effects, such as preventing mitochondrial dysfunction, inhibiting Aβ toxicity, and reducing the effects of circadian dysregulation. Melatonin also has antioxidant and neuroprotective properties, which may help in decreasing Aβ formation. Melatonin may also attenuate the formation of NFTs.[14]

Improving sleep quality is another way to reduce the effects of AD pathology. This can be done by keeping a regular sleep schedule, engaging in daily exercise, minimizing daytime napping, reducing caffeine and alcohol intake, and restricting the use of light close to bedtime. An especially important circadian disruptor is artificial light from electronic devices, which emits monochromatic blue light that activates ipRGCs. This artificial light reduces melatonin secretion, which in turn lowers the quality of sleep.[17]

Additionally, since the hypothalamus is affected early on in AD pathology and is responsible for the regulation of circadian rhythms in numerous risk factors of AD, factors contributing to hypothalamic dysfunction should be investigated and managed, such as nutritional deficiencies and causes of neuroinflammation.[29] Specifically, alterations to metabolic system, immune system, and HPA axis should be considered when observing the causes and factors of AD progression.

Conclusion

This paper investigated the role of circadian and sleep-wake dysfunction within the hypothalamus in AD. To conclude, there is a complex relationship between circadian rhythms and AD pathogenesis. Involvement of

circadian rhythms has been observed in the growth and progression of AD, and changes in sleep patterns caused by circadian dysfunction can help identify certain biomarkers in AD. The hypothalamus, which regulates circadian rhythms through the SCN, also contributes to AD progression. The hypothalamus is affected very early in AD pathogenesis, which is demonstrated in structural, pathological, and physiological changes. The hypothalamus is highly influential in AD due to protecting against certain biomarkers and interacting with systems involved in AD development. Since circadian and sleep alterations are observed in AD progression, a bidirectional relationship has been proposed due to both perpetuating the other's development. Other hypothalamic processes are involved in the dysfunction of circadian rhythms, which include metabolism, stress, and hormonal axes such as the HPA axis. Certain hormones produced by the hypothalamus follow a circadian rhythm and can exacerbate or improve AD pathology, such as melatonin, insulin, and orexin.

Potential therapeutics for circadian dysfunction in AD include bright-light therapy and melatonin. Circadian dysfunction may also be resynchronized by regulating certain stimuli, which includes appropriate exercise and meal timing. Because circadian rhythms vary for certain groups of the population, such as those in women and men, treatments should reflect this and be personalized to the individual. Based on this new avenue for understanding AD, further progress can be made to better treat patients with AD, opening pathways to new knowledge and therapeutics.

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