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Therapeutic Strategies Targeting the Serotonergic System and Circadian Rhythm in Alzheimer's Disease Treatment

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Abstract. Alzheimer's disease (AD) is a neurodegenerative disorder characterized by progressive cognitive decline, circadian rhythm disturbances, and loss of serotonergic function. While there is no cure for AD, emerging research suggests that targeting the serotonergic system and circadian rhythms may offer novel therapeutic avenues. Serotonin, a key neurotransmitter involved in regulating mood, cognition, and circadian rhythms, plays a critical role in maintaining brain function. However, serotonin levels decline with age and are further reduced in AD, exacerbating circadian disruptions and contributing to the disease's progression. This review explores the connection between the serotonergic system and circadian rhythm regulation in AD, examining the impact of serotonin depletion on the suprachiasmatic nucleus and its influence on amyloid-beta accumulation and tau pathology. Additionally, the potential therapeutic benefits of serotonin-targeted treatments, such as selective serotonin reuptake inhibitors and melatonin supplementation, are discussed. Restoring circadian and serotonergic balance may help delay AD onset and mitigate symptoms, though further research is needed to fully understand these mechanisms and develop effective interventions.

Keywords: Alzheimer’s disease, Serotonergic system, 5-HT receptor, Circadian rhythm.

1. Introduction

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter in vertebrates' central nervous system. It plays a crucial role in brain functions like learning, memory, and emotion regulation. It's also essential for basic physiology integration. [1]5-HT production begins with l-tryptophan transport from the bloodstream to the brain, converted by tryptophan hydroxylase in the brain. Despite its creation in a small subset of CNS (central nervous system) neurons, 5-HT affects the entire brain. [1] Serotonin is released at synapses from the axon of a pre-synaptic nerve and binds onto the serotonin receptor on the post synaptic neurons. Above certain threshold, the dendrite fires the electrical stimuli, then serotonin is sucked back to the SERT (Serotonin re-uptake transporter) for recycling. There are 7 types of 5-HT receptors in our body, and each receptor generally has 3 serotonin subtypes with different functions. The 5-HT1 receptor, located in the prefrontal cortex and hippocampus, controls neurotransmitter release and mood, anxiety, and aggression. It is involved in excitatory transmission and affects thought processes and sleep patterns. The 5-HT2 receptor affects mood, thought processes, and sleep. The 5-HT3 receptor impacts anxiety and gastrointestinal function. The 5-HT4 receptor affects gut motility and cognitive processes. The 5-HT5 and 5-HT7 receptors control circadian rhythm and neurotransmitter release.

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Alzheimer's disease (AD) is a brain ailment that gradually impairs thinking and memory abilities as well as the capacity to perform even the most basic tasks. AD accounts to more than 50 million patients in the world, yet there is no cure for the disease. Symptoms typically appear in mid-60s for late-onset patients, affecting memory-evolving brain parts like the entorhinal cortex and hippocampus, and the cerebral cortex, responsible for language, reasoning, and social behaviour. [2] The major features of AD include formation of amyloid plaques and Tau tangles in the brain and the loss of connections between nerve cells in the brain. Recent research indicates serotonin's role in cognition and memory, leading to increased interest in its therapeutic targets. Current drug discovery programs focus on the serotonergic system due to its close relationship with brain areas. However, no clear evidence exists for novel pharmacological entities [3,4].

This review is to explore the role of the serotonergic system in the progression of AD, with a particular focus on its influence on cognition, memory, and circadian rhythm regulation. By examining recent research on serotonin's involvement in AD pathology, including its interaction with amyloid plaques and tau tangles, this review aims to highlight potential therapeutic targets within the serotonergic system. The review also seeks to evaluate the current state of drug discovery efforts targeting serotonin receptors and pathways, while addressing gaps in evidence for novel pharmacological interventions. Ultimately, this review aspires to provide a comprehensive understanding of the therapeutic potential of serotonin modulation in mitigating AD progression.

2. The disruption of circadian rhythm in AD

Disruptions in circadian rhythms play a critical role in the progression of AD, particularly in the early stages of the condition. These disruptions are closely related to the dysfunction of the brain's central biological clock, specifically the suprachiasmatic nucleus (SCN) located in the hypothalamus. The SCN regulates vital physiological processes, such as the sleep-wake cycle, body temperature, and hormone secretion, by controlling circadian rhythms. Recent research by Faizan Ahmad and colleagues has revealed a precise molecular mechanism by which SCN regulates circadian rhythm. Reverb (NR1D1 and NR1D2), Period (PER 1-3), and Cryptochrome (CRY1 and 2) are negative feedback regulators that stifle the positive limb. In humans, the SCN aids in the synchronization of cellular oscillators throughout the body. The SCN receives light and dark impulses from the retina and further regulates it. It synchronizes the oscillations of the neurons' core clock, which is then translated into oscillatory synaptic output and sends signals to the various hypothalamic nuclei.

In AD, clock genes in peripheral tissues often become misaligned with the central clock. This misalignment leads to physiological dysregulation, including abnormalities in blood vessel function, hormone levels, and the expression and activity patterns of antioxidant enzymes [5]. Furthermore, circadian dysregulation may also exacerbate the neurodegenerative processes characteristic of AD. Subsequent loss of synapses and neurons (changes in neurotransmitters), the synthesis of amyloid-beta, aberrant tau protein phosphorylation, can all result in oxidative stress in AD. [6]

Although the more precise mechanisms connecting circadian rhythms to AD remain under investigation, evidence indicates that circadian disruptions may not only be an early indicator of the disease but also a significant factor in its advancement. Understanding this relationship is crucial for developing early intervention and treatment strategies. For example, therapies aimed at realigning circadian rhythms, such as melatonin supplementation or light therapy, may help slow the progression of AD and improve cognitive function in affected individuals. Further research is needed to clarify these mechanisms and explore novel therapeutic approaches targeting circadian regulation in AD.

3. The role of serotonin in AD

3.1. Serotonin Loss in AD and Aging

AD is associated with alterations in the serotonergic neurotransmitter system, which has been linked to emotional and cognitive dysfunction. Changes in serotonin levels, particularly in the cerebrospinal fluid (CSF), are correlated with decreases in overall serotonin, especially in the temporal and frontal cortex.

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Post-mortem studies of AD patients reveal significant losses of serotonin type 1 and 2 receptors, with a relationship observed between low serotonin levels and aggressive or depressive symptoms. Selective serotonin reuptake inhibitors (SSRIs) have been found to alleviate behavioural and cognitive symptoms in AD patients, with long-term antidepressant use showing potential to reduce dementia risk [7]. The loss of serotonin is also evident in normal aging and in neuropsychiatric conditions common in the elderly. This decline affects multiple aspects of the 5-HT (serotonin) system, including: The density of 5-HT-positive neurons in the raphe nuclei. 5-HT metabolism and corresponding serotonin levels in the central nervous system (CNS). The density of 5-HT projections across the brain and spinal cord. Expression of the 5-HT transporter (SERT) and 5-HT receptors [8]. After-mortem studies show a marked reduction in serotonergic neurons in the dorsal and median raphe nuclei of AD-affected brains. These regions are often riddled with amyloid plaques and neurofibrillary tangles [8].

3.2. Serotonin dysfunction and brain protein accumulation in AD

3.2.1. Impact on Amyloid-β (Aβ) accumulation

The aggregation of amyloid-β (Aβ) as toxic oligomers and plaques is a key pathological event in AD. Lowering Aβ levels has been a therapeutic focus to prevent this accumulation. Serotonin signalling appears to play a role in modulating Aβ metabolism. A study by Cirrito et al. examined the effects of serotonin signalling on brain Aβ levels in both human and mouse models of AD. In mice, administration of SSRIs led to a 25% decrease in brain interstitial fluid (ISF) Aβ levels. Direct infusion of serotonin into the hippocampus also reduced ISF Aβ levels, while inhibitors of the ERK signalling pathway reversed serotonin-dependent reductions in Aβ. Chronic treatment with citalopram resulted in a 50% reduction in brain plaque accumulation in mice [9]. Further human studies examined brain amyloid load in elderly individuals who had taken antidepressants within the past five years. Participants receiving antidepressant therapy had significantly lower amyloid loads, as assessed by Pittsburgh Compound B positron emission tomography imaging. A longer duration of antidepressant use correlated with reduced Aβ accumulation [9].

3.2.2. Impact on Tau protein aggregation

Although the direct relationship between serotonin and tau protein aggregation is still under investigation, studies suggest melatonin—a neurohormone linked to serotonin—affects tau aggregation. The pathological hallmark of AD, tau protein aggregation into neurofibrillary tangles (NFTs), has been a target for synthetic and natural small-molecule therapies. Research has demonstrated that melatonin inhibits the formation of higher-order tau oligomeric structures, though it does not significantly alter overall tau aggregation kinetics. Melatonin's cytoprotective and anti-aggregation effects have been modest, but it still shows potential as a therapeutic option in tauopathy [10].

3.3. Hormonal and metabolic changes associated with serotonin loss in AD

Melatonin, synthesized from serotonin, plays a crucial role in regulating circadian rhythms and gastrointestinal functions. The enterochromaffin (EC) cells in the gastrointestinal tract are primarily responsible for producing extraspinal melatonin [11]. Two enzymes, AANAT and HIOMT, catalyse the conversion of serotonin to melatonin during the night, a process controlled by the pineal gland. The interplay between serotonin and melatonin is critical for maintaining circadian balance [12].

Melatonin levels naturally decline with age and are further reduced in AD patients. Clinical trials have shown that melatonin supplementation can improve sleep quality, reduce sundowning (late-day confusion and agitation), and delay cognitive impairment. Its neuroprotective effects include inhibiting Aβ accumulation and oxidative stress in neuronal cells. Melatonin's structure-dependent interaction with Aβ prevents the formation of amyloid fibrils, though the exact mechanisms remain unclear [12]. Given the concurrent loss of serotonin in aging and AD, the decline in melatonin levels further facilitates Aβ generation and the formation of amyloid fibres [12-14].

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4. The function of serotonin and its receptors in circadian rhythms

Serotonin plays a crucial role in regulating circadian rhythms, particularly in controlling the sleep-wake cycle and modulating light-induced phase shifts. Ongoing research seeks to clarify the mechanisms by which serotonin contributes to these processes. It is believed that serotonin is primarily responsible for triggering phase shifts and inhibiting light-induced disruptions, thereby helping synchronize the body's internal clock with environmental rhythms. According to research by L.P. Morin, serotonergic input from the dorsal raphe nucleus to the intergeniculate leaflet (which projects to the suprachiasmatic nucleus, or SCN, via the geniculohypothalamic tract) and from the median raphe nucleus directly to the SCN is vital for circadian rhythm regulation [13].The 5-HT1A and 5-HT1B receptors, two subtypes of serotonin receptors, play complex roles in sleep-wake regulation, involving both presynaptic and postsynaptic activity in other neurotransmitter systems. These receptors provide inhibitory feedback to serotonergic raphe neurons, modulating the circadian rhythm's sensitivity to light [14]. Research indicates that stimulating postsynaptic 5-HT1A receptors, for instance through systemic injection of high-dose agonists, tends to enhance wakefulness while reducing sleep. Conversely, localized delivery of low-dose 5-HT1A agonists into the dorsal raphe nucleus promotes alertness while increasing REM sleep by disinhibiting mesopontine neurons involved in REM promotion.

Similarly, systemic administration of 5-HT1B receptor agonists significantly promotes wakefulness and reduces REM sleep, like the effects of 5-HT1A agonists. The proposed mechanism underlying this regulation involves the activation of presynaptic 5-HT1B receptors in the retina-hypothalamic tract, which attenuates light input to the SCN, reducing the circadian system's sensitivity to light [13].

In summary, 5-HT1A and 5-HT1B receptors are integral to circadian rhythm regulation, primarily by influencing the SCN's response to light and modulating melatonin production in the pineal gland. While their roles in state regulation and arousal are not fully understood, these receptors are part of a network of neurotransmitter systems that collectively sustain wakefulness and modulate the sleep-wake cycle. Further investigation is required to fully understand how these receptors influence circadian rhythms and overall arousal states.

5. Secretion as the bridge between circadian rhythm disruption and AD

The secretion of key hormones and neurotransmitters plays a crucial role in linking circadian rhythm disruptions to AD pathogenesis. While both melatonin and serotonin are independently important for the regulation of circadian rhythms and cognitive function, their secretion patterns form a dynamic feedback loop that integrates circadian biology with the neurodegenerative processes seen in AD. Understanding how this secretion process functions as a bridge between circadian dysregulation and AD progression can provide new insights into early intervention strategies.

5.1. The Role of Melatonin and Serotonin Secretion in Circadian Rhythm Disruption and AD

Melatonin and serotonin secretion are closely intertwined in the regulation of circadian rhythms, and disruptions in their secretion are key contributors to AD progression. Melatonin is essential for synchronizing the sleep-wake cycle with the external environment. Its secretion follows a circadian pattern that is tightly regulated by serotonin, the precursor to melatonin. Serotonin, in turn, is regulated by the light-dark cycle and plays a pivotal role in modulating mood, cognition, and sleep—all functions that deteriorate in AD.

In AD patients, both melatonin and serotonin secretion are impaired, leading to a breakdown in circadian regulation. Decreased melatonin levels not only disrupt sleep but also reduce its neuroprotective effects, which include inhibiting amyloid-beta accumulation and oxidative stress. At the same time, lower serotonin levels—common in aging and exacerbated in AD—further limit melatonin production, creating a feedback loop of worsening circadian dysregulation. This disruption in the secretion of both hormones directly contributes to the pathological processes in AD, including cognitive decline and neurodegeneration. Thus, the interconnected secretion of melatonin and serotonin forms a critical link between circadian rhythm disruptions and the progression of AD.

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5.2. The Feedback Loop Between Secretion and Circadian Dysregulation in AD

The interplay between melatonin and serotonin secretion forms a feedback loop that is disrupted in both circadian rhythm disorders and AD. As circadian rhythms become misaligned, serotonin levels decline, leading to reduced melatonin production and further disturbances in the circadian system. This vicious cycle not only aggravates cognitive decline but also promotes the pathological accumulation of amyloid-beta and tau protein, which are central to AD pathology. Thus, the breakdown of this secretion feedback loop is a key factor linking circadian rhythm disruptions to AD progression. In summary, the secretion of hormones like melatonin and neurotransmitters like serotonin serves as a critical link between circadian rhythm disruptions and AD progression. Understanding and manipulating these secretion processes may provide new strategies for managing AD, particularly through treatments aimed at restoring circadian and neurochemical balance.

6. Therapeutic Strategies to Regulate Circadian Rhythms in AD

Melatonin therapy has shown promise in treating circadian rhythm disruptions, particularly in AD, by improving sleep quality and reducing symptoms such as sundowning. Its neuroprotective effects, including reducing amyloid-beta accumulation and oxidative stress, make it a valuable option in early-stage interventions for AD. However, its effectiveness can vary, particularly in older adults, due to differences in absorption and potential drug interactions. Given the central role of serotonin in modulating melatonin production, exploring serotonin-targeted treatments, such as SSRIs, may offer an additional approach to regulating circadian rhythms and mitigating AD progression.

6.1. Potential drugs affecting serotonin receptors and their effectiveness

SSIRs is the major antidepressant drug that affects serotonergic system and has potential to treat AD. Inhibiting presynaptic reuptake of serotonin at the serotonin transporter is the main way that SSRIs work. This results in an increase in serotonin at the postsynaptic membrane in the serotonergic synapse. Predictive serotonin reuptake inhibitors have been shown to have a positive effect on pathophysiological biomarkers of AD, such as tau deposits, neurogenesis, and amyloid burden, based on data from animal studies. Studies conducted on individuals with a history of depression in humans also revealed that those receiving treatment with most selective serotonin reuptake inhibitors had a delayed onset of AD. Strong anticholinergic effects of paroxetine have been linked to higher mortality, mixed effects on amyloid and tau deposits in mice, and higher risk of developing AD in humans. [15] Because SSRIs affect plaque formation rather than plaque clearance, it is important to start using those antidepressants as soon as possible in people who are cognitively intact, ideally before plaque deposition starts. Human studies have successfully illustrated this, demonstrating that the longest SSRI treatment period significantly reduced the chance of developing AD and establishing the necessity of treating depression as a risk factor for AD.

6.2. Exploring alternative therapeutic strategies to restore serotonin and its receptor and regulate circadian rhythms

The primary enzyme responsible for the enzymatic breakdown of 5-hydroxytryptamine, or 5-HT, is monoamine oxidase (MAO), an enzyme that is bound to the mitochondria and needs Flavin adenine dinucleotide as a cofactor. The oxidative deamination of 5-HT is catalysed by MAO, which transforms it into 5-hydroxy-3-indolacetaldehyde (5-HIAL). Aldehyde dehydrogenase then converts 5-HIAL into 5-hydroxy-3-indolacetic acid (5-HIAA). [16] Serotonin levels can be naturally increased by consuming certain foods, engaging in physical activity, managing stress, and spending time in sunlight. Additionally, some herbal supplements, medications, and alternative therapies may help boost serotonin levels. However, there is no research available on methods to restore serotonin receptors once they are lost or impaired.

Future research on the serotonergic system in AD should aim to clarify the exact mechanisms by which serotonin and its receptors influence cognitive impairment, particularly how brain protein accumulation interacts with serotonin pathways. While serotonin levels can be restored through lifestyle

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changes and medications like SSRIs, current research has not found an effective method to regenerate or restore serotonin receptors, which degrade with age and AD progression. Additionally, it remains unclear whether circadian rhythm disruptions contribute to AD development or if the disease itself causes these disruptions, making this an important area for future investigation. Understanding these relationships could pave the way for more targeted therapies that address both serotonin signaling and circadian regulation in AD.

7. Conclusion

In conclusion, AD is a multifaceted neurodegenerative disorder marked by cognitive decline, circadian rhythm disturbances, and dysfunction within the serotonergic system. The role of serotonin in regulating mood, cognition, and circadian rhythms, alongside its involvement in the aggregation of amyloid-beta and tau proteins, makes it a crucial target for therapeutic intervention. Selective serotonin reuptake SSRIs show promise in alleviating symptoms and potentially slowing disease progression by modulating serotonin levels and reducing amyloid-beta accumulation. Additionally, restoring circadian rhythms through therapies such as melatonin supplementation may further mitigate AD symptoms. Despite these advances, significant gaps remain in our understanding of the precise mechanisms by which serotonin depletion and circadian dysregulation contribute to AD progression. Further research is essential to develop strategies that restore serotonin receptor function, prevent circadian disruption, and explore lifestyle factors that influence serotonin regulation. Ultimately, future therapeutic approaches integrating serotonin signalling and circadian rhythm regulation hold promise for delaying the onset and progression of AD, improving outcomes for individuals affected by the disease.

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