Melatonin as Treatment and Prophylaxis for Alzheimer's Disease

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Abstract

Alzheimer's is a very prevalent disease that has no true dependable and effective treatment. Through research and trials melatonin has been seen as a potential therapeutic option for both structural and behavioral changes in Alzheimer's. Studies have shown low levels of natural melatonin in CSF are a strong indicator of Alzheimer's Disease. This suggests melatonin could be used as a prophylactic measure as well as a treatment for slowing the disease's neuropathological changes. Results showed that melatonin improves circadian rhythm and sleep quality leading to more effective glymphatic clearing of free radicals, improving cognition, and decreasing behavioral disturbances.

Introduction

Alzheimer's disease is a neurodegenerative disease that affects over 55 million people worldwide.[1] Individuals with Alzheimer's develop dementia which leads to cognition and memory loss affecting their daily activities.[1] The diagnosis of Alzheimer's began in the early 1900's and continues to have limited effective treatments to slow progression or reverse effects of neurologic degeneration.[1] Genetic dispositions along with age-related changes such as oxidative stress, inflammation, and amyloid plaques deposited in the brain are thought to be the main causes of this devasting disease.[1]

Melatonin is a natural hormone produced by the brain to guide sleep and circadian rhythms.[2] The natural production of melatonin decreases with age therefore Alzheimer's patients may be at risk for lower levels. The glymphatic system which is activated during sleep plays an important role in neurological function, reduction of oxidative stress and buildup of misfolded proteins.[3] The goal of this review is to discuss the role of melatonin as a preventative measure in the development of Alzheimer's disease, as well as discuss if melatonin is an effective medication to decrease neurologic degeneration for those with preexisting Alzheimer's disease.

Pathophysiology of Melatonin

Melatonin (N-acetyl-5-methotryptamnie) is a natural hormone synthesized in the pineal gland.[5] Melatonin regulates circadian rhythms and clears free radicals; these physiologic functions improve immunity and inhibit oxidation of biomolecules.[5] Melatonin will function in the brain as a "free radical scavenger" and has antioxidant properties which play a protective role in neurodegenerative diseases.[6]

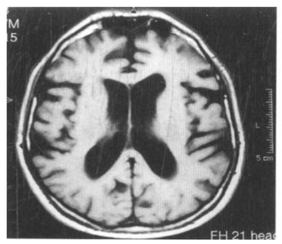
In Alzheimer's disease there is a decrease in serotonin, the precursor to melatonin, by dysregulation of noradrenergic innervations and upregulation of monoamine oxidase. Monoamine oxidase is responsible for the degradation of serotonin and norepinephrine in the central nervous system. This decrease in norepinephrine increases cerebrospinal fluid in the perivascular spaces of the brain, leading to dilation and disruption of the glymphatic systems ability to clear neurotoxic proteins.[5] The increase of REM sleep with the ingestion of melatonin could be indicative of an increase in glymphatic system activity.[7] Norepinephrine regulates Melatonin's release from the pineal gland, supplementing Melatonin in patients with Alzheimer's disease will override deficiency, while improving sleep time and quality that further supports the glymphatic system.[8]

Neurological Changes in Alzheimer's Disease

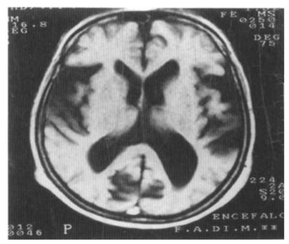
The glymphatic system moves cerebral spinal fluid into the brain parenchyma and functions to eliminate waste consisting of soluble proteins and metabolites.[3] Alzheimer's disease is characterized by an accumulation of neurotoxic proteins specifically, extracellular amyloid plaques. These amyloid plaques are composed of Amyloid-β and intracellular neurofibrillary tangles composed of hyperphosphorylated tau.[1] The neurofibrillary tangles of hyperphosphorylated tau are 3-4-fold higher in Alzheimer's patients than in healthy adult brains[1]. They are also responsible for the decline in cognitive memory and altered behavior witnessed in Alzheimer's disease.[1, 6] A dysregulation between the clearance and production of Amyloid-β leads to neurotoxicity, oxidative stress, inflammation, and apoptosis.[2] These changes decrease the number of neural cells and damage their ability to relay connections within the entorhinal cortex and hippocampus, the part of the brain responsible for memory.[2] The inability to clear the neurofibrillary tangles in the brain by the glymphatic system is hypothesized to be an initiating factor in Alzheimer's disease.[1]

The defective drainage of the glymphatic system in neurodegenerative diseases has been linked to the primary water channel that supports cerebrospinal fluid and interstitial fluid exchange. It is the Aquaphorin-4 water channel located in the central nervous system.[4] Aquaphorin-4 channel is responsible for the homeostasis of the brain and waste clearance during sleep. This finding is due to decreased natural levels of norepinephrine during sleep, allowing for expansion of the extracellular space and decreased resistance of flow into the glymphatic system.[5] Quiescent sleep is a stage of sleep without- rapid eye movements and this stage is characterized by slow oscillatory brain waves.[5] Slow oscillatory brain waves increase the amount of cerebrospinal fluid within the perivascular space of the brain, increasing the glymphatic clearance compared to an awake state.[5] Sleep disturbances such as decreased sleep time, and slow oscillatory brain waves seen in quiescent sleep occur early in the progression of neurodegenerative diseases.

A major genetic link in Alzheimer's disease is the elevated levels of apolipoprotein E (APEO). Apolipoprotein E also plays a role in dilating the perivascular spaces of the brain, and disruptions to the blood-brain barrier have been linked to the dysfunction of the AQP4 channel of the glymphatic system in both neurodegenerative diseases of Alzheimer's Disease .[4] With these findings, the glymphatic system may be a target for therapeutic treatment to slow the progression of Alzheimer's disease. Melatonin can improve the length of time in quiescent sleep and is linked to restored glymphatic system function by polarizing the aquaphorin-4 water channel.[6] Improving the function of the glymphatic system with the use of melatonin may decrease plaque accumulation, oxidative stress, and inflammation seen in Alzheimer's disease.



Patient NN



Patient ZZ

Fig. 1. Comparison of MNR of monozygotic twins with Alzheimer's disease of 8 years duration, one of them (patient N.N., left) treated with melatonin (6 mg/day) during 36 months. A generalized cortical atrophy was found in both patients, with a more important bitemporal atrophy and ventricular enlargement in patient .Z.Z (right) who did not receive melatonin.

Figure 2. Table of Melatonin Implementation and Sleep Studies in AD patients.

This table shows the results in sleep, structural or behavioral changes after various studies between AD patients, healthy patients, treatment with melatonin, or placebo/control.

Patient	Treatment	Structural Changes	Behavior Changes	Source
AD	6 mg Melatonin 36 months	-Cortical Atrophy -Decreased secretion of Amyloid Plaques	-FAST stage 5 -10/30 MMSE -Slight impaired speech	#12
AD	N/A (Placebo)	-Cortical Atrophy -Bitemporal atrophy and ventricular enlargement -Amyloid Plaques	-FAST stage 7b -0/30 MMSE -Severely impaired speech -Pacing -Sundowning -Insomniac	#12
Healthy	N/A	-Within normal limits of spindle sleep fibers	-Normal immediate memory recall	#10
AD	N/A	-Reduced fast spindle sleep fibers quantity and intensity	-Decreased immediate memory recall	#10
AD	3 mg Melatonin 4 weeks or 2.5 mg for 7 weeks	N/A	-Improvement of behaviors -Decrease in symptoms of depression, anxiety, hallucinations, irritability, apathy, agitation	#11
AD	N/A (Placebo)	N/A	-No improvement	#11

Discussion/Conclusion

Through the analysis of various research articles, it was discovered that melatonin plays a large role in Alzheimer's disease. Due to the decreased levels of serum melatonin found in AD patients, testing could be implemented in clinical practice and the diagnosis of Alzheimer's. The implementation of melatonin as a treatment or prophylaxis should also be considered. The increased sleep from melatonin supplementation could improve sleep spindle intensity in AD patients therefore improving the memory recall.[10]

Some studies have indicated that melatonin may not be useful in the treatment of the pathophysiological changes seen in the brain that result from Alzheimer's disease but is advantageous in the treatment of the psychopathologic behavior disturbances that come from Alzheimer's.[11] Though, this is contradicted in other research trials who state there are changes within the brain after melatonin implementation. The study from source 12 in figure 1 and 2 shows the comparison Alzheimer's Disease and the positive effects of melatonin on both structural and behavioral changes between two monozygotic twins. Therefore, this research would state there is both a behavior and cognitive aspect to the treatment of Alzheimer's with melatonin.

Future Directions

Further research could explore if melatonin is more beneficial in improving the physiologic changes in the brain or cognitive improvement in Alzheimer's disease and prophylaxis. In addition to more research conducted on the usefulness of melatonin in treatment of Alzheimer's, there should be trials exploring the effects of long-term melatonin use and if there are any safety hazards associated with prolonged exposure to the drug.[13] The implementation of these studies may further help conclude if the application of melatonin in a clinical setting would be recommended for the prophylaxis or treatment of Alzheimer's disease.

Sources

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