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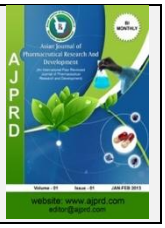

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Review Article

Role of Copper and Melatonin in the Pathogenesis and Therapy of Alzheimer's disease

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A B S T R A C T

Alzheimer's disease (AD) is a neurodegenerative ailment that results in dementia and the death of neurones. It also causes cognitive impairment. Neurofibrillary tangles and amyloid-beta (Aβ) plaques are two of the pathological findings associated with this condition. A study that was conducted not too long ago revealed that Copper (Cu) dysregulation plays a significant role in the aetiology of Alzheimer's disease (AD) by producing oxidative stress and increasing the aggregation of Aβ. In the meanwhile, melatonin, a neurohormone that possesses powerful neuroprotective and antioxidant properties, has garnered interest due to the possibility that it might be used as a therapy for Alzheimer's disease (AD). Within the scope of this review, a comprehensive assessment of the most current research on the intricate connections that exist between Alzheimer's disease, melatonin, and copper homeostasis is presented. We investigate how an excessive amount of copper might exacerbate the pathogenesis of Alzheimer's disease (AD), as well as how the unique properties of melatonin can mitigate these effects. Through the chelation of excess copper and the reduction of oxidative stress, melatonin is a potential chemical that has a dual approach to addressing major aspects of Alzheimer's disease. A better understanding of the interaction between copper dysregulation and the protective mechanisms of melatonin may lead to the development of novel therapeutic approaches, which holds the potential to improve the treatment of Alzheimer's disease (AD).

Keywords: Alzheimer's Disease; Copper; Melatonin; Neurofibrillary Tangles; Amyloid-Beta (αβ) Plaques.

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INTRODUCTION

Alzheimer's disease (AD), the primary cause of dementia, has rapidly become one of the most lethal diseases in the 21st century. This neurodegenerative illness, known as the "*Silver Tsunami*," causes brain dysfunction due to the progressive loss of neurons in the cortex and hippocampal regions (1). The most common early symptom is memory impairment and cognitive decline, which can impact behavior, speech, motor function, and visuospatial orientation. AD is rarely encountered alone with other neurodegenerative co-pathologies (2). Familial hereditary genetic mutations, such as Apolipoprotein E (APOE), presenilin-1 (PS1), presenilin-2 (PS2), and the amyloid precursor protein (APP), account for only 5% of documented instances of AD (3). The remaining 95% are irregular and mostly affect elderly persons. AD affects around 50 million people globally and is expected to triple by 2050 due to population aging (4). In Europe, the prevalence is estimated at 4.4% in people over 65, while in the US, it has reached 9.7% in those over 70 years old. Mortality rates are also increasing, making AD the sixth leading cause of death in the USA (5-7).

Researchers have identified limitations and challenges in using melatonin in Alzheimer's disease (AD) treatment, highlighting the need for further research to optimize its therapeutic potential. Adverse effects in clinical trials were often mild to moderate, self-limiting, or resolved quickly after treatment ended. Out of 50 papers, 26 found no significant adverse events, while 24 reported at least one serious adverse event. Uncontrolled melatonin consumption in children is a growing health risk (8-10). This study provides valuable insights into the dynamic interplay

between Cu, AD, and melatonin, adding to our understanding of melatonin's potential use as a therapeutic intervention. It serves as a valuable resource for researchers, clinicians, and policymakers, guiding future investigations and clinical trials.

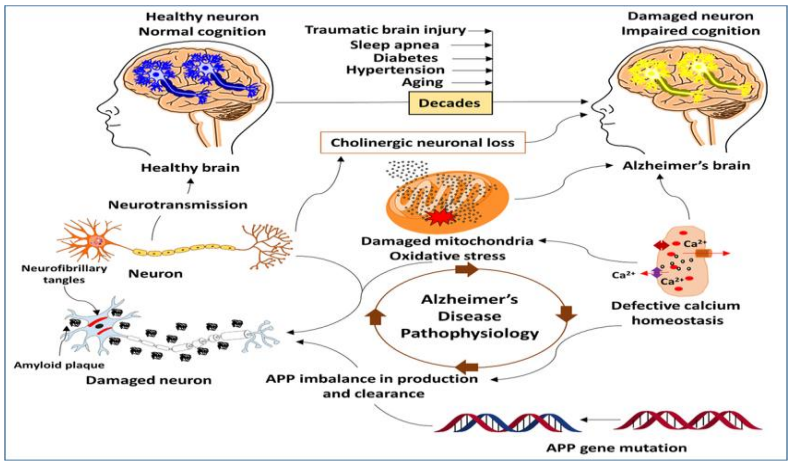

Figure 1: Pathophysiology of Alzheimer's disease (AD)

Role of Copper in the Pathogenesis of Alzheimer's disease (AD)

Cu is a crucial trace element in the central nervous system, playing a vital role in neurological processes. It is a necessary metal ion for biological functioning, but excessive amounts can be hazardous. The recommended daily allowance (RDA) for Cu is between 0.9 and 1.3 mg, which is the consumption amount required for 97-98% of the population (11).

Consuming 2-3 mg daily is safe and prevents Cu insufficiency. Cu is abundant in the cell bodies of cortical pyramidal and cerebellar granular neurons, basal ganglia, hippocampus, cerebellum, and synaptic membranes. Cu has a direct or indirect etiology connected to several neurological disorders, including aceruloplasminemia, Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's disease, Menkes disease, occipital horn syndrome, Parkinson's disease, prion disease, and Wilson disease (12).

Cu is essential for understanding the physiology of the central nervous system and is believed to be mediated by brain cell lineages other than neurons, such as capillary endothelial cells, which are linked to the development of AD neuropathology and its altered distribution (Figure 2). Copper ions play a crucial role in these pathological processes, particularly through crosslinking mechanisms. The interaction between copper and Aβ promotes oxidative stress, leading to neuronal damage and cognitive decline (13).

Tau proteins, crucial for maintaining microtubule stability, can undergo abnormal phosphorylation and aggregation in AD. Cu may influence tau pathology by altering its conformation and promoting toxic oligomerization. Understanding these interactions is crucial for developing therapeutic strategies to mitigate the effects of metal dysregulation in AD (14). Cu chelating medications, which eliminate amyloid deposits in transgenic mice's brains and stop oxidative stress in senile plaques and neurofibrillary tangles, provide evidence for the critical involvement of copper in the etiopathogenesis of AD (15).

Two key explanations for Cu disturbance in AD are the loss of functional Cu from protein-bound pools, which reduces energy generation and oxidative stress management, and the rise in redox-toxic function, reflected by a bigger pool of loosely connected Cu to proteins (16).

Transition metals like iron, zinc, and copper are essential for various bio-processes and brain neuronal functions. Alzheimer's disease (AD) patients have higher levels of these metals in their amyloid plaques compared to healthy brains (17).

Cu, an essential micronutrient, accelerates electron transport to key enzyme pathways and is crucial for aerobic processes. It accounts for 7.3% of the body's total Cu content and can significantly impact brain function. High Cu levels have been linked to various neurological conditions, and chronic exposure can reduce depression-like behaviors and anxiety (18). There are conflicting reports about Cu concentrations in AD, with some suggesting a link between AD manifestation and Cu deficiency. Most studies reveal a higher level of Cu in AD, indicating the need to reduce it (19).

Cu can also contribute to the formation of Aβ plaques, a hallmark of AD, and generate reactive oxygen species (ROS), leading to oxidative stress and potentially causing neuronal damage. However, the exact mechanisms by which Cu contributes to Alzheimer's pathology remain unexplored (20).

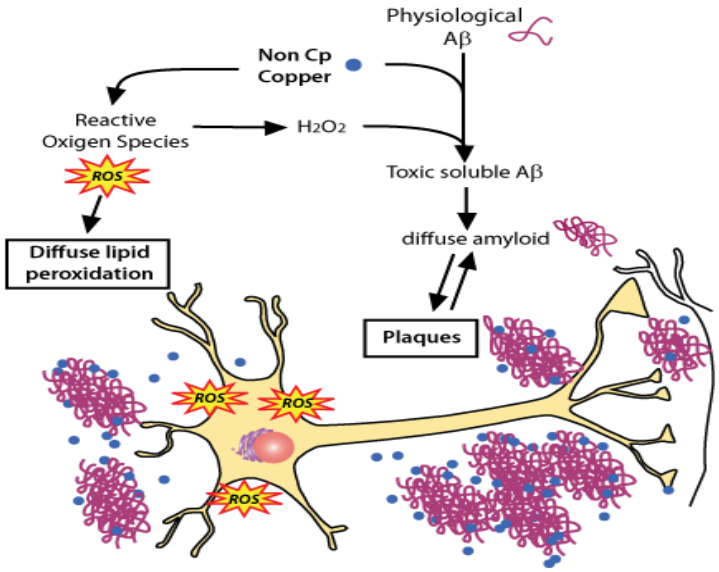

Figure 2: Role of Copper in the Pathogenesis of Alzheimer's disease (AD)

Role of Melatonin in the Management of Alzheimer's disease (AD)

Melatonin, a tryptophan metabolite, is primarily found in the pineal gland in animals and is found in bacteria, plants, and unicellular eukaryotes (21). It has evolved to serve various functions and is produced in various cells, tissues, and organs. Melatonin levels in the cerebrospinal fluid (CSF) of older individuals with early neuropathological AD-related alterations in the temporal cortex are lower than in young control subjects (22).

Melatonin has been studied for its potential therapeutic implications in Alzheimer's disease (AD), particularly in modulating sleep abnormalities (Figure 3). Melatonin supplementation has been proven to increase sleep quality and decrease overnight awakenings, improving overall sleep-wake patterns and cognitive function (23).

Melatonin also has powerful antioxidant and anti-inflammatory capabilities, scavenging free radicals, protecting neurons from oxidative damage, and regulating immunological responses to minimize inflammation (24). These neuroprotective properties make it an excellent option for managing neurodegenerative conditions like AD. Additionally, the antioxidant properties of melatonin may lessen neuronal damage caused by tau tangles and Aβplaques in AD (25).

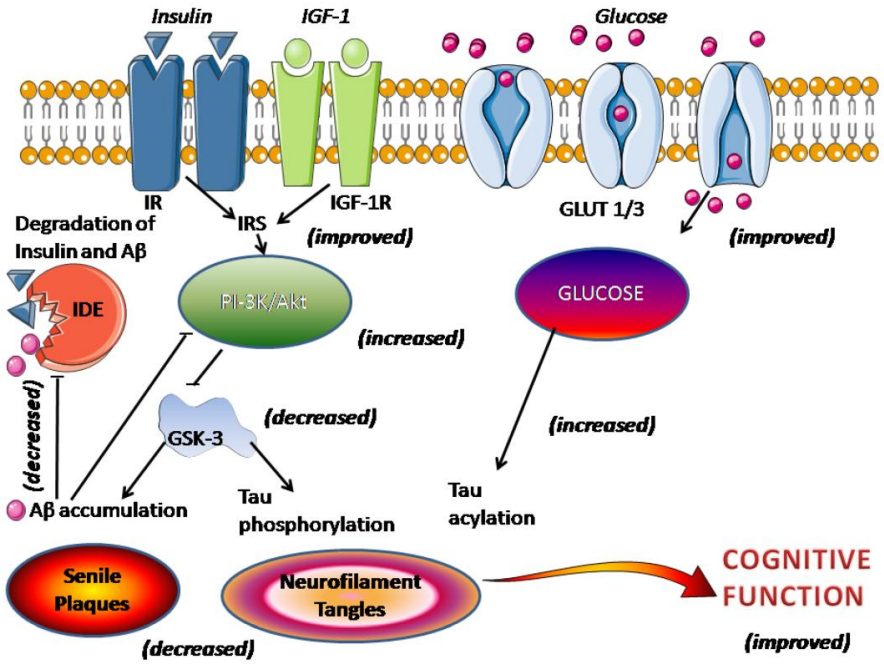

Figure 3: Role of Melatonin in the Management of Alzheimer's disease (AD)

Melatonin is a natural active molecule with strong antioxidant properties that protects nerve cells. Its levels rise from birth, peaking during teenage or puberty, and fall with age, with elderly people exhibiting the lowest levels (26). Age-related decreases in melatonin synthesis are thought to be a major risk factor for Alzheimer's Disease (AD) (27).

In healthy individuals, melatonin levels are lowest during the day and highest at night. Circadian disturbance and irregular sleep-wake cycles are strongly linked to the advancement of AD (28-30). Patients with AD have lower levels of melatonin in their serum and cerebrospinal fluid (CSF), as well as a loss of melatonin's circadian pattern (31).

Melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2) are two distinct high-affinity membrane receptors via which melatonin exerts some of its functions in mammals. The hippocampal regions of AD patients have been shown to exhibit elevated MT1 immunoreactivity and decreased MT2 immunoreactivity (32-34). Melatonin has been demonstrated in clinical trials to enhance mood and cognitive function in Alzheimer's patients. One target of AD treatment is inhibition of tau hyperphosphorylation.

Melatonin effectively reduces the hyperphosphorylation of tau caused by wortmannin (35). Haloperidol, an inhibitor of 5-hydroxyindole-O-methyltransferase, was injected into the brains of rats to stop changes in tau phosphorylation that would occur from a decrease in melatonin. Melatonin production inhibition not only caused rats to have impaired spatial memory but also increased tau phosphorylation and decreased PP-2A activity (36).

In experimental AD animal models, melatonin may interfere with the development of plaques and tangles, two pathological markers of AD. Melatonin can also improve synaptic plasticity and connectivity in brain circuits affected by AD. Oral melatonin therapy (0.04 mg/kg/day) dramatically improves synaptic function in sporadic AD (OXYS) rats, as seen by increased synapsin I and PSD-95 levels (37).

Melatonin is more beneficial than other antioxidants due to its amphiphilic nature. Other antioxidants have a limited solubility and are hydrophilic or lipophilic, such as glutathione, flavonoids, and vitamins C and E. Due to its antioxidant properties, it prevents free radical overproduction and reduces neuronal damage caused by various pathogenic processes (38). However, melatonin can also indirectly effect by enhancing the body's natural antioxidant defenses, which include glutathione peroxidase (GSH-Px), catalase, and SOD, which are all downregulated in AD (39-42). In conclusion, melatonin has been shown to lessen the impact of several AD diseases, including impaired neurogenesis and neuroinflammation and oxidative stress. All disorders associated with AD can be affected by melatonin overall.

Conclusion and Future Perspective

This review sheds light on the complex interaction that exists between copper dysregulation, Alzheimer's disease, and melatonin by concentrating on significant biochemical relationships and potential therapies associated with these conditions. By boosting oxidative stress and Aβ aggregation, an imbalance in copper in Alzheimer's disease (AD) serves to worsen neuronal damage. Melatonin is a well-known chemical that is both neuroprotective and antioxidant, and it has shown a great deal of promise in potentially lowering the neurotoxicity that is induced by copper.

Because of its ability to chelate copper and reduce oxidative damage, melatonin has the potential to be used as a therapy for Alzheimer's disease. The antioxidant effect of melatonin and the modulation of copper work together to address crucial pathogenic aspects of Alzheimer's disease in a dual approach. Melatonin has been shown to have the ability to greatly reduce oxidative stress and Aβ aggregation, which may therefore have the effect of delaying the advancement of the condition and improving cognitive function. This is supported by research conducted in preclinical settings. In spite of the fact that preclinical results have been encouraging, further clinical studies are necessary to validate the safety and efficacy of melatonin in Alzheimer's disease patients.

In the future, research should focus on refining treatment procedures, including dosage and delivery methodologies, as well as conducting comprehensive evaluations of patients' copper levels. This will allow for the creation of individualised treatment programs. Overall, it appears that this review has a lot of promise for the creation of innovative treatments for Alzheimer's disease.

Conflict of Interest

None

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