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Melatonin Improves Cognitive Impairment in Alzheimer's Disease

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Melatonin is synthesized in the pineal gland, retina, and organs. Melatonin has a variety of physiological functions on free radicals, circadian rhythms, immune system. In addition, melatonin is relevant for various pathologies in central nervous system disorders such as cerebral ischemia and Alzheimer's disease (AD). Particularly, AD has hallmarks including both aggregation of senile plaques derived from amyloid beta peptides and neurofibrillary tangles, especially in hippocampus or cerebral cortex relevant to learning and memory. In addition, insulin signal dysfunction resulted in cognitive decline is a typical pathology in AD brain. Decreased melatonin in cerebrospinal fluid is observed in AD patients. Melatonin has the ability to regulate amyloid precursor protein metabolism and prevent Aβ pathology. Moreover, melatonin is involved in insulin secretion in animals and humans and melatonin receptor deficiency influences insulin resistance in brain. In conclusion, melatonin contributes to improvement of learning and memory processing in AD. Thus, melatonin may serve as a potential therapeutic factor for cognitive decline in AD. Here, we aim to summarize recent studies that suggest the relationship between melatonin and cognitive impairment in AD.
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Key Words Melatonin, Alzheimer's disease, Amyloid beta, Insulin resistance, Cognitive impairment.

Introduction

Melatonin is a hormone synthesized and secreted in the pineal gland and in a number of peripheral organs and tissues.[1,2] Melatonin has a variety of physiological functions including clearing free radicals, regulating circadian rhythms, improving immune responses, modulating autophagy, and regulating insulin signal pathway in the central nervous system (CNS).[3-10] By virtue of its amphiphilicity, melatonin can easily cross the blood-brain barrier[11,12] and can enter the CNS and the cerebrospinal fluid (CSF) via the choroid plexus.[13] In Alzheimer's disease (AD) patients, decreased melatonin in CSF and the loss of melatonin diurnal rhythm are observed.[14-19] Several studies suggest that a reduced CSF melatonin level serves as an early marker for the very first stages of AD.[14,15,19] The action of melatonin is transmitted through the activation of two specific transmembrane receptors, namely melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2).[20-24] These melatonin receptors are strongly involved in insulin pathway.[25-27] Previous studies demonstrated that cognitive decline in AD relates with amyloid beta (Aβ) aggregation and insulin signal dysfunction.[25,28-34] Melatonin decreases in patients with AD and melatonin treatment enhances the various pathologies in patients with AD.[14,15,35] Specifically, melatonin reduces Aβ-induced learning and memory impairment in rats and human by inhibiting aggregation of Aβ.[36-39] In addition, melatonin is involved in insulin signal pathway and improves insulin resistance in AD.[27,28,40] In conclusion, melatonin contributes to improvement of cognitive impairment in AD.[41,42] Thus, melatonin is a potential target to cure learning and memory dysfunction in AD.

The Importance of Melatonin Receptor in Alzheimer's Disease

Melatonin controls various physiological functions by binding to the specific G protein-coupled receptors, MT1 and MT2 which are widely distributed in the CNS.[25] In addition, MT1 and MT2 express in the islet of Langerhans of rats[20] and humans[21] and involve in glucose regulation in other organs such as mouse hepatocytes.[22-24] In AD patients, Savaskan et al. demonstrates that MT2 expression decreases and MT1 expression increases in the hippocampus and also suggests that two melatonin receptor subtypes appear to be differentially affected by the course of AD.[43-45] Mitochondrial dysfunction is commonly

observed in postmortem brains of AD patients and contributes to cognitive dysfunction in AD patients.[46] The MT2 signaling contributes to the restoration of Aβ-mediated mitochondrial dysfunction. Treatment that stimulate MT2 signaling is beneficial for restoring mitochondrial function in AD and for delaying progression of cognitive dysfunction in AD.[47] Hence, melatonin receptors are strongly relevant for cognitive dysfunction in AD.

The Relationship between Melatonin and Aß Pathology

Aβ, composing 39-43 amino acid residues derived from amyloid precursor protein (APP), plays a crucial role in the pathogenesis of AD.[48,49] Aβ also regulates insulin signaling in the brain. Soluble Aβ binds to the insulin receptor and disrupts its signaling capacity and induces neuronal insulin resistance in AD.[50] Insulin like growth factor 1 administration results in decreased Aβ levels in brains of AD mouse models accompanied by elevated Aβ levels in the CSF.[51] Administration of melatonin efficiently attenuates Aβ generation and deposition both *in vivo*[52,53] and *in vitro*.[38,39,54,55] Melatonin inhibits Aβ generation in mouse neuroblastoma N2a cells harboring APP695.[39,56] Melatonin interacts with Aβ40 and Aβ42 and interrupts the progressive formation of β-sheet and amyloid fibrils.[37,57,58] In addition, PKC activity increases soluble APP secretion and involve the activation of the secretases that mediated APP cleavage. Several studies indicate the inhibitory regulation by GSK-3 inhibition on Aβ generation.[59-61] The inhibition of GSK-3 and up regulation of c-Jun *N*-terminal kinase resulted in elevated matrix metalloprotease activity and increased degradation of Aβ.[62] Assuming that melatonin treatment arrests AD by targeting the activated GSK-3β,[63] melatonin regulates APP processing through the PKC and GSK-3 pathways known as the signal pathway increasing Aβ generation. Thus, melatonin has the ability to regulate APP metabolism and prevent Aβ pathology in AD.

The Relationship between Melatonin and Insulin Resistance

In AD, brain insulin resistance was demonstrated and was associated with clinical symptoms of cognitive decline.[32] Patients with AD show lower insulin levels in CSF, higher plasma insulin levels, and reduced CSF to plasma insulin ratios compared to healthy controls.[40] Insulin degrading enzyme knockout mice also have reduced insulin in brain as well as muted degradation of Aβ and insulin in brain.[29,64,65] Several studies demonstrate that melatonin influences insulin secretion in animals.[66-68] Robeva et al. confirmed a significant relationship between melatonin and insulin levels in patients with multiple sclerosis.[69] Previous studies also demonstrates that melatonin receptor deficiency influences on insulin signal pathway in knock-out mouse models with targeted deletions of MT1, MT2 and MT1/MT2 (double-knockout) receptors.[70,71] In addition, altered regulation of insulin secretion and glucose homoeostasis has been detected in melatonin receptor knockout mice.[23] Hence, melatonin is associated with insulin resistance in AD brain.

The Therapeutic Effect of Melatonin for Cognitive Impairment in AD

Recent studies show the evidences that melatonin plays an important role in modulating learning and memory processing.[72-75] Several studies indicate that melatonin treatment protected against cognitive impairment in a transgenic mouse model of AD.[41,76] In both rat models and human studies, acute insulin administration reliably improves learning and memory function.[28,30,31] Insulin also regulates the expression of the neurotransmitters such as acetylcholine and norepinephrine influencing cognition.[77,78] Further, insulin acts to increase cortical cerebral glucose metabolism in brain regions important for learning and memory.[79] As mentioned relationship between melatonin and insulin, melatonin modulates insulin signal mechanism and finally contributes to learning and memory dysfunction in AD. Melatonin administration is also reported to attenuate Aβ-induced learning and memory impairment in rats, along with a significant decrease in positive glial cells expressing NF-κB-induced IL-1β in addition to complement 1q in hippocampus.[36] Melatonin supplementation slows down the progression of cognitive impairment in AD patients.[42,80] Melatonin is involved in memory formation in the hippocampus[5] and structural remodeling of synaptic connections during memory and learning processes.[81] In conclusion, melatonin attenuates learning and memory dysfunction in AD.

Conclusions

Melatonin has a variety of physiological functions in the CNS. In AD, melatonin has the ability to regulate APP metabolism and prevent Aβ pathology. In addition, melatonin is involved in insulin signal pathway and improves insulin resistance in AD brain. By virtue of these effects, finally, melatonin protects against cognitive impairment in AD. Hence, melatonin is a potential therapeutic target to improve cognitive impairment in AD.

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