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Genetic Links Between Melatonin and Neurological Diseases

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1. Abstract

Emerging evidence demonstrates the potential neuroprotective function of melatonin against neurodegenerative diseases. In a recent genome-wide association study for melatonin secretion, we identified five genetic loci associated with melatonin secretion, including *ZFHX3*, *GALNT13*, *GALNT15*, *LDLRAD3*, and *SEPP1*. Here we review the biological function of these genes in respective of neuroprotection. The *ZFHX3* gene encodes a transcription factor highly expressed in the suprachiasmatic nucleus. Mutation of *Zfhx3* in mice modulates circadian rhythm through direct interaction with the AT motifs of downstream circadian genes. ZFHX3 also activates ATM, a kinase that activates multiple downstream proteins important for DNA repair. The activation of ATM in cytoplasm protects cerebellar neurons from genotoxic damage. GALNT13 and GALNT15 are implicated in mucin-type O-glycosylation, but whether they have a role in neurodegenerative diseases is to be elucidated. The *LDLRAD3* gene belongs to the low-density lipoprotein receptor gene family. LDLRAD3 associates with C99, the β-secretase product of amyloid precursor protein, which may shift the non-amyloidogenic α-secretase pathway to the amyloidogenic β-secretase pathway. In addition, C99 accumulation in neurons contributes to neuronal death. C99 is degraded through the endosomal-lysosomal pathway and the association of LDLRAD3 with C99 may modulate the degradation of C99 and accumulation in neurons. The *SEPP1* gene encodes the selenoprotein P, a transporter of selenium for maintaining the selenium pool, which is subsequently taken up by neurons via the apolipoprotein E receptor 2. Selenium is the essential component of many anti-oxidative proteins, such as glutathione peroxidases and thioredoxins. Mutation of *Sepp1* causes extensive brain damage, including poor motor coordination, impaired spatial learning, cognitive decline, and increased tau phosphorylation. These data provide a genetic link between melatonin and neurodegenerative diseases.

2. Introduction

Melatonin has received increasing attention beyond its conventional role in circadian rhythm because of its potential protective function for neurodegenerative diseases [1-8]. The biological pathways for its neuroprotective action include anti-inflammation, anti-oxidative stress, anti-excitability activity through glutamate and gamma-aminobutyric acid (GABA) receptors, improvement of mitochondrial functions, alternation of neurotransmitters, and modulation of apoptosis and autophagy [9-20]. Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) are mostly irreversible. However, emerging evidence shows that melatonin potentially reverses their symptoms [1,9-20]. The neuroprotective action of melatonin has been extensively reviewed and is beyond our scope of this mini-review.

In a recent genome-wide association study (GWAS) for melatonin secretion, we identified five genetic loci associated with melatonin secretion, including *ZFHX3, GALNT13, GALNT15, LDLRAD3*, and *SEPP1* [21]. Here we focused on the biological function of these five genes in the pathogenesis of neurodegenerative diseases and other neurological diseases.

2.1 ZFHX3

The *ZFHX3* gene encodes a zinc finger homeobox 3 transcription factor and the human cardiac Na^+ channel (Nav1.5). ZFHX3 is highly expressed in the suprachiasmatic nucleus (SCN), a small group of hypothalamic nerve cells located in the anterior part of the hypothalamus [22]. The SCN regulates circadian rhythm by a series of transcription-translation feedback loops that manage the periodic expression of the clock genes [22]. SCN processes input from environmental signals, and then SCN transmits temporal response through downstream signals for physiological reactions, such as sleep-wake, body temperature, and locomotor activity.

A dominant missense mutation of *Zfhx3*, termed "short circuit" (Zfhx3Sci) accelerates circadian rhythms and modulates retinal sensitivity to light in mice through direct interaction with the AT motifs of downstream genes [23,24]. Inducible or hypothalamus-specific knockout of *Zfhx3* in mice also caused abnormality in the light-dark cycle [25, 26]. These data indicate a crucial role of ZFHX3 in circadian rhythm (Figure 1).

Furthermore, ZFHX3 is involved in cell cycle regulation, development, and cellular differentiation. ZFHX3 activates ATM (ataxia telangiectasia, mutated), a kinase that phosphorylate multiple downstream proteins to regulate cell cycle arrest, repair of double-stranded DNA breaks, apoptosis, and autophagy. The activation of ATM in cytoplasm protects cerebellar neurons from oxidative stress and shows progressive loss of deep cerebellar nuclei neurons in the cerebellum in mice [27]. ZFHX3 was also shown to be required for differentiation of neurons including the medium spiny neurons in the striatum expressing dopamine receptors [28]. These data imply that ZFHX3 is involved in cerebellar function and the dopaminergic pathway (Figure 1).

2.2 GALNT13 *and* GALNT15

In the GWAS for melatonin secretion, we identified genetic loci within *GALNT13* and near *GALNT15* [21]. Both genes belong to the UDP-GalNAc: polypeptide N-acetylgalactosaminyltransferase family important for mucin-type O-glycosylation [29-31]. Mucin-type O-glycosylation proximal to β-secretase cleavage site has been shown to affect amyloid protein precursor (APP) processing and the accumulation of amyloid-β peptides (Aβ) [32]. Glycosylation also influences several biological processes in the central nervous system, such as cell adhesion, signal transduction, molecular trafficking, and neuronal differentiation. It has been implied to be involved in the pathogenesis of AD, PD, HD, multiple sclerosis, and amyotrophic lateral sclerosis [33] (Figure 1). However, the direct link between these two genes and neurodegenerative diseases is currently unknown.

2.3 LDLRAD3

The low-density lipoprotein receptor gene family encode a class of structurally related cell surface receptors that is most commonly associated with cholesterol homeostasis. Low density lipoprotein receptor class A domain containing 3 (*LDLRAD3*) is one of the top five differentially expressed microglial genes that are related to familial AD [34] and increased *LDLRAD3* expression in microglia suggested that lipoprotein metabolism may contribute to pathogenic APP processing and amyloid deposition [35]. The Aβ peptide, produced through sequential cleavage of the β-amyloid precursor protein (APP) by β- and γ-secretases, has also been postulated to be a hallmark of AD [36].

LDLRAD3 is found in microvascular endothelial cells and neurons of the cortex and hippocampus. Solid-phase binding assays that demonstrated that LDLRAD3 did not bind to the soluble APP fragment (sAPPα) released after α-secretase cleavage. In contrast, LDLRAD3 associate with C99, the

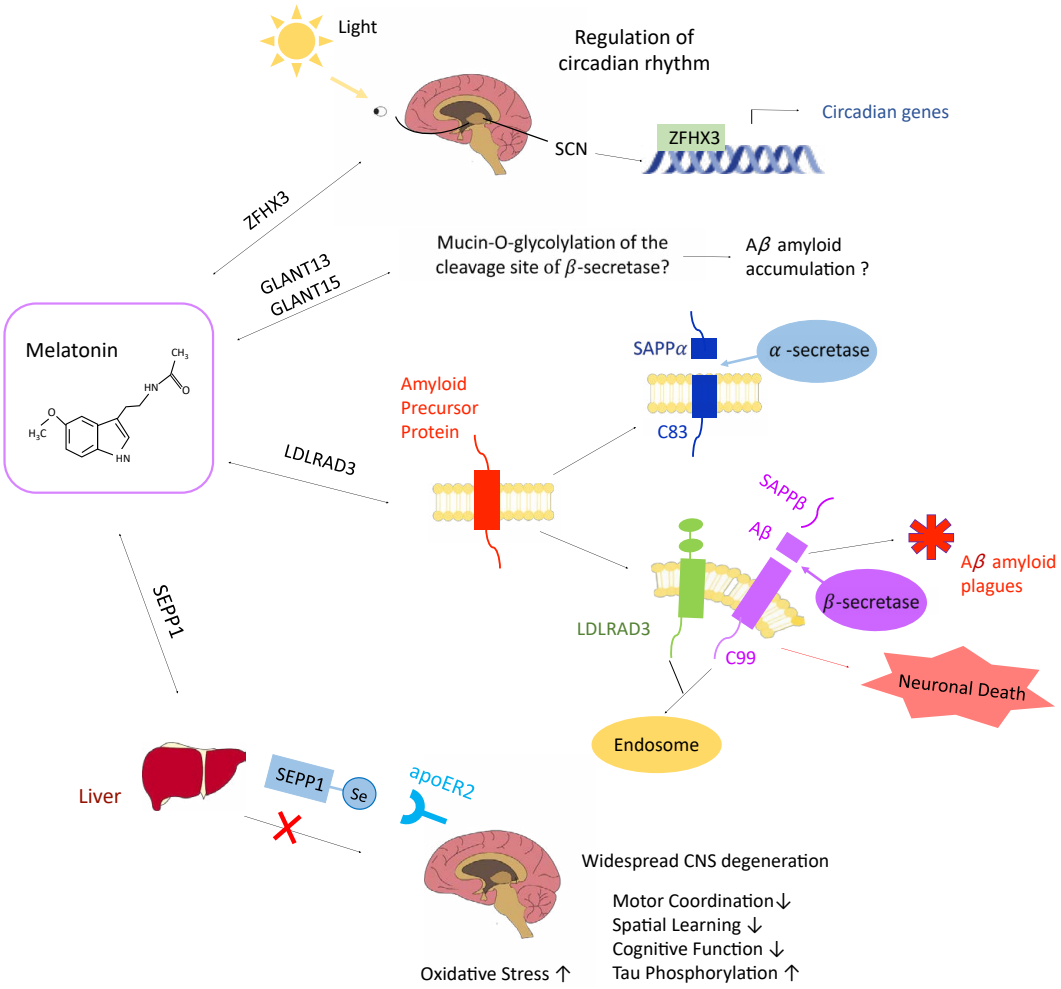

Figure 1.A graphic summary depicting the mechanism by which *ZFHX3*, *LDLRAD3*, *GALNT13*, *GALNT15*, and *SEPP1* were related to neurodegenerative diseases and neurological dysfunction.

β-secretase product of APP. Pulse-chase experiments confirm that LDLRAD3 significantly decreases the cellular half-life of mature APP, suggesting the association of LDLRAD3 with C99 may shifting the α-secretase pathway to the β-secretase pathway, resulting in enhanced Aβ production [37]. Growing evidence also demonstrated that C99 accumulation in neurons contributes to neuronal death in AD [38]. C99 is degraded through the endosomal-lysosomal pathway [39]. The association of LDLRAD3 with C99 may influence the degradation of C99 and accumulation in neurons.

Many LDLR family members act as receptors for apolipoprotein E (APOE), whose are also strongly associated with AD, further implicating the involvement of LDLR family members in AD [40] (Figure 1).

Venezuelan equine encephalitis virus (VEEV) is a neurotropic alphavirus transmitted by mosquitoes that causes severe encephalitis and death in humans. Gene editing of mouse *LDLRAD3* or human *LDLRAD3* results in markedly attenuated viral infection of neuronal cells, which is restored upon complementation with *LDLRAD3*. LDLRAD3 binds directly to VEEV particles and enhances virus attachment and internalization into host cells [41]. A cryo-electron microscopy reconstruction revealed the complex of VEEV virus-like particles and the ectodomains of *LDLRAD3*. Atomic modeling of this interface is supported by mutagenesis and anti-VEEV antibody binding competition assays [42].

The outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created a huge global crisis. The virus primarily targets lipid-producing cells due to viral tropism [43]. LDLRAD3 was one of the functional receptors for SARS-CoV-2 by a genome-wide barcoded-CRISPR screen. All these membrane proteins bind directly to spike's N-terminal domain. Their essential and physiological

roles have been confirmed in either neuron or liver cells. In particular, LDLRAD3 mediates SARS-CoV-2 entry and infection in an ACE2-independent fashion. The identification of the novel receptors and entry mechanisms could advance our understanding of the multi-organ tropism of SARS-CoV-2[44]. Besides providing natural veils for viral materials against host immunity, the inherent properties of some of these endogenous lipid particles to traverse the blood-brain barrier (BBB) also offer alternative routes for SARS-CoV-2 neurotropism. Importantly, virus-driven neurological aberrations mediated by HDLs and exosomes are fueled by lipid rafts, which are implicated in the production and transmigration of these lipid particles across the BBB [43].

2.4 SEPP1

Selenocysteine is recognized as the 21st amino acid, and is the component of many antioxidant selenoproteins including glutathione peroxidases and thioredoxins, which protect cells against oxidative damage [45]. SEPP1 (Selenoprotein P), a transporter for selenium, and its receptor, apolipoprotein E receptor 2 (apoER2) are essential for retaining selenium in the brain [46,47]. SEPP1 is mainly produced by hepatocytes and is distributed to peripheral tissues to main selenium pool, which is subsequently taken up by neurons via the apolipoprotein E receptor 2 [47,48]. A study has shown that *Sepp1*-knockout mice lost weight and developed poor motor coordination fed a basal diet supplemented with 1.0 mg selenium/kg [49]. Another study showed that Sepp1-deficient mice fed a diet containing selenium at or below the recognized dietary requirement of 0.10 mg/kg developed motor dysfunction including wide stance, waddling gait, walking backward, hopping gait, tense rear legs, uncoordinated running episodes, inability to right from a lying position, hyperactivity with extended limbs, and inability to walk [48]. Sepp1-deficient mice had impaired performance on standardized tests including stride length, pole climb, and rotarod tests. Raising the dietary selenium supplement to 0.25 mg/kg prevented the impairment [48, 49] (Figure 1).

Furthermore, Sepp1-deficient mice fed a selenium-deficient diet have extensive degeneration of the medial forebrain, somatosensory cortex, brainstem, thalamus, and hippocampus. The neurodegeneration was predominantly axonal with decreased dendritic length [50]. Sepp1-deficient mice fed a high-selenium diet (1 mg/kg) still developed disrupted spatial learning [51]. In addition, severe alterations were observed in synaptic transmission, short-term plasticity, and long-term potentiation in the hippocampus area [51]. Another study using Sepp1-deficient mice showed that SEPP1 and its receptor low-density lipoprotein receptor-related protein 8 (LRP8) are required for the exercise-induced increase in hippocampal neurogenesis [52]. Dietary selenium supplementation restored neurogenesis and reversed the cognitive decline associated with aging and hippocampal injury [53].

Additional deletion of selenocysteine lyase, an enzyme essential for selenium homeostasis, aggravates the phenotype of Sepp1-deficient mice [53]. These mice needed supraphysiological selenium supplementation to maintain survival and survived mice exhibited impaired motor coordination, audiogenic seizures, and brainstem neurodegeneration [53]. Interestingly, deletion of the *SEPP1* gene in dogs also leads to CNS atrophy and pronounced cerebellar ataxia [54]. Collectively, SEPP1 deficiency leads to a range of neurodegenerative changes, including impaired motor coordination, spatial learning, and cognitive function demonstrated in animal models.

SEPP1 was also found to be highly expressed in substantia nigra and with its expression localized within the centers of Lewy bodies, the pathological hallmark of PD. *SEPP1* expression was significantly reduced in substantia nigra from patients with PD compared with controls [55]. Furthermore, Sepp-1 knockout mice displayed increased tau phosphorylation in the hippocampus, possibly resulting from intracellular zinc changes. These data suggest that SEPP1 potentially participates in the pathogenesis of PD and AD [56] (Figure 1).

3. Conclusion

Candidate genes regulating melatonin secretion were identified via GWAS [21]. Disruption of these genes is associated with disturbed circadian rhythm, cerebellar dysfunction, impaired motor coordination, impaired spatial learning, decreased cognitive function, increased Aβ accumulation and tau phosphorylation, brainstem degeneration, and severe viral infection of the central nervous system. Whether these effects are direct or are mediated through secretion of melatonin is current unknown. These findings provide additional genetic evidence supporting the relationship between melatonin and neurodegenerative diseases.

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