Molecular Neurobiology (2019) 56:8255–8276
https://doi.org/10.1007/s12035-019-01660-3

Melatonin in Alzheimer's Disease: A Latent Endogenous Regulator of Neurogenesis to Mitigate Alzheimer's Neuropathology

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Received: 14 February 2019 / Revised: 20 May 2019 / Accepted: 22 May 2019 / Published online: 17 June 2019

Abstract
Melatonin, a pineal gland synthesized neurohormone is known as a multifunctioning pleiotropic agent which has a wide range of neuroprotective role in manifold age-related neurodegenerative disorders especially Alzheimer's diseases (AD). AD is a devastating neurodegenerative disorder and common form of dementia which is defined by abnormal and excessive accumulation of several toxic peptides including amyloid β (Aβ) plaques and neurofibrillary tangles (NFTs). The Alzheimer's dementia relates to atrophic changes in the brain resulting in loss of memory, cognitive dysfunction, and impairments of the synapses. Aging, circadian disruption, Aβ accumulation, and tau hyperphosphorylation are the utmost risk factor regarding AD pathology. To date, there is no exact treatment against AD progression. In this regard, melatonin plays a crucial role for the inhibition of circadian disruption by controlling clock genes and also attenuates Aβ accumulation and tau hyperphosphorylation by regulating glycogen synthase kinase-3 (GSK3) and cyclin-dependent kinase-5 (CDK5) signaling pathway. In this review, we highlight the possible mechanism of AD etiology and how melatonin influences neurogenesis by attenuating circadian disruption, Aβ formation, as well as tau hyperphosphorylation. Furthermore, we also find out and summarize the neuroprotective roles of melatonin by the blockage of Aβ production, Aβ oligomerization and fibrillation, tau hyperphosphorylation, synaptic dysfunction, oxidative stress, and neuronal death during AD progression.

Keywords Melatonin · Alzheimer's disease · Amyloid β · Neurofibrillary tangles · Circadian rhythm

Introduction

Alzheimer's disease (AD) is a chronic neurodegenerative disease which is characterized by progressive loss of cognition and memory [1, 2]. The pathological hallmarks of AD are extracellular senile plaques [3], primarily composed of amyloid β (Aβ), and intracellular neurofibrillary tangles (NFTs), composed of tau protein [4, 5]. Aging is one of the most pathological risk factor of AD, accountable for 60–80% dementia cases for people aged 65 and over [6, 7]. The main cause of AD is still obscure and about 70% of the risk is believed to be genetic [8]. AD deteriorates over time, and symptoms of dementia progressively exacerbate [9, 10]. In the initial stage of Alzheimer's, memory defect is mild and gradually, mild symptoms arise to cause cognitive functions and, finally, symptoms become more severe resulting dementia [11, 12]. According to Alzheimer's Disease International (ADI) organization, nowadays, 44 million people are living

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with dementia and this amount will rise to 135 million by 2050 [13]. Therefore, the required steps should be taken to control AD during its early stage.

Melatonin (N-acetyl-5-methoxytryptamine), a circadian rhythm–regulated hormone which plays a protective role against neurodegenerative event of AD [14]. The main source of melatonin secretion is the pineal gland of the brain and other organs are also involved including the retina, bone marrow, glial cells, pancreas, kidneys, and skin [15], as well as plant kingdom [16]. The level of melatonin increases from birth and shows its peak around teenage years or puberty [17] and declines with aging, and elderly individuals provide the lowest value [12, 13]. It is well established that melatonin is known as a multifunctional hormone included in the regulation of circadian rhythm [18]and anti-inflammatory, cytoprotective [19, 20], and antioxidant effects [21, 22]. Noticeably, melatonin is regulated by the circadian clock, and plasma melatonin level is highest at midnight in rat [23] and mice [24] models. Melatonin shows lowest level at early day time around 12:00–18:00 and highest peak at midnight around 23:00–02:00 [25].

With aging, the production of melatonin is decreased in aged person, which is considered as a crucial factor for developing AD [26, 27]. Due to abnormality or impairment of the suprachiasmatic nucleus (SCN), pineal hormone melatonin is reduced and circadian rhythm is altered [1]. With the increased reduction in the cerebrospinal fluid (CSF), melatonin assists to progress AD resulting in oxidative damage in AD brains [28, 29]. Studies revealed that AD patients had a lower level of melatonin compared to normal subjects [30, 31]. Melatonin shows anti-amyloidogenic as well as free radical–scavenging properties which promise a therapeutic candidate to inhibit AD progression [32, 33]. Concomitantly, in AD patients, the expression level of free radical production, oxidative DNA damage, lipid peroxidation, reduction of ATP, and cell death is higher compared to healthy individuals [34, 35]. Melatonin has the ability to inhibit the soluble amyloid precursor protein (APP) secretion in various cell lines by interfering with *APP* maturation [36]. Furthermore, for in vivo [37, 38] and in vitro [36, 39–41] models, melatonin supplementation efficiently attenuates Aβ generation as well as deposition. Melatonin administration suppresses Aβ elevation and abnormal nitration of proteins. Interestingly, Zhu et al. [42] in an in vivo study proved that stoppage of melatonin synthesis in rat model resembles AD pathology. Furthermore, melatonin dose at 10 mg/kg recovered cognitive impairment and reduced Aβ generation in AD transgenic (TG) mice model [43].

Sleep-awake is a crucial factor in pertaining to the production of Aβ and it is also proved that Aβ levels are raised during awakening and dropped during sleep, which might occur due to the pattern of day-night melatonin secretion [44]. Chronobiological disturbances like sundowning play a vital role in enhancing mental decline [45] and agitation as well as confusion in patients with AD, while melatonin treatment not only reduces the symptoms of sundowning but also raises cognition [46–48]. AD pathological hallmarks including plaques and tangles formation might be disrupted by melatonin appearing in experimental AD animal models [49–51]. In addition, melatonin supplementation contributes to inhibiting sleep disorders associated with AD progression and also alleviates impairment of memory and cognition in patients with AD [52]. In this review, we discuss and evaluate the neuroprotective functions of melatonin to abate AD pathogenesis by influencing neurogenesis.

Discovery and Synthesis of Melatonin

Melatonin is an ancient molecule which subsists since 3 billions of years ago. In addition, structurally, melatonin was first identified in 1958 [53]. Melatonin is mainly secreted by the pineal gland, activated by the central biological clock, and SCN which controls the circadian rhythm in mammals, including humans. Melatonin is a light-sensitive hormone; as a result, photoperiod plays an important role in synthesizing melatonin as well as its secretion pattern. The SCN is a critical relay center that offers to convey a neuronal signal to the pineal gland, and the neural message reaches the pinealocytes via the regulation of the central and peripheral sympathetic nervous system [54]. Firstly, the retina of the eye absorbs light (Fig. 1), which makes a signal and passes through the retinohypothalamic tract to the SCN, in the hypothalamus, which is then mounted in the optic nerve. After that, this signal passes to the paraventricular nuclei, then forward to the intermediolateral cell column located in the spinal cord, and finally reaches to the superior cervical ganglion (SCG). By the help of norepinephrine, SCG transfers signal to the pineal gland and synthesizes melatonin from its precursor, serotonin. Norepinephrine, a neurotransmitter which is released from the postganglionic sympathetic fibers, plays an important role for melatonin synthesis; too little norepinephrine may lead to synthesize lower melatonin, and too much norepinephrine involves higher melatonin production that makes a person awake [55, 56].

Briefly, norepinephrine stimulates its alfa-1/beta adrenoceptors leading to the activation of membrane-bound adenylate cyclase-cAMP system, resulting in not only the activation of adenylate cyclase-cAMP but also the increase of the intracellular concentrations of cAMP as well as calcium (Ca^{2+}), diacylglycerol, phosphatidylinositol, and protein kinase C [57]. The enzymatic biosynthesis pathway of

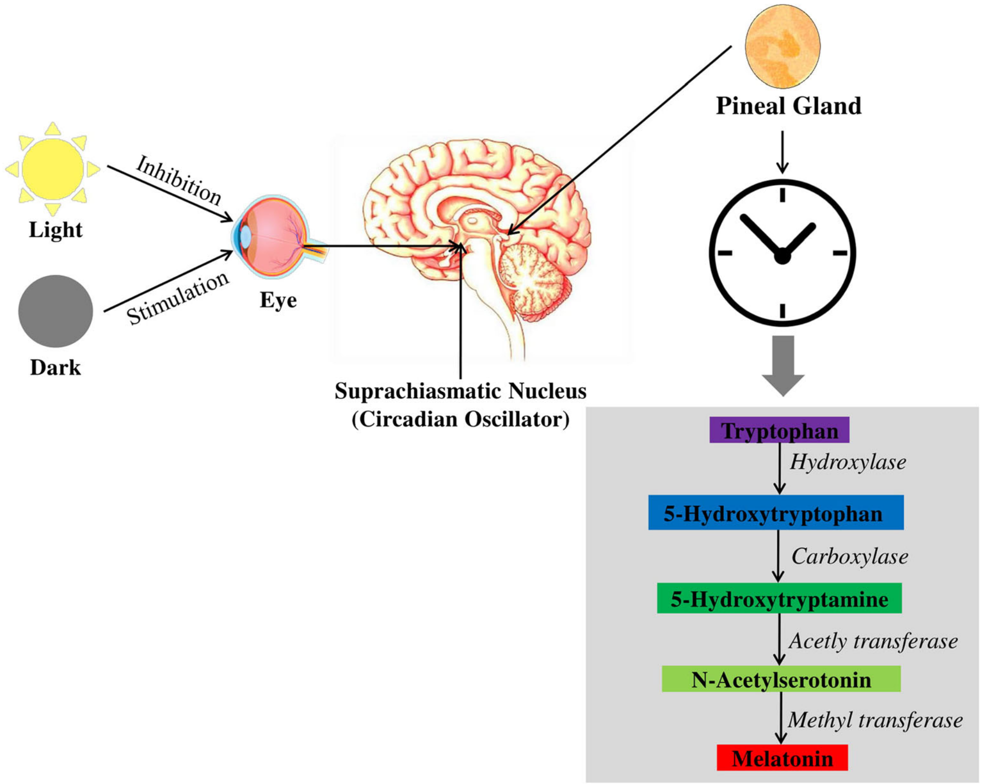

Fig. 1 Regulation of melatonin synthesis by the pineal gland to control circadian rhythms in the brain

melatonin from serotonin was discovered by Axelrod [58]. In a biochemical point of view, melatonin is synthesized from its precursor named tryptophan. The whole synthesizing procedure is mainly involved in three steps including hydroxylation, decarboxylation, and acetylation. The first step of this biosynthesis is to comprehend hydroxylation of the tryptophan (i.e. in the 5th position of the indole ring) by tryptophan hydroxylase which turns into 5-hydroxytryptophan (5-HTP). The next step is the removal of the carboxyl group from the side chain, which is then decarboxylated through aromatic amino acid decarboxylase (AAD) into serotonin. In the final step, serotonin is acetylated to N-acetylserotonin by arylalkylamine N-acetyltransferase (AANAT) and thereafter, by the presence of hydroxyindole-O-methyltransferase (HIOMT); this acetylated form of serotonin, N-acetylserotonin, is converted to melatonin, which is generally suspected the rate-limiting step regarding melatonin biosynthesis [15, 55].

Melatonin and Longevity

The resilience of circadian rhythms is linked with improved longevity in several organisms, whereas rhythms disruption leads to opposite effects. Interestingly, circadian rhythms are synchronized by pineal melatonin [59–61] and may qualify to reduce the prevalence of age-related neurodegeneration [26]. Consolidated evidence apprises that melatonin acts as an anti-aging, senescence-delaying [62], and strong-antioxidant [63, 64] in the brain [65]. For instance, melatonin supplementation escalates the lifespan in several species including *Paramecium tetraurelia* and *Drosophila melanogaster* [66–68].

A study showed that administration of melatonin to aged animals enhanced their life expectancy by nearly 20% [69]. However, experimental results in rodent models are fairly impressive; extended studies will be warranted to other species to emphasize presumed association. Previously, it was uncovered that melatonin accelerated the expression of sirtuin 1 (SIRT1), a longevity protein, [70] that stimulates the expression of a host of self-healing genes [1, 71]. It is not surprising that SIRT1 promoted longevity and attenuates the Aβ peptides not only in cell cultures but also in TG mouse models of AD [72, 73]. In AD patients, SIRT1 RNA and protein levels appeared notably lower [74] that connotes that the overexpression of SIRT1 might be beneficial against AD phenotypes.

Furthermore, SIRT1 encouraged α-secretase activity and decreased Aβ content in the brain [75] through the actuation of disintegrin and metalloproteinase domain-containing protein-10 (ADAM10) [76]. The DNA methylation [77] and histone modifications [78] are the most popular epigenetic switching observed in both AD and aging brain. On the other hand, melatonin tightly regulated these epigenetic changes in the neurons [79] and in this way, melatonin delays aging and increases lifespan in healthy and diseased states.

Melatonin and Circadian Disruption of Alzheimer's Patients

The sleep-wake abnormalities and circadian disruption (Fig. 2) are closely associated with the progression of AD resulting in reduced strength of environmental synchronizer and mental and physical activity and loss of circadian clock functionality. Irregular sleep or sleep disturbance increases the risk of memory and cognitive impairment that leads to AD progression [52]. Approximately, more than 80% of individuals 65 years old or over show circadian abnormalities and internal desynchronization of circadian rhythm that effects a negative impact on sleep pattern, body temperature, hormonal secretion, and other biological functioning [80, 81]. In addition, aged people fall asleep and wake up earlier due to the improper secretion of melatonin which alters the circadian system resulting in a strong reduction of actual sleep time and sleep efficiency and increased sleep latency [82].

Sleep disturbance and fragmented sleep-wake pattern increase not only nocturnal awakenings but also daytime nap [83]. Furthermore, increased sleep propensity in day time accounts for cognitive impairment in moderate to severe AD patients [84]. Sundowning, a chronobiological disturbance which is related to reduced attention to external stimuli, disorganized thinking and making confusion, change of behavior, increased arousal and agitation, and decreased body temperature cycle in the late afternoon or early evening in demented patients [48–50]. Melatonin is controlled by the circadian clock and plays a vital role against AD. However, circadian disruption alleviates melatonin secretion and also exerts higher degree of abnormalities in melatonin rhythm's pattern that results in losing clock setting and synchronizing time cue.

Alteration of SCN in Alzheimer's Disease

In mammals, including humans, SCN is a circadian master clock of the brain which consists of clock cells and its function is to synchronize circadian clock by regulating the retinohypothalamic tract [85]. According to neuropeptide content, the SCN neurons are classified as vasoactive intestinal peptide (VIP) neuron, an important part for generating entrainment which receives the input of retinohypothalamic tract [86]. In addition, arginine vasopressin (AVP), a neuropeptide of SCN's neuron is located in the remaining part of the SCN that modulates rhythmicity not only within the SCN but also in other regions of the brain [87]. The number of circadian fluctuations in AVP-expressing neuron decreases with aging [88] and the severe reduction was obtained during the age of 80–100 years [89, 90]. Concomitantly, VIP-expressing

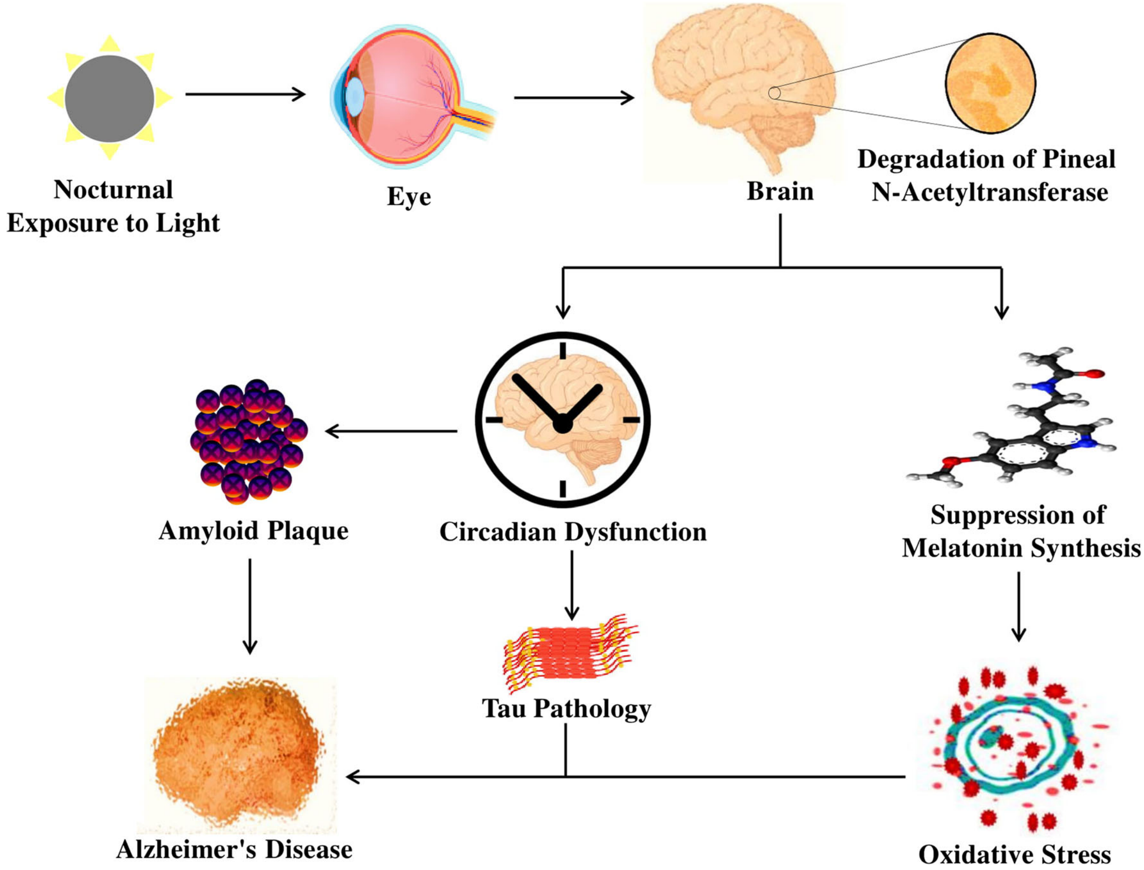

Fig. 2 Nocturnal exposure to light can acutely suppress melatonin synthesis and disrupt circadian rhythm that leads to Alzheimer's disease

neurons showed the same results, the number of these neurons decreased more in middle-aged compared to young subjects [91]. Some studies revealed that, in AD patients, the number of AVP- and VIP-expressing neurons was dramatically decreased compared to age-matched normal subjects. Additionally, the density of astrocytes, a glial fibrillary acidic protein, increases while the expression of vasopressin and neurotensin neurons decreases in the SCN, which helps to progress AD pathogenesis [89, 92, 93]. Surprisingly, the AVP mRNA total amount in AD patients is 3 times lower than age-matched normal subjects and there is no clear and spontaneous diurnal rhythm of AVP mRNA in AD patients [94]. Therefore, alterations of SCN and aging play a crucial role in AD pathology via AVP and VIP pathway.

The circadian oscillator consists of a series of clock genes including the brain muscle ARNT-like 1 (*BMAL1*), circadian locomotor output cycles kaput (*CLOCK*), cryptochrome (*CRY*), period circadian protein homologue 1 (*PER1*), and period circadian protein homologue 2 (*PER2*), which contributes to engage transcriptional or translational feedback loops intracellularly [85, 95]. Clock genes express widely in the brain regions and peripheral tissue (i.e., pineal gland) which are synchronized in the SCN of the hypothalamus [96, 97]. Furthermore, SCN directly controls the clock genes like *PER1* and *CRY2* through the β-adrenergic signaling pathway [98]. Aging is a risk factor associated with the alleviation of *BMAL1*, *CLOCK*, *PER1*, and *PER2* expressions in the SCN [99, 100]. In the peripheral tissue, such as the liver and heart, the expression of clock genes also changed due to aging. The level of *PER* gene was significantly reduced in the liver and heart in old rats compared to middle-aged rats, while the *BMAL1* level increased at night [101].

It is well established that aging progresses the pathological events of AD. Wu et al. [102] tried to find out the correlation between clock genes and AD pathology. They examined the rhythmic expression of clock genes (i.e. *BMALl*, *CRY1*, and *PER1*) in control, preclinical, and clinical AD patients. The preclinical (i.e. Braak I–II) and clinical AD (i.e. Braak V–VI) patients showed the reduced rhythmic expression of these clock genes named *BMALl*, *CRY1*, and *PER1*, while control subjects (i.e. Braak 0) exerted the normal diurnal rhythmic expression of those clock genes. Moreover, in AD mouse model, Aβ directly degrades the circadian clock gene expression of *BMAL1* and *PER2*, which alters the circadian rhythm [103]. This result denotes that disrupted clock gene expression in the pineal gland is related to AD progression.

Decreased Melatonin Levels in Alzheimer's Disease

Melatonin regulates circadian rhythm in both SCN and peripheral organs, which are widely negotiated by MT1 and MT2 receptors [104]. MT1 melatonin receptor is found in the entire body including in the hypothalamus, hippocampus, and CNS [105], and *MT1* gene expression is detected in SCN, while MT2 is unable to be detected due to very low expression in the hypothalamus [106, 107]. Previous studies observed the immunoreactivity of the MT1 receptor in the post-mortem hypothalamus SCN [108, 109], which is consistent with melatonin's feedback role on SCN rhythmicity [110]. In addition, the MT1 receptor appeared to be co-located with a portion of the AVP-expressing neurons located in the SCN, which indicates that this neuron subpopulation is comprised of melatonin action in the SCN. However, MT1-expressing neurons into the SCN is strongly diminished in aged controls than in young controls and same results also showed in the last stage of AD (i.e. Braak stages V–VI), but not in normal controls (i.e. Braak stage 0) [109].

Melatonin level's in CSF decreases with AD progression which is cleared by examination of Braak stages [111]. Additionally, another study proved that the level of CSF melatonin in AD patients is only one-fifth if compared with age-matched normal control individuals [112]. The melatonin levels of patients with apolipoprotein (*APOE*)*e4/4* type were even momentously lower rather than those expressing *APOEe3/4* [112]. With the progression of AD neuropathology, as determined by the Braak stages, melatonin level is decreased in CSF [111]. More strikingly, CSF melatonin's level is already momentously decreased in preclinical AD individuals that exposed the earliest signs of AD (i.e. Braak stage I–II) in comparison with old-aged controls without neuropathology of AD (i.e. Braak stage 0) [111], which is assured by pineal studies of human [30]. Pineal melatonin level in preclinical AD (i.e. Braak stage I–II) and late clinical AD (i.e. Braak stage V–VI) is reduced in comparison with controls (i.e. Braak stage 0), with loss of pineal melatonin content in the diurnal rhythm. In addition, the content of pineal melatonin was found to be immensely correlated with levels of CSF melatonin [30].

During aging, melatonin secretion and the levels of the MT1 receptor in the SCN are reduced sharply and more in AD pathology. Interestingly, reduced levels of melatonin are associated not only with AD but can also play a role in AD neuropathology. Melatonin has been shown to be a powerful in vivo and in vitro antioxidant and neuroprotector [113–115]. In a previous study, TG AD mouse model has been shown to suppress oxidative and amyloid pathology and to enhance survival rates [37]. In addition, in neuroblastoma cells and rats, melatonin significantly reduces tau or neurofilament hyperphosphorylation [116]. Melatonin supplementation significantly improved memory retention deficits, arrested tau hyperphosphorylation and oxidative stress, and restored melatonin synthesis-induced protein phosphatase-2A (PP-2A) activity in the rat [42]. The deficiency of melatonin may, therefore, be involved in AD's pathogenesis.

Decreased Input to the SCN in Alzheimer's Disease

The endogenous circadian clock is driven by environmental indications, especially light/dark cycles, to a 24-h environmental cycle. Light is regarded as the SCN's strongest stimulus. Additionally, melatonin exerts its potent activity to the SCN in the presence of melatonin receptor [104, 117, 118]. Melatonin supplementation significantly improves sleep disorders and provides free-running circadian rhythm in blind individuals—those who have deficiency synchronizing input between light and SCN [119, 120]. To retrain free-running rhythms activity by melatonin, two factors are involved including melatonin administration and subjects' circadian phase [121]. Melatonin's circadian effect plays a vital role in the therapeutic application of jet lag and shift work, as well as circadian-based sleep disorders [122, 123]. During aging and AD, the degeneration of SCN occurs and may result in reduced strength of zeitgebers and also neuronal pathways become dysfunctional or less reactive. These changes may boost the disturbances of circadian rhythm in these conditions [122].

Light is regarded as crucial to the SCN's entry, acting through the photic input pathway (i.e. retinohypothalamic tract). A noticeable dose-response relationship is addressed between illuminance and melatonin rhythm's phase shift. The phase shift response to moderate light levels during aging is decreased, particularly to short wavelengths, which can contribute to the progression of age-related circadian rhythm diseases [124, 125]. During aging, many reasons have been demonstrated to reduce the light projection to the circadian timing system and for AD in an even more pronounced manner. Owing to more nocturnal awakenings and more daytime sleepiness, older people, especially AD patients are exposed to lower levels of illumination in their diurnal lives [126, 127] rather than young people [128, 129]. In addition, the lens' ability to transmit light gradually decreases during aging. Furthermore, the circadian effects of melatonin on the SCN may be affected in aged patients and AD patients as their melatonin contents are decreased and MT1 receptor in the SCN has decreased significantly [109]. In addition, it is well known that physical activity and social contacts are significantly decreased during aging and particularly in AD, which can also contribute to circadian rhythm disturbances [130, 131]. Taken together, the reduced input to the SCN can clearly contribute to the SCN's deactivation during AD.

Melatonin and Alzheimer's Hallmarks

Melatonin in Aβ Toxicity

APP is the precursor of Aβ composing 39–43 amino acid residues. Amyloidogenic beta-amyloid precursor protein (βAPP), one of the most risk factors for the production of Aβ peptides, is shown in Fig. 3. Interestingly, Aβ42 is the most neurotoxic form of Aβ [132] which is produced by improper proteolytic cleavage in the presence of γ-secretase that helps to form β-pleated sheets, resulting in the formation of senile plaques in the brain. These produced plaques in the brain to exert and produce an aggregation of peptides and formation of amyloid fibrils which are responsible for synapse disruption and abnormalities of neuron functioning, as well as the loss of neuron integrity [33]. In addition, the imbalance between the clearance and production of Aβ is responsible for its accumulation, which plays a crucial role in the brain pathology and disrupting the cellular homeostasis. Aβ enables to generate free radicals, oxidative stress, tau hyperphosphorylation, activation of GSK3β and CDK5 resulting in DNA, and protein disruption along with lipid oxidation and diminished metabolism of energy which leads to AD pathology [1, 133].

As previously discussed, melatonin has neuroprotective, antioxidant, and anti-amyloidogenic functions in the brain which leads to decrease the possibilities of Aβ formation in the brain [134]. Melatonin actively reduces Aβ toxicity and inhibits the formation of β-sheet by showing the preventive effects on fibrillary amyloid. Melatonin shows the preventive effects against lipid peroxidation, oxidative stress, circadian alteration, cellular death, and DNA damage in Aβ-induced both in vivo [37] and in vitro models [40, 135].

Regulation of Caspase-3/Bcl-2/GSK-3β/PP2A

Some key enzymes including caspase-3, B cell lymphoma-2 (Bcl-2), PP2A, and glycogen synthase kinase 3 beta (GSK3β) are closely associated with AD pathogenesis by exerting either increasing or decreasing expression level [136–138]. These enzymes may regulate the signaling pathway of Aβ and tau hyperpolarization as well. Among these, activation of caspase-3 ameliorates β-secretase activity that leads to increased Aβ production in AD brains, and it is well known that the level of caspase-3 is higher in AD patients than the normal and age-matched individuals [139]. Concomitantly, GSK3 can progress tau hyperphosphorylation, while increased PP2A enables to inhibit the enhanced hyperphosphorylation of tau protein [140, 141].

Upregulation of caspase-3 is directly responsible for cell death in AD [142] but melatonin has the ability to downregulate caspase-3 and also elevate anti-apoptotic Bcl2 level in AD TG mice model [143, 144]. In contrast, melatonin alleviates not only activation of caspase-3 [145] but also inhibits apoptosis [146] in Aβ-induced animal model. Furthermore, melatonin treatment significantly reduces the expression level of GSK-3β and caspase-3 and increases PP2A and Bcl-2 level in Aβ_{1-42}-induced mice. Altogether, it can be concluded that melatonin might a candidate for reducing tau hyperphosphorylation and damaging toxic compounds

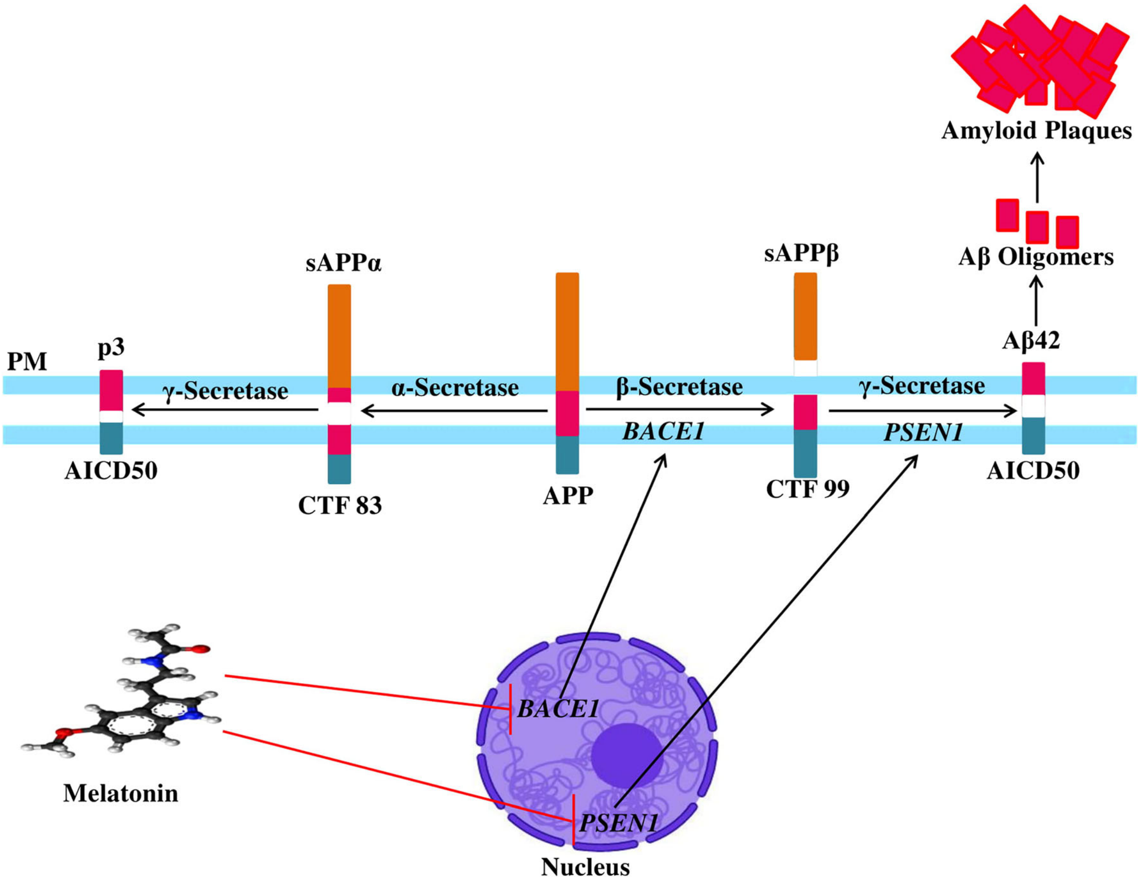

Fig. 3 The role of melatonin in the processing of APP and cleavage products that leads to the formation of amyloid plaques. PM, plasma membrane; APP, amyloid precursor protein; sAPPα, soluble amyloid precursor protein-α; sAPPβ, soluble amyloid precursor protein-β; CTF, C-terminal fragment; AICD, amyloid precursor protein intracellular domain

through the regulation of PP2A and GSK-3β, as well as caspase-3 and Bcl-2 for the inhibition of cell apoptosis.

Attenuation of Memory Impairment and Aβ Accumulation

AD mainly occurred due to the impairment of episodic memory resulting in progressive deficits in many areas such as language, attention, and working memory as well [147, 148]. Gong et al. [149] performed the behavioral test to determine cognitive function on $A\beta_{1-42}$-induced mice model. To assess spatial learning capability and memory ability, oriented navigation trail was executed in control, $A\beta_{1-42}$-injected group, and melatonin-treated group. In fact, melatonin-treated group showed a shorter latency comparison with $A\beta_{1-42}$-injected group. To get better cognitive and memory function, the mice have to stay in III quadrant for a longer period and frequently cross the central arena. Melatonin treatment group exhibited significant result by staying in III quadrant for a longer time and increased the line crossing in the central square arena rather than $A\beta_{1-42}$-injected group. They also performed the open-field test to determine locomotive activity, while step-through test and the step-down test was used to assess spontaneous activity. Melatonin group reduced the making error and exerted a momentous improvement in latency when compared with $A\beta_{1-42}$-induced model. So, these results denote that melatonin has the ability to recover cognitive function and spontaneous activity efficiently [149]. Additionally, melatonin treatment improves the learning capacities in 2 × AD mice examined by Morris Water Maze (i.e. the probe test) and Barnes Maze (i.e. circular platform test) [150].

Melatonin in Tau Pathology

Tau is denoted as a microtubule-associated protein which is involved in microtubule assembly progression and maintains microtubules stability [151]. Hyperphosphorylated tau, the prime component of intracellular NFTs, plays a crucial role in declining the memory and cognition in patients with AD [10, 152]. Due to hyperphosphorylation, tau protein becomes unable to sustain its biological activities [153] which lead to contribute tauopathies by disrupting microtubules [154, 155]. Thus, neurodegeneration occurs in AD patients upon tau hyperphosphorylation and during this period, 3–4-fold higher level of hyperphosphorylated tau in AD patients in comparison with normal individuals [156–158]. Melatonin has special characteristics such as water [159] and lipid [158] solubility that easily permits it to penetrate and pass through the blood-brain barrier; this feature is totally different from other antioxidant agents. Melatonin itself can function as a free radical scavenger and activates antioxidant enzymes which are given in Fig. 4. Melatonin attenuates tau hyperphosphorylation and protein kinase-A (PKA) overactivation in isoproterenol-induced rat brain [33]. Melatonin significantly attenuates tau hyperphosphorylation in N2a and SH-SY5Y neuroblastoma cells induced by wortmannin [160], okadaic acid [161], and calyculin A [42]. Interestingly, melatonin exerts a pivotal preventive effect on the progression of hippocampus degeneration and enhances cognitive effects [48] by regulating the activities of GSK3 and CDK5 in hippocampal neurons [162]. Additionally, melatonin inhibits the expression level of caspase-3, BCL2 associated X (Bax), and prostate apoptosis response-4 (Par-4), which contributes to suppressing the progression of neuronal apoptosis [163].

Regulation of PI3K/Akt/GSK3

The improper regulation of protein kinase or protein phosphatases plays a crucial role in tau hyperphosphorylation; among them, GSK3 is one of the key kinases for the pathogenesis of AD [164]. The overexpression of GSK3 leads to tau hyperphosphorylation in in vivo and in vitro methods [165–167]. Wortmannin is a phosphatidylinositol 3-kinase (PI3K) inhibitor, which activates the expression of GSK3 through inhibiting PI3K pathway [168]. Deng et al. [160] demonstrated that the tau hyperphosphorylation occurred through the activation of GSK3 in wortmannin-induced neuroblastoma N2a cell line, which is widely used in Alzheimer's pathology. Wortmannin treatment not only activated the tau hyperphosphorylation but also initiated lipid peroxidation, oxidative stress, c-JUN N-terminal kinase (JNK), extracellular signal-regulated kinase (ERK), and p38, as well in N2a cell line. In this regard, melatonin treatment exerted a positive effect to rescue tau hyperphosphorylation induced by overactivation of GSK3. Similarly, melatonin inhibited the level of oxidative stress, lipid peroxidation, JNK, and p38 through the activation of antioxidant properties, mainly superoxide dismutase (SOD). In addition, melatonin inhibits tau hyperphosphorylation by regulating PI3K/Akt/GSK3 pathway [169, 170].

Mitigation of Tau Hyperphosphorylation and Memory Deficits

Kainic acid (KA) is familiar as an analog of glutamate which causes memory loss and neurodegenerative disorder [171]. Shi et al. [172] revealed that the expression of tau phosphorylation at Ser199 and Ser396 in the hippocampus increased in

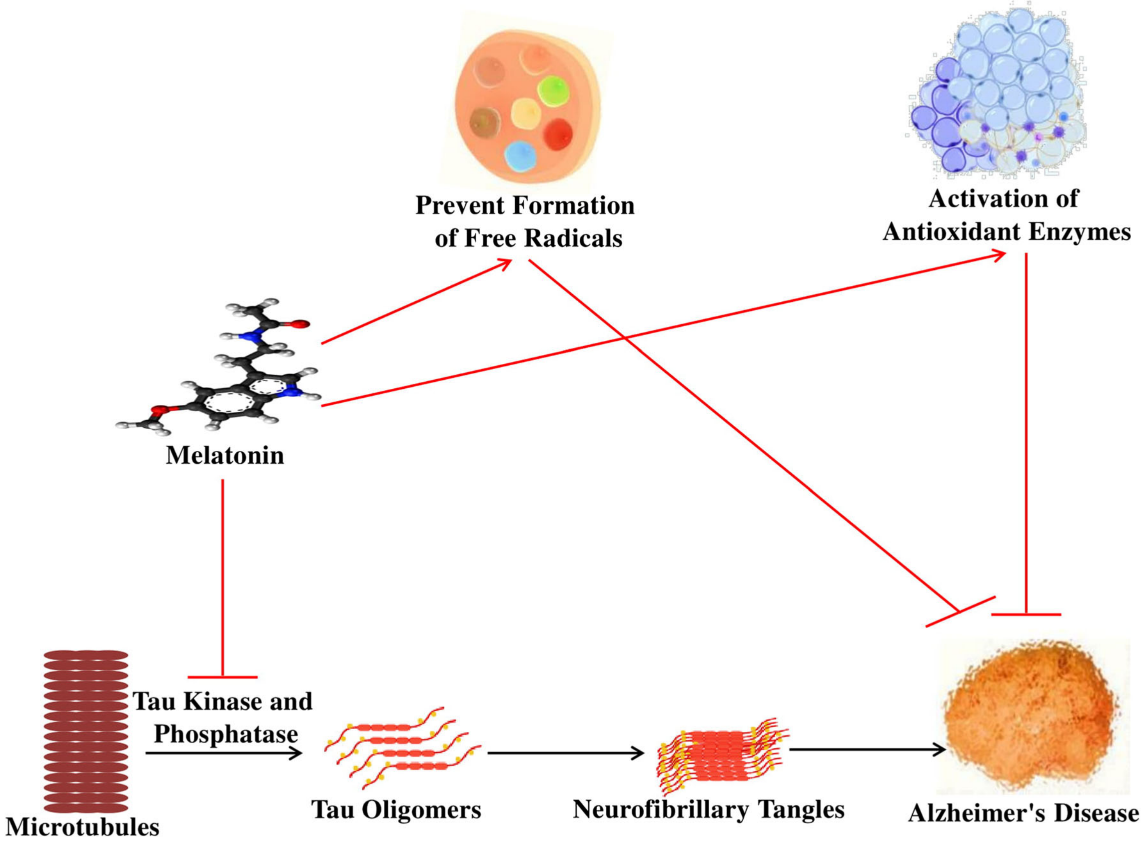

Fig. 4 The role of melatonin against oxidative stress and neurofibrillary tangles that lead to Alzheimer's disease

KA-induced both in vivo and in vitro methods. To assess the memory impairment, they used the Morris Water Maze test to determine the learning capacity in KA-induced mouse. The mean escape latency was higher in KA-treated group than the control group, and melatonin-treated group (Mel+KA) reduced the escape latency in comparison with KA-treated group. Taken together, KA-treated mice spent the lesser time to reach target quadrant compared to control group, while Mel+KA group took better time compared with KA group, and the same result was also noticeable to calculate the percent distance in the target quadrant. So, these results proved that melatonin treatment decreases memory deficits in KA-induced animal model and alleviates tau phosphorylation underlying the protective effect of melatonin as memory impairment is efficiently related to tau hyperphosphorylation [173]. In addition, melatonin remarkably alleviated the tau phosphorylation at Ser396 and Ser199 in KA-induced hippocampal neurons. Furthermore, insufficient supplementation of melatonin is highly associated with the development of cognitive impairment but melatonin treatment has the ability to inhibit the progression of neuronal degeneration and also enhances cognitive function [111, 112].

Endoplasmic reticulum (ER) stress is closely related with AD progression and during that moment, the level of ER chaperone protein, GRP78, was increased in the temporal cortex and hippocampus in AD patients [174, 175]. KA treatment induces the activation of ER stress which leads to hippocampal cell death [176, 177]. In addition, KA-induced ER stress triggers two major kinases including GSK3β and CDK5, which lead to tau hyperphosphorylation. SB216763 and roscovitine are specific inhibitors for GSK3β and CDK5 respectively. These inhibitors were treated in KA-induced hippocampal neurons that were candidates for inhibition of tau hyperphosphorylation. So these results suggest that ER stress triggers GSK3 and CDK5 expressions which lead to assist tau hyperphosphorylation. Interestingly, melatonin treatment inhibits KA-induced ER stress by alleviating the activation of GSK3 and CDK5. Furthermore, melatonin significantly relieves KA-induced increased hippocampal GRP78 level [172]. So, melatonin might be a promising candidate to execute preventive role against neuronal disorder and tau hyperphosphorylation through the regulation of GSK3 and CDK5, as well as easing of ER stress.

Melatonin in Neuroinflammation of Alzheimer's Disease

Rosales-Corral et al. [28] reported that melatonin strikingly downregulated fibrillar amyloid β (fAβ)–induced proinflammatory molecules, including interleukin-1-β (IL1-β), interleukin-6 (IL6), and tumor necrosis factor-α (TNF-α). Interestingly, experimental data is evidence that melatonin suppressed NF-κB DNA binding activity [178, 179]. Recently, a study revealed that melatonin inhibits NF-κB-commenced IL-6 in a concentration-dependent fashion in Aβ-treated brain slices [180]. Furthermore, in rats, after the administration of melatonin, has shown the suppression of Aβ-associated learning and memory loss, and significant reduction of NF-κB-related IL-1β in addition to complement 1q (C1q) in the hippocampus [181].

Inflammatory cytokines, such as IL-1, IL-6, and TNF-α, play a pivotal role in the progression of chronic inflammatory and neurodegenerative disorder like AD [182–185]. IL-1 and IL-6, synthesized by microglia and astrocytes, are responsible for generating Aβ and senile plaques, resulting in neurodegeneration in TG mice [186, 187]. Inflammation, reactive oxygen species (ROS) generation, and Aβ and senile plaques are the major risk factors for AD pathogenesis which are accelerated by the presence of IL-1 and IL-6 [183, 188, 189]. In addition, oxidative stress ameliorates Aβ production in in vivo [190] and in vitro [191] models that contributes to AD progression. In this circumstance, melatonin exerts a positive effect to inhibit IL-1β, IL-6, and TNF-α on mesenchymal stem cells by showing SOD activity [192, 193].

Melatonin reduces oxidative stress by exerting the activity of antioxidant enzymes [194, 195]. In addition, exogenous administration of melatonin (i.e. 500 μg/kg) enhances mRNA expression not only in copper-zinc superoxide dismutase (CuZnSOD) but also in manganese superoxide dismutase (MnSOD) in female Syrian hamsters [196] and melatonin injection (i.e. 5 mg/kg) enhances the SOD activity in rat kidney, liver, and brain [196]. Either Aβ peptide (i.e. 25–35) [197] or D-galactose [198]–induced rodents (rats and mice) cause oxidative damage in the brain, melatonin (i.e. 0.1 to 10 mg/kg) brings back SOD and glutathione peroxidase (GPx) activities. Similarly, melatonin (i.e. 10 mg/kg) also has been shown to be protective against oxidative mitochondrial damage by increasing ATP production in the fetal brain and also stimulates GPx activity in rat brain [199]. So, based on this evidence, melatonin may inhibit the risk of AD by showing its antioxidant and anti-inflammatory effects.

Melatonin on the Cholinergic System of Alzheimer's Disease

Impairment of the cholinergic system is also considered as early sequel pathogenesis of AD [200, 201]. Neurons in the nucleus basalis, a principle origin account for cholinergic innervation of the cerebral cortex and hippocampus, experience an overwhelming and fastidious degeneration in AD brain [202–204]. Surprisingly, at an early phase, AD acetylcholine (ACh) level appeared to decrease, on the contrary, the activities of the synthesizing enzyme and the hydrolyzing enzyme, choline acetyltransferase (ChAT) and acetylcholinesterase

(AChE) respectively, remain unchanged until the late stage of AD [205–207]. Both the biopsy and autopsy examination had been observed that ChAT activity in the neocortex of AD patients reduced significantly, correlating with the predominance of dementia [208]. Though the molecular mechanism implicated to the ACh deficit is still elusive, the AChE inhibitor has been used as a treatment for mild-to-moderate AD [209].

Melatonin has defensive effects on the cholinergic system. Guermonprez et al. [210] reported that melatonin slightly dissuaded peroxynitrite-dependent inhibition of choline transport and ChAT activity in several neuronal proteins. In addition, after 4 months of melatonin treatment in APP695 transgenic mice, Aβ deposition notably ameliorated the learning and memory deficits, and melatonin treatment also showed improved ChAT activity in the frontal cortex and hippocampus [211]. Likewise, another study also demonstrated that melatonin significantly improved spatial memory deficit and decreased ChAT activity in the frontal cortex and hippocampus of ovariectomized adult rats [212]. However, melatonin was impotent to recover ChAT activity, while intracerebroventricularly infused Aβ-induced ChAT activity is significantly reduced [213]. Melatonin showed the inhibition only on the lipopolysaccharide (LPS)-induced increase in AChE activity, whereas no changes were observed in CSF treated rats. These results are in agreement of the inhibitory effect of melatonin on AChE activity in streptozotocin (STZ)-induced dementia model [33, 214].

Systematic review and meta-analysis of placebo-controlled trials have ascertained that the cholinesterase inhibitors (i.e. donepezil, tacrine, rivastigmine, and galantamine) drugs can show acetylcholine deprivation, as a consequence, to stabilize or slow reduction in cognition, function, behavior, and global change [215]. Disorganization of circadian rhythm leads to reduced melatonin secretion in AD, resulting in a decrease in sleep quality and cognitive function impairment. Melatonin replacement was uncovered effectively to treat sundown syndrome, mild cognitive impairment (MCI), an etiologically heterogeneous syndrome that precedes dementia and other sleep-wake disorders in AD patients. Besides inhibition on AChE activity, melatonin also plays as a potent scavenger of reactive oxygen and nitrogen species in the treatment of restoring sleep disturbance and reducing Aβ toxicity in AD [33, 216].

Either AChE inhibitors or melatonin, which is the best choice for AD patients, still remains an unsolved question; therefore, further study is warranted to elucidate this clinical evidence. Notwithstanding, an amalgamation of these two molecules may have synergistic effects. Lately, a hybridization approach has been employed to design and synthesize tacrine-melatonin hybrids as novel multifunctional drug candidates for AD [217, 218]. By combining these, compounds exhibit improved both cholinergic and antioxidant features, implicating better than their individual does. Furthermore, their combination shows lower toxicity and may be capable of penetrating the CNS [217]. Surprisingly, direct intracerebral administration of one of these hybrids, N-(2-(1H-indol-3-yl)ethyl)-7-(1,2,3,4-tetrahydroacridin-9-ylamino) heptanamide, reduced Aβ-induced programmed cell death and amyloid burden in the APP/PS1 mice brain. Moreover, the diminished in Aβ pathology was linked to the recovery in cognitive function [218].

Melatonin and Neurogenesis in Alzheimer's Disease

Typical aging changes neurogenesis, and Aβ accumulation inhibits the proliferation of progenitor cells and neuronal differentiation in animal models as well as cell culture [219–221]. Due to neuronal dysfunction, neuronal vulnerability turns into memory impairment resulting in AD [222]. Previous studies in TG animal model demonstrated that attenuated hippocampal neurogenesis in subventricular zone (SVZ) as well as sub-granular zone (SGZ) [220, 223, 224] related with Aβ peptides [225, 226] and progressed APP expression, spontaneously decreases not only progenitor cell proliferation but also cell survival in hippocampus [227].

Oligomeric Aβ suppresses cell proliferation [228] and reduces neurogenesis through β-catenin downregulation and apoptosis, which activates GSK3β to stimulate Aβ production as well as tau phosphorylation [229]. Clinical studies revealed that in AD brains [230], reduced expression of β-catenin [231, 232] and Wnt/β-catenin were found compared to control subjects. Interestingly, Wnt/β-catenin not only inhibits neuronal toxicity and apoptosis but also suppresses tau phosphorylation [233]. As a result, new neuron production or sustaining neuron might be considered as an effective therapeutic criterion to protect AD.

Interestingly, melatonin plays a positive role to regulate neurogenesis and also some experimental studies proved that it increases cell proliferation and neurogenesis which is impeded in AD [234]. As stated earlier, MT1 and MT2 are present in the neuronal cell as well as adult brain [235]. Melatonin has the ability to develop dendritogenesis [236], maturation of dendrite, and melatonin combined with exercise increases neurogenesis [237, 238]. Deprivation of sleep is directly related to melatonin reduction in AD patients, which increases Aβ generation resulting in memory dysfunction. Melatonin enhances the proliferation as well as differentiation of neural stem cells [239] and accelerates new neuron survival [240] proved by animal studies. It also prevents pyramidal neuronal loss [241] and enhances neurogenesis in pinealectomized rat model [242]. Melatonin enhances adult hippocampal [243] and cell proliferation of subventricular zone [244] via ERK signaling pathway, which also prevents dexamethasone-mediated alterations in hippocampus [244]. Melatonin increases the expression of β-catenin protein and also stimulates PLC/DAG, PI3K/Akt, and PKC [245] which results in phosphorylation and GSK-3β inactivation. Melatonin attenuates AChE activity and shows anti-amnesic effect [245] and also stimulates α-secretases [246] and soluble amyloid precursor protein-α production, which is responsible for promoting neural progenitor cell (NPC) proliferation [247], as well as survival of neurons [248]. In addition, oxidative stress is associated with neuronal death during aging [249] while melatonin treatment prevents impairment of oxidative stress and also improves proliferation as well as differentiation [250] by α-secretase.

Melatonin Levels in Alzheimer's Patients

Compelling evidence has shown that melatonin levels decreased in AD patients compared to age-matched control subjects [112, 129, 251–253]. CSF melatonin levels were decreased in AD patients, suggesting a reduction in mainstream melatonin production. Interestingly, in preclinical phases when the patients do not appear with any cognitive impairment (at Braak stages I-II), even a decrease in CSF melatonin levels have been observed, thereby suggesting that the reduction in CSF melatonin may be an early biomarker for detecting the first stages of AD [30, 111]. To explore the molecular mechanisms behind the reduction of melatonin levels, Wu et al. [30] have conducted a study; the results showed the disruption of noradrenergic regulation, as well as the depletion of 5-hydroxytryptamine by increased monoamine oxidase A (MAO-A) activity, resulting in an imbalance of melatonin rhythm. Alteration of the light transmission pathways from physical characteristics of the dioptric apparatus to faulty retinohypothalamic tract (RHT) or SCN-pineal associations has been discussed as feasible reasons of decreases in melatonin amplitude and corresponding changes in the circadian system [254].

However, the pineal hormone is inhibited by light [255, 256] thereby dysfunction in the transmission of light would not easily interpret as a reduction in melatonin levels. With any possible cases, if the melatonin secretion changes, it will contribute to sleep disturbance, nightly restlessness, and sundown syndrome seen in AD patients [257]. Another reason may be investigated in changed metabolism of AD patients. The appearance of *APOE-ε4/4* that linked with escalated Aβ toxicity and more swift disease development is also leading noticeably stronger decreases in melatonin in the particular AD subpopulation than in patients with several *APOE* subtypes [258]. According to this point of view, the relative melatonin insufficiency may become visible as a consequence rather than one of the reasons for AD, albeit the deficiency in melatonin may exasperate the disease. Decreased nighttime melatonin levels had also been demonstrated that linked with the mental impairment of demented patients [259].

Melatonin as a Target for Alzheimer's Therapy

In a number of performed in vivo studies [37], in vitro studies [40, 135], case reports [46], pilot studies [260], and small-scale clinical studies [261], melatonin was considered to be beneficial for the inhibition of Aβ toxicity and fibrillogenesis, free radical scavenging, prevention of mitochondrial damage, and circadian disturbances, such as sleep disturbance and sundowning in AD-demented patients (Fig. 5). Noticeably, melatonin represents several advantages such as balanced amphiphilicity, blood-brain barrier crossing capacity, the entrance of any cellular compartment (mitochondria), as well as antioxidant properties over other comparable components [115, 262].

Blocking Aβ Production

Aβ, derived from APP, is the most studied risk factor associated with pathogenic mechanisms of AD by forming senile plaques [134]. Melatonin directly interacts with Aβ and prevents the aggregation of Aβ [263] proved by thioflavin fluorescence assay. *APP* gene promoter takes on the cAMP-responsive region, which induces APP synthesis and also enhances prostaglandin synthesis. Increased prostaglandin stimulates the overexpression of APP mRNA, resulting in neuroinflammation and neurodegeneration [264]. Interestingly, melatonin and/or its metabolites suppress prostaglandin by interfering with PEG/COX-2 pathway and also blocks cAMP production by inhibiting adenylyl cyclase which finally alleviates APP synthesis [32].

Melatonin, through its MT2 receptor, enables to stimulate phospholipase C (PLC) and activates protein kinase C (PKC), a promoter of α-secretase-mediated cleavage of APP, which in turn phosphorylates and inactivates the expression of GSK-3 [245, 265]. Furthermore, melatonin inhibits JNK production that enriches the preventive mechanism of GSK-3 activation [266]. So inhibition of GSK-3 activation might be a crucial factor for interrupting APP synthesis and reducing tau hyperphosphorylation.

Additionally, Aβ elevates AChE activity which in turn is related to increases in intracellular Ca^{2+}, resulting in oxidative stress and ROS production, while melatonin prevents the increased AChE expression by reducing ROS generation and intracellular Ca^{2+} levels in Aβ -induced mice model [263]. Moreover, melatonin at a concentration of 5–50 μM prevents cell death and oxidative stress in $Aβ_{25–35}$- and $Aβ_{40}$-induced rat PCL2 pheochromocytoma and mouse N2a neuroblastoma cell model [267]. Melatonin treatment improves cognitive impairment and reduces apoptosis in $Aβ_{1–42}$-induced mice model [149].

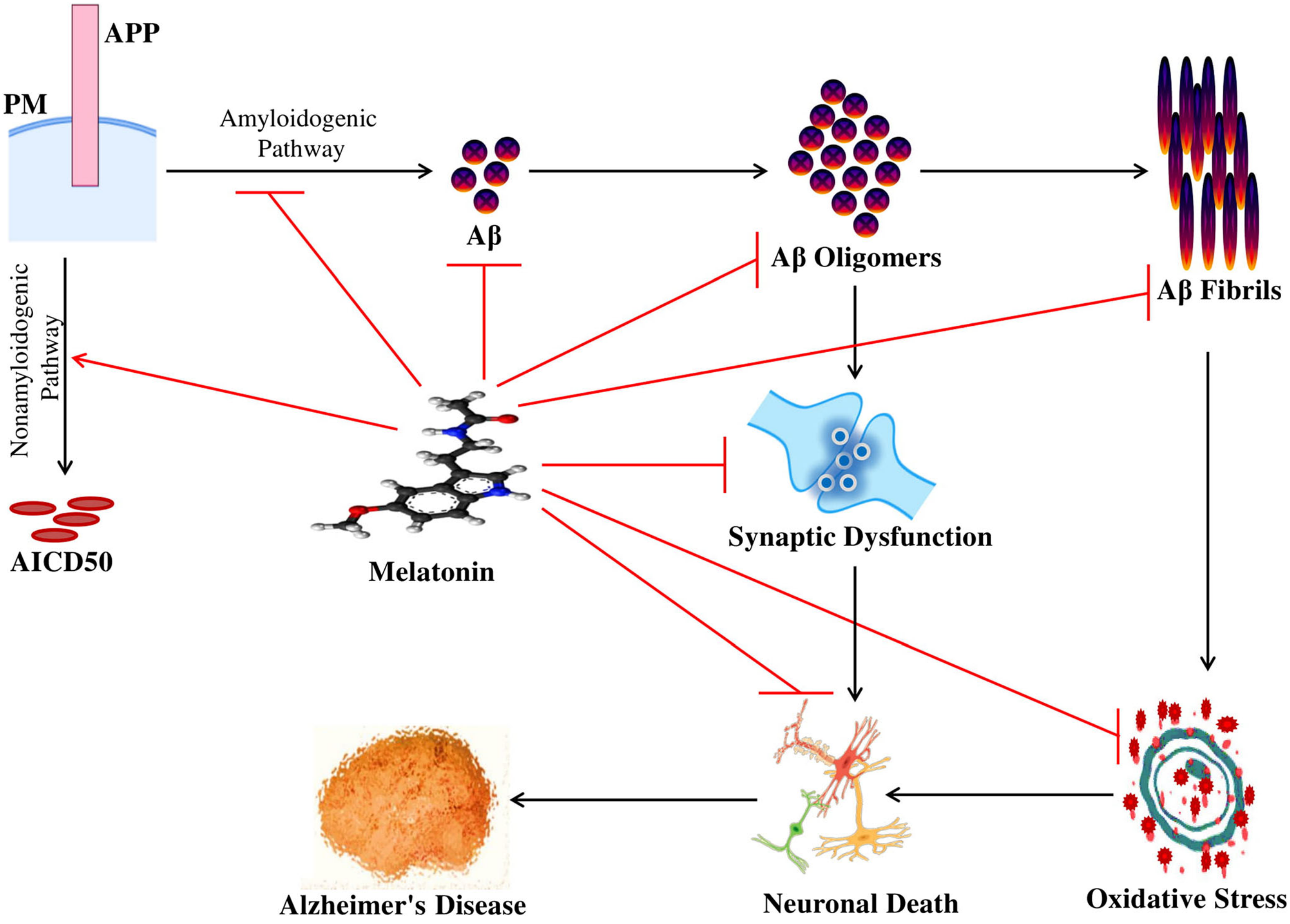

Fig. 5 Therapeutic strategy targeting melatonin to abate Alzheimer's pathogenesis. *PM* plasma membrane, *APP* amyloid precursor protein, *AICD50* amyloid precursor protein intracellular domain 50

Blocking Aβ Oligomerization and Fibrillation

There are three major groups of Aβ assemblies including monomers, soluble oligomers, and insoluble fibrils which are referred to as Aβ pool [268]. Each pool encircles multiple structures of Aβ aggregation based on mers range such as toxic oligomers (i.e. 8–24 mers), α-synoligomers (i.e. 6–18 mers), and tau oligomers (i.e. 3–15 mers) which offer neuronal toxicity by the process of making aggregates [269]. These aggregates turn into fibrils. Soluble Aβ oligomers exhibit various structures including dimmers, trimers, tetramers, pentamers, and decamers [270–272]. The most toxic Aβ is familiar as $A\beta_{1-42}$ which is responsible for producing amyloid plaque and is associated with nerve death. Interestingly, $A\beta_{1-42}$ sustains its consistency with a mix-up of monomer, trimer, and tetramer before altering to fibrillation. $A\beta_{1-42}$ promotes neuronal death by alleviating N-methyl-D-aspartate receptors (NMDARs) desensitization, resulting in overexpression of intracellular Ca^{2+} [273] and decreases the density of AMPA synaptic receptors [274].

Melatonin spontaneously binds with protofibrils, which prevent ROS generation and protects neuron by exerting its antioxidant properties. Melatonin treatment reduces oxidative damage in Aβ protofibril-induced mice. Concomitantly, due to affinity on Aβ peptide, melatonin shows a preventive effect on amyloid fibril formation proved by in vitro fibrillization assay [263]. Pappolla et al. [275] proved that melatonin has the ability to interact with $A\beta_{1-40}$ and $A\beta_{1-42}$, and decreases the amount of β-sheet-structured peptides, thereby inhibiting the formation of $A\beta_{1-40}$ and $A\beta_{1-42}$ fibrils. Melatonin directly interacts with *APOE*, a risk factor of developing the onset of AD progression by showing its anti-fibrillogenic properties which result in $A\beta_{1-40}$ inhibition [49, 276].

Another study revealed that melatonin involves the hydrophobic region (i.e. 17–28) of amyloid peptides and forms non-covalent complexes which helps to mitigate Aβ fibrillogenesis [277]. Furthermore, soluble Aβ produces excessive ROS in astrocytes that contributes to the destruction of basal forebrain neurons [278]. Interestingly, melatonin attenuates not only ROS generation but also reverses reduced activities of antioxidant enzymes (i.e. catalase and GPx) in $A\beta_{1-42}$-induced mice model [263].

Blocking Synaptic Dysfunction

Synaptic impairment is one of the most familiar signs of AD which assists to trigger dementia [279]. In AD patients, excessive Aβ, which suppresses long-term potentiation (LTP), a synaptic stimulator in the hippocampus and neocortex, improves the induction of long-term depression (LTD) [280], smashes synaptic transmission, plasticity, as well as neuronal death, through activating NMDARs [281, 282]. Additionally, the total number of synapse is fewer in AD patients than normal individuals [283]. Melatonin significantly enhances LTP and promotes synaptic transmission [284]. Corrales et al. [285] revealed that melatonin reduces the synaptic inhibition and recovers hippocampal LTP through increasing the density and activating glutamatergic synapse. By improving the activity of a presynaptic protein, synaptophysin, melatonin increases the number of synapses [286] and also ensures a proper dendritic structure in hippocampal neurons [287]. Rudnitskaya et al. [288] proved that melatonin administration (i.e. 0.04 mg/kg) not only alleviated the expression of Aβ accumulation in frontal cortex and hippocampus but also decreased the damaged and dead neurons in OXYS rats. They also revealed that the total number of synapses was increased and synaptic pathological change was also prevented after melatonin administration. Furthermore, the peak level of melatonin in CSF at night time improves the dendrite number and their length as well as thickness [236]. Benleulmi-Chaachoua et al. [289] confirmed that the MT1 receptor is located in presynaptic membrane and it is a part of presynaptic protein network hippocampus, hypothalamus, and cortex. On the other hand, the MT2 receptor contributes to functional axonogenesis in central neurons by activating 3β/CRMP-2 signaling pathway [290].

Recently, Ali et al. [291] demonstrated that Western blot results ensure the reduced expression of memory-related presynaptic protein synaptophysin, SNAP25 and postsynaptic protein PSD95, and p-GluR1 (Ser 845) in D-galactose-induced mice model as compared to vehicle group. Interestingly, these decreased effects were reversed by melatonin treatment (i.e. 10 mg/kg) and significantly increased the protein marker. P-CREB Ser 133, a transcription factor which is associated with synapse formation as well as memory function [292]. The level of p-CREB Ser 133 level is decreased in D-galactose-treated mice while melatonin treatment elevates p-CREB Ser 133 level and also prevents memory impairment [291].

Blocking Oxidative Stress and Neuronal Death

Oxidative stress, a key protagonist, is associated with age-related neuronal decline including AD [293]. Oxidative stress accumulates Aβ by an amyloidogenic pathway which results in mitochondrial damage, neuroinflammation, ROS generation, and advanced glycation end products (AGEs) formation [294–296]. These results are associated with loss of memory and cognition and also involve the activation of inflammatory mediators in AD brains [297]. Moreover, accumulation of Aβ generates free radicals in AD patients, which alter oxidative damage leading to increasing intraneuronal Ca^{2+} levels and intraneuronal free radical generation. Increased free radical is associated with mitochondrial dysfunction which leads to ATP depletion and neuronal death [298].

Melatonin directly detoxifies the progression of hydrogen peroxide (H_2O_2) and nitric oxide (NO) in the cerebral cortex [299]. 8-Oxoguanine, an oxidative stress marker, is distributed in patients with AD and dementia. To assess the oxidative stress, Ali et al. [291] performed immunofluorescence staining in D-galactose-induced mice model. They found that the 8-oxoguanine level was higher in D-galactose-treated mice as compared to the vehicle-treated mice in the hippocampal region including DG, CA1, and CA3. Melatonin treatment not only reduces the overexpression of 8-oxoguanine in DG, CA1, and CA3 region but also overcomes oxidative stress in D-galactose-induced model. Additionally, they also revealed that the expression of the level of p-IKKβ, nuclear factor kappa beta (NF-κB), cyclooxygenase-2 (COX-2), nitric oxide synthase 2 (NOS2), IL-1β, and TNF-α were increased in D-galactose-induced model as compared to vehicle group but melatonin treatment reduced that elevated expression [291].

Furthermore, melatonin prevents the NF-κB expression in Aβ model [300] and also suppresses p52 acetylation by inhibiting p300 HAT pathway [263]. The JNK pathway is involved with the activation of GSK-3, which is noticeably associated with AD progression. Melatonin inhibits JNK activation under oxidative stress condition and also exhibits anti-GSK activities by playing antioxidant properties [301]. Receptor for advanced glycation end products (RAGE), glial fibrillary acidic protein (GFAP), and ionized calcium-binding adaptor molecule 1 (Iba1) are responsible for microgliosis and astrocytosis. However, melatonin plays a vital role in reducing the expression level of RAGE, GFAP, and Iba1 and also suppresses several apoptotic mediators such as cytochrome (Cyt) c, caspase-9, caspase-3, and cleaved poly(ADP-ribose) polymerase-1 (PARP1) contributing neuronal death in D-galactose-induced mice model [291]. Moreover, melatonin neutralizes free radicals by exerting their antioxidant properties that reduce the possibilities of Aβ formation in AD patients [302]. Melatonin administration at a dose of 10 mg/kg attenuates neuronal death, microglial activation, and lipid peroxidation in KA-induced adult rat model [302]. Meanwhile, melatonin protects the neuronal cell death by inhibiting free radical formation, as well as Aβ generation, in in vitro model [303]. So melatonin might be a promising therapeutic target during AD progression.

Conclusion

The pineal product melatonin is a potent antioxidant and has a free radical scavenging power. Noticeably, by inhibiting oxidative stress, melatonin reduces the expression of proinflammatory cytokines, mitochondrial dysfunction, neuroinflammation, as well as neuronal cell death, in AD brain. It has been often proved that with aging, the progression of AD is increased concomitantly with melatonin level is slowly decreased. Therefore, a lower level of melatonin might be another risk factor for AD pathology. Melatonin also exerts the anti-Aβ aggregation effects and prevents tau hyperphosphorylation and neurotoxicity in Aβ-induced various species including humans. Through controlling SCN and CLOCK genes, melatonin protects circadian fluctuation, which may assist to attenuate AD. Melatonin contributes to stabilizing the structure of synapse and its plasticity, which further elevates memory and cognitive function. Therefore, melatonin might be a promising, safe, and compatible antioxidant for a future potent therapeutic target against AD.

Acknowledgments The authors are grateful to the Pharmakon Neuroscience Research Network, Dhaka, Bangladesh.

Author Contributions This work was carried out in collaboration between all authors. MSU and GMA conceived the original idea and designed the outlines of the study. MFH, MSU, GMSU, and DMS wrote the draft of the manuscript. MSU prepared the figures of the manuscript. GEB, MSI, and BM reviewed the scientific contents of the manuscript. All authors read and approved the final submitted version of the manuscript.

Funding The author(s) received no financial support for the research, authorship, and publication of this manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Abbreviations AD, Alzheimer's disease; Aβ, amyloid β; APP, amyloid protein precursor; AANAT, N-acetylserotonin by arylalkylamine N-acetyltransferase; AVP, arginine vasopressin; ACh, acetylcholine; AChE, acetylcholinesterase; AGEs, advanced glycation end products; ADAM10, a disintegrin and metalloproteinase domain-containing protein-10; AAD, aromatic amino acid decarboxylase; BMAL1, brain muscle ARNT-like 1; CSF, cerebrospinal fluid; CRY, cryptochrome; CLOCK, circadian locomotor output cycles kaput; COX2, cyclooxygenase-2; ChAT, choline acetyltransferase; C1q, complement 1q; CuZnSOD, copper-zinc superoxide dismutase; CDK5, cyclin-dependent kinase 5; ER, endoplasmic reticulum; GPx, glutathione peroxidase; H_2O_2, hydrogen peroxide; HIOMT, hydroxyindole-O-methyltransferase; IL1-β, interleukin-1-β; IL6, interleukin-6; KA, kainic acid; LPS, lipopolysaccharide; LTP, long-term potentiation; LTD, long-term depression; MCI, mild cognitive impairment; MnSOD, manganese superoxide dismutase; NFTs, neurofibrillary tangles; NO, nitric oxide; NOS2, nitric oxide synthase 2; NF-κB, nuclear factor kappa beta; PLC, phospholipase C; PKC, protein kinase C; PI3K, phosphatidylinositol 3-kinase; PER, period circadian protein homologue; PSEN1, presenilin-1; PSEN2, presenilin-2; ROS, reactive oxygen species; RHT, retinohypothalamic tract; SOD, superoxide dismutase; SCN, suprachiasmatic nucleus; SCG, superior cervical ganglion; SIRT1, sirtuin 1; TNF-α, tumor necrosis factor-α; VIP, vasoactive intestinal peptide; 5-HTP, 5-hydroxytryptophan; Bcl2, B cell lymphoma 2; PP2A, protein phosphatase 2A; GSK3β, glycogen synthase kinase 3 beta; PKA, protein kinase-A; Bax, BCL2 associated X; Par-4, prostate apoptosis response-4; JNK, c-JUN N-terminal kinase; ERK, extracellular signal-regulated kinase; MAO-A, monoamine oxidase A; RAGE, receptor for advanced glycation end products; GFAP, glial fibrillary acidic protein; Iba1, ionized calcium binding adaptor molecule 1; APOE, apolipoprotein E; PARP1, poly(ADP-ribose) polymerase-1

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