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REVIEW ARTICLE

Mechanisms of Melatonin in Alleviating Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a chronic, progressive and prevalent neurodegenerative disease characterized by the loss of higher cognitive functions and an associated loss of memory. The thus far "incurable" stigma for AD prevails because of variations in the success rates of different treatment protocols in animal and human studies. Among the classical hypotheses explaining AD pathogenesis, the amyloid hypothesis is currently being targeted for drug development. The underlying concept is to prevent the formation of these neurotoxic peptides which play a central role in AD pathology and trigger a multispectral cascade of neurodegenerative processes post-aggregation. This could possibly be achieved by pharmacological inhibition of β- or γ-secretase or stimulating the non-amyloidogenic α-secretase. Melatonin the pineal hormone is a multifunctioning indoleamine. Production of this amphiphilic molecule diminishes with advancing age and this decrease runs parallel with the progression of AD which itself explains the potential benefits of melatonin in line of development and devastating consequences of the disease progression. Our recent studies have revealed a novel mechanism by which melatonin stimulates the nonamyloidogenic processing and inhibits the amyloidogenic processing of β-amyloid precursor protein (βAPP) by stimulating α-secretases and consequently down regulating both β- and γ-secretases at the transcriptional level. In this review, we discuss and evaluate the neuroprotective functions of melatonin in AD pathogenesis, including its role in the classical hypotheses in cellular and animal models and clinical interventions in AD patients, and suggest that with early detection, melatonin treatment is qualified to be an anti-AD therapy.

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1. INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and the cause of premature senility, resulting in progressive mental deterioration and neurobehavioral deficits. Histopathologically, AD is characterized by extracellular deposits of Aβ in plaques [1] and intracellular neurofibrillary tangles mainly composed of an abnormally hyper-phosphorylated form of the microtubule-associated protein tau [2]. Additionally, cholinergic dysfunction in the central nervous system (CNS) contributes significantly to the cognitive decline associated with advanced age and AD [3, 4]. Melatonin (*N*-acetyl-5-methoxytryptamine) is a neuro-hormone produced by the pineal gland. It is highly pleiotropic, acting as a local regulatory molecule in probably all tissues [5]. This molecule was initially found to influence circadian rhythms [6, 7] and seasonal breeding [8, 9]. More recently, it was discovered to be a potent antioxidant and free

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radical scavenger [10, 11]. Its nuclear localization suggests its possible genomic actions [12-14].

Melatonin levels in individuals increase from birth and peak around puberty [15]. Its synthesis [16] and levels decline in middle-aged and most elderly individuals [17] along with a simultaneous reduction in the urinary excretion of its metabolites [18]. The functional versatility of this natural ubiquitous molecule enables it to regulate numerous aspects of biological and physiological functions [19], and its decline consequently alters related biological functions during aging and in diseased conditions [20]. In addition to its low level of intrinsic toxicity, studies have shown melatonin's ability to reduce the side effects and increase the efficacy of large number of drugs [21]. Moreover, it stimulates antioxidant defense systems in the brain [22, 23]. Melatonin easily diffuses through all morphophysiological barriers [24] and reaches every subcellular organelle [25]. It has been speculated that melatonin may actually be produced in all cells, *i.e*., in mitochondria [26].

The decline in melatonin production in aged individuals [27] is itself a significant factor that may contribute to age-related neurodegenerative disease processes [28] and has been suggested as one of the primary reasons for the development of AD. This is possible because as the pineal gland becomes impaired, most likely due to dysfunction of the suprachiasmatic nucleus (SCN), decreased melatonin levels and altered circadian rhythms may contribute to aging. A decline in cerebrospinal fluid (CSF) melatonin levels parallels the progression of AD neuropathology [29], which makes the brain cells more vulnerable to the oxidative damage that is observed to be more severe in AD brains [30, 31]. The high melatonin concentrations in the CSF supports the likelihood that melatonin would have exceptional protective effects in the CNS [32, 33]. Of interest is that the melatonin levels are lower in patients with AD than in age-matched control subjects [34, 35].

As a powerful free radical scavenger [36, 37], melatonin also displays anti-amyloidogenic properties, which qualifies it to be a promising therapeutic candidate for AD [38, 39]. Interestingly, inhibition of melatonin biosynthesis in rats causes signs that resemble AD pathology [40]. Many studies report increased free radical production, lipid peroxidation, oxidative DNA damage, oxidative protein damage, decreased ATP production, and reduced cell viability in postmortem AD brains compared to brains from age-matched healthy subjects [41, 42]. In this context, melatonin exhibits a broad diversity of effects to reduce neurodegenerative changes in the CNS [38, 43, 44].

An interesting fact regarding the circadian pattern of Aβ production is that Aβ levels reportedly rise when awake and fall during sleep [45], which could possibly be due to the day-night melatonin rhythm. Chronobiological disturbances such as sundowning contribute to mental decline [46], agitation and confusion in AD patients, and melatonin supplementation alleviates symptoms of sundowning and improves cognition [47-51]. Experiments in animal models of AD suggest that melatonin may disrupt the production and accumulation of both plaques and tangles, which are pathological hallmarks of AD [52-54]. Melatonin supplementation also helps combat sleep disorders associated with AD [55, 56] and prevents memory and cognitive impairment in AD patients [57]. Although many therapeutic investigations are underway to provide brain protection against AD, the most challenging is the regulation of disease initiation and prevention of the progression of neuropathology. In this review, we thoroughly discuss the likely preventive role of melatonin in AD and its remarkable function in controlling the progression of this devastating disease.

2. MELATONIN IN AGING AND AD: PROSPECTS FOR LIFE EXPANSION AND DELAYING SENESCENCE

2.1. Is Melatonin the Key to Unraveling the Incomprehensible Connection between Genetically Programmed Aging and AD?

The onset of puberty initiates a slow decline in blood melatonin levels. This decrease in the secretion of melatonin continues with advancing age [58], and by middle age, the levels drop to the point where they may trigger and initiate neurodegenerative changes in the brain. A number of clinical investigations and experimental studies have been performed that may partially explain this association. The pineal gland is part of the central biological system that some believe to be the initiation site for senescence [59]. Alterations in the retina-SCN-pineal axis and disrupted receptor-mediated effects of melatonin at the level of the SCN [60] leads to desynchronized melatonin rhythms and reduced melatonin production during aging; this also occurs in patients with AD [61-64]. These changes contribute to the deterioration of the structural, physiological, molecular and biochemical functions of the nervous system. The severe degenerative changes in the SCN result in abnormal nocturnal melatonin levels in AD patients [65]. In comparison to normal aging individuals [58, 66], the nighttime melatonin concentrations are reported to be especially low in AD patients [63]. Decreased melatonin levels in the CSF [29] and in the serum [67] of AD patients suggests dysfunction of the sympathetic regulation of pineal melatonin synthesis by the SCN during the early stages of AD [34, 35]. A diminishing level of melatonin may be a predisposing factor for AD [68], with this decline paralleling disease progression in AD patients [62].

The neurological markers of AD begin to develop after puberty [69], which coincides with the onset of melatonin synthesis decline. Additionally, there is a significant loss in the melatonin precursor serotonin in preclinical AD stages [70]. Melatonin concentrations in the ventricular CSF are reduced to one-fifth of those in elderly controls [71]. This difference is even more significant in (APOE) e4/4 type patients [71]. Furthermore, neurodegeneration in AD modulates the expression and physiological actions of both melatonin receptors (MT1/MT2) [72, 73], and interestingly, a reduced number of melatonin receptors in the pineal and cortical brain areas are found in AD [74]. Studies have demonstrated that chronic melatonin treatment slows the functional decline in the aging brain [75-78].

2.2. Aging Women More Prone to AD than Men

AD affects women earlier and more severely than men [79, 80]. Genetic evaluation reveals that female ApoE-4

carriers have twice the risk compared to male carriers for eventually developing AD, and studies have implicated the ApoE-4 gene-estrogen interaction in this marked increase in the risk. Prior to menopause, estrogen enhances neuronal cell division and proliferation [81, 82] and delays the onset and progression of neurological diseases. After menopause, the degree of impaired neurogenesis increases with age and is more pronounced in females, which could possibly be due to the dysregulation of the circulating levels of estrogens in aging women [79, 80, 83]. As there is a natural decline of estrogen levels during menopause, it is hypothesized that the loss of estrogens might predispose to AD pathology by increasing the risk and advancing the onset of the disease in aging women. In this context, animal studies have demonstrated that the cessation of fertility increases the vulnerability of brain cells to oxidative damage and dysfunction and that melatonin supplementation reverses these deleterious effects by preventing inflammation and apoptotic processes in a similar manner to estrogens [84].

2.3. Melatonin and Longevity

Well-regulated circadian rhythms correlate with improved longevity of several organisms. Melatonin synchronizes circadian rhythms [85-87] and may reduce the probability of age-associated neurodegenerative disorders [27] associated to altered biological rhythms [88]. The extensive therapeutic applications of melatonin are based on its anti-aging, senescence-delaying [89], antioxidant functions [90-92] and substantial protective and regenerative properties in the CNS [93]. Experimental studies have demonstrated the life extending property of melatonin [94-96]. When administered to aging animals [97], melatonin increased their life span by almost 20%. Although results in rodent models provide evidence for a melatonin/longevity connection, these studies must be extended to other species to strengthen the presumed association.

Melatonin increases the expression of the "longevity protein" sirtuin 1(SIRT1) [98, 99] which triggers the expression of a host of self-healing genes [98]. SIRT1 attenuates the amyloidogenic processing of βAPP both in cell cultures and in transgenic mouse models of AD [100, 101]. SIRT1 RNA and protein levels are significantly reduced in AD patients [102], which implies that the over expression of SIRT1 may be protective against AD phenotypes. In Tg2576 neuron cultures, SIRT1 promoted α-secretase activity and attenuated Aβ content in the brain [103] *via* the activation of ADAM10 [104]. Altered DNA methylation [105, 106] and histone modifications [107] are common epigenetic changes observed in aging and AD brains. Melatonin regulates these epigenetic processes in the neurons [108] which is one of the possible mechanisms by which it delays senescence and increases lifespan in healthy and diseased states. Herein, we thoroughly review the therapeutic role of melatonin as it relates to various hypotheses of AD (Fig. **1**). This summary includes data from cell culture and animal models to clinical investigations in AD patients. Collectively, the actions of melatonin as a neuroprotective agent are consistent with it having anti-AD effects.

3. COMPREHENSIVE REVIEW OF MELATONIN THERAPY IN DIFFERENT CLASSICAL HYPOTHESES OF AD PATHOGENESIS

Among the classical hypotheses that attempts to explain AD, the "cholinergic hypothesis" [109] was developed because of the role of acetylcholine (ACh) in learning and memory; it is well established that the loss of cholinergic neurotransmission and reduced levels of ACh [110] contribute significantly to deterioration in cognitive functions as observed in AD patients [3] and, in older patients [4] due to an impairment in ACh release [111]. Melatonin and its metabolites [36, 37] are powerful free radical scavengers [112, 113], and melatonin supplementation is beneficial and protective of the cholinergic system. It promotes choline transport [114], prevents the reduction of choline acetyltransferase (ChAT) activity by reducing ChAT nitrosylation and/or oxidation [115] in the frontal cortex and hippocampus [53, 115] and inhibits the increase in acetylcholinesterase (AChE) activity [116].

Neurofibrillary aggregates containing phosphorylated tau are another major hallmark of AD; their number correlates with the severity of dementia in this disease. The toxic pathological modifications [117] of tau contribute significantly to neurodegeneration and play a central role in AD pathogenesis [118]. Melatonin efficiently attenuates tau hyperphosphorylation by affecting the most relevant protein kinases involved in tau modifications in neurofibrillary degeneration; these enzymes include glycogen synthase kinase 3 beta (GSK3β) [119-122] and cyclin-dependent kinase 5 (Cdk5) [123]. These kinases are significantly elevated in aged [124] and AD brains [125]. This has been documented in a number of experimental models [126-131]. Interestingly, a comparative study between AD pathology and rat models with melatonin inhibition, which may activate cdk-5 [132], revealed similarities between the two, supporting the idea that reduced melatonin levels correlate with AD pathology [40].

The CNS is lipid-rich and therefore highly vulnerable to oxidative damage since lipids are easily oxidized. Free radicals are involved in the pathogenesis of neuronal degeneration, and in AD the brain is under increased continuous oxidative stress [133]. The oxidative damage prior to the onset of pathology in AD patients exceeds the levels observed in elderly controls, which could possibly be related to diminished melatonin levels. Melatonin is a chronobiotic-cytoprotective agent [134] that prevents oxidative stress due to its direct and indirect antioxidative actions [11, 135, 136]. Melatonin is highly lipid soluble and enters all subcellular compartments with ease [137], and along with its ability to directly scavenge highly toxic free radicals [11], it downregulates prooxidant enzymes [138] and upregulates antioxidant enzymes by transcriptionally regulating nuclear factor (erythroid-derived 2)-like 2 (Nrf2) [139, 140], thus protecting against increased oxidative damage [141] in the brain. Finally, melatonin chelates transition metals which *via* the Fenton/Haber-Weiss reactions, generate the highly toxic hydroxyl radical [142].

Melatonin is more potent than vitamins C and E [36] and provides remarkable protection against oxidative stress in the

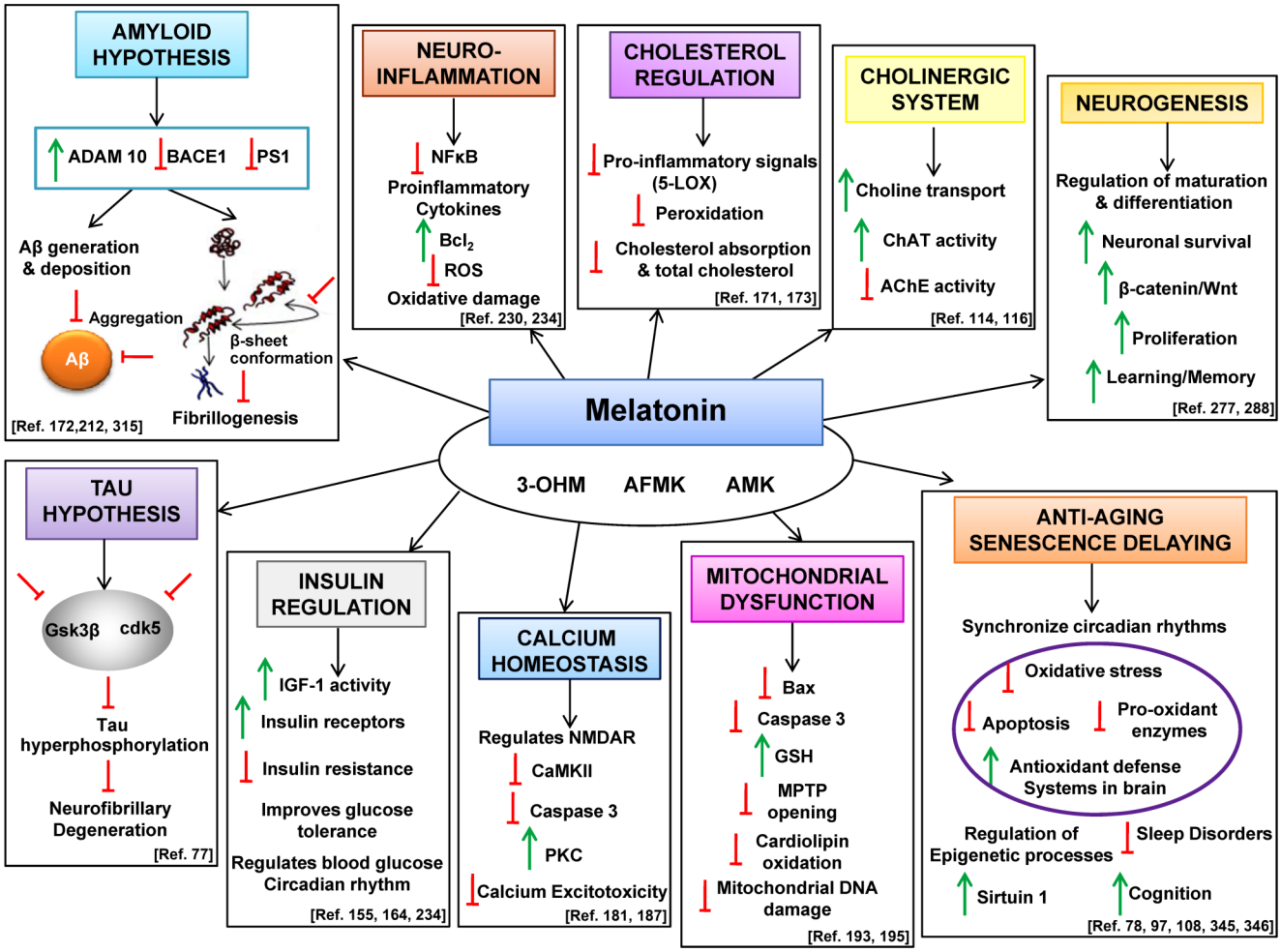

Fig. (1). Comprehensive summarization of melatonin therapy in different classical hypotheses of AD pathogenesis. This figure summarizes the potential therapeutic targets of melatonin in AD treatment. Melatonin is metabolized into its kynuramine derivatives AFMK (N1-acetyl-N2-formyl-5-methoxykynuramine), AMK (N1-acetyl-5-methoxykynuramine) and 3-OHM (cyclic 3-hydroxymelatonin) which also possess neuroprotective biological and pharmacological properties. Melatonin levels strongly decrease with advancing age and patients with AD exhibit lower melatonin levels than age matched controls. In this context, melatonin *via* its action on the circadian oscillators modulate and synchronize the rhythms, regulates the epigenetic processes and stimulates the anti-oxidant defense system in the brain thereby improving cognition and sleep disorders. Melatonin also promotes neuronal survival by stimulating neurogenesis. Among the classical hypotheses of AD, melatonin has a protective effect on the cholinergic system by stimulating both choline transport and ChAT activity and down regulating AchE activity. By regulating the important kinases (GSK3β, cdk5) melatonin attenuates hyperphosphorylation of tau thereby precluding tangle formation. Melatonin stimulates the non-amyloidogenic and down regulates the amyloidogenic processing of βAPP thereby precluding the formation of Aβ peptides. Aβ-induced microglial activation is an important factor in AD pathogenesis and in this frame of reference melatonin attenuates proinflammatory cytokines, inhibits NFκB activity and reduces oxidative damage. Melatonin regulates blood glucose circadian rhythm by stimulating IGF-1 activity and modulating insulin resistance. Melatonin regulates Aβ-induced altered calcium and mitochondrial homeostasis thus protecting cells against oxidative stress and cell death and also regulates cholesterol homeostasis further preventing peroxidation of neuronal membrane lipids. Therefore, the diverse biological and physiological properties of melatonin employ it to be a neuroprotective drug in the treatment of AD. (↑ = stimulation, ⊥ = inhibition).

brain, even at physiological concentrations [19, 143, 144]. Melatonin and its metabolites function as broad-spectrum antioxidants [145-147], and under enhanced oxidative stress in aging and AD [148] the role of melatonin in providing brain protection has been extensively reviewed and critiqued [135, 149-151], making this molecule a promising therapeutic candidate with regard to AD pathology [38, 39]; in addition to the protection it affords the brain, in senescent mouse models, chronic melatonin treatment increased lifespan [152].

The age-related melatonin decline induces insulin resistance, glucose intolerance, sleep disturbance, and metabolic circadian disorganization [153], which are commonly observed in AD pathology. Melatonin reduces brain damage by enhancing IGF-1 activity [154, 155], probably due to melatonin-induced sleep improvement [156]. The activation of protein kinase B (Akt) by melatonin [157] reactivates IGF-1, thereby reducing insulin resistance [158, 159] and Aβ accumulation [160-162]. Melatonin influences the circadian blood glucose rhythm [163], improves glucose tolerance and

increases insulin receptors in addition to glucose clearance from the blood [164].

Cholesterol modulates and enhances Aβ production [165-167] and negatively regulates α-secretase activity [168] with augmentation of both β- and γ -secretase activities, resulting in increased Aβ production. Exposure to cholesterol-lowering agents [169, 170] reduces the amyloid load in cultured cells and in the brain of mammalian models. Melatonin significantly reduces cholesterol absorption [171], and the most widely known effect of melatonin on lipids is to prevent their peroxidation [143, 172, 173]. The protein levels and enzyme activity of *5-lipoxygenase*-activating protein (5-LOX), an active Aβ inducer [174], and 12/15-LOX are increased in AD brains [175]. 5-LOX overexpression in elderly subjects may be related to the age-associated melatonin deficiency [176] since melatonin suppresses 5-LOX gene expression through its high-affinity nuclear receptors [177], even in the nanomolar range [178, 179]. This reduces the proinflammatory response [180], which contributes to oxidative stress.

The Ca^{2+} overload in neurons results in excitotoxicity, thereby inducing cell death and neurodegeneration. The activation of the amyloidogenic pathway leads to a remodeling of the neuronal Ca^{2+} signaling pathway [181, 182], which alters the normal Ca^{2+}-dependent mechanisms responsible for learning and memory. Ca^{2+}/calpain activity declines during aging, which makes βAPP more vulnerable to attack by β- and γ-secretases, resulting in Aβ formation. Over activation of N-methyl-D-aspartate receptor (NMDAR) also stimulates the amyloidogenic processing of βAPP. Aβ selectively interacts with the NMDA receptor [183], leading to dysregulation of Ca^{2+}. Melatonin controls the NMDA receptor [184], possibly by redox modulation [185], and regulates intracellular free Ca^{2+} by directly binding to calmodulin [186, 187], thereby decreasing the activity and autophosphorylation of Ca^{2+}/calmodulin-dependent protein kinase II (CAMK II) and activating protein kinase C (PKC), even in the nanomolar range [188]. This protects cells from calcium-dependent caspases. Calreticulin, another calcium regulator, functions as a molecular chaperone for the Aβ precursor protein [189], and its relationship with melatonin [190] may be relevant in AD.

Mitochondrial dysfunction has an early and predominant role in AD [191, 192]. Melatonin provides mitochondrial protection by preventing cardiolipin oxidation, avoiding 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) opening and restoring Ca^{2+} balance [193-195]. Caspase-3 levels are higher in AD brains than in age-matched controls [196], and the activation of caspase-3 accounts for increased β-secretase activity, thereby augmenting Aβ production [197]. In contrast, melatonin downregulates caspase-3 [198], which is linked directly to cell death in AD [199] and enhances anti-apoptotic bcl-2 expression in AD transgenic mice and in ischemic brains [200].

Glucocorticoids and corticotropin-releasing hormones induce AD-associated pathologies [201], possibly related to hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis. Melatonin modulates the activity of this axis [202], and its nocturnal elevation influences the cortisol rhythm, which indicates the importance of the melatonin/corticoid relationship [203]. Furthermore, a significant rise in serum cortisol levels has been demonstrated in elderly individuals and is more pronounced in demented subjects compared to young controls during the night [204].

3.1. Melatonin in Aβ Toxicity

Aβ peptides are produced *via* the amyloidogenic processing of βAPP, and the imbalance between the production and clearance of Aβ leads to its accumulation; this triggers a cascade of pathological mechanisms in the brain, disturbing the overall cellular homeostasis. Relative to this, several anti-amyloid processing effects of melatonin have been demonstrated in *in vitro* and *in vivo* studies. Aβ by itself is capable of generating free radicals, resulting in protein, DNA and lipid oxidation along with diminished energy metabolism. Melatonin prevents $Aβ_{25–35}$-induced circadian alterations [205] and Aβ-induced oxidative stress [150], lipid peroxidation [206], cellular death and DNA damage in neuroblastoma cell cultures [172, 207] and human platelets [47]. Melatonin also protects the APP + presenilin 1 (PS1) double-transgenic mouse model of AD from cognitive impairment [208]. Melatonin reduces Aβ generation and deposition both *in vivo* [209] and *in vitro* [210-212] and prevents Aβ aggregation *via* direct interaction [213, 214]. Melatonin also exhibits antifibrillogenic effects [52, 215], alleviates behavioral deficits associated with apoptosis and cholinergic system dysfunction [216, 217], inhibits amyloid pathology [218] and increases survival in transgenic mouse models [209]. ApoE4 aggravates the effects of Aβ. Melatonin reversed the profibrillogenic activity of ApoE4 and neutralized its neurotoxic combination with Aβ [52]. Aβ activates caspase 3 and induces apoptosis [219], while melatonin alleviates the Aβ-induced rise in caspase-3 activity [220, 221].

N1-acetyl-N2-formyl 5-methoxykynuramine (AFMK) [145], a melatonin metabolite, prevented Aβ-induced toxicity [222] though such effects were not observed in old transgenic mouse models. Melatonin reduced Aβ-induced AChE activity and prevented acetylcholine degradation [214]. Accumulated Aβ activated microglia [223-225], induced an inflammatory response *via* stimulation of the NFκB-dependent pathway leading to cytokine release [226]. NFκB stimulation was followed by neuritic injury, hyperphosphorylation of the tau protein, and the formation of neurofibrillary tangles, leading to cognitive impairment [227] and ultimately to neuronal dysfunction and cell death.

Cytokines transcriptionally upregulate beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) mRNA, protein and enzymatic activity [228]. *Via* this means, a vicious cycle forms between Aβ-induced cytokines, which further increase Aβ production by upregulating BACE1. Melatonin possesses anti-inflammatory properties [229, 230]. By inhibiting NFκB [231, 232], melatonin suppresses the production of proinflammatory cytokines [30, 233-235] and also attenuates the Aβ-induced secretion of IL-1β and IL-6 [236] in transgenic mouse models. Melatonin prevents Aβ-induced depletion of bcl-2 [221] and enhances bcl-2 expression in AD transgenic mice and in ischemic brains [200]. Based on studies by [237], melatonin may impair the

Aβ-induced assembly of phagocytic oxidase (PHOX) by inhibiting the translocation of the p47phox and p67phox subunits of PHOX from the cytosol to the plasma membrane, thus eventually preventing the subsequent production of ROS.

Melatonin restores insulin/insulin receptor mechanisms and increases PI3-K/Akt signaling activity, resulting in the inhibition of GSK-3β and less Aβ accumulation and reduced tau hyperphosphorylation [238]. Acting through its MT2 receptor, melatonin stimulates phospholipase C (PLC) and activates PKC *via* diacylglycerol (DAG) [239], which in turn phosphorylates and inactivates GSK-3β. Thus, by activating PKC, melatonin might impair Aβ overproduction. It has been speculated that melatonin, which prevents JNK activation under oxidative stress conditions [240], may also employ this mechanism to prevent the activation of GSK-3β. Studies have shown that melatonin potentiates the neuroprotective properties of resveratrol against beta-amyloid-induced neuro-degeneration by modulating 5'AMP-activated protein kinase (AMPK) pathway [241]. Melatonin controls apoptosis and stress-mediated events by regulating Bcl2/Bax, glutathione and its enzymes [242] and increases the activation of the prosurvival PI3K/Akt pathway, inhibiting GSK-3β and resulting in an increase in Forkhead box protein O1 (FOXO-1) phosphorylation [243]. Overall, melatonin protects the brain from an Aβ-induced cascade of neurodegenerative processes, thus likely playing a critical role in preventing disease progression.

4. MELATONIN: AN ENDOGENOUS REGULATOR OF NEUROGENESIS IN AGING AND AD

Adult neurogenesis contributes positively to learning and memory [244]. The potential of hippocampal precursor cells to proliferate and differentiate marks cellular plasticity and cognitive health of any organism, and low proliferation and differentiation capacities of adult hippocampal stem cells correlate with memory dysfunction [245]. Physiological aging alters neurogenesis, and the accumulation of Aβ suppresses the proliferation of neural stem and progenitor cells and neuronal differentiation in cell culture and animal models [246-248]. Dysfunctional neurogenesis exacerbates neuronal vulnerability to AD and contributes to memory impairment [249]. Studies in transgenic animal models have reported reduced hippocampal neurogenesis [249] in the sub-ventricular zone (SVZ) and sub-granular zone (SGZ) [247, 250, 251] associated with Aβ peptides [252, 253] and increased amyloid precursor protein intracellular domain (AICD) expression, which consequently reduces hippocampal progenitor cell proliferation and survival [254]. Oligomeric Aβ inhibits proliferation [255] and decreases neurogenesis *via* the downregulation of β-catenin [256] and apoptosis, thereby leading to Wnt/β-catenin signaling impairment [257]; this further activates GSK3β, resulting in stimulation of Aβ production and tau phosphorylation [258]. Evidence from other clinical studies showed decreased expression of β-catenin [259, 260] and reduced Wnt/β-catenin signaling in AD brains [237]. Wnt/β-catenin prevents Aβ-induced toxicity and apoptosis and inhibits GSK-3β activity and tau phosphorylation [261]. Therefore, sustaining or enhancing the production of new neurons is now regarded as a potential therapeutic strategy to prevent AD-associated cognitive decline.

Melatonin is a positive endogenous regulator of neurogenesis during aging [262], and experimental studies have shown that it prevents the abatement in proliferation and neurogenesis that occurs in aging and AD. The melatonin receptors MT1 [263] and MT2 [264] are expressed in neural stem cells and in the adult brain [265]. Interestingly, the MT1 and MT2 agonists agomelatine [266, 267], in the adult rat hippocampus, and buspirone potentiate neurogenesis in combination with melatonin in major depressive disorder (MDD) [268]. Melatonin enhances dendritogenesis [269], dendritic maturation of doublecortin (DCX)-positive cells [270] and, in combination with exercise, enhances neurogenesis and neuronal survival [271, 272]. Sleep deprivation, which is directly linked to reduced melatonin levels in AD, leads to depressed hippocampal neurogenesis and increased Aβ generation; this contributes to memory dysfunction. Interestingly, animal studies demonstrated that melatonin modulates the proliferation and differentiation of neural stem cells [273] and promotes the survival of new neurons [274]. Its administration also prevented the loss of pyramidal neurons *in vivo* [275] and induced neurogenesis in the dentate gyrus of adult pinealectomized rats [276].

A variety of clinical investigations and animal studies have revealed the possible mechanisms by which melatonin regulates neurogenesis. It increases adult hippocampal [277] and subventricular zone [278] progenitor cell proliferation and neurogenesis *via* melatonin receptor-mediated ERK signaling and by enhancing BDNF-like growth factors. Melatonin also prevents methamphetamine-induced [279] and dexamethasone-mediated alterations in hippocampal neurogenesis in the mouse brain [280]. A comparative clinical investigation in AD patients and healthy controls revealed that Aβ-induced interruption of β-catenin signaling may contribute to the impairment of neurogenesis of hippocampal progenitor cells in AD [257]; similar results were observed in AD transgenic mouse models. In this context, melatonin has been shown to increase β-catenin protein expression and activation in human neuroblastoma cell cultures [281], and *via* its receptors, melatonin stimulates the PI3K/Akt [264] and PLC/DAG pathways and activates PKC [239]; this in turn phosphorylates and inactivates GSK-3β.

Cholinesterase inhibitors promote the survival of newly generated neurons and increases neurogenesis in adult mice [282], while melatonin decreases AChE activity and exhibits an anti-amnesic effect [283]. Our recent findings demonstrate that melatonin stimulates the α-secretases [284] at the transcriptional level and increases sAPPα production, which is known to promote neural progenitor cell (NPC) proliferation [285] and advance the survival of neurons [286]. Oxidative stress impairs adult neurogenesis during aging [287]. In contrast, melatonin supplementation prevents oxidative stress-induced impairment and induces neuronal stem cell proliferation and differentiation [288] by stimulating the α-secretases. While collectively the findings support melatonin as an anti-AD agent, additional mechanistic studies would help to validate this association.

5. ROLE OF MELATONIN IN REGULATING THE NON-AMYLOIDOGENIC AND AMYLOIDOGENIC PROCESSING OF βAPP: PREVENTION OF AB PRODUCTION

The non-amyloidogenic α-secretase cleavage of βAPP is mainly performed by two enzymes (ADAM10 and ADAM17) responsible for the constitutive and PKC-regulated pathways [289-291] that thereby preclude the formation of Aβ. In contrast, the amyloidogenic cleavage of βAPP by BACE1 consequently results in the formation of Aβ peptides [292]. Many examinations of the AD brain have shown a reduction in α-secretase or an increase in β-secretase, or both [293]. Clinical investigations in AD patients have reported reduced α-secretase activity and lower levels of ADAM10 [294, 295] and sAPPα levels in the CSF [296, 297] and platelets [295]. This perturbed balance favors β-secretase cleavage, releasing proapoptotic sAPPβ [298] along with Aβ overproduction and the associated decline in cognitive functions. Interestingly, elevated BACE1 expression is associated with aging and oxidative stress [299]. The enhanced BACE1 protein and activity has also been documented in the brains of AD patients [300-303]. In this context, α-secretase-promoting therapeutic agents are neuroprotective by enhancing sAPPα formation [304-306] Enhanced α-secretase activity [307] and the overexpression of ADAM10 (Postina *et al*., 2004, Schroeder *et al*., 2009) andADAM9/ADAM17 (Kuhn *et al.*, 2010, Weskamp *et al.*, 2002) increased the release of sAPPα and limit sAPPβ, thereby reducing the formation of Aβ40 and Aβ42; this further reduces Aβ peptide levels [307].

A reduction in BACE1 prevents cholinergic dysfunction, neuronal loss and memory deficits, along with a reduction in Aβ40/42 levels [308, 309]. Studies in AD mouse models have shown that knockout of BACE1 reduced Aβ production [310, 311], amyloid plaque load and AD-related symptoms [308, 312]. As discussed previously, many earlier studies focused on the ability of melatonin to protect against Aβ deposition, aggregation, fibrillogenesis, pro-inflammatory effects, and oxidative and apoptotic neurotoxicity. Cell culture studies show that melatonin inhibits sAPPβ secretion [210, 313] and reduces the levels of Aβ peptides in the murine cerebral cortex [314].

We recently investigated whether melatonin directly controls the secretases responsible for βAPP processing. We documented that near physiological concentrations of melatonin positively control the α-secretases ADAM10 and ADAM17 at the transcriptional level and downregulate the BACE1 protein and mRNA levels and activity [284, 315] (Fig. **2**). We also investigated the underlying signaling mechanisms by which melatonin regulates βAPP proteolytic cleavage. Activation of ERK/MAPK signaling in the CNS is critical for synaptic plasticity and memory, and PKC-dependent α-secretase competes with β-secretase for cleavage of β-APP and thus prevents its amyloidogenic processing. Interestingly, melatonin regulates PKC [316, 317], and PKC also mediates the circadian entrainment effects of melatonin in the master biological clock [318]. *Via* stimulation of its plasma receptors, melatonin induces ERK phosphorylation through three distinct signaling pathways (Gq/PLC/PKC, Gi/PI3K/PDK1/PKC or Gs/cAMP/PKA), which leads to the activation of transcription factors, including CREB, Oct-1, and HIF-1. This activation further stimulates ADAM10 and ADAM17 promoter transactivation and mRNA levels [284]. Moreover, the melatonin-dependent activation of α-secretase would likely suppress Aβ production, as previously discussed, and would also impair AICD production by favoring the α/γ over the β/γ pathway [319-321] and reducing AICD-dependent GSK3β expression [322]. This may explain the previously-described inhibitory effect of melatonin on this tau-phosphorylating kinase [323]. The phosphorylation of GSK-3β by PKC leads to γ-secretase inactivation. GSK-3 may be one of the common signaling pathways that increases Aβ generation and tau hyperphosphorylation; thus melatonin could regulate βAPP processing through the PKC and GSK-3 pathways. BACE1 and PS-1 are key enzymes in neuronal Aβ formation and in their absence, Aβ synthesis is either abolished or considerably reduced [324]. We also demonstrated that in the amyloidogenic pathway, melatonin attenuates BACE1 and PS1 protein expression and mRNA levels *via* melatonin receptors (MT1/2) [315], possibly by inhibiting NF-κB activation.

Aging is the major risk factor for AD, and the phenomenon of Aβ accumulation and aggregation is similar to what is observed in the AD brain, with significant increases in the Aβ42:Aβ40 ratio [325]. Studies in aged animal models have confirmed elevated BACE1 [326] and γ-secretase [327] activities, which ultimately lead to increased Aβ accumulation. We found that in the hippocampus of aged mice melatonin upregulated the aged-induced loss in ADAM10 and downregulated the rise in BACE1 and PS1 protein levels through transcriptional regulation [328]. NF-κB upregulates BACE1 expression [329], whereas melatonin downregulates NF-κB activation in SH-SY5Y cells by inhibiting the translocation of the NF-κB subunit (p65-p50) into the nucleus [139]. This suggests that the melatonin-induced reduction in BACE1 levels may occur through the inactivation of the NF-κB pathway. Moreover, melatonin upregulates ADAM10 through the SIRT1 pathway activation [243]; this is an alternate mechanism by which melatonin may upregulate ADAM10 expression, as observed in aged mouse models [328]. Deregulation of the proteolytic processing of βAPP by secretases is an early event in AD pathology, with a melatonin deficiency having serious effects [330]. This suggests that melatonin supplementation should be started at a very early stage of AD to provide maximum brain protection and prevention. Studies in transgenic animals also support the view that melatonin should be given at an early phase to regulate Aβ metabolism, mainly by preventing formation of Aβ [331]. Moreover, enhancing α-secretase activity by increasing the expression and activity of ADAM10 and 17 and/or downregulating BACE1/PS1 is a promising means of the treatment of AD.

6. MELATONIN REGULATION OF EPIGENETIC MECHANISMS-IMPLICATIONS IN AD

The main epigenetic modifications that contribute to disease pathogenesis are bizarre patterns of DNA methylation, histone modifications and RNA-based mechanisms controlled by non-coding RNAs and microRNAs (miRNAs) which are heritable but reversible changes in gene function without causing any alteration in the DNA sequence. These

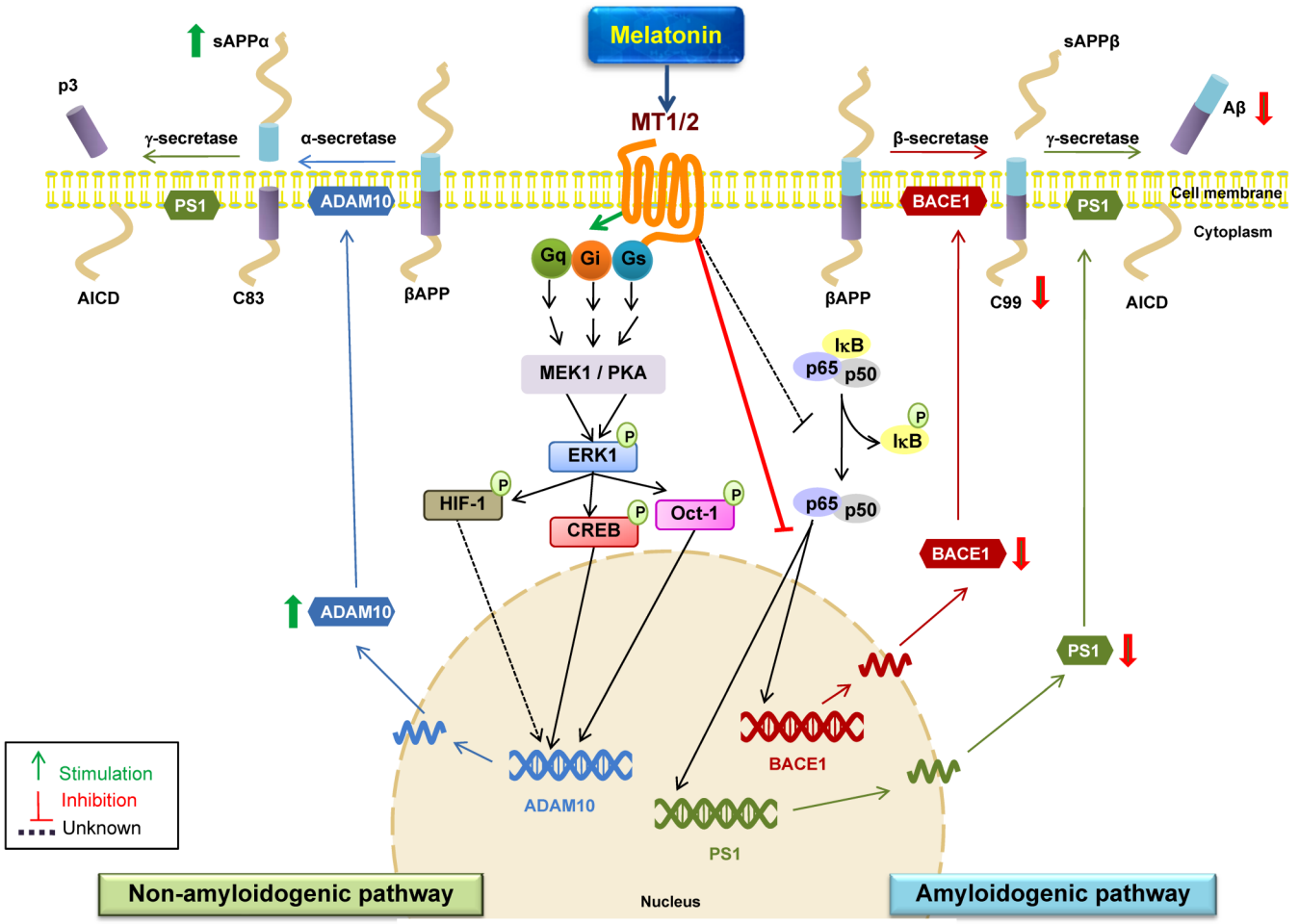

Fig. (2). Schematic representations of melatonin-dependent regulation of βAPP processing secretases and its possible underlying mechanisms. The proteolytic processing of βAPP by the non-amyloidogenic pathway precludes Aβ formation. Cleavage by α-secretase (ADAM 10) releases sAPPα and C83 which further undergoes cleavage by γ-secretase to generate P3 and AICD fragments; thereby preventing the generation and release of Aβ peptides. In amyloidogenic pathway, βAPP is cleaved by β-secretase (BACE1) releasing sAPPβ and C99 which is subsequently cleaved by γ-secretase to produce Aβ 1-40 and Aβ 1-42 peptides. Stimulation of the melatonin receptors located at the plasma membrane induce ERK phosphorylation probably *via* three distinct signaling pathways (Gq/PLC/PKC, Gi/PI3K/PDK1/PKC or Gs/cAMP/PKA) thus triggering the activation of transcription factors CREB, Oct-1, and HIF-1 which further increase ADAM10 promoter transactivation and mRNA levels consequently granting more α-secretase activity and sAPPα production fomenting neuroprotection. In the amyloidogenic pathway, melatonin in a receptor-dependent manner attenuates BACE1 and PS1 protein expression and transcriptional levels and decreases levels of C99 which is further cleaved by γ-secretase to generate Aβ peptide. BACE1 promoter region has multiple transcription factor binding sites like for NF-κB. Melatonin inhibits NF-κB activation which could possibly regulate melatonin induced decrease in BACE1 and C99 expression. Thus melatonin-dependent transcriptional activation of α-secretases and down regulation of BACE1 and PSI levels strongly indicates the beneficial role of melatonin in AD pathology thereby precluding Aβ production. Aβ, beta-amyloid; ADAM10, α-secretase; BACE1, β-secretase; Mel, melatonin; MT1/2, melatonin receptor; NF-κB, nuclear factor- kappa light-chain enhancer of activated B cells; PS1, presenilin1; PKA, Protein kinase A; MEK1, mitogen-activated protein kinase kinase 1; AICD, The amyloid precursor protein intracellular domain.

mechanisms are involved in learned behavior, cognition, formation and maintenance of memory and neuro-degenerative pathology [332-334]. Epigenetic alterations like differentially DNA methylated genes and histone acetylated genes in AD have been extensively reviewed [335, 336]; these aberrant epigenetic changes trigger alterations at the transcriptional level of genes like βAPP [337], BACE1 and PS1[338] which are involved in the pathogenesis leading to dementia/AD. Neuropathology-associated with the hyper-methylation of the gene ankyrin 1 (ANK1) implicates cortical deregulation which is a primary site of AD pathogenesis [339] suggesting that epigenetic changes might contribute to AD beyond expectation [340]. Therapeutics for epigenetic alterations in AD is by itself challenging and therefore early diagnosis would aid in successful treatments. PET imaging allows noninvasive visualizations of differential HDAC activity, neuronal hypomethylation, and imaging Aβ plaque deposits and tangles [341] which are the epigenetically influenced events and would thus provide beneficial insights for preventing, early diagnosis, and treating AD. Likewise, epigenetic therapeutic approaches for AD include HDAC inhibitors, Sirtuins, HATs, DNA methylation modulation and miRNAs [342].

Interestingly, melatonin possesses all of the above required properties in being a comprehensive future epigenetic therapy for AD [108, 343]. Concerning the mechanisms of epigenetic regulation by melatonin in AD, there are many studies demonstrating various targets and signaling pathways involved, which would provide a better understanding in this particular area of research. Epigenetic mechanisms might work through the circadian clock to regulate neuronal function and influence disease states [344] which suggests a potential role of melatonin in epigenetic regulation [345, 346]. Extended sleep disturbances causes histone modifications along with significant alterations in the levels of DNA methylation [347]. Sleep and circadian disorders in AD appear early in the course of the disease [348] which might be due to decreased melatonin levels which supposedly parallels AD progression. As such melatonin has been known to regulate sleep/circadian rhythm disorders. It also regulates antioxidant and pro-inflammatory genes *via* epigenetic on/off mechanisms [349], reverses tumor growth through the epigenetic mechanism of global DNA methylation [350] and ameliorates prenatal dexamethasone induced epigenetic alterations in the rat hippocampus [351]. HDAC inhibitors reverse the abnormal histone acetylation and improve cognitive function and memory in transgenic mouse models of AD [352, 353]. In this context, melatonin has been shown to inhibit HDACs [354] which shows it capability of reversing the observed epigenetic changes.

MicroRNAs (miRNAs) are post-transcriptional regulators involved in numerous biological processes involved in AD pathogenesis. It has been speculated that melatonin mediates the regulation of gene expression at the post-transcriptional level through its effect on miRNA expression. The profiling of the pineal miRNAs (miR-182, miR-96, miR-183, miR-483) notified that melatonin synthesis also somehow lies under the epigenetic control [355]. Regarding AD, several miRNAs have been identified which directly regulate βAPP expression and processing along with its secretases thus regulating Aβ load. These miRNAs are also involved in regulation of BACE1 cleavage and expression which has been comprehensively reviewed [356]. One of them is miR-124 which not only controls BACE1 gene expression [357] but is also the most abundant miRNA in the brain and affects a broad spectrum of biological functions in the CNS [358]. Interestingly, melatonin by regulating miR-124 attenuates memory and synaptic disorder thereby aiding drug discovery in AD [359]. Surprisingly of interest is the fact that melatonin receptor 1 has been identified as a direct target of miR-29b [360] suggesting possible regulatory mechanisms of melatonin *via* miR-29b. The miRNAs (miR-103, miR-107 and miR-1306) possibly regulate ADAM10 expression [361] and as melatonin stimulates ADAM10 activity which simultaneously prevents amyloidogenic processing of βAPP, it might have an epigenetic control over this processing *via* the above mentioned miRNAs.

Measurements of miRNAs in the CSF has emerged as a novel diagnostic tool for various neurological conditions. Interestingly melatonin has been recently reported to be involved in controlling miR-497 expression [362]. Down regulation of miR-125b, miR-23a, miR-26b has been shown in serum from AD patients [363] out of which miR-23a has been shown to regulate ER stress and melatonin has the ability to regulate expression of miR-23a [364]. miR-34a is a potential therapeutic target for AD as its alteration is associated with dysfunction of synaptic plasticity, energy metabolism, and resting state network activity [365]. It is over expressed in specific brain regions of AD patients which correlate with the severity of the disease. Melatonin modulates miR-34a/SIRT1 pathway [366] which adds on to another regulatory function of this neurohormone in mi-RNAs involved in AD. Expression of long interspersed element-1 (LINE-1) can introduce genomic instability and its methylation is increased in AD patients [367] and melatonin regulates LINE-1 in a receptor dependent mechanism [368]. A very recent investigation [369] provided the first evidence of PIWI-interacting RNAs (piRNAs) in the human brain and its dysregulation in AD. Interestingly, piRNA effects the expression of melatonin receptor type1A [370] and as DNA methylation pattern and chromatin remodeling *via* histone deacetylation may be associated with changes in melatonin receptor expression therefore it becomes reasonable to suggest that melatonin might also control epigenetic mechanisms in AD *via* interacting with piRNAs.

Extracellular miRNAs (miR-9, miR-34c, miR-101, miR-132) in CSF and serum from AD patients correlates with the status, progression and characteristic features (neurofibrillary tangles and amyloid plaques) of AD pathology [371]. Overexpression of α-synuclein has been reported in the CSF of AD patients [372] and this increase contributes to cognitive dysfunctions and memory impairments similar to that of AD mice model [373]. Significant down-regulation in miR-132 expression has been associated with α-synuclein accumulation and neuronal malfunction in α-synuclein (A30P)-transgenic mice [374, 375]. Melatonin prevents up regulation of α-synuclein in amphetamine-treated rats [376] which might aid in regulating miR-132. miR-9 also targets SIRT1 which is reduced in AD [102, 377]. Decreased SIRT1 levels would indicate a potential increase in miR-9, or the increase of another miRNA targeting SIRT1. Interestingly, elevated miR-34c also correlates with decrease in SIRT1. As melatonin naturally enhances SIRT1, it might affect the expression patterns of both miR-9 and miR-34c.

Cyclooxydenase-2 (COX-2) and βAPP are known miR-101 targets implicated in AD [378]. It is possible that miR-101 down-regulation might contribute significantly to AD pathology by enhancing βAPP expression, tau phosphorylation and contributing to inflammation through the up regulation of COX-2 expression. Melatonin suppresses COX2 by inhibiting p52 acetylation and binding [234] and by inhibiting COX-2/iNOS and NF-κB/p300 signaling pathways [379] which implicate that melatonin might regulate these mechanisms *via* modulating miR-101. The proliferation, fate specification and differentiation of adult neural stem cells are regulated by epigenetic mechanisms which are relevant to AD etiology and pathogenesis [380]. In this context, melatonin has been known to promote neurogenesis [278], so it could be envisioned how melatonin by regulating epigenetic mechanisms could modulate both degenerative and regenerative processes in AD pathogenesis thus meeting the preventive and curative parameters of anti-AD regime.

7. MELATONIN CLINICAL INTERVENTIONS IN AD-FUTURE PROSPECTS IN ANTI-AD DRUG DEVELOPMENT

A number of clinical trials with melatonin supplementation have been successful in terms of the prognosis of AD. Diminished levels of melatonin correlate with AD pathology; therefore, the replacement of physiological levels of melatonin in the brain could impede the progression of this disease [150, 381]. Mild cognitive impairment (MCI) is an etiologically heterogeneous syndrome that precedes dementia. It has been shown that melatonin significantly retarded the progression of MCI patients to AD over time, and melatonin is beneficial in AD and MCI patients [47, 49, 381-384] by significantly improving cognitive and emotional performance [385]. Clinical investigations of the efficacy of melatonin in treating patients with MCI and AD have been extensively reviewed and discussed by [70, 331, 383]. As early diagnosis and preventive therapeutic implementation guard against the development of neurodegenerative diseases such as AD, studies have shown that the time of melatonin supplementation may be crucial in AD pathogenesis [217]. Investigations in patients showed the efficacy of prolonged melatonin release in elderly and insomnia patients, which would consequently decrease Aβ levels [386, 387]. Human clinical interventions for AD usually begin only after the symptoms appear, but the actual degeneration is initiated much earlier before these symptoms appear; therefore, along with a preventive therapeutic strategy, the early detection of AD is equally important for the successful outcome of this devastating disorder. In this context, our previous studies suggest that melatonin is a potential therapeutic agent for preventing and thereby reducing the risk of AD. Melatonin should be advanced as an anti-AD drug for humans. Importantly, the inter-individual pharmacokinetics in relation to the concentration of melatonin [388] in the plasma and the proposed treatment doses should also be investigated, and new dosage paradigms should be explored for use in clinical trials.

CONCLUDING REMARKS

In summary, this review emphasizes on the diverse roles of the pineal hormone melatonin as an anti-AD regime. We have done a comprehensive evaluation of various experimental and clinical investigations regarding the therapeutic effects of melatonin in AD. Along with its neuroprotective roles in the three classical hypotheses (cholinergic deficits, tau integrity and β-amyloid aggregation and deposition) we also discuss the underlying molecular mechanisms of melatonin action in the multispectral degenerative cascade triggered during the progressing stages of AD. Inhibiting β-secretase and/or enhancing α-secretase processing of βAPP is a preventive strategy in combating this disorder and our recent studies demonstrated that melatonin qualifies to be a defensive and preventive anti-AD drug. The rationale of the therapeutic approach in AD must be focused on its early detection as the stage of the disease and its irreversible nature is critical in terms of the relevant clinical outcomes of any medications prescribed. Although there are ethical issues when it comes to the toxicity parameters and precautionary methods during clinical trials with different therapeutic strategies in the diseased and non-AD control groups, it should be noted that the toxicity of melatonin is almost negligible. Therefore, melatonin could be considered as a broad-spectrum strategy in AD, although a substantial amount of clinical interventional trials with melatonin should be implemented to validate its overall efficacy and be clinically accepted as an anti-AD drug.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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