Review

Role of melatonin in regulating neurogenesis: Implications for the neurodegenerative pathology and analogous therapeutics for Alzheimer's disease

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ABSTRACT

The revelation of adult brain exhibiting neurogenesis has established that the brain possesses great plasticity and that neurons could be spawned in the neurogenic zones where hippocampal adult neurogenesis attributes to learning and memory processes. With strong implications in brain functional homeostasis, aging and cognition, various aspects of adult neurogenesis reveal exuberant mechanistic associations thereby further aiding in facilitating the therapeutic approaches regarding the development of neurodegenerative processes in Alzheimer's Disease (AD). Impaired neurogenesis has been significantly evident in AD with compromised hippocampal function and cognitive deficits. Melatonin the pineal indolamine augments neurogenesis and has been linked to AD development as its levels are compromised with disease progression. Here, in this review, we discuss and appraise the mechanisms via which melatonin regulates neurogenesis in pathophysiological conditions which would unravel the molecular basis in such conditions and its role in endogenous brain repair. Also, its components as key regulators of neural stem and progenitor cell proliferation and differentiation in the embryonic and adult brain would aid in accentuating the therapeutic implications of this indoleamine in line of prevention and treatment of AD.

Key words: melatonin, neurogenesis, neurodegeneration, Alzheimer's disease.

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1. INTRODUCTION

Neurodegenerative diseases are characterized by functional disintegration of newly generated neurons which are associated with cognitive and memory dysfunctions. The theory of Alzheimer's disease (AD) pathogenesis as an event of deregulated cellular differentiation was first proposed by Santiago Ramon and Cajal, S. and has been discussed in terms of degeneration and regeneration of the nervous system (1). The dramatic decrease in neurogenesis during adulthood and its further decline with advance aging (2) suggest that reduced proliferation of neural progenitor cells might be one of the important mechanisms associated with the cognitive decline observed in AD subjects and the fact that cell cycle kinetics and the transition from proliferation to cell cycle exit and differentiation governs

major aspects of neurogenesis (3) with recent evidence of drastic decrement in adult hippocampal neurogenesis in AD patients (4), strongly recommends this area to be a key target for developing anti-AD therapeutics (5).

Melatonin, the multifunctional indolamine acts as an endogenous factor that modulates and promotes plasticity in the brain and has been identified in the regulation of hippocampal neuronal development during adulthood. Along with promoting endogenous neurogenesis (6, 7), melatonin also regulates hippocampal plasticity (8, 9) both at structural and functional levels (10). Studies have affirmed that exogenous melatonin acts during different events of the neurogenic process which involves the activation of its membrane receptors distributed abundantly in the hippocampal neurogenic niches (11). Additionally, cumulative evidence has pointed out that melatonin receptors not only play important physiological roles in sleep, anxiety, pain and circadian rhythm, but might also be involved in the pathogenesis of several neurodegenerative diseases including AD (12). The significance of melatonin in brain can be marked by a study which demonstrated that how the absence of maternal pineal melatonin might determine abnormal brain programming in the offspring with implications for brain function and behavior (13). Nonetheless, melatonin exerts neuroprotective effects in the central nervous system (CNS) and its age-related decline itself explains its regulatory effects on both neurogenesis and neurodegeneration (14). Also, melatonin has been acclaimed in enhancing the efficacy of peripheral nerve regeneration in nerve defect of Wistar rats (15) which manifests its diverse therapeutic paradigm.

Concerning the neurodegenerative pathology, melatonin has been recognized to alleviating pathogenic mechanisms in AD (16) and its regulatory actions in controlling neurogenesis (17-19) with modulation of crucial signaling pathways (20) makes this remarkable indoleamine as one of the most efficient candidates in regulating the development and progression of many neurodegenerative disorders. Moreover, AD neuropathology in propinquity with pineal gland dysfunction and altered melatonin secretion has emerged to somehow discern the complexity of AD pathogenesis suggestive of impaired neurogenesis due to reduction in melatonin secretion (21). Therefore, owing to the multifactorial nature of AD which involves complex heterogeneous pathophysiological pathways, a broad-spectrum therapeutic paradigm should be considered. Melatonin stimulates early and late stages of neurodevelopment in the adult brain and significantly enhances memory and cognitive functions in aging, mild cognitive impairment (MCI) and AD. The conceivable factors mediating melatonin-induced adult neurogenesis are comprehensive (Figure 1). Therefore, melatonin pharmacotherapy strategy is pragmatic in combating the multispectral pathology of AD (22).

2. MELATONIN IN REGULATION OF THE PHYSIOLOGICAL HOMEOSTASIS OF NEUROGENIC NICHES

The insight that neurogenesis occurs in human brains throughout life led the understanding of learning and memory in a different direction (23, 24); contrary to the theory that neurogenesis was limited to embryonic development. This supervened as a complete scientific turn around as cognitive health of an organism is maintained by the capacity of hippocampal precursors to proliferate and differentiate.

2.1. Melatonin and neural stem cells.

Neural stem cells (NSCs) are immature progenitor cells in the CNS that are capable of self-replication and multipotent differentiation into neurons and glial cells. Adult mammalian neurogenesis occurs throughout life in the sub granular zone (SGZ) of dentate gyrus in the

hippocampus and in the subventricular zone (SVZ) of the lateral ventricle (25-28). The newborn cells are incorporated into the extant circuitry of neurons which have been associated with the accretion of memory processes and cognitive functions (29) with phenomenal plasticity (30) thus boosting the total brain power. Therefore, the level of neurogenesis in the adult human hippocampus significantly contributes to the brain function (31).

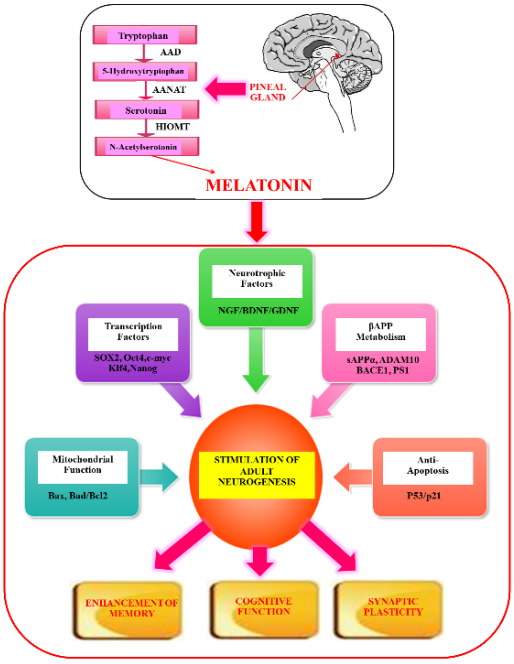

Fig. 1. Potential factors mediating melatonin-induced adult neurogenesis.

Melatonin stimulates adult neurogenesis by upregulating neurotrophic factors and transcription factor network. By regulating βAPP metabolism, metabolic homeostasis, stimulating anti-apoptotic and down regulating pro-apoptotic genes, melatonin boosts neurogenesis thus enhancing overall memory and cognitive functions. Abbreviations: βAPP, Beta-amyloid precursor protein.

Melatonin has been extensively investigated in regulating neurogenesis via multiple pathways (Figure 2). This indoleamine regulates the viability and guides directional differentiation of NSCs as evidenced in rat midbrain NSCs (32). It remarkably maintains and augments neurogenesis and has also been known to enhance the survival of new neurons, boost growth and maturation of dendrites and increase volume of the granular cell layer in the hippocampus of adult mice. Also, the regulatory action of melatonin in generation of new neurons in the dentate gyrus is evidenced by the enhancement in the volume of mossy fiber projections (9). Cultured C17.2 cells originally cloned from mouse cerebellar neural stem cells constitutively express several neurotrophic factors including nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF), which play pivotal roles in neuronal development and differentiation (33). Physiological concentrations of melatonin increased neurite-like extensions and induced mRNA expression of the neural stem cell marker, nestin, the early neuronal marker beta-III-tubulin and the orphan nuclear receptor nurr1 in C17.2 cells (34). In addition, melatonin plays an important role in determining cell fate during neural commitment, thus promoting the differentiation of P19 mouse embryonic carcinoma cell line (P19) cells octamer-binding transcription factor 4 ($Oct4^+$) SRY (sex determining region Y)-box 2, $SOX2^+$) into neural stem cells via activation of the melatonin receptor subtype 1 (35). Interestingly, P19 cells

originate from an embryo-derived teratocarcinoma, can differentiate into the three germ layers and is broadly used for examining the molecular mechanism of neurogenesis.

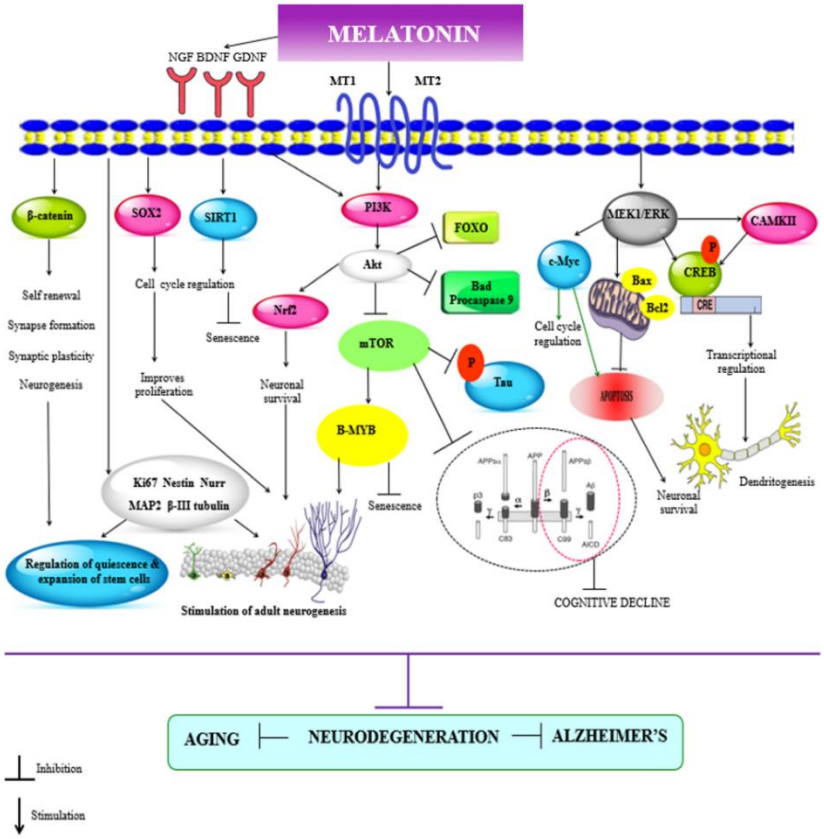

Fig. 2. Schematic illustration of melatonin mechanisms in regulating cellular proliferation and neuronal survival.

Melatonin regulates cellular proliferation and neuronal survival by both receptor dependent and independent mechanisms. It enhances the levels of β-catenin thereby regulating self-renewal, synaptic formation and plasticity, stimulates SOX2 levels which cross talks with cell cycle regulatory proteins and improves proliferation and by increasing SIRT1 blocks senescence. Melatonin regulates proliferation and differentiation of stem cells by enhancing stem cell markers. By instigating MEK1/ERK signaling pathway, melatonin 1) activates CaMKII and phosphorylates CREB thereby eliciting dendritogenesis 2) controls c-Myc which regulates cell cycle events and apoptosis (green arrows) 3) regulates mitochondrial function and blocks apoptosis, altogether promoting neuronal survival. Melatonin via PI3K/Akt signaling pathway; 1) stimulates Nrf2 and down regulates FOXO and procaspases thereby promoting neuronal survival 2) represses mTOR signaling pathway which in turn blocks tau hyperphosphorylation and regulates B-MYB which is involved in proliferation and senescence related phenomenon. Overall, it can be speculated that melatonin by regulating the above-mentioned mechanisms could possibly prevent neurodegenerative pathologies like aging and AD. SOX2, SRY (Sex determining region Y)-box 2; SIRT 1, silent mating type information regulation 2 homolog) 1; MEK1/ERK, Mitogen-activated protein kinase kinase 1 /extracellular signal-regulated kinases; CAMKII, Calcium/calmodulin-dependent kinase type II; CREB, cAMP-response element binding protein; c-Myc, master regulator of cell cycle entry and proliferative metabolism; PI3K/Akt, phosphatidylinositol-3-kinase/protein kinase B; Nrf2, nuclear factor erythroid 2-related factor 2); FOXO, Members of the class O of forkhead box transcription factors; mTOR, mammalian target of rapamycin; B-MYB, Myb-related protein B.

Melatonin stimulated NSC proliferation; increased the viability of cells, DNA synthesis (36) and significantly increased the number of neurospheres along with upregulation of multipotent stem cell markers (19). This indoleamine increased neural stem/progenitor cell proliferation in the dentate gyrus of rat pups (37) and increased the survival of neuronal progenitor cells in the dentate gyrus of adult mice (38, 39). Melatonin also stimulated the neural stem cells in adult mouse SVZ via its receptor activation by promoting βIII-Tubulin expression without affecting the levels of glial cell markers (17) and maturation of dendrites in new neurons formed in the dentate gyrus of mice (40).

The multiple actions of melatonin are modulated by many factors including Mitogen-activated protein kinase (MAPK)/Extracellular signal-regulated kinase (ERK) signaling pathway, histone acetylation, neurotrophic factors, transcription factors, and apoptotic genes (41). It has been reported that melatonin enhances NSC differentiation by increasing mitochondrial function (42). Growth factors are the main components for neurogenic induction in basic neural stem cell culture. A study by (18) compared the synergistic effects of epidermal growth factor (EGF) and basic fibroblast growth factor (bFGF) along with melatonin using neurosphere proliferation assay suggesting that the observed effects resulted due to activation of ERK/MAPK pathway. Another study in PC12 cell cultures also demonstrated that sub micromolar concentrations of melatonin exert a positive effect on neural differentiation involving the MEK/ERK1/2 signaling pathway (43). Importantly, melatonin membrane receptors are involved in the transition from NSCs and proliferative cells to the developmental stages as observed in the hippocampal neurogenic process of adult female mice (11) suggesting the pivotal involvement of melatonin in such mechanisms.

2.2. Melatonin acts via different transcription factors.

The specific transcription factors (Oct4, SOX2, c-Myc, and Krueppel-like factor 4 (Klf4)) dedifferentiate somatic cell lineages into a pluripotent state (44, 45). Melatonin induces mouse fibroblasts into induced pluripotent stem cells (iPSCs) possessing the same characteristics typical of embryonic stem cells (ESCs), including expression of the pluripotency markers Oct4, SOX2, and Nanog. Melatonin also promotes the expression of SOX2 and activates the phosphatidylinositol-3-kinase (PI3K)/Akt/ Nuclear factor erythroid 2–related factor 2 (Nrf2) signaling which authenticates its importance in survival and proliferation of NSCs (46). In addition, treatment with melatonin during the early stage of reprogramming downregulated the expression of the apoptosis-related genes p53 and p21 compared with the untreated controls (47). Melatonin administration also modulated primary cultured bovine NSCs isolated from the retinal neural layer by down regulating both p53 and p21 and increased reprogramming efficiency of N-iPS cell generation from primary cultured bovine NSCs via activation of ERK1/2 pathway (48). Melatonin not only enhanced the reprogramming efficiency but also significantly upregulated gene and protein expression of Nestin and Microtubule associated protein 2 (MAP2) in a receptor dependent manner (49) thus enhancing the proliferation and differentiation of iPSCs via activating ERK1/2 and (PI3K)/Akt signaling pathway.

Endogenous stem/progenitor cells have been investigated for enhancing cognition in the diseased brain (50). Neurons produced within canonical stem cell niches play a significant role in cognitive tasks (learning/memory) operated by specific neural systems (51, 52). Due to its remarkable protective potential and positive regulation of anti-aging mechanisms (53) and neurogenesis (14), melatonin has numerous applications in physiology and medicine pertaining to neurogenesis. Moreover, its involvement in regulation of important signaling pathways constitutes its role as a neurogenesis promoting agent (20). Nonetheless, a technical research patent on dendritogenesis and neuronal maturation has been drafted on the use of

the melatonin molecule in stimulating neuronal maturation and dendritogenesis in adult mammals (54).

3. MELATONIN IN REGULATION OF NEUROGENESIS IN DIFFERENT PATHOLOGICAL CONDITIONS

Neurodegenerative diseases are associated with an exponential decrease in brain neurogenesis. The immature precursors of the CNS have self-renewal and multipotential differentiation abilities and their modulation with controlled pharmacological stimulation of these endogenous NSCs niches can be a promising therapeutic approach for many neurodegenerative disorders and other pathologies counteracting the neuronal loss. Melatonin has been accredited as a promising therapeutic approach for stimulating neurogenesis (55) by influencing proliferation and differentiation of NSCs in different physiological and pathological conditions (56).

3.1. Aging.

Maintaining healthy brain function in old age is an extremely critical aspect as both natural aging and age-related diseases are essentially comprised of pathological changes. The age-related decline in neurogenesis has been attributed to a decreased pool of NPCs because aging cells divide less in a given period of time, and the ones that do are more likely to re-enter the cell cycle within a day, both *in vitro* and *in vivo* (57). With advancing age there is an overall decrease in proliferation, growth factors, neuronal output and plasticity required for brain repair. NSCs undergo age-associated remodeling and dysfunction (58); therefore, therapeutic interventions targeting these niches could revitalize neurogenesis in the aged brain (59) .

Melatonin has been found to increase cell proliferation and survival in the hippocampus of aging mice (38, 39, 60). Its administration enhanced neurogenesis in old rats without modification of the total number of neurons and was able to reduce inflammation and apoptosis in the hippocampus (61, 62). As impaired neurogenesis and neurodegeneration promote the aging process in the nervous system, the recognition of melatonin as an anti-aging agent (53) with neurogenesis enhancing properties could have important therapeutic implications in aging (14) and neurodegenerative diseases (36).

3.2. Circadian dysrhythmia and sleep deprivation.

Circadian dysrhythmia has adverse impacts on body and mind. The circadian rhythm disorder "jet lag" disturbs hippocampal neurogenesis and spatial cognition, which represents morphological and functional adult brain plasticity. Moreover, altered circadian rhythms coincide with reduced nocturnal melatonin response in subjects with cognitive impairment (63). Melatonin promotes neurogenesis in circadian disruption (64), restores hippocampal neural precursor cell proliferation and prevents cognitive deficits induced by jet lag simulation in adult mice (65).

Sleep deprivation is associated with changes in hippocampal neurogenesis and cognitive processes causing a significant reduction in the number of new neurons in the SGZ, which may impair learning and memory performance (66). The prophylactic administration of melatonin increases the number of neural precursor cells in the adult SGZ. The possible mechanisms implicated in this induction involve circadian rhythm, melatonin receptors, and growth factors (67). Interestingly, melatonin promotes an increase in the tissue levels of B-cell lymphoma 2 (Bcl-2) in sleep-deprived animals. (68), using transgenic animals showed that Bcl-2 promotes neuronal maturation and hippocampal neurogenesis in the adult brain

which gives a clear indicative of one of melatonin's mechanism of action in enhancing neurogenesis. To add on, a recent study observed that melatonin administration enhanced $SOX2^{+}$/5-bromo-2'-deoxyuridine $(BrdU)^{+}$ cells in the SGZ of the sleep-deprived group (69). This study also explained the underlying mechanism according to which melatonin possibly modifies the expression of epigenetic mediators which in turn further regulate the proliferation of neural progenitor cells in the adult dentate gyrus under long-term sleep-deprived conditions.

3.3. Metabolic disorders.

Accumulating lines of evidence have marked that metabolic disorders like diabetes affect adult neurogenesis (70) where insulin/insulin like growth factor (IGF) signaling plays a pivotal role in modulating in NSC self-renewal, neurogenesis and cognition as evidenced in the CNS of mammalian models (71). Such involvement of disruptions in insulin/insulin receptor signaling, brain glucose uptake and tolerance in AD bridges the adult neurogenesis with energy metabolism and AD (72). Interestingly, it has also been evidenced in rodent and zebrafish models that diabetes impairs brain cell proliferation and differentiation thus affecting the overall brain cell survival (73). Type 2 is the most common form of diabetes reflected by peripheral blood hyperglycemia and one of the most prevalent risk factors for AD (74). Noteworthy, even the number and function of brain insulin receptors were found to be decreased clinically and in animal models of aging and AD (75).

In this frame of reference, melatonin prevented hyperglycemia induced detriments in brain of rat (76) and its receptors (Melatonin receptors 1 and 2) are associated pivotally in regulating glucose metabolism (77, 78). Recently, it has been established that melatonin prevents high glucose-induced apoptosis involving crucial signaling pathways like NF-κB, mTOR and Wnt in Schwann cells (79). Recently, it has been advocated that melatonin by restoring the brain insulin signaling substantially exerts neuroprotective effects on cognition in aged rats fed with high fat diet (80), herein, melatonin also prevented the increase in tau phosphorylation and amyloid beta (Aβ) accumulation in the hippocampus of rat brains.

Many previous studies have reported an inhibitory effect of melatonin on insulin release and contrary to this inference some studies have also demonstrated stimulatory effects. Therefore, based on the above congregated information there are some especially important aspects which needs to be mentioned and considered for elaborative investigations. Cohort studies have provided exceptional insights into such mechanisms where melatonin and its receptor (melatonin receptor 1B) play an important role in type 2 diabetes *mellitus* pathogenesis via directly acting on the β-cells (81) analyzing that the nocturnal melatonin secretion is independently and inversely associated with the insulin resistance (82). However, the melatonin induced decrement in glucose tolerance involved differential mechanisms during daytime and evening by either decreasing insulin release or by decreasing insulin sensitivity (83). Also, a human meta-analysis revealed that rs1387153, rs4753426, and rs10830963 variants of melatonin receptor 1B might serve as genetic biomarkers of gestational diabetes *mellitus* (84). As such both improved and impaired glucose tolerance has been reported after melatonin therapy. These discrepancies might have been alleged due to the different experimental models and species. One important reason is that melatonin is inversely correlated to activity/food intake in the human, as compared to species like nocturnal rodents. Furthermore, standards like the genetic background and time of the day play an important role in explaining the outcomes in human studies (85).

Although several studies are undergoing in order to investigate the underlying mechanisms, (86), demonstrated of late that melatonin augments proliferation and regulates differentiation of NSCs via autophagy in hyperglycemia. Moreover, an interesting study

determined that co-treatment of bone marrow mesenchymal stem cells and melatonin improved the structural and functional efficiency of β-cell in streptozotocin diabetic male albino rats where melatonin by its own nature increased the vitality of stem cells (87). In a similar streptozotocin rat model, (88) , showed the therapeutic role of melatonin in protecting against diabetic central neuropathy, oxidative stress and neurodegeneration. In addition, this indoleamine enhanced the proliferation of NSCs derived from the brains of embryos from diabetic pregnant mice (89) which suggests that melatonin supplementation in diabetic pregnancy might prevent neural malformations in the offspring and when treated with Wnt-4 and retinoic acid, melatonin changed their morphology and enhanced expression of neural and glial cell markers (90).

The beneficial role of melatonin has also been demonstrated in mouse model of D-galactose-induced aging where it significantly restored the D-galactose-induced reduction of proliferating cells (Ki67-positive cells) and differentiating neuroblasts (doublecortin-positive neuroblasts) in the dentate gyrus (91) and attenuated the reduction of neurogenesis, synaptogenesis and the induction of astrogliosis induced by high-fat diet and streptozotocin in rat models (92).

3.4. Neurotoxic insults.

During embryonic stem cell self-renewal, growth factor deprivation and stress can lead to apoptosis and cell death (93). Dexamethasone is a synthetic glucocorticoid and exerts a neurotoxic action on rodent hippocampus. A study by (94) indicated a protective effect of melatonin on glucocorticoid neurotoxicity in the rat hippocampus. This indoleamine also protected hippocampal neurons from damage and reversed neurogenesis after chronic dexamethasone by activating BDNF and ERK1/2 cascades which indicates that melatonin possesses anti-stress and neurogenic actions (95). Apparently, melatonin regulates the cell viability, proliferation, and differentiation of NSCs from different brain regions (32, 36) and fosters neuroprotection against hypoxia (96), inflammation (46, 97) along with increasing the percentage of myelin basic protein (MBP)-positive cells in NSCs derived from mouse embryonic cortex (98).

Environmental stressors including irradiation have been shown to inhibit neurogenesis and are associated with the onset of cognitive impairments. Melatonin protects against radiation-induced impairment of neurogenesis and cognitive functions (99). Also, melatonin treatment recovers scopolamine-induced spatial learning and short-term memory impairments and restores or increases scopolamine-induced decrease of cell proliferation and neuroblast differentiation in the mouse dentate gyrus (100).

In a very recent study(101), demonstrated that melatonin prevented valproic acid induced spatial and non-spatial memory impairments and an abatement in hippocampal neurogenesis in male Sprague-dawley rats. Valproic acid is an anti-epileptic drug and it adversely affected hippocampal neurogenesis and memory. Whereas, methotrexate which is a chemotherapy agent is linked to cognitive deficits associated with decreased cell proliferation in the hippocampus in cancer patients. Interestingly, the neuroprotective potential of melatonin in diminishing the detrimental effects of methotrexate on memory and neurogenesis was validated (102). Besides, the neurotoxic effects of pesticide fenvalerate are well known. Melatonin significantly debilitated fenvalerate induced upregulation of pro-apoptotic genes like Bax, Fas, caspase 8, caspase 9, and caspase 3 and downregulation of anti-apoptotic gene Bcl-2. In addition, melatonin also prevented the decrease in the expression of neurogenesis-related genes (Distal-Less Homeobox 2 (Dlx2), Sonic hedgehog protein A precursor (Shha), Neurogenin1 (Ngn1), ELAV Like RNA Binding Protein 3 (Elavl3), and Glial fibrillary acidic protein (GFAP) in a zebrafish model (103).

On the other note, several studies have demonstrated that methamphetamine, a psychostimulant drug of abuse causes neurotoxic effects. Methamphetamine induces alterations in hippocampal neurogenesis (104, 105) and has been reported to disrupt development of neural progenitor cells in young adult nonhuman primates (106). In this context, melatonin administration attenuated methamphetamine induced inhibition of neurogenesis in the hippocampus of adult mouse (107). Melatonin also prevented a methamphetamine-induced reduction in cell proliferation (108) and abrogated dexamethasone-induced reductions in Ki-67 and alterations in G1-S phase cell cycle regulators in progenitor cells derived from the adult rat hippocampus (109).

To date, many different mechanisms have been proposed to cause dendritic spine dysfunction and loss in AD (110). Structural abnormalities in AD are characterized by decreased hippocampal volume and shrunken cortex. These structural changes are associated with diminished memory performance. The hilar neurons of the hippocampus integrate spatial memory and are lost in dementia. Melatonin increases dendrite maturation and complexity in new neurons formed in the dentate gyrus of adult mice (40) and repaired the loss of hippocampal dendrites by increasing calmodulin levels, activating $Ca2^{+}$/calmodulin-dependent protein kinase II (CaMKII) thereby, eliciting dendritogenesis via protein kinase C (PKC) and its receptor activation (111).

Information from preclinical studies has shown that compounds with antidepressant effect possibly regulate adult hippocampal neurogenesis where enhancing the adult neurogenesis has been suggested to treat depression and anxiety (112). A human study in depressed subjects revealed that the decreased levels of melatonin corresponded to the diminished levels of neurotrophin-3 (NT-3), BDNF and NGF when compared to healthy controls (113). In this context, melatonin also possesses antidepressant like effects (114) along with its ability to regulate adult hippocampal neurogenesis.

Furthermore, in combination with exercise, melatonin increased the number of BrdU-positive Nestin-expressing endogenous neural stem cells in a rat model of spinal cord injury (115) and potentiated running wheel-induced hippocampal neurogenesis by enhancing neuronal survival suggesting that the combination of physical exercise and melatonin may be an effective treatment for diseases affecting the hippocampus neurogenesis (116). The fact that agents promoting BDNF signaling might be effective in treating and preventing AD (117) supports the probability of melatonin as an anti-AD compound based on the study by (100) which showed that melatonin treatment increased BDNF and tropomyosin receptor kinase B (TrkB) expressions in the mouse dentate gyrus.

Ischemia affects the neurovascular complex of the AD brain by altering the cholinergic system in concomitance with vascular pathology as observed in mice models (118). Whereas, melatonin pretreatment increased survival of mesenchymal stem cells *in vitro* and reduced apoptosis after transplantation into ischemic rat brain (119) and played a role in protecting the cholinergic system (120). Moreover, treatment with melatonin after stroke dramatically enhanced endogenous neurogenesis and cell proliferation in the peri-infarct regions of mice by activating melatonin receptors (6) and has been beneficial for treating cerebral infarction (36). Melatonin also upregulated GDNF expression (121) and enhanced glial cell survival in case of cerebral ischemia (122) which depicts yet another therapeutic mechanism of melatonin action in alleviating pathological mechanisms in AD.

3.5. Melatonin analogs in inducing neurogenesis in pathological conditions.

Neurons produced within canonical stem cell niches play a significant role in cognitive tasks (51, 52); therefore, endogenous stem/progenitor cells have been investigated as a way of enhancing cognition in the diseased brain (50). Cognitive health of an organism is

maintained by the capacity of hippocampal neurogenesis which plays an important role in ameliorating the deficits in neurodegenerative diseases.

The immunological mechanisms in the brain have diverse interactions with the AD pathogenesis where aggregated proteins trigger release of inflammatory mediators, which are responsible for disease progression and severity (123). Interestingly, niche-derived inflammatory signals induce quiescence as observed in aging brain which is accompanied by a systematic drop in the NSCs which is considered as a rescue response that prevents exhaustive depletion of these resting cells (124). Systemic neuroinflammation induced enhancement of proinflammatory cytokines pose negative impact on neurogenesis and on the cognitive reserve as observed in progressive aging and neurodegenerative disorders like AD (125, 126). An additional mechanism through which inflammation could disrupt cognitive function is through altering levels of neurotrophic factors in the brain such as BDNF etc. which are known to be critically involved in supporting memory formation, neurogenesis and LTP (127). In this context, melatonin has been known to immensely affect the immune cells functioning. As the pro-/anti-inflammatory aspect concerning neurogenesis extends to the role of macrophage/microglia polarization (128) and the capability of melatonin of favoring polarization, i.e., anti- vs. proinflammatory behavior (129) may be of substantial relevance. Our previous study demonstrated how melatonin significantly attenuated the pro-inflammatory cytokines and enhanced BDNF in the hippocampus of aged mouse brain (97). Moreover, melatonin also reduced Aβ42 induced NFκB activation in neuroblastoma cell cultures (130) which gives a clear indication of its anti-inflammatory role in an aging and diseased brain.

Investigations have manifested that melatonin-based compounds promote the differentiation of NSCs into neuronal phenotype (131). N-Acetylserotonin is a precursor of melatonin involved in its biosynthesis. Not only this compound stimulates proliferation of neural progenitor cells in the hippocampus but also prevents sleep deprivation induced harmful effects (132, 133). Melatonin pretreatment and treatment with its metabolite N(1)-acetyl-N(2)-formyl-5-methoxykynuramine (AFMK), significantly ameliorated the radiation-induced decline in the anti-doublecortin and Ki-67 positive cells in mouse brain (134, 135) and since oxidative stress is reported to be implicated in impaired neurogenesis, it is likely that antioxidants such as melatonin and its metabolites could restore or minimize cellular death in the hippocampal dentate gyrus (99). Agomelatine is a novel antidepressant acting as a melatonergic receptor agonist and serotonergic (5-HT (2C)) receptor antagonist. In adult rats, chronic agomelatine treatment enhanced cell proliferation and neurogenesis in the ventral hippocampus. Agomelatine increased the ratio of mature vs. immature neurons and enhanced neurite outgrowth of granular cells, suggesting an acceleration of maturation. The influence of agomelatine on maturation and survival was accompanied by a selective increase in the levels of BDNF (136) and it also increased hippocampal neurogenesis and ameliorated apoptosis in the hippocampus of rat brains exposed to stress (137). Previous studies have demonstrated that piromelatine (a melatonin and serotonin 5-HT1A and 5-HT1D agonist) exerts an antidepressant activity in rodent models of acute stress and improves cognitive impairments in a rat model of AD. Piromelatine ameliorates memory deficits in rats and this effect may be mediated by restoring hippocampal BDNF, cAMP-response element binding protein (CREB), and cytogenesis deficits (138). Recently, it has been shown that the melatonin analog 2-(2-(5-methoxy-1 H-indol-3-yl) ethyl)-5-methyl-1,3,4-oxadiazole (IQM316) induced hippocampal neurogenesis with concurrently preserving previously attained memories in adult mice (139).

4. ROLE OF MELATONIN IN REGULATING NEUROGENESIS VIA BETA AMYLOID PRECURSOR PROTEIN (βAPP) PROCESSING PATHWAYS (Figure 3)

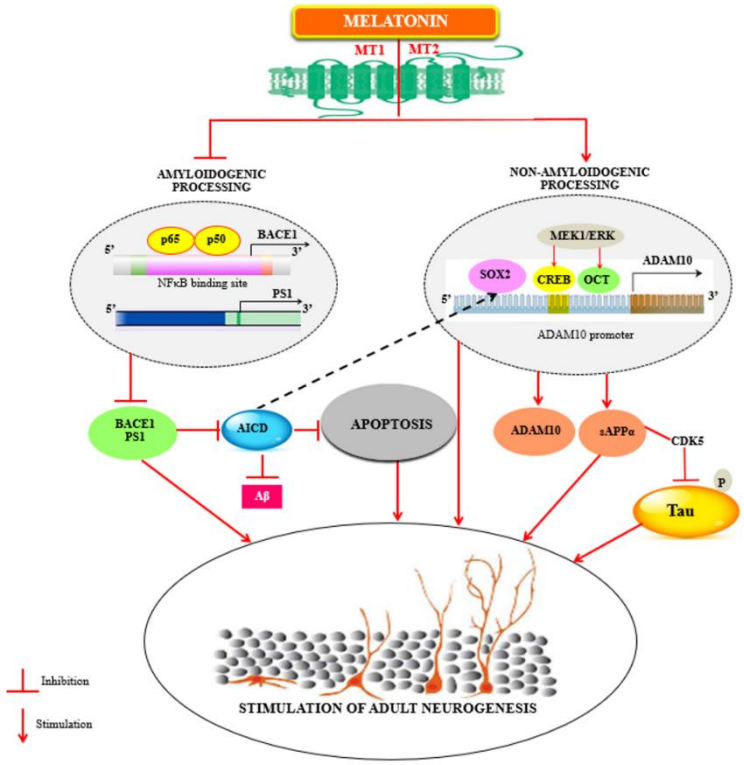

Fig. 3. Melatonin regulates adult neurogenesis by regulating βAPP metabolism.

As increase in amyloidogenic cleavage of βAPP triggers an overproduction of AICD, which not only initiates the apoptotic process but also inhibits SOX2 expression at the transcriptional level (black lines) further leading to a diminution of ADAM10 transcription (for review; Sarlak et.al, 2016) subsequently impairing neurogenesis. Melatonin regulates the non-pathological βAPP homeostasis by stimulating the non-amyloidogenic processing and down regulating the amyloidogenic processing of βAPP. By decreasing the mRNA levels of both BACE1 (via NFκB) and PS1, melatonin might preclude the production of AICD and Aβ which implies its anti-apoptotic effects and simultaneous regulation of Aβ induced alterations in neurogenesis. Parallelly melatonin enhances sAPPα and stimulates ADAM10 levels by increasing its promoter transactivation. Increase in sAPPα down regulates CDK5 induced tau hyperphosphorylation. By stimulating SOX2 levels which are involved in transcriptional regulation of ADAM10, melatonin thereby augments the neurogenic processes. AICD, amyloid precursor protein intracellular domain; SOX2, SRY (Sex determining region Y)-box 2; ADAM10, A disintegrin and metalloproteinase domain-containing protein 10; BACE1, Beta-site amyloid precursor protein cleaving enzyme 1; NFκB, Nuclear factor kappa-light-chain-enhancer of activated B cells; PS1, Presenilin 1; AβAmyloid beta -peptide; sAPPα, Soluble amyloid precursor protein alpha; CDK5, Cyclin-dependent kinase 5.

The neurodegenerative events of AD progress throughout the temporal, frontal and parietal lobes (140) of the brain and it has been well known that hippocampus which is affected during early stages of AD is one of the two neurogenic niches of the adult brain (141). Therefore, impairment of neurogenesis is quite related to the disease progression itself. Beta amyloid precursor protein (βAPP) the precursor of amyloid beta (Aβ) is important for neuron generation, differentiation and neural migration (142, 143) as the embryonic

expression of βAPP peaks during neuronal differentiation and neurite outgrowth period (144, 145). The studies performed on transgenic animals expressing mutant βAPP demonstrated decreased neurogenesis in adult brains (146-149). Noteworthy is that melatonin levels are decreased in blood and cerebrospinal fluid (CSF) of AD patients and this reduction runs parallel with the progression of AD pathogenesis (150). Accumulation of hyperphosphorylated and aggregated tau reduces adult neurogenesis (151) and melatonin ameliorated Aβ and wortmannin-induced tau hyperphosphorylation (152, 153), neurodegeneration and memory deficits in mouse hippocampus. In *vitro* studies demonstrated that melatonin concentration dependently prevented Aβ induced apoptotic mechanisms in neuronal cell cultures due to its anti-amyloidogenic properties (154, 155). Interestingly, melatonin reduced Aβ accumulation in hippocampus and entorhinal cortex and prevented the cognitive impairment in APP + presenilin1 (PS1) double transgenic (Tg) mouse model (156). Diminished α-secretase activity leads to AD-related pathology (157), whereas sAPPα is persistently involved in specific regulation of gene expression in hippocampus as demonstrated in rat experimental models (158).

4.1. Nonamyloidogenic pathway.

In this context, the first demonstration that melatonin upregulates the nonamyloidogenic constitutive and regulated A Disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) and ADAM metallopeptidase domain 17 (ADAM17) proteases which enhances the neuroprotective sAPPα through melatonin receptor was provided by (159). Additionally, melatonin also prevented $A\beta_{42}$ induced reduction in ADAM10 protein expression via its receptor activation involving Pin1/GSK3β/NF-κB pathway (130). An increase in ADAM10 activity shifts the balance of βAPP processing toward soluble α-APP (sAPPα) (160) and protects the brain from amyloid deposition and tau pathology in the brain (161). As such the levels of ADAM10 are reduced in AD patients (162) and blocking sAPPα secretion or down regulating βAPP synthesis impairs the proliferation of epidermal growth factor responsive cells, which leads to decrease in number of neuronal progenitor cells in SVZ (163, 164). Whereas, both βAPP and PS1, the catalytic core of one of the enzymes that cleaves βAPP, play a role in regulation of neurogenesis during development and postnatally and how βAPP regulates neurogenesis in physiological conditions and in AD has been reviewed extensively (165). Neurogenesis declines with aging and sAPPα rescues age associated decline in neural progenitor cell proliferation (2). sAPPα protects neurons and promotes neurogenesis (166, 167), enhances neurite outgrowth and presynaptic bouton density in differentiating NPCs isolated from both embryonic and adult brains (168, 169) and promotes neuronal differentiation. sAPPα protects neurons and promotes neurogenesis, possibly mediated by its ability to prevent over activation of cyclin-dependent kinase 5 (CDK5) and tau hyperphosphorylation (170).

sAPPα binds to SVZ progenitor cells expressing the EGF receptor and increase their proliferation (171) along with eliciting neuroprotection, synaptic plasticity, memory formation, neurogenesis, and neuritogenesis, while reducing amyloid and tau pathology in the brain (161). Melatonin enhances the α-secretase processing of βAPP and increases sAPPα levels (159) and increases reprogramming efficiency of NSC-derived pluripotent stem cells (N-iPS) cell generation (48).

4.2. Amyloidogenic pathway.

Conversely to sAPPα function, amyloid precursor protein intracellular domain (AICD) has been shown to be a negative regulator of proliferation in neural progenitor cells (NPCs).

AICD negatively regulates the transcription of the epidermal growth factor receptor (EGFR), a receptor that drives NPCs proliferation (149, 172). Adult neurogenesis is functionally associated with AD-like neurodegeneration (173) as the increase in amyloidogenic processing of βAPP triggers an overproduction of AICD which has been shown to decrease hippocampal progenitor cell proliferation and survival in transgenic mice (174) and this increase in AICD expression after a certain point leads to apoptosis simultaneously inhibiting SOX2 expression at a transcriptional level which subsequently leads to an impairment of neurogenesis together with neurodegeneration thereby reducing ADAM10 transcription and sAPPα secretion (175, 176) Melatonin enhances the expression of pluripotent genes-including (POU Class 5 Homeobox 1 (Pou5f1), SOX2, Klf4, c-Myc, Nanog, Lin28a, and surface marker proteins from embryonic stem-like cells from rabbit blastocysts (177).

Although it has been shown that β-Site amyloid precursor protein cleaving enzyme 1 (BACE1) inhibition improves cognitive functions and reverse amyloid deposition in an 5xFAD mouse model (178), but due to its involvement in regulation of adult hippocampal neurogenesis the complete therapeutic inhibition of BACE1 activity would certainly dysregulate neurogenesis in adult mouse hippocampus (179). Therefore, it would be more reasonable to opt for partial inhibition of BACE1 activity for therapeutic purposes. Whereas, PS1 is the catalytic core of the aspartyl protease γ-secretase which is also involved in regulation of the differentiation of adult NPCs (180). It has been demonstrated that knockdown of PS1 in NPCs in the sub granular layer of dentate gyrus induces learning impairments (181). As PS1 effect on neurogenesis is mediated via β-catenin phosphorylation and notch signaling, it is therefore speculated that inhibiting PS1 completely would affect the neurogenesis processes. Considering the above parameters, it would be meaningful to assess the therapeutic potential of melatonin. In this context, it has been shown that melatonin also down regulates the amyloidogenic processing of βAPP by regulating both β- and γ-secretases at the transcriptional level (182) without complete inhibition. Moreover, melatonin has been shown to reverse the age dependent alteration of βAPP cleaving secretases in hippocampus of aged mouse (183). Overall, it could be speculated how this multifunctional indoleamine could possibly regulate neurogenesis in pathological conditions like AD.

5. MELATONIN DOSES AND CONCENTRATIONS EMPLOYED *IN VITRO* WITH THE PRESUMPTIVE THERAPEUTIC DOSES IN HUMANS

Therapeutic effects of melatonin have been reported in large number of disorders of different etiologies such as neurodegenerative disorders, cardiovascular diseases, sleep disorders, psychiatric disorders etc. Regarding its production nearly 80% of the melatonin is synthesized at night, with serum concentrations varying between (80-120 pg/ml) whereas low serum concentrations (10-20 pg/ml) are present during the daylight hours. In humans, 1-5mg has been considered as an average dosage range where the bioavailability also depends upon the route of administration (184, 185). An important retrospective study on the efficacy of melatonin in AD patients revealed that 9 mg gelatin melatonin capsules p.o. daily at bedtime for 22 to 35 months stabilized the sleep and cognitive disorders (186). However, melatonin as high as 20mg have also been used in malignancies. Several *in vitro* studies have shown that the pharmacologic concentrations of melatonin is 1 mM, but the physiological concentration in humans is about 70 pM.

Furthermore, on investigating in different animal models, melatonin at subacute dose of 4 mg/kg/day for a continuous period of 29 days improved neuronal survival and enhanced neurogenesis in a stroke model of mice (187). Another study in adult Balb/C mice demonstrated that administration of oral melatonin at a dose of 10 mg/kg of body weight per day enhanced neurogenesis (188). Similarly, in the dentate gyrus of adult C57BL/6 mice *in*

vivo, exogenous melatonin (8 mg/kg) also increased the survival of neuronal progenitor cells and post-mitotic immature neurons (189). The administration of both physiological (5-10 microg/kg) and pharmacological (20-320 microg/kg) doses produced different effects on sleep efficiency in three species of diurnal nonhuman primates as these could possibly serve as adequate animal models for studying the mechanisms of melatonin's action on such disorders (190).

Referring to the brain, a number of evidence which have been accumulated from studies on various neurodegeneration models and clinical reports support the use of melatonin for the preventive treatment of major neurodegenerative disorders like AD, Parkinson disease, Huntington's disease and Amyotrophic Lateral Sclerosis (191). Additional studies are required to identify the specific therapeutic concentrations and the dose-response relationships to test the clinical efficacy of melatonin supplementation (192) in various disorders in order to extend the use of melatonin in clinical practice, prevention and treatment. However, regarding the therapeutic aftermath of melatonin use in enhancing neurogenesis in humans need substantive clinical evidence before any precise recommendations can further be formulated.

6. SUMMARY

The complex circuitry between neuroregenerative and neurodegenerative processes revolves around the mechanisms interlinked between the parameters coupled with neurogenesis. The homeostatic balance between these variables goes awry in degenerative diseases like AD. The phenomenal regulation of neurogenesis by melatonin reveals a remarkable regulatory network of this indoleamine in governing not only the molecular events which occur during the development of the disease but also regulating stem cells which have the potential to repair brain damage and may aid in developing novel strategies for neurodegenerative disease therapy.

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AUTHORSHIP

MS drafted the first version of manuscript, prepared figures, AS and PG revised the manuscript critically and PG approved it.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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