The Mechanisms of Melatonin's Regulatory Functions on Neural Stem Cells' Survival, Proliferation and Differentiation

Asuku Abraham Olufemi[1], Ayinla Maryam Tayo[2], Ajibare Ayodeji Johnson[3], Adeyemo Michael Bolaji[4], Adeyemo Racheal Oluremi[5], Olajide Tobiloba Samuel[2]

[1]Department of Medical Biotechnology, Bioresources Development Centre, National Biotechnology Development Agency, Ogbomoso, Nigeria
[2]Department of Physiology, Faculty of Basic Medical Sciences, University of Ilorin, Ilorin, Ilorin, Nigeria
[3]Department of Physiology, Faculty of Basic Medical Sciences, College of Medicine, Lead City University, Ibadan, Oyo State, Nigeria
[4]Joint Universities Preliminary Examinations Board, Anyigba, Kogi State University, Nigeria
[5]Department of Medical Laboratory Science, Kogi State College of Health Sciences and Technology, Idah, Nigeria

Correspondence: Asuku Abraham Olufemi, Email: asufem2017@gmail.com

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Abstract

Neural stem cells (NSCs) are cells that can self-replicate and differentiate in the central nervous system into neurons and glial cells. The sub granular zone (SGZ) in the hippocampal dentate gyrus (DG) and the sub ventricular zone (SVZ) are the two principal locations where NSCs are discovered in the adult brain. The recent identification of NSCs in adult mammalian brains has sparked a flurry of preclinical and translational research to examine brand-new strategies for treating neurodegenerative illnesses. Therefore, mobilizing endogenous NSCs has become a possible therapeutic strategy for brain repair. The main secretory substance produced and released by the pineal gland is melatonin, which has a wide range of biological functions. Melatonin has recently been shown to play a significant role in NSCs, including their proliferation, differentiation, and survival. These processes are regulated by a variety of factors such as the MAPK/ERK signaling pathway, histone acetylation, neurotrophic factors, and apoptotic genes that are discussed in this review.

Key words: *Neural stem cells; melatonin; proliferation; survival; differentiation*

Introduction

A neuro-hormone called melatonin is released from the pineal gland, which is located in the middle of the brain (Tan *et al.*, 2010). It has a variety of regulatory and protective functions, including synchronizing the circadian cycle, fending off oxidative stress, controlling energy consumption, modifying the immune system, and delaying the aging process (Hardeland *et al.*, 2010). The retina, testicles, ovary, placenta, glial cells, and lymphocytes are additional extra-pineal sources (Tan *et al.*, 2007). Melatonin is discovered to be highly released between

the time three and four in the morning (Clausrat and Leston, 2015). The developing and adult brains both include multipotent cells called neural stem cells (NSCs). They can produce glia and neurons in the developing brain, and they also explain the adult brain's very low capacity for regeneration. NSCs provide a special and potent tool for regenerative medicine and basic research in the central nervous system (CNS). Our understanding of the flexibility and function of the brain has significantly changed as a result of the identification of NSCs and neurogenesis in adult mammalian CNS. This has sparked interest in the potential use of intrinsic neurogenic activity to treat CNS disorders and restore function to the brain after damage or dysfunction. Therefore, mobilizing endogenous NSCs has become a possible therapeutic strategy for brain repair (Honmou, 2015). Melatonin's antioxidant activity has garnered a lot of interest in addition to its many physiological activities (Reiter *et al.*, 2009). According to studies, melatonin's free radical-scavenging processes decreased neuronal cell death brought on by toxins such amphetamine (Klongpanichpak *et al.*, 2007), 6-hydroxydopamine (Sharma *et al.*, 2006), 1-methyl-4-phenylpyridinium ion (MPP+), and -amyloid protein (A) (Gunasingh *et al.*, 2008). Melatonin has thus been suggested as a hormone that may contribute to the emergence of conditions linked to oxidative damage. It's interesting to note that recent research indicates melatonin receptors are expressed in neural stem cells and neural progenitor cells, or NSCs and NPCs (Ramirez-Rodriguez *et al.*, 2009), which begs the question of whether melatonin also plays a significant role in the development of NSCs and NPCs. Additionally, it is known that the dentate gyrus-DG has diurnal rhythmic neurogenesis. Proliferating cells tagged with BrdU exhibit a cycle-dependent pattern (Guzman-marin *et al.*, 2009) According to Tamai *et al.* (2008), M-phase cells multiply more during the night, and prolonged exposure to light reduces neurogenesis in the DG (Fujioka *et al.*, 2011).

NPCs in the DG of the hippocampus express the clock genes (Per1, Per2, Cry1, Cry2, Bmal1, and Clock), which can control the differentiation transcription factors NeuroD1, Id2, Hey1, and Olig1 (Kimiwada *et al.*, 2009). According to these researches, melatonin, which is secreted in response to light/dark rhythms, may be crucial for the growth of NSCs. In order to shed fresh light on the effects and their processes of melatonin on NSCs and to promote the development of new therapeutics for neurodegenerative illnesses, a deeper understanding of the potential interaction between melatonin and NSCs is necessary.

The Physiology of Melatonin

Inhibiting the tendency to wakefulness coming from the suprachiasmatic nuclei (SCN) in the late evening is how melatonin "opens the doors of sleep" (Lewy *et al.*, 2006). Melatonin is the chemical equivalent of darkness, providing the neuroendocrine system with important information (Pandi-Perumal *et al.*, 2008). In mammals, the pineal gland provides almost all of the circulating melatonin (Clausrat and Leston, 2015). Since melatonin plays a role in the regulation of immune response and the removal of free radicals to accomplish cytoprotection (Hardeland *et al.* 2011), there is now compelling evidence that it is produced in every animal cell with mitochondria (Tan *et al.*, 2019). Melatonin's chronobiotic activity is mediated by the MT1 and MT2 receptors, members of the superfamily of membrane receptors linked to G proteins (G-protein coupled receptors, GPCR) (Dubocovich *et al.*, 2010). The SCN, hippocampus, thalamus, retina, vestibular nuclei, cerebral cortex, and cerebellar cortex have all been found to contain MT1 and MT2 receptors (Ng *et al.*, 2017). Another member of the melatonin receptor subfamily, GPR50, was included because of its strong sequence homology with MT1 and MT2 (Cecon *et al.*, 2017)

In addition to having inherent free radical scavenging activity, melatonin is converted into substances with enhanced antioxidant capacities. Melatonin has greater antioxidant protection than vitamins C and E (Galano *et al.*, 2011). Melatonin also has cytoprotective effects in ischemia (independent of the removal of free radicals), most likely by stabilizing the mitochondrial membrane (Reiter *et al.*, 2018). Melatonin has both pro- and anti-inflammatory effects on the immune system (Hardeland, 2018). Melatonin does indeed have calming and anti-excitatory properties (Caumo *et al.*, 2009).

Neural Stem Cells and Neurogenesis

The process through which new neurons are produced is known as neurogenesis. Once the primary brain networks have formed and are established during embryonic development and the first few weeks following birth, neurogenesis starts to slow down. The lateral wall of the lateral ventricle and the subgranular zone of the dentate gyrus of the hippocampus are the only two regions of the adult brain where neurogenesis is currently occurring. Adult neural stem cells (NSCs) can produce new neurons throughout life, and these new neurons can be integrated into the hippocampal formation's existing neural circuits. This process is known as adult hippocampal neurogenesis. A growing body of research indicates that adult hippocampal neurogenesis may play a role in cognitive functions like memory, learning, mood control, and cognitive flexibility that occur under physiologically normal circumstances. The integration of adult-born neurons into the hippocampus circuitry is a unique example of plasticity, and as a result, adult hippocampal neurogenesis is thought to promote cognitive functions that enhance survival. Adult NSCs are typically in a quiescent state with a reversible cell cycle arrest, low metabolic rate, and high sensitivity to the local signaling environment. However, they can be activated by a variety of physiological stimuli, including extrinsic factors (morphogens, growth factors, cytokines, neurotransmitters, and hormones), intracellular factors (transcription factors and epigenetic modulators), and environmental factors like diet and exercise (Surget and Belzung, 2022). Neuronal regeneration in the brain is negatively impacted by aging, neurodegenerative diseases, stroke, and/or ischemia. The quantity and maturation of neurons decrease over the course of Alzheimer's and Parkinson's diseases (AD and PD). Indeed, a drop in neurogenesis may contribute to the course of the disease, suggesting that treatments aimed at reversing this decline may postpone the start of AD/PD or lessen symptoms (Moreno-Jimenez *et al.*, 2019; Seki *et al.*, 2019). When these illnesses arise, adult quiescent NSCs are not routinely activated to replace dead neurons. Because of this, a great deal of study has been done to comprehend the molecular processes involved in neurogenesis and to explore ways to encourage the growth of new neurons in the adult brain. In this situation, neuroregeneration destiny and regeneration mechanisms are governed by the endogenous environment. Since various factors, including neurotrophic support and endogenous chemicals like melatonin, can modify this procedure, the intrinsic neurogenic potential and its potential modulation through therapeutic measures constitute a promising therapeutic strategy. The job of promoting neurogenesis for neuronal repair is difficult given the rise in neurodegenerative illnesses. By using this potential therapeutic strategy, it might be able to stimulate adult NSCs and direct neural precursors to the site of the damage where lost neurons will eventually be replaced. The majority of our knowledge of the functional relevance of adult hippocampus neurogenesis is based on retrospective analysis utilizing post-mortem tissues and in vitro animal models due to the technological limitations of human investigations. We need to understand the intricate interactions between the components of neurogenic niches and the dynamics of adult neurogenesis in order to better comprehend the physiological roles played by neurogenesis, which serves as a permanent reservoir of plasticity in the brain. Some

compounds are being researched as potential therapeutic agents to boost neurogenesis because their characteristics are promising.

In the mammalian brain, neurogenesis occurs continuously throughout life (Wang *et al.*, 2011), as NSCs successively proliferate, migrate, and differentiate into new neurons (Wade *et al.*, 2014), astrocytes, and oligodendrocytes.

Since the discovery of possible NSC advantages in multiple animal models of various neurological disorders, such as stroke, Parkinson's disease (PD), and Alzheimer's disease (AD), NPCs-based therapy has been seen as a promising therapeutic method to protect and heal the injured CNS (Martino *et al.*, 2011). Therefore, more research into the mechanisms underlying NSC proliferation and differentiation is required.

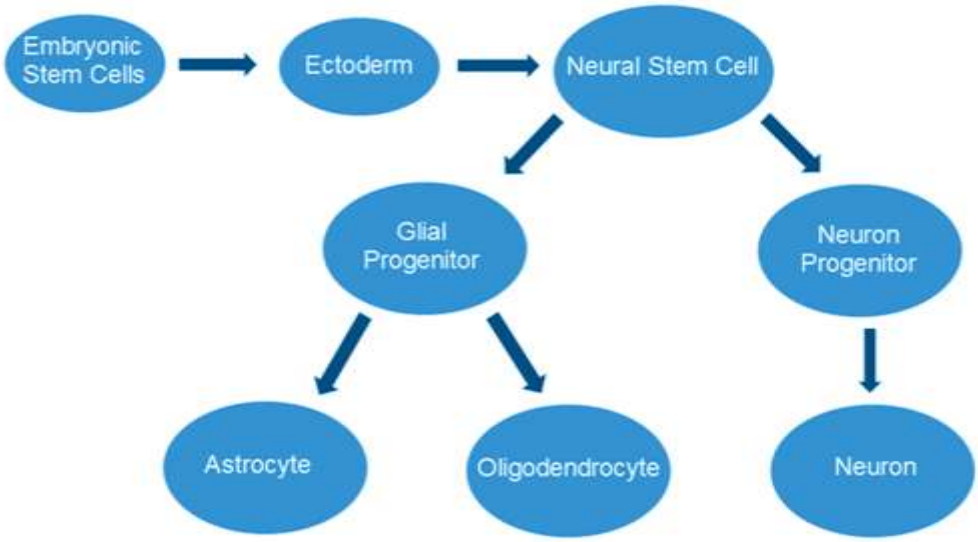

Fig 1: Neurogenesis

Effects of Melatonin on Neural Stem Cells

The roles of NSCs in the developing or adult brain as well as in pathological situations depend heavily on their survival, proliferation, differentiation, and migration. A growing body of research has shown that melatonin is crucial to these processes.

Melatonin Plays a Modulatory Function on the Survival of Neural Stem Cells

The future of NSCs is crucial. It was revealed that melatonin controls the cell survival of NSCs from various parts of the brain, which is consistent with other studies showing that melatonin protects injured neurons. By using the MTT assay, Kong *et al.* discovered that melatonin (0.05–1 nM) significantly improved the vitality of cultivated NSCs taken from rat midbrain (Kong *et al.*, 2008).

In addition, after 14 days of treatment with BrdU-labelling, melatonin improved the survival of neonatal neurons in the dentate gyrus (DG) of adult mice. Compared to mice treated with vehicle, mice treated with melatonin (8 mg/kg) had a 63% higher number of surviving cells in the DG (Ramirez-Rodriguez *et al.*, 2009). Melatonin improved cell survival in vitro and safeguarded NSCs from hypoxia, according to studies. The cell viability of NSCs was

significantly increased by melatonin (0.001-100 M) in a dose-dependent manner. As seen by Hoechst staining, melatonin (100 nM) dramatically reduced the mortality of cells exposed to hypoxia (Fu *et al.*, 2011). Melatonin has been shown to shield NSCs from inflammation brought on by lipopolysaccharides. Lactate dehydrogenase (LDH) assay revealed that melatonin (100 nM) reduced the cytotoxicity level of NSCs treated with 100ng/mL and 1g/mL Lipo-polysaccharides by around 20% and 35%, respectively. This reduction may be connected to reducing NO generation in LPS-treated NSCs (Song *et al.*, 2015). The messenchymal stem cells generated from human bone marrow were likewise discovered to have protective properties. Bone marrow-messenchymal stem cells' senescent phenotypes caused by hydrogen peroxide could be successfully corrected with the help of pretreatment with melatonin (0.01-100 M) (Zhou *et al.*, 2015).

Melatonin Promotes Neural Stem Cells Proliferation and Differentiation

During neuronal commitment, melatonin is crucial for specifying cell fate (Chen *et al.*, 2014). It encouraged the conversion of pluripotent P19 cells into NSCs, a process that may have been aided by the activation of the MT1 receptor and the phosphorylation of ERK1/2. Melatonin also promoted neural differentiation of NSCs produced by foetal bovine serum without influencing astroglial differentiation during the proliferation phase, while suppressing neural differentiation during the differentiation phase (Moriya *et al.*, 2007). Hypoxia in culture has the potential to reduce neural differentiation of NSCs. In this regard, melatonin not only encouraged NSC proliferation during hypoxia but also caused NSCs to differentiate into neurons, with no discernible impact on astrocyte differentiation (Fu *et al.*, 2011). Furthermore, melatonin-induced NSC proliferation was mediated by MT1 receptor and extracellular signal-regulated kinase (ERK) 1/2 phosphorylation. In NSCs, melatonin significantly enhanced the number of neurospheres and upregulated the levels of phospho-cRaf, phospho-ERK1/2, and nestin protein, according to Tocharus *et al.* (2014). These effects were countered by luzindole or PD98059, a mitogen-activated protein kinase (MEK) inhibitor. Melatonin's immediate precursor is N-acetylserotonin (NAS). Sompol and associates (Sompol *et al.*, 2011) demonstrated that NAS boosted neural progenitor cell proliferation in adult mice throughout both the awake and asleep states, as well as in mice with sleep deprivation. Neuronal progenitor cells treated with chronic NAS have their TrkB receptors activated. According to these results, melatonin could promote NSC proliferation through activating TrkB and the c-Raf-MEK-ERK1/2 pathway. Sharma and colleagues (Sharma *et al.*, 2008) demonstrated that nestin, a marker for neuroectodermal stem cells, was expressed at higher levels in C17.2 NSCs at physiological melatonin concentrations (nanomolar range). Melatonin also enhanced the early neuronal marker -III-tubulin and the orphan nuclear receptor nurr1 in NSCs and encouraged neurite-like extensions. More significantly, melatonin markedly boosted histone H3 acetylation-linked gene transcription and chromatin remodeling. The MT1 receptor was assumed to mediate these biological effects since the melatonin MT2 receptor was absent from C17.2 NSCs cells.

The Mechanisms of Melatonin Regulatory Functions on Neural Stem Cells Survival, Proliferation and Differentiation

Melatonin regulates NSCs, according to studies from many sources, by a variety of pathways that include melatonin receptors, MAPK/ERK signaling, histone acetylation, neurotrophic factors, basic helix-loop-helix (bHLH) factors, and others. Following is a discussion of the evidence:

Neurotrophic Factors

Proteins called neurotrophic factors are secreted by the body and have a significant impact on the formation of different neuronal populations as well as the survival and neuritic arbors of mature neurons throughout adulthood (Hegarty *et al.*, 2014). Through its downstream signals, which include phosphoinositide 3-kinase (PI3K)/Akt, ERK, and phospholipase pathways, brain-derived neurotrophic factor (BDNF) can maintain neuronal survival and modulate synaptic plasticity (Numakawa *et al.*, 2013). According to Hong *et al.* (2008), glial cell line-derived neurotrophic factor (GDNF) regulates neuronal survival by activating cellular signaling, mRNA translation, and new protein synthesis. GDNF is thought to protect neurons in Parkinson's disease by promoting the survival of dopamine and other neurons. Additionally, GDNF protects neurons by inhibiting the death receptor-caspase pathway, moving the apoptogenic protein Bax, and increasing the levels of the anti-apoptotic proteins Bcl-2 and Bcl-XL (Maruyama *et al.*, 2013). According to studies, melatonin treatment of cultured NSCs led to a considerable rise in neurotrophic factors, particularly BDNF and GDNF. It suggests that by raising the levels of BDNF and GDNF, melatonin may help NSCs remain viable and aid neural development (Kong *et al.*, 2008; Sharma, 2008).

MAPK/ERK signaling

A series of proteins in the cell called the MAPK/ERK pathway, sometimes referred to as the Ras-Raf-MEK-ERK pathway, transmits signals from a receptor on the cell's surface to the DNA inside the nucleus of the cell. The signal is activated when a signaling molecule connects to a receptor on the cell surface, and it is shut off when DNA in the nucleus expresses a protein, causing a change in the cell, such as cell division. With the addition of phosphate groups to a nearby protein, which functions as a "on" or "off" switch, MAPK (mitogen-activated protein kinases; formerly known as extracellular signal-regulated kinases) communicate with other proteins in the pathway. A critical step in the formation of many cancers is when one of the proteins in the pathway is altered and becomes trapped in the "on" or "off" position. Intricate cellular processes like proliferation, differentiation, development, transformation, and death depend heavily on MAPK families.

In order to trigger an appropriate physiological response, such as cellular proliferation, differentiation, development, inflammatory reactions, and death in mammalian cells, MAPK pathways relay, amplify, and integrate information from a variety of stimuli. ERK 1 and ERK 2 are members of the ERK kinase family. They become active in response to various mitogens and growth stimuli. MEK phosphorylation comes first, then the phosphorylation of the theronine and tyrosine residues, before ERK is activated. ERK goes to the cytoplasm and nucleus after becoming activated to phosphorylate other proteins. These proteins control cell proliferation, differentiation, and mitosis (Fey *et al.*, 2012).

Melatonin has been shown to phosphorylate ERK1/2 and activate it in neural cell cultures (Roy and Belsham, 2002). Studies have demonstrated that melatonin-induced NSC proliferation and differentiation are mediated by the MAPK/ERK pathway, which has been associated with histone acetylation (Cohen-Armon *et al.*, 2007). Studies revealed that the primary MAPK (ERK1/2) and c-Raf protein kinases, which are involved in the MAPK signaling pathway, were highly phosphorylated by melatonin, and that this phosphorylation was significantly decreased when melatonin receptor antagonist was pretreatment (Fu *et al.*, 2011; Niles, *et al.*, 2013;Tocharus *et al.*, 2014).

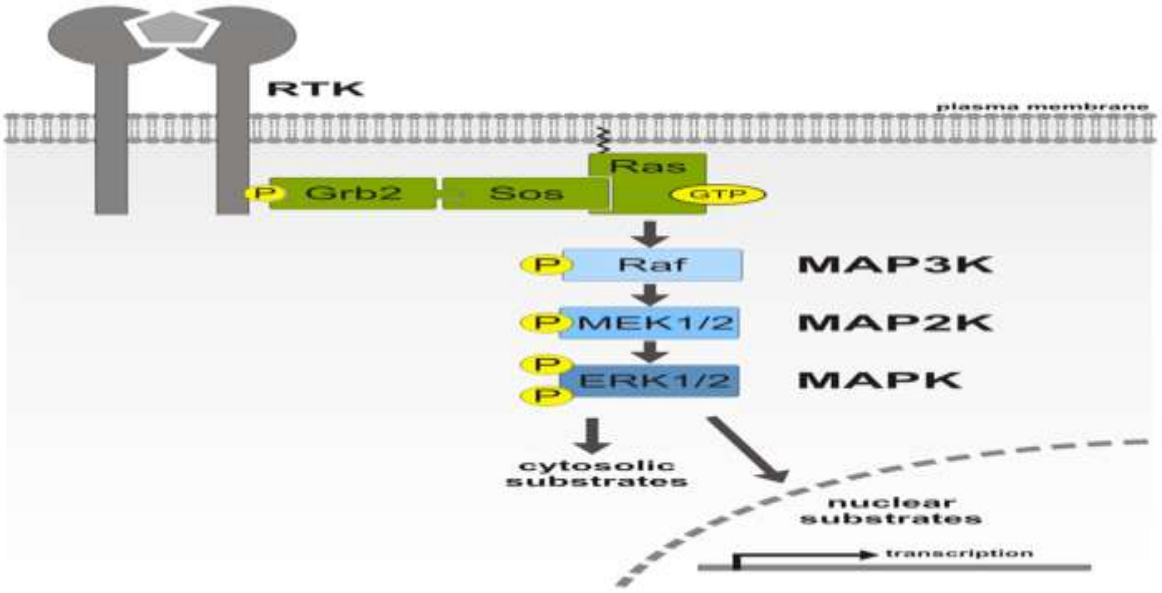

Fig.2: MAPK/ERK cascade,

Histone Acetylation

The DNA, H2A, H2B, H3 and H4 core histones make up the nucleosome core particle's crystal structure. The superhelical axis is visible from the top of the structure. The processes by which the lysine residues in the N-terminal tail extending from the histone core of the nucleosome are acetylated and deacetylated as part of gene regulation are known as histone acetylation and deacetylation. Acetylation and deacetylation of histones are critical processes in gene regulation. Enzymes having "histone acetyltransferase" (HAT) or "histone deacetylase" (HDAC) activity often catalyze these processes. Acetylation is the transfer of an acetyl functional group from one molecule to another, in this case, Acetyl-Coenzyme A. Simply put, deacetylation is the reaction in which an acetyl group is taken off of a molecule.

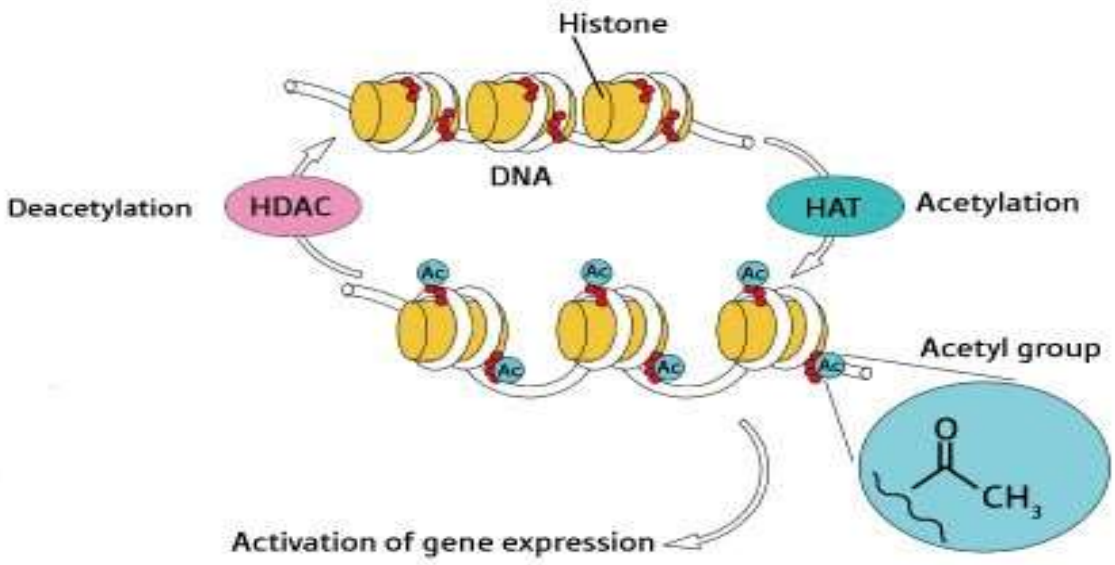

Fig.3: Histone acetylation, TF: transcription factors; Ac: acetylation; Me: methylation; HAT: histone acetyltransferase; HDAC: histone deacetylase; HMT: histone methyltransferase; DNMT: DNA methyltransferase.

Because of histone acetylation, transcription factors can access DNA and the chromatic structure is made accessible. Histone deacetylation, histone methylation, and DNA methylation all lead to closed chromatin, which prevents transcription factors from accessing DNA and causes gene silencing. Gene expression is changed as a result of epigenetic alterations to DNA and/or histones through methylation. There is proof that melatonin's effects on NSCs are related to gene change (Kim *et al.*, 2010; Sarlak *et al.*, 2013). Nucleosomes, which are made up of DNA and an octamer of histones, are involved in the epigenetic mechanisms that modify DNA without changing genomic sequences. For the nervous system to develop and cells to differentiate, transcription must be tightly controlled. In the past ten years, it has become clear that histone changes regulate a wide range of transcriptional processes, including higher order chromatin structure and gene expression (Lilja *et al.*, 2013). It is discovered that histone acetylation is associated with neuronal differentiation (Stockhausen *et al.*, 2005). It has been demonstrated that histone hyperacetylation in progenitor cells promotes neuronal differentiation while preventing the emergence of a glial phenotype (Balasubramaniyan *et al.*, 2006). Melatonin increased the mRNA expression of HDAC3, HDAC5, and HDAC7, according to Sharma et al. Increased HDAC mRNA levels most likely indicate a compensatory feedback mechanism in response to melatonin-induced histone hyperacetylation (Sharma *et al.*, 2008). Niles LP, *et al.* (Niles *et al.*, 2013) found that melatonin significantly increased histone H3 and H4 acetylation in the hippocampus and striatum but not in the midbrain or cerebellum. This finding suggests that the hippocampus and striatum may be the targets for the epigenetic effects of melatonin and also demonstrates the regional differences in melatonin signaling. In addition to acetylation, histone methylation is also intimately linked to the development of NSCs. In stem cells and progenitors, the methylation of histones, particularly at the residues H3K4, H3K9, and H3K27, is becoming one of the most important epigenetic marks that regulate transcription (Lilja *et al.*, 2013). The alteration of histone and the enzymes controlling these changes can be a focus of attention when analyzing the epigenetic processes by which melatonin influences the status and fate of NSCs, even if the interaction between melatonin and histone methylation has not yet been reported.

Anti-apoptotic Bcl-2 Family Proteins

The Bcl-2 family of regulator proteins controls cell death (apoptosis) by either promoting (pro-apoptotic) or inhibiting (anti-apoptotic) apoptosis. Bcl-2 (B-cell lymphoma 2) is encoded in humans by the BCL2 gene. BCL-2 is found on the outer membrane of mitochondria, where it exerts significant influence on cellular survival by preventing pro-apoptotic proteins from doing their job. The mitochondrial membrane is generally affected by the pro-apoptotic BCL-2 family proteins, such as Bax and Bak, to encourage permeabilization and the release of cytochrome C and ROS, which are critical signals in the apoptosis cascade. The actions of BH3-only proteins, which in turn activate these pro-apoptotic proteins, and BCL-2 and its related BCL-Xl block them (Hardwick *et al.*, 2013). It has clinical importance in lymphoma, just like BCL3, BCL5, BCL6, BCL7A, BCL9, and BCL10. The intrinsic or "mitochondrial" apoptosis pathway is controlled by members of the B-cell lymphoma 2 (Bcl-2) protein family. Bax and Bak are frequently produced

constitutively in cells, and pro-apoptotic Bcl-2 proteins have the ability to trigger several cell death processes, including apoptosis, via activating the mitochondrial apoptosis pathway (Kilbride *et al.*, 2013). Numerous academic studies demonstrate that Bcl-2 is crucial for starting or preventing apoptosis during neuronal growth and damage. Bcl-2 overexpression, for instance, shielded hippocampal neurons from glutamate-mediated excitotoxicity and prevented Bax-mediated cytochrome-c release, caspase activation, and cell death (Wong *et al.*, 2005). Intriguingly, melatonin was also discovered to significantly raise the ratio of Bcl-2/Bax and suppress caspase-3 activation (Fu *et al.*, 2011), suggesting that the overexpression of the Bcl-2 family proteins may be a factor in how well the hormone protects wounded NSCs.

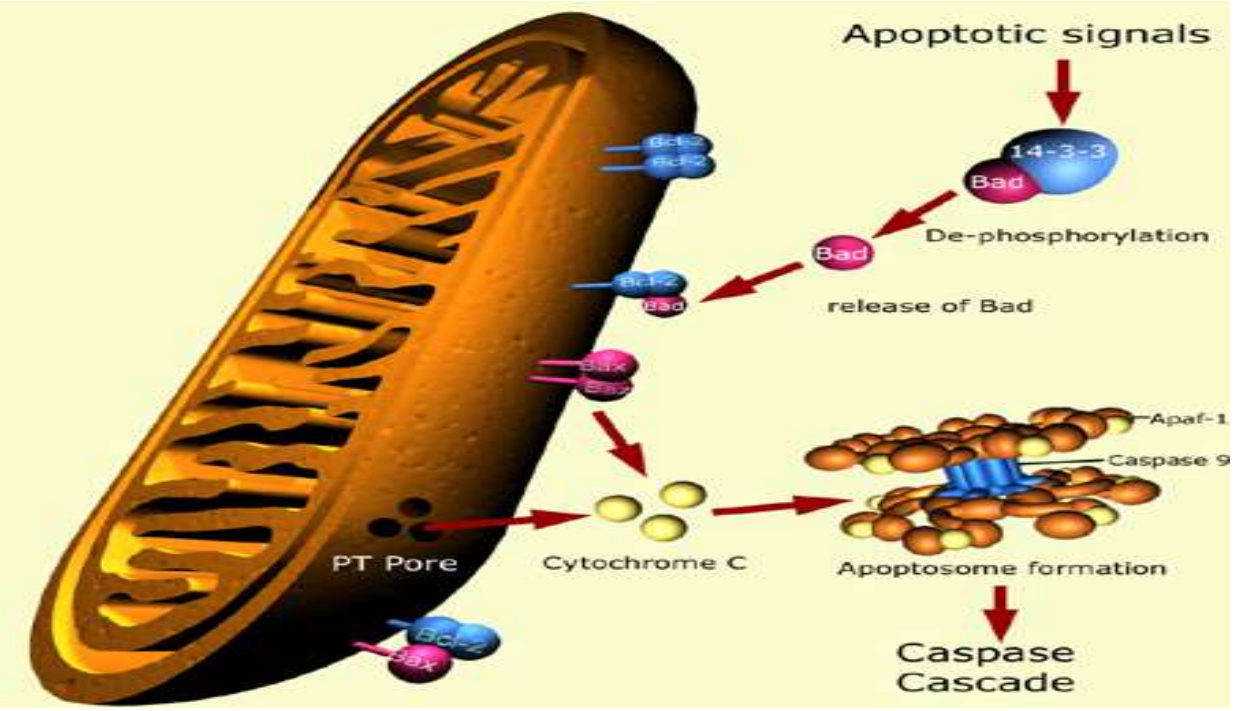

Fig.4: Pro- apoptotic and anti- apoptotic proteins in apoptosis

Nrf2 Signaling

Through its capacity to control the expression of thousands of antioxidant and detoxifying genes, the nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant response element (ARE) pathway serves as both a key sensor and a master regulator of oxidative stress (Johnson *et al.*, 2008). To control this pathway, Nrf2 binds to the ARE, an enhancer element found in the 5flanking region of numerous phase II detoxifying and antioxidant genes. Under normal circumstances, the cytoplasmic kelch-like ECH associating protein 1 controls Nrf2 negatively (Keap1). Keap1 serves as an adapter protein to E3 ligase to facilitate Nrf2's destruction by the ubiquitin proteasome system (UPS), preventing Nrf2 from translocating into the nucleus (Gan and Johnson., 2014). When the Keap1-Nrf2 interaction is broken, Nrf2 moves to the nucleus and interacts with the tiny Maf proteins. In order to maintain redox equilibrium, the produced heterodimer binds to the ARE and coordinates the transcription of genes involved in phase II detoxification and antioxidant defense. Findings have revealed

how the Nrf2/ARE pathway dynamically changes during disease, demonstrating the accumulation of oxidative damage and exerting neuroprotection against oxidative stress as well as protecting against protein oxidation and misfolding, such as A and tau neurofilament tangles (NFTs) in AD (Gan *et al.*, 2014).

Studies have also suggested that the Nrf2 pathway protects NSCs and NPCs from oxidative damage (Abdanipour *et al.*, 2014; Ni *et al.*, 2014). Accordingly, some studies have shown that melatonin protects cells from oxidative stress, brain damage, and neurotoxicity by activating the Nrf2/ARE signaling pathway (Wang *et al.*, 2012; Deng *et al.*, 2014; Ding *et al.*, 2014). However, few studies have shown that Nrf2 is involved in the mechanism of melatonin in NSCs/NPCs, raising the question of whether the pathway plays a role regulating the NSCs survival and development.

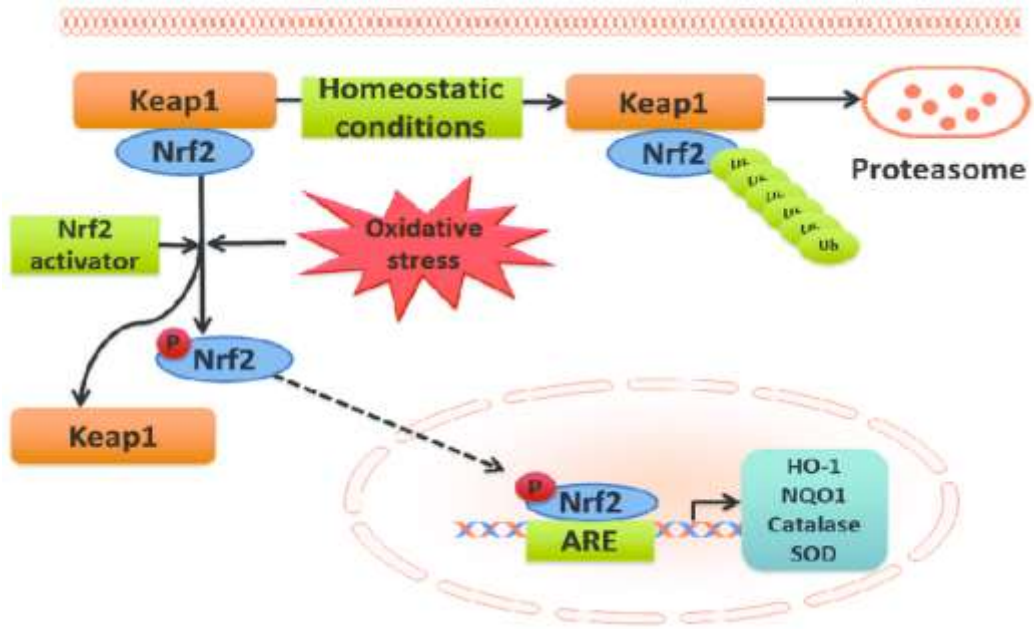

Fig.5: Schematic representation of NF-E2-related factor 2 (Nrf2)- antioxidant response element (ARE) pathway.

Conclusion and Future Perspective

Melatonin has the potential to replace neural stem cells as an adjuvant in the treatment of neurodegenerative illnesses due to its stimulating effects on the proliferation and neuronal differentiation of neural stem cells. Melatonin's protective effects on NSCs through promoting cellular survival, proliferation, and neural differentiation have been the subject of an increasing number of studies. Melatonin protects brain cells from potentially damaging assaults such hypoxia, inflammation, and too much glucocorticoid production. These allow for the optimal neuronal development and enable the adjunct use of melatonin in NSC grafting. To paint a more accurate picture of the regulatory networks, additional research is needed to clarify the as-of-yet unidentified molecular pathways. The identification of potential treatment targets should result from this.

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