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REVIEW ARTICLE

Melatonin and Melatonergic Influence on Neuronal Transcription Factors: Implications for the Development of Novel Therapies for Neurodegenerative Disorders

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Abstract: Melatonin is a multifunctional signalling molecule that is secreted by the mammalian pineal gland, and also found in a number of organisms including plants and bacteria. Research has continued to uncover an ever-increasing number of processes in which melatonin is known to play crucial roles in mammals. Amongst these functions is its contribution to cell multiplication, differentiation and survival in the brain. Experimental studies show that melatonin can achieve these functions by influencing transcription factors which control neuronal and glial gene expression. Since neuronal survival and differentiation are processes that are important determinants of the pathogenesis, course and outcome of neurodegenerative disorders; the known and potential influences of melatonin on neuronal and glial transcription factors are worthy of constant examination. In this review, relevant scientific literature on the role of melatonin in preventing or altering the course and outcome of neurodegenerative disorders, by focusing on melatonin's influence on transcription factors is examined. A number of transcription factors whose functions can be influenced by melatonin in neurodegenerative disease models have also been highlighted. Finally, the therapeutic implications of melatonin's influences have also been discussed and the potential limitations to its applications have been highlighted.

Keywords: Melatonin, glial, neurons, gene expression, transcription factors, neuroinflammation, neurodegeneration.

1. INTRODUCTION

Worldwide, an emerging economic burden and arbiter of death to the rapidly-expanding population of aged people is a failing brain [1, 2], which is characterised by age-related neurodegeneration, and the onset of neurodegenerative disorders [3-5]. Genetics play crucial roles in brain development and functioning either under physiological or pathological states; and there are genetic blueprints that modulate the proper development and functioning of the human brain [6]. In the last decade, investigating the roles of alterations in gene expression in the pathogenesis of traumatic, ischaemic and neurodegenerative brain diseases has continued to receive attention. This is important to first understand the possible mechanisms that alter gene expression profiles resulting in cell death; and second to assist in the development of novel therapies to manage neurodegenerative diseases.

Neurodegenerative diseases are a heterogeneous group encompassing conditions such as Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD) and frontotemporal dementia (FTD). These diseases generally share similarities in pathologies that include progressive and selective neuron loss linked to protein aggregation, neuroinflammation, mitochondrial dysfunction and genetic alterations [7-9] resulting in irreversible loss of brain function [9]. The mechanisms involved in the development of neurodegenerative diseases include oxidative stress [10, 11], vascular pathologies [12] and previous traumatic brain injury [13]. The presence of genetic mutations in autophagy-related genes [14], mitochondrial genes [15], genes involved in ribonucleic acid (RNA) processing [4, 9, 16]; and protea-

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somal dysfunction [17] has also been investigated extensively. Findings indicate that there is a multistep process of neuronal transition from stem cells to adult neurons which is regulated by transcription factors to facilitate differential genetic expressions [18-20]. Transcription factors function as regulators and integration centres for the different signal-transduction pathways involved in the expression of a given gene; they also induce and maintain stem cell pluripotency [21, 22]. The transcription regulators are themselves regulated to allow for differential gene expression during neuronal development and in terminally-differentiated adult cells [23, 24].

One of the endogenous ligands known to play a role in the control of transcription factors is melatonin. The roles of melatonin in gene regulation and the regulation of transcription factors have been proposed by several studies [22, 25]. Findings indicate that melatonin has the ability to regulate activities of transcription factors through its interaction with its surface receptors (MT1, MT2), leading to the activation of intracellular signalling cascades. The activation of transcription factors results in the modulation of DNA in a manner that either leads to apoptosis or reduced angiogenesis (processes important in tumour suppression [25]), or increased antioxidant defense mechanisms, immune modulation and decreased age-related pro-inflammation [25], processes which are relevant in the prevention of neurodegeneration (Fig. **1**). Melatonin homeostasis has been reported to be disrupted in many neurodegenerative conditions including Alzheimer's and Parkinson's disease, suggesting its involvement in the pathophysiology of these diseases. The different attributes of melatonin as an antioxidant, anti-excitotoxicity, anti-inflammatory, and anti-misfolding molecule; and its ability to cross the blood-brain barrier make it a promising neuroprotector. However, its ability to regulate the activities of transcription factors, and alter neurodegenerative and pathophysiological events is yet to be fully explored. Also of interest is how the interaction between exogenous melatonin and transcription factors could directly or indirectly alter the course and outcome of neurodegenerative disorders. The first part of the review discusses transcription factors gene expression and regulation in the brain. In addition, gene expression patterns transcriptome analyses, the regulation of genes expression and neuronal transcription factors in neurodegenerative diseases have been highlighted. In the second part, melatonin and melatonergic influences in neuronal transcription in neurodegenerative diseases with an emphasis on mechanistic relationships between melatonin and transcription factors will be discussed. Finally, how this can be translated to alter or prevent the course and outcome of neurodegenerative disorders will then be highlighted.

1.1. Transcription Factors and Gene Expression

Transcription factors are proteins with domains that bind to the DNA of the promoter regions of specific types of genes. Moreover, they possess a domain that interacts with other transcription factors resulting in the regulation of messenger RNA (mRNA) produced by the gene. Some transcrip-

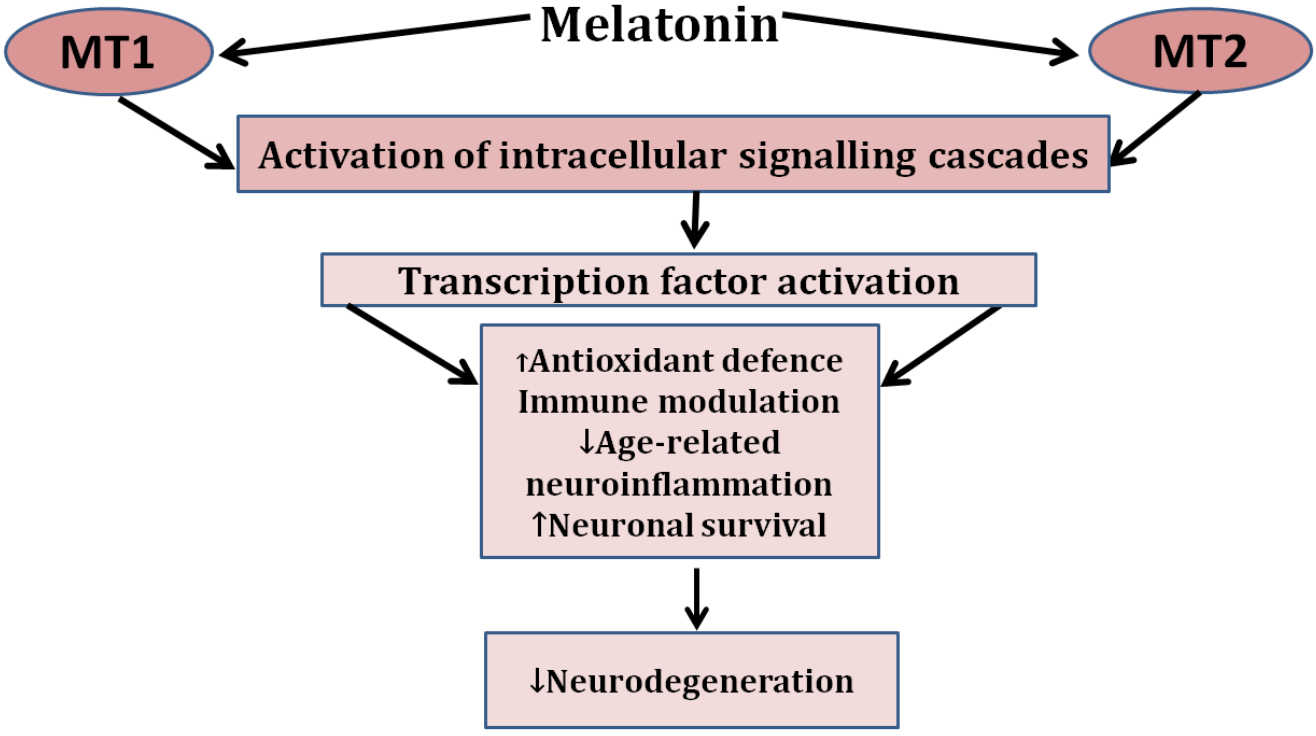

Fig. (1). Showing the mechanisms by which melatonin prevents the development of neurodegenerative changes or mitigates neurodegeneration *via* its activities at Melatonin (MT) 1 and 2 receptors. The *via* this receptors melatonin causes the activation of intracellular signalling cascades which goes on to activate transcription factors responsible for antioxidant defense mechanisms, immune modulation, age related neuroinflammation and neuronal survival. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

tion factors are found in almost all cells of an organism, while other transcription factors are specific for some types of cells and stages of development. The specific type of transcription factor is most of the time very significant in initiating patterns of gene expression that result in significant developmental changes. This occurs when they act on promoters to activate or repress the transcription of specific types of genes. In humans, they function by modulating the transcription phase by up or downregulation of gene expression [26]. The mechanisms by which this is done include; a) catalysing the acetylation or deacetylation of histone proteins [27], b) regulating the binding of RNA polymerase to DNA, and c) controlling the recruitment of cofactors to the transcription factor-DNA complex [28].

The presence of DNA binding domains (DBD) is a characteristic feature of transcription factors [29]. With the aid of DBDs, *transcription factors are able to* recognise specific motifs or nucleotide sequences located on the chromosome (up or downstream) before or after the gene. It is also important to point out that transcription factors represent one of the means by which different cells including neurons, express different combinations of genes, allowing for differentiation into the various types of cells. This mechanism of regulation is very important, considering the findings that several neurodegenerative pathways are expressed in particular cell types [30], and neurodegeneration involve specific combinations of genetic predispositions [31]. Accordingly, selective neuronal vulnerability may involve neuron-specific combinations of dysfunctions including genetic, intrinsic morphological, electrophysiological, and biochemical factors aggravated by advancing age. These determinants are not likely to be independent, and they may play synergistic roles in the selective loss of particular neurons in vulnerable regions of the brain. In this context, the role of specific transcription factors in selective neuronal vulnerability needs to be thoroughly investigated. It has been shown that transcription factors can as well control gene expression by creating a "*cascade*" effect [32], such that the occurrence of small amounts of one particular protein activates the production of larger amounts of a second, and this triggers production of *larger* amounts of a third *etc*. This represents the mechanisms through which major effects are induced by small amounts of the initial material. This reveals that an important general principle of the transcription factor in its regulatory function is not working alone, but work together with other specifically bound transcription factors and cofactors [33]. Moreover, it suggests more detailed mechanistic approaches for understanding the regulation of transcription factors and multiplicity of biochemical effect or functions

Within the concept of cross-talk, the demonstration that transcription factors may interact with each other resulting in inhibition or enhancement of transcriptional activity at a site distinct from the specific target for a particular transcription factor, is significant [34]. This allows cross-talk between different signal transduction pathways at the level of gene expression and provides coextensive activation of several transcription factors, which is necessary to have maximal gene expression. This provides the explanation for how transcription factors that are universal in distribution may regulate particular genes in certain types of neuronal cells.

1.1.1. Regulation of Gene Expression in the Brain and Regulation of Neurodegenerative Disease

The human brain is a complex structure (with several functional subdivisions) whose differentiation and continued functioning are directly linked with the expression and regulation of genes [35]. For instance, the functional and cellular differentiation of the neuron is ensured by variations in gene expression, which are regulated by transcriptional and post-transcriptional processes during the different phases of human brain development [36]. Moreover, the process of brain development involves the coordinated expression of several genes [37, 38] that control the differentiation of the neural plate through several phases into distinct brain regions [39, 40]. Studies have also shown that during brain maturation, functional compartments of the brain also exhibit unique transcriptome signatures [41, 42].

The importance of genetics in the development of neurodegenerative diseases has been studied extensively in the last two or more decades [43-47]. These studies have demonstrated the central role played by genes in the aetiopathogenesis of these disorders. In some cases, identified genes are directly involved in the aetiology or act as modulators of disease susceptibility. Candidate genes associated with the development of monogenic neurodegenerative disorders like AD or PD have been identified [8, 48], and specific genes or susceptibility loci associated with heterogeneous and/or heritable disorders like the ataxias, have also been [49-52]. Moreover, the results of genome-wide association studies identified an estimated ninety-four genes associated with the development of neurodegenerative diseases, including AD, PD, Multiple sclerosis and Amyotrophic lateral sclerosis [53]. It has been shown that few of these genetic variations are linked to the control of disease susceptibility and expression [52]. These studies continue to identify susceptibility and disease risk loci that are related to neurodegenerative diseases such as AD and PD [54-56]. Ongoing large-scale genome-wide association studies enabled the assessment of the extent of the involvement of gene-environment interactions, genetic variants, and shared gene-related mechanisms in the development of neurodegenerative diseases. Specific risk variants such as associations between genetic variations in cell adhesion molecule pathways and the development of AD [57, 58], as well as the presence of genetic associations between the immune system and certain AD variants [52, 59] or multiple sclerosis [60] have been identified. Using expression quantitative trait locus analysis to examine genes linked with the development of some neurodegenerative diseases, Ryan *et al*. [50] showed that genetic variants present in six genes loci including PILRB, METTL21B, NUP160, LRRK2, CD33 and RGS1 not only altered the expression of contiguous genes but were also associated with determining disease susceptibility [50]. In general, existing studies [50, 52, 58, 61, 62] provided scientific evidence that the presence of genetic variants modulates gene expression and neurodegenerative diseases susceptibility. Also, such genetic variants may be important determinants of onset/progression of neurodegenerative disorders, and differences in their clinical phenotype or expression.

1.1.1.1. Transcriptome Analyses in Neurodegenerative Diseases

In recent years, advances in molecular techniques have significantly impacted our understanding of the science underlying the pathogenesis and therapeutic options in neurodegenerative disease management [63, 64]. These advances paved the way for pathway-based gene expression and multiple pathway analyses studies [57, 59, 63] that allowed the in-depth study of complex diseases; thereby, broadening our knowledge base as well as providing a framework for measuring mechanism, and disease outcome [57-59, 63, 64]. Moreover, transcriptome analysis enabled the identification of alterations in the splicing patterns and genes expression that occur either before the onset of or during the course of the neurodegenerative disease process; helping to define key factors in the molecular pathogenesis of these disorders [65, 66]. This provides the opportunity for molecular backtrack studies and the formulation of different hypotheses on possible transcription factors that could have been involved in or be responsible for the dysregulation. Using ribonucleic acid sequencing in both wild-type and transgenic mice, Kim *et al*. [66] identified age-dependent alterations in neuroinflammatory gene loci in the cerebral cortex in both mouse models, and also associated this with the over-expression of tau proteins. They reported that the over-expression of tau induced a number of transcriptomic changes in the immune and inflammatory system [66]. In addition, transcription analysis to profile human microglia isolated from normal-looking regions of the post-mortem brains of donors with or without multiple sclerosis reported evidence of white and grey matter transcriptomic changes. Variations in the gene expressions in the white and grey matter were also observed [67]. Transcriptome profiling also enabled the discovery of shared gene expression pathways between and within neurodegenerative diseases [4, 67, 68]. A deeper understanding of the shared gene expression pathway will be beneficial to the potential development of an integrative approach to the prevention or therapy of neurodegenerative disorders.

1.2. Neuronal Transcription Factors in Neurodegenerative Diseases

The progression in understanding the molecular pathogenesis of neurodegenerative diseases has enlightened us that more important than protein aggregation in neurodegenerative diseases is the contribution of altered RNA processing to these disorders [69, 70]. Studies have implicated defects at different levels of gene regulation with disease-specific alterations in noncoding RNAs and RNA-binding proteins. Neurons have also been shown to be extremely sensitive to perturbations in transcription trafficking [71]. While transcription factors are critical to normal brain development, a number of transcription factors have been implicated in the development of neurodegenerative diseases. Several lines of evidence indicate that transcription factor-induced changes in neurodegenerative diseases occur not only as a result of alterations in transcription factor levels but also as a consequence of disruptions in phosphorylation and subcellular distribution within neurons in the brain abounds [71, 72]. There have been reports of the existence of distinct overlaps between transcription factor changes that occur in health and neurodegenerative diseases like AD. For example, the abnormal expression of amyloid-β (Aβ) peptide and tau proteins resulting in the accumulation of neurofibrillary tangles that is characteristic in AD has been associated with transcriptional down-regulation of genes that control biochemical pathways and encode proteins metastable to aggregate [73, 74].

A number of transcription factors (Table **1**) have been implicated in neurodegenerative diseases. The restrictive element-1 silencing transcription factor (REST), also known as the (neuron-restrictive silencing factor (NRSF), is a re-

Table 1. Transcription factors implicated in neurodegenerative diseases.

Transcription Factor	Function	Refs.
REST	The loss of REST has been associated with the onset of AD while in Huntington's disease accumulation of REST has been observed striatal neurons	[77-79]
$PARK_2$	Implicated in autosomal recessive juvenile parkinsonism, regulates the expression of apoptosis-related genes modulates the activity of the p53 presenilin-1 and presenilin-2 promoters	[81-85]
ATF_2	Regulates gene expression *via* their ability to form homodimers or heterodimers with a number of other protein partners	[84, 86]
ApoE4	Undergoes nuclear translocation and binds to DNA and gene promoters involved in a number of processes linked to neurodegeneration	[94, 95]
NF-kB	Regulates the expression of genes that encode proteins in processes related to inflammation and immunity	[87-91]
STAT1	Undergoes activation in glial cells. Overactivation results in the activation of inducible nitric oxide synthase cause neurodegeneration	[90, 91]
p53	Regulates important cellular activities including DNA repair and cell death Increased p53 immunoreactivity has been reported in AD, frontotemporal dementia and diffuse Lewy body disease.	[96-98]
Nrf2	Nrf2 regulates cellular response to oxidative stress and xenobiotics. Cytoplasmic accumulation of Nrf2 has been observed in hippocampal neurons INAD and Lewy body dementia	[92, 93]

pressor or silencer of gene which is expressed largely during embryogenesis and is important in ensuring terminal neuronal differentiation [75]. In actively-dividing pluripotent neural cells, REST acting through epigenetic remodelling represses the expression of genes critical to neuron-specific synaptogenesis, structural remodelling, synaptic plasticity and microRNAs that modulate the activities of non-neuronal genes [76, 77]. The dysregulation of REST has been implicated in a number of neurodegenerative diseases. For example, the loss of REST has been associated with the onset of AD, while in Huntington's disease, accumulation of REST has been observed in striatal neurons [77-79].

Parkin or the *PARK2* gene is well known for encoding the E3 ubiquitin ligase, and has been implicated in the development of autosomal recessive juvenile Parkinsonism [80, 81]. It regulates the expression and activities of genes associated with apoptosis and acts as a transcriptional factor directly repressing the activity of the p53 promoter [82-84]. Parkin also modulates the transactivation of presenilin-1 and presenilin-2 promoters [85]. Activation transcription factor 2 (ATF2) is a member of the leucine zipper family of deoxyribonucleic acid-binding proteins and an important member of the activator protein-1 (Ap-1) family that regulate gene expression *via* their ability to form homodimers or heterodimers with a number of other proteins. It regulates the expression of genes involved in cellular processes, including inflammatory signalling and apoptosis, which have been reported to be altered in neurodegenerative diseases [84, 86].

Nuclear factor-κB (NF-kB) is a well-characterised transcription factor that has been shown to regulate the expression of many genes which encode proteins in processes related to inflammation and immunity and more recently it has been shown to be important in the pathogenesis of neurodegenerative diseases including PD, AD and amyotrophic lateral sclerosis [87-89]. Studies have also shown that TF(s) like signal transducer and activator of transcription-1 (STAT1) can undergo activation in glial cells following which they are translocated into the nucleus [90]. Overactivation of STATI with the activation of inducible nitric oxide synthase has been linked to the development of neurodegenerative diseases [91]. Nuclear factor E2-related factor 2 (Nrf2) is also a member of the basic leucine zipper family of transcription factors and has been described as a crucial regulator of cellular response to oxidative stress and xenobiotics [92]. In the post-mortem brains of subjects with AD and Lewy body dementia, cytoplasmic accumulation of Nrf2 has been observed in hippocampal neurons [93].

Proteins like the Alzheimer's disease-associated protein (ApoE4) have also been reported to act as transcription factors by undergoing nuclear translocation and binding to DNA and gene promoters involved in a number of processes linked to the disease pathogenesis [94, 95]. Other TFs include the p53, which has been shown to regulate important cellular activities, including DNA repair and cell death [96]. Increased p53 immunoreactivity has been reported in AD, frontotemporal dementia and diffuse Lewy body disease [97, 98].

A number of novel TF(s) with recent demonstrable involvements in the pathogenesis of AD were described by Vargas *et al*. [84]. These TF(s) which include cysteine and serine-rich nuclear protein 2 (CSRNP2), CCR4-NOT transcription complex subunit 7 (CNOT7), TSC22 domain family member 1 (TSC22D1) and solute carrier family 30 member 9(SLC30A9) were demonstrated to modulate the activity of different genes that encode protein processes related to the development of neurodegeneration, and the activity of the p53-promoter [84].

1.3. Regulators of Transcription Factors (TF)

The transcription of genes is regulated by transcription factors, the activities of which are, in turn, modulated and regulated by TF converging surface-initiated signalling pathways *via* post-translational modifications. Post-translational modifications (PTMs) regulate every aspect of transcription factor activity and also controls access of RNA polymerases to the respective promoter templates [99]. This provides a transcription factor/post-translational modification "switchboard" that allows coordination of the activities that occur upstream (signalling) and downstream (transcription) [99, 100]. Transcription factor post-transcriptional modifications include acetylation, phosphorylation, sumoylation, methylation, ubiquitination and glycosylation [99, 101-104]. Some of these PTMs occur at the same frequency as observed in other proteins, while a few occur less frequently [99]. There have been suggestions that distinct patterns of post-transitional modifications are directed by the activities of external and internal stimuli [105, 106].

Apart from post-translational modification of transcription factors, genome-wide studies are showing that while the loss of chromatin dynamics occurs in both the aging and neurodegenerative states, the chromatin landscape of the neurodegenerative brain is quite different from that of the healthy ageing brain. Recent discoveries point to the fact that chromatin function is critical in the ageing brain and the maintenance of health relies heavily on epigenetic mechanisms [107]. While epigenetic changes in the neurodegenerative brains have been characterized, the impact of these changes is not all clearly understood. Animal models show that reversing abnormal chromatin structure reduces the toxicity of disease-associated proteins [107], indicating that epigenetic changes are likely to contribute to transcriptional dysregulation in the degenerative brain.

The circadian rhythm involvement in gene transcription has also been described, with suggestions that the biological clock modulates the availability of gene transcripts by either its effects on post-transcriptional modifications of transcription factors or transcription factor activity [105, 108]. Melatonin, a modulator of the circadian clock rhythm has also been reported to suppress the expression of some transcription factors (AP-1, NF-kB and Parkin) or modulate their activities [109-111]. How melatonin or melatonergic influences directly or indirectly fits into this puzzle would be discussed in the succeeding sections.

2. MELATONIN

2.1. Melatonin in Neurodegenerative Diseases

Over the past few decades, there has been an increase in research and reviews examining the benefits of melatonin on

the brain in health or disease [112-127]. Findings from these studies and reviews indicate that a decrease in the level of melatonin and the expression of melatonin receptor expression occur with normal ageing, and that an acceleration of these reductions is directly linked with the pathogenesis of some diseases. For instance, the depletion in melatonin and melatonergic signalling has been associated with impairment in cognition and memory, the development of neuropsychiatric dysfunction and alterations in the processes responsible for neurogenesis and neuro-restoration [128].

Along this line, the therapeutic benefits of the neuroprotective and antioxidant properties of melatonin in neurodegenerative diseases have also been examined in animal models of AD and PD [114-116]. Findings reveal melatonin's ability to arrest the neurodegeneration process, by reducing the generation of free radicals and regulating mitochondrial homeostasis Melatonin's role in mitigating or ameliorating the neurocognitive decline associated with aging and/or neurodegenerative disorders have also been investigated extensively [117-119, 122]. These studies reveal evidence of improvement in sleep, amelioration of bouts of confusion, evening-time anxiety, aggression and agitation (observed a number of AD patients), and slowing down the progression of cognitive impairment in Alzheimer-type dementia following melatonin supplementation. This result indicates the possibility that melatonergic agents are likely agents in dementia management [122].

There have also been reports suggesting that melatonin could function directly as a trophic factor that promotes adult neural precursor cell proliferation (in the mouse hippocampal subventricular zone) through the activation of the ERK/MAPK pathway [129]. However, the direct clinical application of melatonin in dealing with the pathogenesis and brain morphological alterations of neurodegenerative diseases is still an area of continuous research.

2.1.1. Melatonin, Mitochondria and Neurodegenerative Diseases

It is becoming increasingly evident that the mitochondria play crucial roles in the pathogenesis of neurodegenerative diseases [130, 131]. This knowledge comes from studies that have associated mitochondrial oxidative injury, increased production of mitochondrial mutant proteins, and mitochondrial biogenesis with cellular alterations in neurodegenerative diseases [132-141]. Also, an increase in mitochondrial fragmentation, and a decrease in mitochondrial fusion have been shown to be crucial to the development of mitochondrial dysfunction and cell death that occurs with aging and in age-related diseases [15, 142, 143]. Recent evidence demonstrating that in addition to the pineal secretion of melatonin, circulating levels of melatonin also derive from the mitochondria which are present in a number of cells [144, 145] further emphasises the importance of melatonin and/or the mitochondria in neurodegenerative diseases. Reports that the mitochondrial concentration of melatonin far exceeds blood melatonin levels [144] has led to recent evidence which demonstrates the presence (within the mitochondria membranes) of oligopeptide transporters that assist in the rapid uptake of melatonin against a gradient [146]. Inside the mitochondria, melatonin exerts strong antioxidant effects [144, 146] possibly through melatonin receptors that have also been localised in the mitochondria [145]. The presence of these receptors in the mitochondria could also be linked to the neuroprotective effects of melatonin [145]. However, the importance of the relationships between melatonin and the mitochondria, and how these relationships might affect the influences that melatonin exert on neuronal transcription and transcription factors is a field that requires extensive research. Also, the knowledge acquired will further our understanding of the pathogenesis, possible prevention, and management of neurodegenerative disorders.

2.2. Melatonin and Melatonergic Influences in Neuronal Transcription

Advances in neuro-genetics and genomics reveal that the therapeutic potential of melatonin in brain disease may go beyond its effects on free radicals, with a potential to modulate transcription factors, messenger RNA and/or different components of transcription factor genes [22, 109, 147]. It was initially believed that melatonin may act through a nuclear signalling pathway that is mediated *via* a transcription factor (RZR/ROR) to influence neuronal differentiation. Along this line, studies in staggerers (which are natural RZR/RORα "knockout" mice) have reported defects in cerebellar Purkinje cell development [148, 149]. However, recent findings cast doubts on the validity of RORs acting as nuclear melatonin receptors [150].

A recent study by Franco-Iborra *et al* [151] demonstrated that exogenous melatonin decreased the expression of mitochondrial transcription factors mRNA, and interfered with the transcription of mitochondrial DNA in malignant glioma cell line [151]. The importance of melatonin and melatonergic influences in neuronal transcription and gene regulation has also been buttressed by studies that have demonstrated the significance of melatonin receptor upregulation (specifically Melatonin II receptor) by agents like valproic acid on memory, learning and neural stem cell proliferation; suggesting the existence of therapeutic benefits in neurodegenerative disorder management [128, 152, 153].

Over the past few years, experimental evidences continue to support the notion that melatonin can prevent or modulate the processes involved in neuronal degeneration by exerting influence on a number of transcription factors. In a number of cases, there is upregulation of molecular modification of such transcription factors. Recent evidences have uncovered more of such influences, and also point us in the direction in which they may be useful in neurodegenerative disorders. In a rat model of Alzheimer's disease (AD) which was induced by intra-hippocampal injection of amyloid peptide Aβ1-42, melatonin was reported to attenuate increases in cortical and hippocampal S-100β and NFκB of treated animals, leading to a partial reversal of the behavioural changes that were caused by amyloid peptide Aβ1-42 treatment [154]. Increased phosphorylation due to the influence of melatonin appears to be the mechanism by which the transcription factor c-Myc stimulates neuronal proliferation in the adult mouse hippocampal sub-ventricular zone (SVZ). The action of melatonin on its receptor activates the ERK/MAPK signalling pathway which leads to stability of c-Myc and trig-

gering of the proliferative signal [129]. The nuclear factor erythroid 2-related factor 2 (Nrf2) also has a gene-dependent antioxidant mechanism that can be influenced by melatonin. In an experimental paradigm using acute ethanol-induced elevated reactive oxygen species (ROS)-mediated neuroinflammation and neurodegeneration in the developing rodent brain, biochemical, immunohistochemical, and immunofluorescence evidences showed that melatonin significantly upregulated endogenous Nrf2 and heme oxygenase-1 leading to a reversal of the acute ethanol-induced elevation in ROS and oxidative stress [155]. Also, acute melatonin reduced the activation of the MAPK-p-P38-JNK pathways, attenuating neuroinflammation; and decreasing the expression of activated gliosis and inflammatory markers in both the developing rodent brain and BV2 cells. All these led to the attenuation of neuronal apoptosis [155].

The inhibition of activating transcription factor 6 (ATF6) by melatonin has been shown to alleviate secondary brain injury occurring through apoptosis after intracerebral hemorrhage (ICH) in rats. Melatonin administration led to a significant decrease in the mRNA and protein levels of ATF6; also, downstream targets like CHOP and cleaved caspase-3 were reduced while the Bcl-2/Bax ratio increased, all leading to improved neurological functions [156]. In primary cortical neurons cultured with Aβ25-35, there was decreased expression of miR-132 and elevation of PTEN and FOXO3a; however, administration of melatonin led to the upregulation of miR-132, and downregulation of level of PTEN and FOXO3a with inhibition of apoptosis. This experimental evidence shows that melatonin can exert a neuroprotective effect in Aβ-induced neurotoxicity through the miR-132/PTEN/AKT/FOXO3a pathway [157]. In high-glucose induced neuronal cell apoptosis model, melatonin had been shown to stimulate the transcription factor PINK1 expression, *via* an MT_2 /Akt/NF-κB pathway; and this stimulation has been shown to be important in the prevention of neuronal cell apoptosis under high glucose conditions [158]. In manganese-induced striatal brain injury in mice, melatonin had been shown to induce the Keap1-Nrf2-antioxidant response elements (ARE) pathway leading to a protection against manganese-induced oxidative injury [159]. Melatonin has also been shown to have a role in the protection, increased survival and proliferation of Neural Stem Cells through its effects on certain transcription factors. *In vitro* experiments on Neural Stem Cell (NSC) cultures with Lipopolysaccharide (LPS) induced inflammation, showed an increase in SOX2 mRNA levels (a marker of NSC survival and proliferation) in melatonin treated NSCs compared to controls [160]. In other experiments using Spinal Cord Injury Rat Models, increased expression of OCT4 (a marker of higher proliferation) was also demonstrated in endogenous Neural Stem/Progenitor Cells (eNSPC) when melatonin was used as compared to controls [161].

In mice with traumatic brain injury, administration of melatonin (at 1-hour post-injury) led to facilitation of recovery and a twofold decrease in size of brain lesion, through a mechanism that involves an increase in brain low molecular weight antioxidants, including ascorbic acid [162]. Melatonin also blocked the late-phase (8 days) activation of NF-kappa B and it decreased activation of AP-1 to below basal levels [162]. In rats with Vitamin A deficiency-induced congenital spinal deformity, whole-embryo expression of miR-363 has been shown to be up-regulated; also, miR-363 has been shown to inhibit the proliferation and neuronal differentiation of primary cultured NSCs, with accompanying down-regulation of Notch-1 [163]. Melatonin administration suppressed miR-363 expression and blocked the effects of miR-363 on NSC proliferation/neuronal differentiation and also restored Notch signalling [163]. Overall, the results of these studies point to the fact that in models of neurodegenerative disorders, melatonin can enhance neuronal proliferation, differentiation and survival through the activation of pathways that promote such processes, and by counteracting cellular pathways that inhibit them.

Table **2** shows a number of transcription factors modulated by melatonin and how the regulation/modulation affects certain measurable outcomes that are related to models of neurodegenerative disorders.

2.3. Therapeutic Implications of Melatonin's Influences on Neuronal Transcription Factors

Current treatment strategies for neurodegenerative diseases are directed predominantly towards alleviating disease symptomatology, rather than halting or reversing the neurodegenerative process. Therefore, the development of more effective treatment options may entail the redirection of therapeutic interventions towards developing novel drugs or repurposing old compounds that directly or indirectly target processes that lead to or sustain neurodegeneration. As highlighted above, the results of a number of preclinical studies using different models of neurodegenerative diseases [164-166] suggest that pharmacological manipulations of transcription factor expression and regulation may become crucial to the management of neurodegenerative disease. Hence, melatonin's influence on neuronal transcription factors can be positively explored in the management of neurodegenerative disorders. From the knowledge of melatonin's actions, we can deduce that its anti-inflammatory, antioxidant and antiapoptotic effects make it potentially beneficial in preventing, delaying and possibly reversing the pathological processes that are involved in neurodegenerative disorders.

A number of studies have highlighted the possible therapeutic benefits of melatonin supplementation in Alzheimer's disease [167, 168], Parkinson's disease [169-171], and motor neuron disease [172]. In a number of clinical studies, administration of melatonin to human subjects with AD, mild cognitive impairment or dementia was associated with improvement in agitation, cognition, mood, sleep latency and sundowning [173-176]; while melatonin prophylaxis was associated with a reduction of AD neuropathology [168]. In the management of PD, results from studies have also demonstrated neuroprotection and improvements in cognition/sleep latency [169-171]. In motor neuron diseases such as amyotrophic lateral sclerosis, melatonin therapy has been associated with a decrease in caspase-mediated cell death, inhibition of melatonin receptor loss, and delay in disease progression [172].

Also, research has shown that a number of transcription factors that are involved in neurodegenerative diseases act

Table 2. Transcription factors modulated by melatonin and the consequences.

Transcription Factor	Model	Consequence	Refs.
c-Myc	Aging mice hippocampus	Enhanced c-Myc stability and cell proliferation in the SVZ	[129]
nuclear factor erythroid 2-related factor 2 (Nrf2)	Ethanol-induced neuroinflammation and neurodegeneration in the developing murine brain, and murine hippocampal cells.	Upregulation of Nrf2, reduction in oxidative stress, neuroinflammation and apoptosis *via* Nrf2-dependent mechanisms	[155]
NFκB	Rat model of AD	Upregulation of hippocampal NFκB and partial reversal of behavioural markers.	[154]
activating transcription factor 6 (ATF6)	Rat model of intracerebral hemorrhage (ICH)	Reduction in secondary brain injury by decreasing mRNA and protein levels of ATF6, CHOP and cleaved caspase-3; and increased Bcl-2/Bax ratio.	[156]
miR-132	primary cortical neurons cultured with Aβ25-35	Upregulation of miR-132, and downregulation of level of PTEN and FOXO3a with inhibition of apoptosis.	[157]
PINK1	high glucose induced neuronal cell apoptosis	Stimulation of PINK1 expression *via* the MT_2 /Akt/NF-κB pathway, and prevention of neuronal apoptosis	[158]
Kelch-like ECH-associated protein 1 (Keap1)	manganese-induced brain striatal brain injury in mice	Activation of the Keap1-Nrf2-antioxidant response elements (ARE) pathway which protects against manganism.	[159]
SOX2	Lipopolysacharide (LPS) induced inflammation in Neural Stem Cells (NSC) *in vitro*	Increase in SOX2 mRNA levels - marker of NSC survival and proliferation.	[160]
OCT4 AP-1 miR-363	Spinal Cord Injury Rat Model Closed head injury in mice Rat model of Vit. A deficiency-iinduced congenital spinal deformity	Increased expression of OCT4 in endogenous Neural Stem/Progenitor Cells (eNSPC) - marker of higher proliferation. Reduction of late-phase (8 days) activation of AP-1 to below basal levels. Decreased lesion size Suppression of miR-363 expression; and rescue of the effects of miR-363 on neural stem cell proliferation and neuronal differentiation.	[161] [162] [163]

through mechanisms that are amenable to modulation by exogenous melatonin. The possible translational application of this knowledge starts with the identification of the specific types and numbers of neuronal or glial transcription factors that are involved in each neurodegenerative disorder, and establishing that their activities can be modulated by melatonin. This may help to categorise neurodegenerative disorders based on the potential to benefit from melatonin therapy. Also, based on this concept, the likely degree of improvement that may be derivable from melatonin therapy can be predicted; hence, paving the way for rational therapy of neurodegenerative disorders using melatonin.

In general, if the observations from animal and cell line studies can be extrapolated to humans; melatonin may be the closest to a single-agent 'ideal' drug for the prevention or management of a number of neurodegenerative disorders, due to its potential ability to alter behaviours and influence processes such as neuroinflammation, neuronal oxidative stress, neuronal proliferation and neuronal apoptosis as well as NSC survival and proliferation by its influence at the genetic level. However, an incomplete knowledge of the number of transcription factors that may be affected by melatonin is a limitation to the prospect of its use in this capacity. Also, a possible multifactorial origin of a number of neurodegenerative disorders may present a challenge to an attempt at using a single agent for management. Finally, the unwanted effects of exogenous melatonin on endogenous melatonin rhythm and functions might also limit application. However, despite the limitations mentioned above, as experimental evidence of benefits continues to accumulate, melatonin might not only emerge as a valuable and widely-accepted adjunct in the management of a number of neurodegenerative disorders, but also as a therapeutic cornerstone for the management of neurodegenerative disorders.

CONCLUSION

Melatonin is a unique molecule that can affect several aspects of the pathogenesis and progression of neurodegenerative disorders through its actions on neuronal and glial transcription factors. Presently, basic research has continued to uncover the roles that melatonin administration may play in neurodegenerative disorders; however, the full potentials of melatonin in the prevention and management of human neurodegenerative disorders is yet unknown.

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CONFLICT OF INTEREST

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

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