International Journal of Medical Science and Research
www.medicaljournals.in
Online ISSN: 2664-8768, Print ISSN: 2664-875X
Received: 13-05-2022, Accepted: 30-05-2022, Published: 15-06-2022
Volume 4, Issue 1, 2022, Page No. 54-60

The physiology and neuroprotective role of melatonin in neurodegenerative diseases

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Abstract
Melatonin is a neurohormone produced by the pineal gland that has a variety of regulatory and neuroprotective properties. Melatonin levels have been found to be disrupted in some neurodegenerative disorders, including stroke, Alzheimer's disease, and Parkinson's disease, implying that it plays a role in the pathophysiology of these diseases. Its properties make it a promising potential therapeutic neuroprotective agent for some neurodegenerative disorders, with no side effects. The role of melatonin in the pathophysiology of some diseases is discussed and pinpointed in this review.

Keywords: melatonin, ischemia, Alzheimer's disease, Parkinson's disease

Introduction
Melatonin is a tryptophan-derived indoleamine that is found in all phyla of multicellular animals. It's a neurohormone with multiple functions and a wide range of distribution [1]. Melatonin is mainly synthesized by the pineal gland in a circadian manner and released into blood and cerebrospinal fluid to exert regulatory roles on seasonal and circadian rhythms which is critical for neuroimmunoendocrine system physiological functions such as sleep-wake cycle, pubertal development, and seasonal adaptation. Melatonin secretion is quite low during the day (below 10 pg/mL), but the concentration rises dramatically at night (10–15-fold increase, up to 120 pg/mL) [2].
The circadian rhythm can be found in all living things. In humans, for example, the rhythm develops during the first few months of birth, peaks between the fourth and seventh years of life, and subsequently declines. [3] As a result, melatonin levels fluctuate throughout life. The fetus uses maternal melatonin that crosses the placenta throughout the fetal stage, and melatonin levels rise from birth to a high around adolescence, and then fall in middle-aged and old people.

Discovery of Melatonin
Melatonin was first found in relation to the mechanism by which certain amphibians and reptiles alter their skin color. Carey Pratt McCord and Floyd P. Allen discovered in 1917 that feeding tadpoles extract from cow pineal glands lightened their skin by constricting the dark epidermal melanophores. In 1958, dermatology professor Aaron B. Lerner and colleagues at Yale University extracted melatonin from bovine pineal gland extracts in the hopes of finding a chemical from the pineal that may be used to treat skin problems [4]. Richard Wurtman of MIT received the first patent for its usage as a low-dose sleep aid in 1995 [5]. Around the same time, the hormone received a lot of attention as a potential cure for a variety of ailments.

Melatonin Biosynthesis and Secretion
The pineal gland produces melatonin, the darkness hormone, from tryptophan, an important amino acid. Melatonin is produced through a multi-step process. Tryptophan is hydroxylated by tryptophan-5-hydroxylase (TPH) to produce 5-hydroxytryptophan, which is then decarboxylated by L-aromatic amino acid decarboxylase to produce 5-hydroxytryptamine (serotonin) (AADC). Arylalkylamine N-acetyltransferase (AA-NAT, commonly known as "Timezyme," is the rate-limiting enzyme for melatonin synthesis), converts serotonin to N-acetyl-5-methoxytryptamine (melatonin), which is then transformed to N-acetyl-5-methoxytryptamine (melatonin) by N-acetylserotonin-O (ASMT, also called hydroxyindole-O-methyltransferase or HIOMT). Because the pineal gland is located outside the blood-brain barrier, it loses its connections with the central nervous system and is primarily supplied by sympathetic nerves. This could explain why the pineal gland can absorb a lot of tryptophan, resulting in a lot of melatonin production and secretion in response to darkness. The action of beta-adrenergic receptors is required for melatonin production. N-acetyltransferase is activated by

norepinephrine, and beta-receptor blockers suppress melatonin release. Noradrenergic and neuropeptidergic projections to the pineal gland regulate both AA-NAT and ASMT activity.
Postganglionic fibers provide input to the pineal gland, which leads to the release of norepinephrine. Norepinephrine activates the adenylate cyclase-cAMP system by inducing its 1/-adrenoceptors. As a result, intracellular concentrations of second messengers such as cAMP, Ca2+, phosphatidylinositol, diacetylglycerol, and protein kinase C rise. AA-NAT and HIOMT expression and activity are induced by these messengers [6].

Melatonin Secretion Regulation

Melatonin is largely produced by the pineal gland in reaction to darkness, but it has also been discovered in extrapineal areas such as the retina, Harderian gland, lymphocytes, gastrointestinal system, bone marrow cells, platelets, and skin [6]. Melatonin, a neurohormone that is released into the bloodstream and can enter all human tissues, is not retained in the pineal gland. Melatonin production has a distinct circadian cycle, with low levels during the day and a peak in secretion at night. The suprachiasmatic nucleus (SCN) clock regulates the pineal gland's nighttime melatonin synthesis and release, which is restricted by illumination conditions [7]. Light sensing activates retinal ganglion cells that project to the SCN in the hypothalamus, prompting the release of inhibitory -amino butyric acid, which suppresses the circuit governing melatonin production and release in humans and other mammals. Melatonin content in the blood peaks between midnight and 3 a.m. (80–150 pg/mL), while it is low during the day (10–20 pg/mL) [8]. Individuals' typical melatonin patterns and the influence of light might differ significantly, either due to personal traits or as a result of aging or chronic disease. [9] Melatonin serum concentrations fluctuate significantly with age, and babies secrete very low levels of melatonin before the age of three months. Between the ages of 4 and 7, the amplitude of the nocturnal surge in melatonin secretion reaches its maximum levels [6].

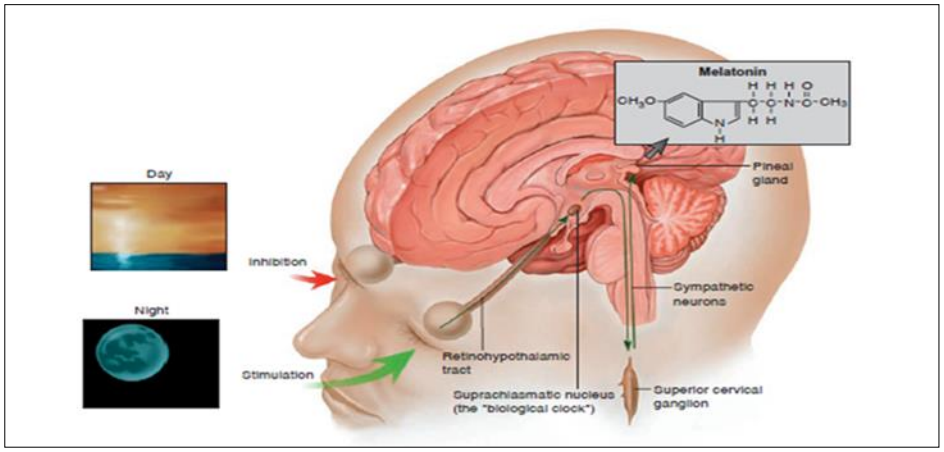

Fig 1: Secretion of melatonin, [10]

Receptors for Melatonin

Melatonin is swiftly released into the systemic circulation after being produced, allowing it to reach central and peripheral target tissues. Melatonin's effects are determined by the location and kind of melatonin receptors. [6] Melatonin activates two G-protein-coupled receptors with high affinity, known as MT1 and MT2. Neuronal firing, arterial vasoconstriction, cell proliferation, immunological responses, and reproductive and metabolic activities are all regulated by the MT1 and MT2. [11] The brain, cardiovascular system, immunological system, testes, ovary, skin, liver, kidney, adrenal cortex, placenta, breast, retina, pancreas, and spleen all have MT1 receptors. The immune system, brain, retina, pituitary, blood arteries, testes, kidney, gastrointestinal tract, mammary glands, adipose tissue, and skin have all been discovered to contain MT2. [11] Unlike the MT1 and MT2 receptors, the MT3 receptor has a low affinity, is not connected to G proteins, has a nanomolar affinity for melatonin, and is not sensitive to Na, Mg, or Ca ions. The enzyme quinone reductase II is similar to MT3. Although the specific nature of the interaction between melatonin's numerous physiological functions and this enzyme is unknown, it is thought to be involved in the control of cellular redox state. Melatonin appears to be a natural ligand for the RZR/ROR receptor family of retinoid-related orphan nuclear hormone receptors. RZR/ROR is found in several organs, whereas RZR is only found in the brain and retina. Melatonin also interacts with intracellular proteins such calmodulin, calreticulin, and tubulin, preventing Ca ions from attaching to calmodulin. ROR/RZR has been proposed to regulate gene expression in collaboration with the plasma membrane receptors MT1/MT2. Melatonin's low-affinity association with calmodulin may play a role in its antioxidant properties as well as other signaling pathways. [6] In many mammalian species, membrane receptors have been identified in the central nervous system and peripheral organs such as the liver, gastrointestinal tract, skin, kidney, heart, adipose and lymphoid tissues. Melatonin also has non-receptor modes of action, such as acting as a scavenger for reactive oxygen and nitrogen species (ROS and RNS) (RNS).

Mechanism of Melatonin Action

The seven transmembrane G protein-coupled receptor family includes MT1 and MT2. The G proteins that mediate adenylyl cyclase inhibition and phospholipase C beta activation are linked to the MT1 melatonin receptor. The MT2 receptor inhibits the soluble guanylyl cyclase pathway as well as inhibiting adenylyl cyclase. Melatonin also suppresses the phosphorylation of the transcription factor cyclic AMP response element binding protein (CREB) in SCN cells, which is triggered by the pituitary adenylate cyclase-activating polypeptide. However, in MT1 receptor-deficient mice, a functional MT2 receptor in the mouse SCN can partially compensate for the lack of the MT1 receptor. This suggests that receptor subtypes play both redundant and non-redundant functions in regulating SCN function. A functioning MT1 receptor is required for the rhythmic synthesis of the clock gene product mPER1 in the pars tuberalis. When melatonin levels drop around dawn, it causes adenylyl cyclase to become sensitized for a long time, amplifying cyclic AMP signaling. Melatonin's effect in the pars tuberalis enhances gene expression rhythms and provides a method for reinforcing rhythmicity in peripheral tissues that lack the ability to sustain self-sustained oscillation. Melatonin directly detoxifies reactive oxygen and nitrogen species (ROS) by nonreceptor-mediated methods, in addition to the numerous activities mediated by its several receptors listed above.

The Brain and Energy Disturbance

Despite accounting for approximately 2% of the human body's weight, the brain consumes roughly 20% of the body's oxygen. This high degree of oxygen consumption can cause oxidative stress, which is a hazardous condition. The emergence of reactive oxygen species (ROS) in excess of the antioxidant action is referred to as oxidative stress. [12] ROS are molecules containing one or more unpaired electrons in their outer layer that are unstable. These compounds are toxic, destroying DNA, proteins, and cell membranes. [12] The brain's high fat content, which is dispersed in cell membranes and the myelin sheath, making it more vulnerable to ROS-targeted damage. An imbalance between ROS production and the opposing impact of antioxidants occurs when antioxidant enzyme levels are lower than in other bodily locations. The blood–brain barrier becomes leaky as a result of ROS damage, which disrupts mitochondrial respiration and changes the tubulin organization. [12] ROS produces excitotoxicity by increasing the release of excitatory neurotransmitters such as glutamate into the extracellular space, which acts on several types of receptors, primarily NMDA receptors. Furthermore, ROS changes gene expression, triggers the apoptosis cascade, and reduces neuronal viability.

Neurodegenerative Disease and Melatonin

Alzheimer's illness and melatonin (AD)

Alzheimer's disease is a neurodegenerative illness that develops with age and is characterized by toxic protein aggregation both inside and outside the neurons. Alzheimer's disease is characterized by extracellular b-amyloid (Ab) and intracellular neurofibrillary tangles (NFTs). [13] These aberrant proteins are known to accumulate in memory-related brain areas like the neocortex and hippocampus, resulting in progressive cognitive deterioration. Oxidative stress, synaptic dysfunction, and neuronal death are all mediated by toxic protein buildup. [14] The disease's aetiology is unknown; however, various factors have been identified as contributing to the disease, including genetic factors, sex, lipid metabolism, ageing, nutrition, and metal ion toxicity. [15] The amyloid precursor protein (APP), apolipoprotein E (ApoE), and presenilins 1 (PS1) and 2 (PS2) are the most common genes linked to Alzheimer's disease (PS2). [16] High Ab production is thought to be the fundamental cause of neuropathology in Alzheimer's disease. [17] Senile plaques are formed up of Ab peptides, which have 40–43 amino acids. The aetiology and subsequent neurodegenerative pathology of Alzheimer's disease are linked to oxidative stress. Several factors contribute to a high number of free radicals in Alzheimer's disease, including Ab deposition, mitochondrial malfunction, inflammation, and activated microglia. [18] Ab plaques are one of the main causes of oxidative stress in Alzheimer's disease, having a two-way effect in which oxidative stress mediates lysosomal Ab synthesis and Ab causes lysosomal membrane breakdown and eventually cell death. Melatonin's antiamyloidogenic impact in Alzheimer's disease has been documented in several research. [19] Melatonin has been demonstrated to decrease the creation of soluble APP in vitro, which may impede the production of Ab [20]. Melatonin has also been shown to interfere with the synthesis of Ab fibrils in vitro by interacting with A 40 and A 42. [21] In a transgenic rat model of Alzheimer's disease, long-term treatment of melatonin (for around two months) reduced immunoreactive Ab accumulation in the hippocampus and cortex by 43 percent and 37 percent, respectively. [22] In a sporadic rat model of Alzheimer's disease, melatonin administration during the active stage of disease progression reduced amyloid deposition in the hippocampus (b1–42 and b1–40) and frontal cortex (b1–42), decreased degenerative changes in the hippocampus, prevented mitochondrial dysfunction, and delayed anxiety and cognitive impairment. [23] Chronic melatonin administration following intracerebroventricular Ab1–42 injection reduced tau hyperphosphorylation and Ab-mediated memory impairments in rats, preventing neurodegeneration. [24] Melatonin is also said to be a powerful antioxidant in Alzheimer's disease. Melatonin lowers Ab-mediated oxidative stress and lipid peroxidase, according to several investigations. [19, 25] In the brain of transgenic AD mice, melatonin has been demonstrated to restore the normal level of mRNA encoding antioxidant enzymes (SOD-1, glutathione peroxidase, and catalase). [22] In Alzheimer's disease brains, oxidative stress end products are plentiful. Long-term oral melatonin therapy improves hippocampus synaptic development and protects neuronal and glial structure in a sporadic rat model of Alzheimer's disease. [26] Furthermore, after intracerebroventricular injections of soluble Ab1–42, melatonin

improves spatial memory, reduces synaptic dysfunction, and reduces astrogliosis in the rat hippocampus [27]. More research on the mechanism and therapeutic potentials of melatonin in Alzheimer's patients is needed. Melatonin protects synaptic dysfunction, neuronal loss, and cognitive impairment by acting as an anti-b amyloid aggregation, antioxidant, and anti-inflammatory.

Parkinson's illness and melatonin (PD)

PD affects several million people worldwide [28]. Several risk variables, including genetic factors, age, lead and manganese exposure, and dairy product consumption, are positively associated with PD incidence. Parkinson's disease is characterized by dopaminergic neuron loss in the substantia nigra pars compacta (SNc), which leads to striatal dopamine depletion, which disrupts smooth, coordinated motor movements, causing rigidity, tremor, bradykinesia, and postural instability [29]. Non-motor symptoms such as impulse control disorders (ICDs), neuropsychiatric, autonomic, sleep, and sensory dysfunction have been observed in PD patients. [30] Dopaminergic neuronal death is a pathogenic feature of Parkinson's disease, and it can impact multiple dopaminergic neurons, impairing connections with other neurons. The location of Lewy bodies and alpha-synuclein protein aggregation on neurons is a histological characteristic of PD. Lewy body aggregation impairs mitochondrial dynamics, which control ROS production and cell death. Several types of PD animal models have been developed to promote dopamine neuronal death and enhance the creation of sensory and motor deficits, which then expose PD symptoms as tremor, rigidity, and akinesia. PD animal models are often induced using two mechanisms: nigrostriatal injections of 6-hydroxydopamine (6-OHDA) and cerebral injections of neurotoxins like MPTP. Melatonin injections have been shown to reduce neuronal death in the nigrostriatal region and interfere with lipid peroxidation in the hippocampus and striatum in an MPTP-induced PD model. [31]. Furthermore, in a 6-OHDA-induced PD animal model, melatonin increases the levels of antioxidant enzymes such as catalase and superoxide dismutase in the nigrostriatal pathway. [32] Another study found that melatonin has a neuroprotective effect in the mouse nigrostriatum of a 6-OHDA-induced Parkinson's disease animal model by suppressing OH production and avoiding glutathione (GSH) decrease. [33]. Melatonin has been found to be a powerful antioxidant that can enhance the prognosis in Parkinson's disease by downregulating the effects of oxidative stress. Toxic alpha-synuclein is made up of oligomerized alpha-synuclein, fibrillated alpha-synuclein, and Lewy bodies, which cause neurodegeneration and cell death. [34] Melatonin has been demonstrated to act as an anti-assembly and interfere with alpha-synuclein toxic oligomer and alpha-synuclein fibril, reducing alpha-synuclein-induced cytotoxicity. [35] Furthermore, PD patients' melatonin rhythm amplitude and 24-hour plasma level have been found to be considerably lower than controls. [36] These findings show that the melatoninergic system is involved in the etiology of Parkinson's disease in people. However, clinical evidence is growing suggesting light therapy that antagonizes the impact of a melatonin receptor improves motor outcomes in PD patients, [37], which is compatible with animal model research. [38] To further understand the role of melatonin in motor functioning, more research employing exogenous melatonin rather than light therapy is needed.

Ischemia and melatonin

Ischaemic stroke is the world's second greatest cause of mortality and the leading cause of disability [39]. Ischemic stroke, which accounts for 85 percent of all strokes, and high mortality haemorrhagic stroke, which accounts for 15% of all strokes are the two forms [40]. During ischaemia, a complicated cascade of cellular damage events is set in motion, including excitotoxicity, ROS generation, and inflammation. Neurons are highly excitable cells that require a high metabolic rate to keep up with their energy-intensive activities. As a result, any restriction in cerebral blood flows, such as in the case of ischemic stroke, is a severe scenario for neurons, as they require a constant supply of oxygen and glucose. Cell viability is damaged by various processes in the case of oxygen glucose deprivation, beginning with energy deprivation, which affects one of the primary ATP-dependent pumps, Na^1/K^1-ATPase, causing its failure and reversing its function. Anoxic depolarization is initiated by a high amount of intracellular Na [Na^1] ions, which activates voltage gated calcium channels (VGCC) and reverses Na^1-Ca^2 ions exchange. As a result, Ca^2 ions travel within the cells, triggering a damage process mediated by Ca2 ions [41]. Muller and Ballanyi discovered that ischaemia caused anoxic depolarization, which was accompanied by a massive increase in intracellular Ca^2 ions [42]. During ischaemia, the extracellular level of glutamate, a primary excitatory neurotransmitter, rises due to the reversal of its absorption and release from presynaptic neurons. Excitotoxicity cell damage is caused by a sustained high amount of glutamate binding to NMDA and non-NMDA receptors. NMDA receptors mediate Ca^2 ion influx and enhance Ca^2 ion overload, whereas AMPA receptors allow Na^1 ion entrance, which causes cell swelling and cerebral oedema. Excitotoxicity is followed by a neurotoxic impact caused by oxidative stress. Multiple oxidative enzymes are activated by high [Ca^2 ions] excess (e.g., phospholipases, cyclooxygenases, NO synthase, and proteolytic enzymes). These enzymes speed up the production of free radicals, which causes a cascade of cellular damaging events such lipid peroxidation, DNA damage, mitochondrial injury, and the collapse of the blood–brain barrier (BBB), which causes brain oedema [43]. Inflammation follows excitotoxicity, a high level of Ca^2 ions, and oxidative stress. The activation of various factors such as NFjB, hypoxia-mediated factor 1, and STAT3, which are responsible for the production of inflammatory cytokines (TNF-a, IL-1b), enzymes (iNOS, COX-2), adhesion molecules (ICAM-1, selectins), and increasing the number of activated phagocytes, kicks off the inflammation stage. The ischemic damage that began at the centre of the injury travels out to the penumbra, a hypoperfused and functionally disturbed but viable tissue, over several days. In the case of an acute ischemic

stroke, thrombolysis or thrombectomy is used to clear the blockage in the blood arteries and restore cerebral circulation to the damaged area. Reperfusion, on the other hand, will increase the production of oxygen free radicals, aggravating oxidative stress and inflammatory injuries. As a result, combining neuroprotective strategies with thrombosis or thrombolysis is an effective way to treat stroke patients and improve their outcomes. The major goal is to prevent the penumbra from dying. Melatonin is one of the most powerful antioxidants, and it plays a crucial function in protecting against ischemic injury. Through the release of melatonin, pineal gland transplantation improves motor function and reduces infarct size in rats with middle cerebral artery occlusion, a model of acute ischaemia [44]. Melatonin injections have also been found to protect against oxidative brain injury in rat models of subarachnoid haemorrhage (SAH) [44]. Melatonin aids in the maintenance of Ca^2 ion homeostasis and the prevention of impairment. Furthermore, in an oxygen glucose deprivation (OGD) model of rat ischaemia, it has been found to reduce the extracellular level of glutamate in hippocampus regions by reversing its release [45]. Melatonin prevents an increase in Ca^2 ions caused by acid. [46] Furthermore, it reduces a glutamate-dependent increase in Ca^2 ions levels in the rat's cerebral cortex by lowering parvalbumin and hippocalcin, calcium-buffering proteins [47]. Melatonin lowers free radical formation by acting on the MT2 receptor following a transient middle cerebral artery ischaemia in mice, according to a fluorescence live-animal imaging system [48]. Melatonin combined with hypothermia reduced plasma-free radicals (nitric oxide [NO]), seizure events, and white matter damages, and improved neurological outcomes in 45 human neonates diagnosed with hypoxic-ischaemic encephalopathy [49].

Conclusion

Melatonin's physiology and putative neuroprotective effect in neurodegenerative illnesses are discussed in this article. It's a well-known antioxidant, as well as an anti-excitotoxicity and anti-inflammatory chemical. Melatonin is also a prospective neuroprotector because of its ability to pass the blood–brain barrier and short half-life with no apparent side effect.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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