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Mini review

Melatonin: A review of its potential functions and effects on neurological diseases

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ABSTRACT

Background. – The aging process is not univocal, both body and brain age. Neurological disorders are a major cause of disability and death worldwide. According to the Global Burden of Disease Study 2015, neurological diseases are the second most common cause of death and 16.8% of total deaths are caused by neurological diseases worldwide. Neurological disease deaths have risen 36% worldwide in 25 years. Melatonin is a neuroregulator hormone that has free radical scavenger, strong antioxidant, anti-inflammatory, and immunosuppressive actions. These major properties of melatonin can play an important role in the pathophysiological mechanisms of neurological diseases. In addition, melatonin is necessary for circadian rhythm. Studies have shown that melatonin levels are low in people with neurological diseases. Both preventive and therapeutic effects of melatonin are known for many diseases, including neurological diseases (e.g., Alzheimer's disease, Parkinson's disease, multiple sclerosis, amyotrophic lateral sclerosis, Huntington's disease, epilepsy, headache, etc.). Based on all these reasons, clinical trials of melatonin were performed and successful results were declared.

Conclusions. – In this review, biological and chemical knowledge of melatonin, its experimental effects, and the clinical impact on patients with neurological disorders were described. According to all of the beneficial results obtained from experimental and clinical trials, melatonin may have a prophylactic and therapeutic effect on neurological diseases. Strong collaboration between neurologists and health service policy makers is needed to encourage use of melatonin in the patients suffering from neurological diseases. Melatonin may be the solution we have been looking for.

1. Introduction

The human body harbors a great balance. This property makes it unique. When the balance breaks down, disease states appear. This is why maintaining balance is so important. At this stage, defense mechanisms play a major role in sustaining perfect balance. Good health implies accepting a life that supports the body's endogenous defense mechanisms [1].

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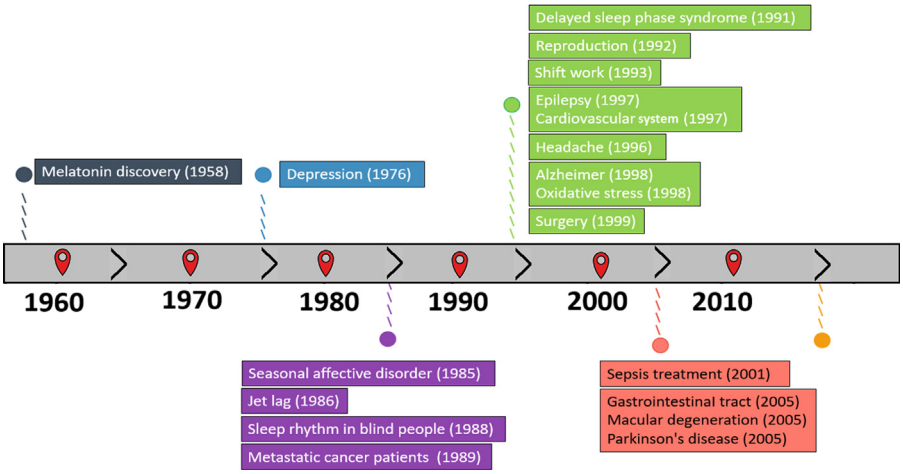

Fig. 1 – Timeline for melatonin's clinical investigation.

Melatonin is one of the substances implicated in the body's endogenous defense mechanisms. Melatonin also plays a neuroprotective role in many central nervous system disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), and ischemic brain injury [2,3]. It is related to memory, and its associations with control of body posture and balance have been demonstrated [4].

In this article, we aimed to review the present literature on the relationship between melatonin and neurodegenerative diseases and the use of melatonin for therapeutic purposes.

2. History

The pineal gland (epiphyseal gland) was defined by Alexander Herophilus (325–280 BC) in the 300s B.C. Rene Descartes (1596–1650), a famous philosopher, physician, and mathematician of medieval times, wrote about melatonin. He called it ''the place where the spirit settles'' and also emphasized its importance in memory functions [5].

The first discovery of melatonin from the pineal gland was made in 1958 by Lerner et al. [6]. The definition of melatonin in this period was ''melanophore-contracting hormone''. In 1958, Lerner and colleagues at Yale University thought that the pineal-secreted material could be beneficial for skin diseases and they managed to get it from the pineal gland. In the mid-1970s, melatonin was advocated by Lynch and his friends, who described the circadian rhythm [7].

In 1993, it was discovered that melatonin was an antioxidant [8]. Richard Wurtman thought that melatonin would help sleep when used in low doses. At the same time, it was predicted that this hormone could cure many diseases [9]. The major discovery dates for melatonin are shown in Fig. 1.

2.1. *Biosynthesis and pharmacology*

Melatonin is synthesized from tryptophan in pinealocytes. This synthesis takes place in four steps [10]. Tryptophan first converts to serotonin, and then melatonin synthesis takes place via a two-step pathway. These enzymes are N-acetyl transferase (NAT), which is an inhibiting enzyme for the melatonin compound, and hydroxyindole-O-methyltransferase (HIOMT) [11] (Fig. 2). The control of this synthesis varies depending on the day/night rhythm and the synthesis reaches the highest level at night [12]. Several factors influence the speed of this process. For example, the induction of β1 adrenergic receptors or the presence of norepinephrine play a key role in this synthesis. Under these conditions, the amount of melatonin production increases [12]. Folate and B6 vitamins also play an important role in this synthesis. Folate is required during the methylation phase. B6 vitamins also play a role in tryptophan decarboxylation. If they are not in the environment, melatonin synthesis will not occur.

2.2. *Mechanism(s) and receptors*

Melatonin can easily be dissolved in both water and lipid. Because of this feature, it can pass through membranes very easily. Recent studies showed that the vast majority of melatonin is found in the cell nucleus, which has specific binding sites for melatonin [13]. In vitro quantitative studies with melatonin agonist 2-[I125] iodomelatonin show that brain and peripheral tissues carry melatonin receptors. Also, melatonin is found in numerous tissues, especially the human brain, intestines, ovaries, and veins.

Three mammalian melatonin receptors have been identified: MT1, MT2, and MT3. Melatonin acts on the object cells either directly or via G-protein-coupled receptors considered to be MT1 and MT2. The MT3 protein has recently been purified and found to belong to the quinone reductase family.

Ramelteon [14] is used for the treatment of insomnia, whereas agomelatine for the treatment of depression [15] and tasimelteon for the treatment of the non-24-hour sleep-wake disorder [16]. All three drugs show their effects by non-selective binding to MT1 and MT2 receptors [17]. All agonists also modulate the circadian rhythm in humans and experimental animals. Ramelteon binds to the MT1 receptor with a 10-fold higher affinity than the MT2 receptor and has 7-fold higher affinity than melatonin [17]. Ramelteon promotes sleep in various mammal species, including humans, without

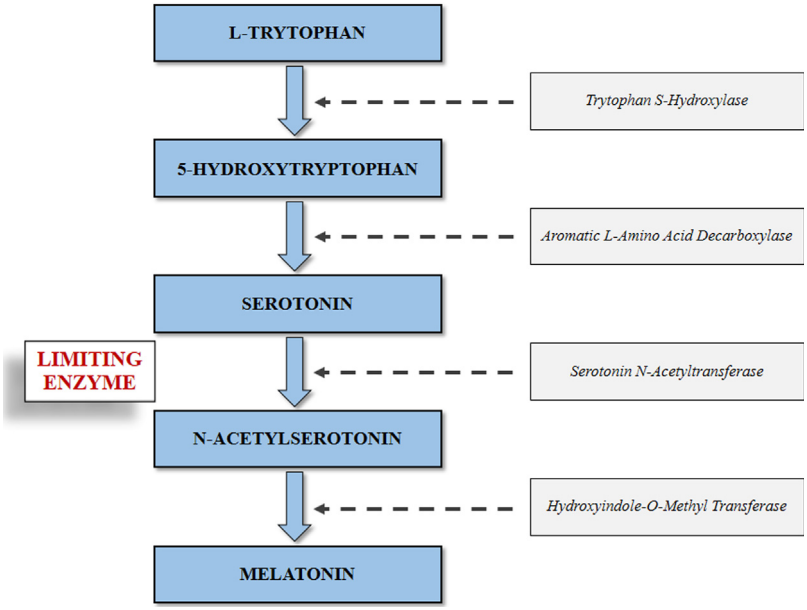

Fig. 2 – Melatonin biosynthesis pathway.

learning, memory or motor dysfunction, or without rewards [18]. Although agomelatin and tasimelteon are non-selective agonists, they have a slightly higher affinity for the MT2 receptor [19]. Furthermore, studies on potential new melatonin receptor targets to treat conditions affecting the central nervous system are ongoing.

2.3. MT1 Receptor

The MT1 receptor which has two subgroups known as MT1A and MT1B shows its effect by inhibiting adenylate cyclase enzyme in the target cell [20]. It is found in the suprachiasmatic nucleus (SCN), cardiac vessels and functions in circadian rhythm regulation and vessel contraction [21,22]. Besides the brain and peripheral tissue, the MT1 receptor is also known to be produced in other regions [23,24].

2.4. MT2 Receptor

MT2 provides phosphoinositol hydrolysis and has low affinity [25]. Receptor involved in retinal physiology causes enlargement of cardiac vessels [22,26,27]. Unlike the MT1 receptor, the MT2 receptor is located in the restricted area of the tissue. Places where they are mainly include the hypothalamus, retina, kidney and heart tissue [28].

2.5. MT3 Receptor

MT3 displays similarity to the MT2 receptor in terms of binding profile and purification from the Syrian hamster kidney. Its structure is very similar (95%) to human quinone reductase 2 enzyme. This enzyme is also involved in detoxification [29,30]. The activity of the MT3 receptor inhibits leukotriene-induced leukocyte adhesion resulting in decreased intraocular pressure [31].

The general properties of these receptors are shown in Table 1. Work on new properties and receptors of melatonin continues.

2.6. Retinoic acid receptor-related orphan receptor (ROR)

Nuclear hormone receptors (NRs) are a family of transcription factors with a variety of physiological functions including regulation of metabolism, immune reaction and stress responses [32] and are currently the molecular targets of approximately 13% of FDA-approved drugs [33]. RORα, RORβ and RORγ are the subtypes of NRs. RORα is the most important of these receptor subtypes RZR/RORα is located both peripherally and in the brain [34].

Melatonin interacts with RORs to reveal its biological effects [35]. In addition RORs also exert metabolic and immune regulation functions [36]. RORs (particularly the RORα subtype) play a crucial role in daily rhythm regulation [37]. Melatonin has been reported to exhibit anti-inflammatory and antioxidant effects by affecting transcriptional factors through RORs present in the cell nucleus. Because of these properties, it is thought that melatonin exerts anti-neurodegenerative properties via ROR receptors [38].

2.7. Receptor-independent effects

Melatonin and its metabolites also prevent free radicals and related reactants, independently of the their receptors [39]. These independently beneficial and protective effects are:

- direct detoxification of radicals and radical products;
- stimulate the activity of several antioxidant enzymes;
- inhibit the activities of oxidative enzymes;
- increase the activity of other important antioxidants;

Table 1 – Properties and types of melatonin receptors.

Melatonin			
Receptor Dependent			Receptor Independent
Cytosol *(MT3, Calmodulin)* Detoxification Enzyme regulation	Nucleus *(ROR, RZR)* Immune modulation Antioxidant enzyme regulation	Membrane *(MT1, MT2, GPR50)* Seasonal reproduction Retinal physiology Circadian modulation Sleep promotion Bone growth Blood pressure modulation	Free Radical Scavenging *(ROS, RNS)* Protection against: Ionizing radiation UV radiation Ischemia/reperfusion Heavy metal toxicity Alcohol toxicity Drug toxicity

Abbreviations: GPR50: G protein-coupled receptor 50; RNS: reactive nitrogen species; ROR: retinoic acid orphan receptor; ROS: reactive oxygen species; RZR: retinoid z receptor.

- show synergistic effect with other antioxidants;
- reduce free radical formation through the mitochondrial effects of melatonin.

Although NO. is not a strongly damaging free radical, it forms a potentially reactive and damaging peroxynitrite anion (ONOO-) when combined with O2. Melatonin inhibits lipoxygenase [40], whereas AMK reduces nitric oxide synthase (NOS) enzyme activity, resulting in NO formation [41]. As a result, free radical and/or toxic reactant formation is mitigated.

2.8. *Regulation*

Dark and light are the most important environmental influences that regulate the synchronization of the human body and regulate the synthesis of melatonin. Melatonin release occurs during the dark period. In the bright process, light information passes through the central pacemaker through the retinohypothalamic tract and inhibits the synthesis of the stimulated melatonin from the retinohypothalamic pathway. Melatonin synthesis does not occur under artificial light at night. The high amount of light inhibits melatonin secretion in the 2 hour time period (03.00-04.00 a.m.) [42,43].

The retinal ganglion cells react with the light causing it to affect the SCN. These melanopsin bearing cells participte in the circadian rhythm photometric process [44]. Release of melatonin is controlled by the SCN. Moreover, this system does not only send information to the endogenous clock in the SCN but also sends information to other brain regions involved in pupil constriction and sleep induction [45]. This region is in the hypothalamus and is responsible for nutrition, thirst, sleep cycle, temperature settings and controlled release of some hormones [46]. From the SCN to the pineal gland, the upper part of the cervical spinal cord is first passed. This part forms the preganglionic part of the superior cervical ganglion (SCG) and has sympathetic chains [47]. Then the cells in the SCG send a warning to the pineal gland. Norepinephrine is known as the most important neurotransmitter regulating the function of the pineal gland. This release occurs at night, replacing the stimulation of the SCN. Blockers of the β1 adrenergic system also inhibit melatonin, which is released at night. Also, clonidine and methyl-para-tyrosine, for example, reduce the synthesis of presynaptic catecholamine and thereby reduce the release of melatonin [48].

Conversely, the synthesis of melatonin can be enhanced using catecholamine, a tricyclic antidepressant, or monoamine oxidase inhibitors. Neuropeptide Y released from the SCG increases the release of melatonin. In this task, the fifth cranial nerve, the trigeminal nerve, is also involved. The substances involved in this process are vasoactive intestinal peptide (VIP) and peptide histidine isoleucine (PHI), substance P (SP) and calcitonin gene-related peptide (CGRP). In animals, VIP and opioid-related receptors stimulate the synthesis of melatonin; however, gamma aminobutyric acid (GABA), neuropeptide Y, dopamine, and glutamate inhibit the synthesis of melatonin.

According to accessible literature, information regarding melatonin is mostly obtained from rats and monkeys; for humans, limited information is available [49,50]. Therefore, it is not clear that these mechanisms are human or not, however, the existence of such a mechanism is contemplated. At night, the stimulation of the GABAergic system by benzodiazepines reduces the level of melatonin [51]. In contrast, dopaminergic agonists or opioid receptor blockers may alter the level of melatonin. This suggests that melatonin levels should be followed after drug use.

2.9. *Pharmacokinetic properties*

Metabolism of melatonin is less understandable compared to synthesis. One of the most important metabolites of melatonin is 6-OH melatonin. Over a few decades, melatonin has been implicated as the sole metabolite of 6-OH melatonin however it is understood that there is no single metabolite. As a matter of fact, metabolism of melatonin has a very complicated mechanism. Melatonin metabolizes by three different pathways: enzymatic, pseudoenzymatic or reactive oxygen species (ROS) interactions [52].

N1-acetyl-N2-formyl-5-methoxy- kynuramine (AFMK) may be the first product of melatonin metabolism to be formed by a pseudoenzymatic process. Iron-containing hemoproteins such as hemoglobin have been reported to interact with melatonin to form AFMK and other metabolites. In this mechanism; the oxophoryl hemoprotein oxidizes melatonin and breaks down to form AFMK [53].

In animals, the main enzyme involved in the metabolism of melatonin is CP450. This enzyme is present in many tissues, especially in the liver. The major enzyme required for the metabolism of melatonin in the brain is indoleamine 2,3-dioxygenase (IDO). As a result of the enzyme activity, AFMK emerges as the product [54].

Surprisingly, melatonin can also be metabolized by a non-enzymatic pathway. Several metabolites are formed as a result of interaction with ROS. These formed metabolites are cyclic 3-hydroxymelatonin, 2-hydroxymelatonin, 4-hydroxymelatonin, N-nitrosomelatonin etc. It is difficult to determine which pathway is more active in vivo. Interactions with ROS under severe oxidative stress are the result of metabolism.

Sixty-seventy percentage of the melatonin binds to albumin in plasma [43]. The half-life of melatonin is 3-45 minutes. It is soluble in water and lipid thus can easily enter the tissues. In addition, the effect is greater with intravenous administration, because the hepatic first pass occurs [55]. Melatonin is converted to 6-sulphateoxymelatonin (or 6-OH melatonin sulfate) as a conjugate with N-acetyl-5-methoxy-6-hydroxytryptamine and then with sulfate or glucuronide by 6-hydroxydopamine, followed by a series of reactions. It is excreted in urine. The excretion of 6-sulfateoxymelatonin in the urine is closely related to the serum melatonin concentration. Approximately 50-80% is converted to sulfate derivates, 5-30% is converted to glucuronide derivates. It is seen as changed by 1% in the urine.

When the daily variation of melatonin is examined, the night concentrations of melatonin in the calm and in the cell are 3-10 times higher than the daytime. Secretion of melatonin usually starts at 09.00-10.00 p.m. and reaches the maximum level between 03.00- 04.00 a.m.[43] It starts to decrease between 07.00 and 09.00 a.m. in the morning. The rate of secretion is 29 mg/day [56].

According to age, melatonin is low in the first three months of life. It rises between three and six months and begins to vary day and night. The nocturnal value at 1 to 5 years is 250 pg/mL, at 5-15 years it is 65 pg/mL, and at age 50-70 is 20 pg/mL. Daytime values are around 20 pg/mL. In the elderly, the mean plasma levels are 50-70 pg/mL. The result of studies on four volunteer healthy men show that when an oral 500 μg dose of melatonin is taken, the plasma values of melatonin range from 2 to 395 nmol/L and the half-life is 47 ± 3 minutes. The bioavailability of melatonin remains within the range of 10 to 56%, on average 33% [57].

2.10. *Circadian rhythm*

It is known that the human body has a unique balance with a temporal distribution. For continuity of life, this system, called the circadian rhythm, must work smoothly. Even in human beings, many constructs have adapted to this circadian system. Endogenously synthesized melatonin is of great importance here. The cause of many diseases is the deterioration of this rhythm that is, in general, associated with a reduction in melatonin secretion. Regular function of the pineal gland depends on the rhythm dictated by the biological clock called the SCN that lies in the center of the body. The activity of the SCN decreases during the night. Decreasing SCN activity in the evening makes melatonin release possible. In mammals, the circadian rhythm is linked to the hierarchical arrangement of the SCN center of the hypothalamus in the brain.

Melatonin plays a role in circadian rhythm regulation as well as in the formation of a sleep regime. It also has a role in balancing body temperature. This situation is seen in children as well as in elderly people, even in healthy individuals [58]. Melatonin is an important mediator of sleep physiology, ffand also regulates the circadian rhythm. Melatonin, found throughout the body, appears to be active in many parts, in the cerebrospinal fluid, in the saliva, in human milk, and in the aqueous humor. İn these body sectors, melanin secretion also obeys a certain rhythm [59].

Melatonin is synthesized in the dark, blocking the production of 7α-hydroxypregnenolone. Thus, spontaneous movements are limited at night. In nocturnal organisms, production of melatonin occurs overnight and the amount of 7α-hydroxypregnenolone increases. Thus, an increase in the number of spontaneous movements is observed. All this evidence shows that melatonin is involved in the synthesis of 7α-hydroxypregnenolone and plays an important role in the formation of the circadian rhythm.

As in many biochemical, physiological and behavioral variables in the human body, melatonin levels in plasma show regular ups and downs within the 24 hour-period. This circadian rhythm is controlled by the central pacemakers in the SCN in the hypothalamus, the main regulator of the rhythm in the bright ambient/dark cycle. Pineal functions are acutely suppressed when exposed to night light [60]. When we look at the intra-day change of melatonin, the night concentrations of melatonin are 3-10 times higher than the daytime. The secretion of melatonin usually starts at 21.00-22.00 h and reaches its maximum level between 03.00-04.00 h. It starts to decrease between 07.00 and 09.00 in the morning. The rate of secretion is 29 mg/day [56].

In addition to its importance in accelerating th aging process, the circadian clock also controls other systems known to be associated with aging, such as oxidative stress response and DNA repair [61]. Melatonin production, amplitude and pulsatile release from the pineal gland are reduced with aging [62]. Impaired circadian rhythm affects melatonin production and adversely affects the health of older individuals [63]. In addition, the aging process results in different changes in the daily rhythms of expression of various clock genes in the SCN, and the therapeutic effects of melatonin in recovering such age-related changes have been demonstrated. It is reported in literatüre that mRNA expression of various clock genes in SCN at 3, 12 and 24 months show that circadian change is age-dependent. In an experimental study, the administration of melatonin for 11 days showed that Per2, Cry1, Cry2, and Bmal1 returned to the normal rhythm [64].

''Clock'' genes (Per1, Per2, Cry1, Cry2, Bmal1, and Clock) act as transcription factors that regulate a variety of functions including cell division, metabolism, immune response and oxidative processes [65]. Circadian clock dysfunction contributes to aging and age-related pathologies. Evidence from individuals with AD, PD, and HD show that these diseases appear to be associated with abnormalities in the rhythms of bmal1 and per2 expressions [66]. However, some findings suggest that the circadian system may actually play a more

direct role in the etiology of neurodegenerative diseases. For example, single nucleotide polymorphisms of bmal1 and perl are associated with an increased risk of PD [67]. In addition, clock genes regulate the expression of other genes directly involved in neurocognitive disorders such as AD [68]. For example, the binding presenylin-2 gene [69] which regulates beta-amyloid peptide levels, is rhythmically expressed in SCN. Mice with Bmal1 deficiency age prematurely, characterized by age-related multiple abnormalities and a nearly three-fold reduction in life expectancy [70]. Clock -/- mice exhibit increased inflammation and a 15% reduction in longevity [71]. After exposure to non-lethal ionizing doses, Clock and Per2 mutated mice have a shorter life span and show certain aging phenotypes [72]. Removal of the fluctuation of these circadian genes may result from a decrease in the number of SCN melatonin receptors [73]. In peripheral tissues, Clock:Bma1l dimers regulate presenylin-2 expression through transcriptional and post-transcriptional mechanisms [74]. These findings suggest that there is a causal accordance between the clock genes and the molecular factors leading to the risk of neurodegeneration.

2.11. *Antioxidant properties*

Today's information confirms that melatonin is a potent antioxidant that is endogenously secreted [75]. Melatonin is not only a free radical scavenger but also a stronger antioxidant which is the reference agent in this field. It is a well-known endogenous biomolecule with potent antioxidant effects [76]. Melatonin and its metabolites, such as AFMK and N1-acetyl-5-methoxykynuramine (AMK), possess high antioxidant properties, allowing them to directly scavenge various free radicals, such as hydroxyl (OH) radical, peroxyl radical, O_2 – radical, hydrogen peroksit (H_2O_2), singlet oxygen (O^12), peroxynitrite (ONOO –) and nitric oxide (NO), in physiological conditions [77–79].

Increased inflammation and oxidant substances are shown due to various diseases. While these are given as examples, melatonin is considered one of the most potent antioxidants, playing an important protective role in the ischemic injury [80]. Melatonin administration after middle cerebral artery occlusion has been shown to play a role as an antioxidant in reducing nitrite and malondialdehyde (MDA) levels and improving motor behavioral outcomes and brain edema [81]. Also, melatonin significantly reversed the oxidative damage caused by neutrophil activation in tissues in various inflammatory models (burn injury, sepsis, ischemia/reperfusion) [82,83].

It has been demonstrated that melatonin can be used in the AD based on its anti-β-amyloid, antioxidant, and anti-inflammatory action. The result of all these effects is toi prevent synaptic function loss and contribute to the recovery of cognitive processes by reducing neuronal loss [84]. The antioxidant activity of melatonin has been suggested for use in AD patients because of its anti-amyloidogenic effect and its inhibitory effect against tau protein hyperpolarysis [85].

Another disease that melatonin may have a positive effect on is PD. Another report showed that indolamine melatonin (N-acetyl-5-methoxytrytamine, aMT) prevents dopamine oxidation, and has neuroprotective features in different types of neurodegeneration, including the MPTP model of PD [86–88]. These reactions of melatonin may be associated with its antioxidant, anti-inflammatory.

There are also a number of studies on multiple sclerosis (MS), another neurological disease that is more common in young and middle-aged women. Melatonin supplementation is known to increase the quality of life in MS patients. These effects of melatonin and its metabolites reduce various oxidant substances such as MDA in serum? thus reducing the Multiple Sclerosis Impact Scale (MSIS) score [89].

It has been announced that melatonin levels are low in endometrium, prostate, lung, gastric and colon cancers, whereas melatonin may be protective against cancer by antioxidant effects [90]. Direct oncostatic effects and anti-cancer effects of melatonin in tumor cells are linked to immunomodulator and antioxidant effects [91,92].

Another reason for the use of melatonin in epilepsy patients is due to its strong antioxidant properties. Studies have shown that administration of melatonin to patients with epilepsy receiving carbamazepine results in a strong therapeutic effect [93]. A more recent study showed that septic newborns who received 20 mg of melatonin exhibited reduced serum inflammation markers, improved patient survival, and improved clinical healing [94].

2.12. *Immune system properties*

The first finding of the immunological role of melatonin belongs to Maestroni and his colleagues (1987). Studies support that melatonin augments immunity response. The effect becomes evident when the immune system is depressed, i.e. during conditions such as aging, infections and use of immunosuppressive agents [95,96]. There is strong evidence that melatonin plays an important role in the regulation of the immune system of the pineal gland. Pharmacological (by propranolol) or functional inhibition of melatonin synthesis causes humoral and cellular immunosuppression in mice.

Wichmann and colleagues showed that the suppression of trauma and hemorrhagic shock-induced immunoreactivity in mice were reversed by melatonin [97]. It is necessary to add, they reported, that chronic melatonin administration increased leukocyte natural killer activity in humans. Melatonin increases macrophage, monocyte and natural killer (NK) cell counts [98]. NK cells promote the regulation of melatonin immunosuppression which induces cell activity [99]. NK cells that are increased by induction of melatonin increase synthesis of mediators such as IL-2, IL-6, and IFN-y from T cells [100].

Also, melatonin has been shown to reduce pathogenic inflammation with various pathways, for example, decreasing Th17 cells and IL-17 cytokines. In addition, melatonin increases the production of inflammatory cytokines such as IL-10 by Tr1 cells [101]. In sum, high melatonin intake increases IL-10 levels while decreasing IL-17 levels [102]. Th1 and Th17 subsets are important in the pathogenesis of MS, which is triggered by infiltration of myelin-specific $CD4^+$ T helper cells and is a chronic neuroinflammatory disease [103]. Increased Th1 and Th17 responses in the brain fluid of MS patients support this association [104]. A previous study has shown that melatonin has a history of reducing Th1 and Th22 responses [105].

Maestroni et al. found that melatonin acts on immune response directly and indirectly [106]. Melatonin affects prostaglandin E2 and IL-2 production in human lymphocyte cells via the MT1 receptor [107]. These studies support the treatment of melatonin to stimulate the immune system in the human body [108]. Melatonin might play a major role in the fight against immunological diseases in the future.

2.13. *Side effects*

Melatonin is a substance which has high safety and efficacy. Nevertheless, a few adverse effects are reported in the literature. When melatonin agonist drugs or supplements are given, side effects such as a headache, vomiting, liver disorders, sleep problems can be seen [109]. Side effects such as increased motion, restless legs syndrome, menorrhagia, pain, or numbness may occur from the first day of use.

2.14. *Medical use*

Melatonin plays a major role in the human body in numerous structures and in the physiology of the system. It has been linked to a wide range of functions including anti-inflammation, antioxidant, oncostatic, circadian rhythm regulation, sleep, mental status, tumor development, aging, etc [43,110,111].

It is now known that not only melatonin but also its products have important effects on the body. Moreover, melatonin and its metabolites inflect enormously antioxidative and pro-oxidative enzymes, leading to a reduction in oxidative damage [79,112]. Along with the developing science, medical use of melatonin has gained importance. It can be used in the treatment or prophylaxis of many diseases. Numerous studies have been conducted on the use of melatonin for the treatment of diabetes, autoimmune disease, sleep disorders, neurodegenerative diseases [98]. For example, according to a study in 2010, it has been shown that melatonin can be used in the treatment of diseases such as cancer, hypertension, obesity, psychiatric disorders, and neurological disorders [113,114].

It has been observed that the application of melatonin together with the known treatment of the diseases may be more effective. In relation to this, in a study on newborns in 2017, less new epilepsy and brain anomalies were observed in newborns receiving melatonin at a dose of 10 mg/kg, 5 times a day, and the lifespan was increased without any neurological deterioration over a 6-month period. For this reason, melatonin is thought to be possibly protective agent against brain damage seen in newborn infants [115]. Melatonin has been shown to be effective even in cases of high mortality. This has promoted the widespread use of melatonin in medical science. When the topic of melatonin on the nervous system is investigated, a large number of studies have revealed this positive effect. Several diseases have been reported improved with melatonin supplementation, including PD [116], depression [117], cerebral ischemia [3], and phenylketonuria [118].

2.15. *Stroke*

Stroke is one of the most important neurological disorders and has subtypes such as subarachnoid hemorrhage (SAH), intracerebral hemorrhage, and etc. Stroke is considered the most common cause of disability in the world [119]. There are two types of strokes, classified as ischemic and hemorrhagic stroke. Numerically, ischemic stroke is more common (85% of all strokes). During ischemia, many events come to the cascade including excitotoxicity, free radical production, and inflammation [120].

Current protocols used in the treatment of stroke have limited effect. For this reason, the treatment method needs to be improved. Melatonin is a strong candidate for stroke therapy. Feng et al. showed the role of autophagy and melatonin during stroke. It is known to be used for prophylaxis in ischemic disease. It accomplishes this by providing inhibition of various pathways such as inhibiting endoplasmic reticulum stress-dependent autophagy via protein kinase RNA-like endoplasmic reticulum kinase (PERK) and inositol-requiring enzyme 1 (IRE1) signaling inhibition [121]. Additionally, melatonin increases mitophagy-associated proteins, PTEN-induced putative kinase 1 (PINK1) and Parkin levels so that it reduces mitochondrial damage and injury of the brain tissue. It also reduces inflammation by decreasing NLRP3 levels after SAH [121].

In another study, melatonin has been shown to reduce early brain damage following SAH in mice. It is thought that the mechanism would involve melatonin causing a decrease in autophagy and apoptosis [122]. Based on this relationship, one study showed that increased pineal calcification in humans increases stroke risk. Similarly, increased pineal calcification increases the risk of intracerebral hemorrhage [123]. In accordance with this result, it is well known that pineal calcification reduces the synthesis of melatonin. This circumstance reflects the importance of melatonin in neurological disorders. It is also involved in the reduction of serious permanent adverse effects of the disease. In another similar study on rats, it was shown that melatonin could reduce auto-phage by increasing PI3 K/Akt activation and could be used as a treatment for middle cerebral artery occlusion [124]. It should be noted that autophagy is necessary for the development of tissues and organs in newborns. In a study of 45 newborns born with hypoxic encephalopathy, the combined use of melatonin and hypothermia has been shown to reduce plasma free radicals, stroke frequency and regulate neurological development [125]. Because of all these reasons, it is thought that melatonin can be used as a treatment for some pathological inflammations in preterm infants. In sum, all these experimental studies and ideas indicate that melatonin may be used in stroke treatment and prophylaxis.

2.16. *Alzheimer's disease (AD)*

AD is an age-dependent neurodegenerative disease with toxic protein accumulation. β-amyloid and neurofibrillary tangles accumulate in this disease. Accumulation in the brain of proteins in this abnormal structure leads to a decrease in cognitive performance [126]. As a result of the cascade arising from the accumulation of β-amyloid structure, toxic substances are formed in the brain. The accumulation of these toxic compounds results in neuronal loss to increase oxidative stress [127,128].

Although the etiological cause of AD has not been fully elucidated yet, many factors play a major role in the emergence of this disease. Some of these factors include genetics, age, gender, and nutrition [129,130]. The genotypes resulting from the emergence of the AD are amyloid precursor protein (APP), apolipoprotein E (ApoE) and presenilins 1 and 2 [131].

Several studies have shown the anti-amyloidogenic effect of melatonin [132]. Melatonin has been shown to inhibit the production of in vitro Aβ and APP formations [133]. Likewise, melatonin protects against fibril production in AD patients [134]. The long-term use of melatonin on rat models with AD has been shown to reduce the hippocampal and cortical Aβ units by 43% and 37%, respectively [134]. Furthermore, the finding that melatonin mitigates degenerative changes in the hippocampus and prevents mitochondrial changes has been proved [135]. Clinical trials have shown that the level of melatonin is reduced in AD patients compared to a control group [136]. Based on this relationship, the theoretical beneficial effects of melatonin on AD seems to be related to the observation that melatonin has a dominant role in the production of certain antioxidant enzymes [134].

In a retrospective study, the use of melatonin has been shown to improve the cognitive subscale of AD assessment scale (ADAS-Cog) and sleep quality in AD patients [137]. It shows the effect of melatonin through the MT1 and MT2 receptors in the mammalian living organism. Despite the increase in MT1 activity in the hippocampus of AD patients, MT2 activity is decreased. This also show that melatonin depletion may cause AD [138,139]. In addition to all of these, there is a need to further study the mechanism(s) and therapeutic potential of melatonin in AD patients. In sum, it is known that melatonin inhibits β amyloid aggregation, it has antioxidant and anti-inflammatory properties. These features are thought to prevent neuronal loss and improve cognitive processes [140]. For all these reasons, melatonin may be an ideal therapeutic agent against AD early on.

2.17. *Parkinson's disease (PD)*

According to the United Nations, the number of people with PD is estimated to reach 2 billion people in 2050. According to the World Health Organization, the number of people with PD is increasingly a major public health problem. PD affects millions of people worldwide and varies depending on gender, social status, ethnicity, and economic level [141]. PD is more common in males, with a ratio of men to women of 3:2 [139].

The main symptoms of PD include tremor, rigidity, bradykinesia, and postural instability. The pathological cause of this disease is that dopaminergic cells in the substantia nigra pars compacta are defective in dopamine production [141]. The factors contributing to the development of age-related PD include increased production of free radicals and increased oxidative processes [142]. Some researchers considered the melatonin-dopamine imbalance in the PD to be a favored prospect for melatonin [143]. Despite these, another study showed that decreasing the level of MT1 and MT2 receptors in specific regions of the brain may also trigger this disease [144]. Thus, PD is thought to be a disease resulting from melatonin imbalance. Based on this relationship, studies on PD models have shown that melatonin not only prevents dopamine reduction but also prevents the loss of dopaminergic neurons [145]. The use of acute and chronic melatonin has been shown to preserve dopaminergic neurons in neurotoxicity [146]. This supplement is formed by the melatonin neuron protective function and inflammation reducing effect. Conversely, a few studies have shown that melatonin triggers the emergence of the PD [147]. Moreover, the antagonism of melatonin receptors may even improve in motor symptoms [148]. Given all these studies, further study is needed to ensure that this intercourse is better understood and that it can contribute to the treatment of the disease.

2.18. *Autism spectrum disorder (ASD)*

ASD is a type of neurodevelopmental disorder that occurs as a result of multifactorial events which begin early in life. Permanent abnormal social intercourse is an important feature of the disease [149]. As a result of epidemiological studies, numerous environmental factors and genetics are involved in the emergence of ASD [150,151]. Among the most important are parental age, fetal distress, multiple births, low birth weight, congenital problems, meconium aspiration, environmental psychology. It is known that melatonin synthesis does not occur in early days of a baby's life and that breastfeeding during the first 9-15 weeks of life fulfils the melatonin requirement, reducing the risk of ASD [152]. Likewise, environmental pesticides increase ASD in infants [153].

Melatonin prevents toxic molecules from disturbing the organ development of the baby. This characteristic of melatonin is achieved via its antioxidant effect [154]. Melatonin is an important factor in the development of neuronal plasticity and in the formation of circadian rhythm [155]. Abnormal melatonin synthesis disrupts the circadian rhythm and causes autistic behaviors to occur. Studies have shown that melatonin equalities are low in patients with ASD [156]. According to another study, the level of melatonin in autistic children was found to be lower than in normal children [157].

It is well known that melatonin deficiency increases neonatal inflammation and oxidative stress, resulting in damage to normal neurological development [158]. The issue to be emphasized is that maternal and placental melatonin have an essential role in the management of fetal brain improvement [159].

Children with normal melatonin levels also suffer from sleep and behavior problems with ASD. In these patients, when the melatonin supplements were started, symptoms dramatically improved [159]. In another study using melatonin in treatment, patients with ASD were given melatonin supplementation for three months. The result of the study showed that sleep latency in patients decreased by an average of 45 minutes and that sleep quality increased with respect to the control group [159]. Studies on ASD patients have shown that low levels of melatonin have increased ASD and mediated the development of sleep and behavioral problems in these patients. There is an increased risk for babies born from mothers that had an insufficient blood level of melatonin.

According to current knowledge, all of these beneficial effects of melatonin are related to its free radical scavenger and antioxidant properties; therefore, melatonin exerts a beneficial effect via neuronal development and circadian rhythm regulation. For all these reasons, melatonin should be considered in the treatment schedule of these patients.

2.19. *Multiple sclerosis (MS)*

MS is a disease associated with immune mediators that often affects white matter and to a lesser degree gray matter [160]. Like many other inflammatory diseases, it often affects women between 20 and 30 years of ages. It is an interesting disease that can display variable symptoms including seasonal changes [102]. The clinical symptoms of this disease affect around 2.5 million people worldwide. Common symptoms include visual and sensory symptoms and motor and coordination problems such as contraction, pain, fatigue and impaired cognitive processes [161].

It has been mentioned above that the metabolites of melatonin itself (AFMK, AMK) are highly potent antioxidants and have an immunological regulatory effect [162]. It is known that melatonin accumulates in various places in the cell, especially in mitochondria. But also, recent studies have shown that the level of melatonin is lower in MS patients [163]. Recently, Sandyk and Awerbuch observed a correlation between the level of melatonin in patients with pineal calcification and MS disease [164]. First, it was found that the level of melatonin was low in 44% of MS patients before steroid administration [165]. In addition, an inverse relationship between melatonin level and disease duration was observed. Subsequently, in a cohort study in which 32 patients were included, it was found that the duration of disease in the low-melatonin level was longer than that in the normal ones by 5 years [166]. Thirdly, it has been found that higher rates of pineal calcification and brain atrophy are seen in MS patients [164].

Melatonin treatment reduces MS disease by inhibiting cytokines that increase inflammation by affecting various receptors. In particular, it decreases the amount of IL-17 secreted by TH17 through the MTNR1A receptor. It also increases the amount of IL-10 secreted from Tr1 cells [102]. Thus, inflammation is reduced. Melatonin also enhances IL-27 release from dendritic cells, leading to IL-10 release [167]. In addition, melatonin decreases cytokines (IL-2, IL-12, IFNγ, and TNF), increases IL-10 levels, and is effective in the treatment of MS patients [105].

Another important part of the issue is night workers. It is known that MS disease is seen more frequently in workers who work at night. In large case-control studies, it was thought that night-time workers had a naturally low level of melatonin, which could trigger the outbreak of MS. For this reason, a low melatonin level may be a risk factor for MS disease [168,169]. There are also studies to examine the effects of melatonin on the quality of life of MS patients. These studies have shown that melatonin improves the quality of life when used in MS patients. In a case-control study involving 102 patients and 20 healthy volunteers, who were given melatonin at 5 mg/day, when the blood of the patients was examined, MDA levels appeared to fall whereas, patients' quality of life improved and the MSIS score decreased [89].

2.20. *Huntington's disease (HD)*

HD is an hereditary neurodegenerative disease that is a deadly and almost untreated disease which affects approximately 30,000 Americans citizens. HD involves progressive motor disorders, cognitive impairment, psychiatric problems, dementia, depression, and weight loss [170,171]. The main reason for this disease is the recurrence of cytosine-adenine-guanine (CAG) in the exon 1, which initially affects the striatum and cortex [172]. The definite task of this huntington protein has not been fully elucidated until now [173].

Since antioxidants are known to be used in the treatment of neurological diseases, melatonin is proposed. When experimental studies are searched, the mitochondrial complex II inhibitor (3-nitropropionic acid) or quinolinic acid are used to create an experimental model of HD disease [174]. The antioxidant property of melatonin has been shown to delay the onset of disease in 3-nitropropionic acid-induced rat model of HD [175]. It has also been declared that melatonin inhibits the death of primary cortical neurons [176].

Another mechanism that plays a role in HD pathogenesis is the accumulation of intracellular calcium that causes mitochondrial blockade, the induction of N-methyl-D-aspartate (NMDA) receptor and the presence of oxidative stress [177].

Experimental studies require further investigation to use the antioxidant, neuroprotective and anti-apoptotic effects of melatonin on HD patients.

2.21. *Amyotrophic lateral sclerosis (ALS)*

ALS is a lethal neurological disease that affects both the first and second motor neuron pathways. This disease progressively affects the anterior horn of the spinal cord and causes problems with motor neuron myelinization. The etiologic cause of ALS is partly understood. When investigated from a pathophysiological perspective, three main reasons were found. The first and major pathophysiological mechanism of ALS is a mutation in the superoxide dismutase (SOD) 1 gene and accumulation of toxic substances (tyrosine nitration). In addition, there is a decrease in the antioxidant effect by affecting zinc binding capacity. Second, selective motor axon degeneration is seen as a result of a mutation in neurofilament genes and phosphorylation of cytoskeletal proteins. The third pathophysiological mechanism is the increasing level of glutamate in the cerebrospinal fluid and the degradation of excitatory amino acid transporters. These conditions also cause excitotoxicity [178].

Still, there is no definitive treatment for ALS patients. Only, riluzole is used to extend survival time. When the pathophysiological processes in ALS patients are examined, ROS/reactive nitrogen/oxygen-mediated oxidative stress seem to be interesting. In this respect, future treatment interventions can focus on suppression of these oxidative stress radicals [179].

Melatonin is advisable for the treatment of ALS patients who may tolerate high doses [180]. First of all, it should be known that even with high doses of melatonin, there is no side effect. For this reason, melatonin can be used in patients at risk for ALS. In addition, it is appropriate to use it in well-defined patients with familial characteristics. Although

melatonin has a fast turnover, it may be effective for about 6 hours in the plasma via slow release preparations. High-dose oral melatonin administration inhibits disease progression and increases survival in SOD1 (G93A)- transgenic mice [181]. In another study, it was reported that the administration of melatonin changed the expression of SOD 1 in the lumbar spinal cord of neonatal rats [182].

The first clinical trials for the use of melatonin in ALS patients were reported in 2002 on three humans [180]. The use of high-dose melatonin has been shown to reduce oxidative parameters [183]. In another clinical trial, high-dose melatonin administration via the rectal route for two years could be tolerated. Importantly, the level of oxidative stress markers that are high in ALS patients is reduced by the addition of melatonin. In humans, the use of high-dose melatonin in the ALS with neuroprotective properties may be appropriate [183].

Considering the efficacy of melatonin in human, animal and cellular experimental ALS models, larger clinical trials are needed to investigate the treatment of ALS patients.

2.22. *Headache*

Headache is a very common neurological disorder that affects a large number of people negatively. It is seen as the seventh disease adversely affecting the life of patients according to the ''Global Burden of Disease Study'' [184]. Primary headache is divided into five groups: migraine, tension-type headache, cluster headache, other trigeminal autonomic cephalalgias, and other primary headaches [185].

Migraine is seen very often in children but in about 28% of people in the middle age group [186]. Patients are treated either by pharmacological or non-pharmacological methods, according to the type and clinical history of headache. Many drugs are used in migraine prophylaxis. Antihistamine, antihypertensive, antidepressant, and antiepileptic drugs are used for migraine prophylaxis in pediatric patients.

There are many theories about the use of melatonin in a headache. Three of these theories are very important:

- the role of the hypothalamus in the formation of a headache;
- the recovery of melatonin intake in patients with sleep impairment;
- reduction of the headache by anti-inflammatory properties of melatonin [187–189].

Melatonin levels decrease during migraine attacks in patients, suggesting that melatonin plays an important role in the pathophysiology of migraine. This chronobiotic substance plays an important role in the treatment of a headache. Possible effects of melatonin on headache include anti-inflammatory, anergic, antioxidative and affecting NOS activity. Stabilization of membranes, protective effect in glutamate neurotoxicity, and involvement in an event such as neurovascular regulation are also important for use as a treatment for migraine [190]. In a case-control study, the level of urinary melatonin in migraine patients was significantly lower than in the control group [191]. Similarly, in a large study involving 146 patients, it was observed that migraine patients had a lower amount of urinary 6-sulfatoxymelatonin than the control group [191]. When agomelatine, a melatonin agonist, is given at 25 mg/day for 6 months, both the number and severity of attacks of migraine patients are severely reduced [192]. In another study, researchers reported that melatonin is a very good and usable agent for migraine headaches. A study that involved 60 children showed that the incidence and duration of migraine frequency were reduced when melatonin was administered prophylactically at 0.3 mg/kg dose for three months. Side effects were reported in only 23% in this study [190]. In another experiment, 37 patients were included and 4 mg melatonin was given 30 minutes before bed every six months and the results compared. It is observed that there is a significant decrease in migraine frequency [193].

When the effect of melatonin on other types of a headache such as a migraine is examined, it has been observed to be useful in its prophylaxis and treatment phase. Experimental and case-control studies in the pediatric age group and elderly group show that the use of melatonin for headache may be both safe and effective.

2.23. *Epilepsy*

Epilepsy is a neurological disorder in which the normal activity of the brain arises as a result of abnormal electrical activity that temporarily occurs in nerve cells. This may be due to oxidative stress, glutamate excitotoxicity, and mitochondrial disorders may be associated with dysfunction [194]. Around 40 million people have been diagnosed with epilepsy worldwide by 2015; 80% of these cases are seen in developing countries [184]. Melatonin has been shown to be an adjunctive treatment in case of severe infantile myoclonic epilepsy. The results of the study show that melatonin may have a beneficial role in the mechanism of neuroprotection untreated epilepsy [195].

The inadequacy of human studies and the small number of controlled clinical trials make up the missing parts of the subject [113]. Currently, known scientific data show that; melatonin can regulate the electrical activity of neurons but its role in the central nervous system is not clear enough [196]. When studies on this subject are investigated, melatonin has often improved the condition of patients with epilepsy. Large randomized, double-blind and placebo-controlled studies seem to be a major need. In a double-blind, placebo-controlled study, consumption of melatonin affected epilepsy in children. Physical function, emotional healing, and behavioral improvement are thought to depend on melatonin. This indicates that melatonin can be used for these purposes in patients with epilepsy [197].

It is clearly known that melatonin shows the anticonvulsant effect by affecting GABA receptors [198]. Melatonin also provides for the closure of the voltage-dependent Ca channel, which can also reduce epilepsy by suppressing neuronal activity [199]. Melatonin restricts the activity of NOS by reducing calcium entry into neurons. According to Acuña-Castroviejo et al., melatonin specifically inhibits glutamatergic receptors in the rat striatum, a NMDA subtype of excitatory activity [200,201].

Melatonin's sleep disorders and circadian rhythm regulating effects are mentioned above, and epilepsy is closely related to sleep. Reducing sleep problems causes positive effects on

epilepsy. The positive effect of agomelatine and other melatonergic compounds on various seizure patterns has been demonstrated by preclinical studies and the anticonvulsant effect of melatonin has been mentioned. However, these findings have not yet been tested in clinical trials [202]. In another experimental study in the rat, when combined melatonin with sodium valproate, this compound showed a potent anticonvulsant effect and reduced the severity of epilepsy [203].

In sum, according to limited human studies and considerable animal studies, it is possible that melatonin will not exacerbate the episode and would be an effective agent with an antiepileptic effect.

2.24. *Subarachnoid hemorrhage (SAH)*

SAH is a hemorrhage formed in the subarachnoid space usually due to arterial occasionally due to venous causes. The incidence of SAH is reported to range from 10-16/100.000 population per year, but these ratios are reported to increase with age. SAH cannot be found in 20% of cases with trauma, aneurysm, vascular malformations, bleeding disorders, brain tumors, and anticoagulant treatment complications [204]. SAH is an important disease that results in high morbidity and mortality [205]. Melatonin has been shown to help reduce early brain injury with its neuroprotective, anti-inflammatory and endothelial regulation properties [3]. It contributes to increasing the quality of life by reducing mortality and morbidity [206].

In a study on rats, inflammation in the brain tissue was investigated after melatonin injection (10 mg/kg, i.p.) into the cisterna magna. It reduced production of lipid peroxidation and release of glutathione deposits in rat brain. Melatonin has also been shown to contribute to the protection of the neurological system 48 h following SAH [206].

When the anti-apoptotic and anti-inflammatory properties of melatonin are examined, brain edema and mortality caused by bleeding are reduced, contributing to the improvement of neurological development [207]. Studies have been conducted on rats in which consumption of melatonin increases NO, improves cerebral vasospasm and oxidative process in the brain [79]. Consumption of exogenous melatonin regulates the levels of MDA and catalase and superoxide dismutase activity in the normal range. Melatonin can inhibit inducible NOS and thus protects the brain tissue by reducing inflammation [78,208]. Recently, it was reported that brain inflammatory parameters were found to be increased after SAH. These parameters were observed to occur with the NF-[kappa] B, NLRP3, and TLR4 pathways and were reduced by the use of melatonin [209,210].

To summarize, melatonin has been shown to enhance cerebral autoregulation following hemorrhage. However, melatonin has antioxidant properties, suppresses the sympathetic nervous system, and thus positive effects can be observed in SAH patients. Despite all these studies, the effect of melatonin use on SAH patients has not been clinically examined. In the future, in the treatment of patients with cerebral hemorrhage, long-term, large-scale, randomized, double-blind, and multicenter clinical trials are needed.

3. Conclusions and future directions

The effects of melatonin on neurological diseases were examined in the light of the accessible literature. There are currently 451 clinical studies conducted on melatonin worldwide (clinicaltrials.gov). The majority of these studies (211 clinical studies) focused on the neurological effects of melatonin and its clinical reflection was investigated.

Low ROS production plays an important role in the fulfillment of many physiological tasks such as cell proliferation and host defense [211]. It is well established that when ROS production occurs more than antioxidant capacity, it makes a great contribution to the formation and acceleration of aging [212]. Aging is a complex process and cannot be attributed to a single factor. The theory of free radical aging has been going on for more than 50 years [213]. Free radical attack on neurons in old age is important in facilitating the formation of many neurodegenerative conditions. It is well documented that melatonin has been very effective in reducing oxidative damage in the last 25 years. It has been clearly described that melatonin neutralizes ROS and directly converts cleaning actions to enzymatically less harmful species [214]. It is clearly reported that melatonin has a beneficial effect on neurological diseases. The common feature of these effects depends on the biological and chemical properties of melatonin. Melatonin as mentioned in this review, is a powerful antioxidant, free radical scavenger, immune system regulator, anti-inflammatory and circadian rhythm regulator [215]. It is known that the metabolites of melatonin exert the same beneficial characteristics. These metabolites are also an important issue because there are many investigations regarding their effects stronger than melatonin alone.

According to the related literature on experimental animal and clinical studies, melatonin can be used in the prophylaxis of many neurological diseases such as AD, PD, and MS. Although there are both positive and negative effects on some neurological diseases such as epilepsy, melatonin is important for other diseases.

In this review, also, the mechanism of melatonin on neurological diseases is mentioned. High doses of melatonin which are effective at low doses are an important feature. Both the lipophilic and the hydrophilic characters of melatonin make it easy to pass through the blood-brain barrier and show its effect on the neurological system. In a study by Cardinali and colleagues, it was shown that the use of 50-100 mg/day was sufficient for the therapeutic efficacy of melatonin in neurological diseases.

As mentioned above there are numerous clinical studies on the usefulness of melatonin for the treatment of neurological diseases. In experimental animal models, melatonin has been shown to be highly effective in reducing neuronal loss and improving cognitive processes. Therefore, it shows that it can be used both in the treatment and prophylaxis of neurodegenerative diseases such as AD, PD, and epilepsy, which include inflammation and ROS in their pathogenesis. One of the biggest challenges in evaluating the effectiveness of melatonin, a neuroprotective agent, is the optimal dose selection. However, the dose of melatonin used in the experimental animals is typically significantly higher than

that used in clinical trials, which affects the result of studies. In addition, new clinical studies are needed to improve therapeutic efficacy and reduce side effects and toxicity of current treatment methods. Further experimental and well-designed clinical studies are required to explore the protective and therapeutic effects of melatonin on neurological diseases.

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