Drug Design, Development and Therapy

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REVIEW

The Role and Therapeutic Potential of Melatonin in Degenerative Fundus Diseases: Diabetes Retinopathy and Age-Related Macular Degeneration

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Abstract: Degenerative fundus disease encompasses a spectrum of ocular diseases, including diabetic retinopathy (DR) and age-related macular degeneration (AMD), which are major contributors to visual impairment and blindness worldwide. The development and implementation of effective strategies for managing and preventing the onset and progression of these diseases are crucial for preserving patients' visual acuity. Melatonin, a neurohormone primarily produced by the pineal gland, exhibits properties such as circadian rhythm modulation, antioxidant activity, anti-inflammatory effects, and neuroprotection within the ocular environment. Furthermore, melatonin has been shown to suppress neovascularization and reduce vascular leakage, both of which are critical in the pathogenesis of degenerative fundus lesions. Consequently, melatonin emerges as a promising therapeutic candidate for degenerative ocular diseases. This review provides a comprehensive overview of melatonin synthesis, its localization within ocular tissues, and its mechanisms of action, particularly in regulating melatonin production, thereby underscoring its potential as a therapeutic agent for degenerative fundus diseases.

Keywords: melatonin, fundus degeneration, oxidative stress, inflammation, anti-apoptotic

Introduction

Fundus degeneration encompasses a spectrum of ocular conditions, notably age-related macular degeneration (AMD) and diabetic retinopathy (DR).[1] In developed nations, AMD stands as the primary cause of legal blindness in individuals aged 60 and above, particularly among those of Caucasian descent.[2] Projections suggest that the number of diagnosed AMD cases will rise to 196 million by 2020 and 288 million by 2040.[3] The etiology of AMD is complex and not yet fully elucidated, although certain risk factors have been identified as potential contributors to the development of the condition.[4] Smoking and sunlight exposure are known to worsen environmental risk factors, with age being identified as the primary demographic risk factor. Additionally, research indicates that nutritional factors, gut microbiota, hypertension, and genetic variability play a role in the development of wet AMD.[5] Advanced wet AMD can lead to severe visual impairment due to choroidal neovascularization.[6]

DR is associated with various microvascular complications, including blindness, particularly in individuals under the age of 40.[7] The estimated prevalence of diabetes is 400 million individuals, with one third experiencing DR and one tenth

Received: 30 March 2024
Accepted: 13 June 2024
Published: 18 June 2024

affected by vision-threatening conditions such as diabetic macular edema and proliferative DR (PDR).[8] Worldwide, DR and AMD are the major causes of vision impairment and blindness.[9] Given the increasing prevalence of diabetes and aging populations, the prevention and treatment of fundus degenerative diseases are of heightened importance.

Melatonin, a neurohormone predominantly produced by the pineal gland, has been the subject of extensive research and application across various disciplines.[10] Eye research has particularly focused on the interaction between melatonin and the eyes, especially retinal ganglion cells. Additionally, studies have explored the impact of eye lesions on the circadian rhythm regulation of melatonin.[11] Besides its role in regulating circadian rhythms, melatonin serves crucial physiological functions in ocular structures. Evidence suggests that a deficiency in melatonin may contribute to the development of AMD, as indicated by reduced melatonin production in AMD patients compared to controls.[12] Furthermore, individuals with AMD exhibit elevated melatonin levels during daytime hours, suggesting a disruption in melatonin's diurnal cycle in individuals with this condition.[13] Consequently, heightened levels of melatonin during daylight hours may have deleterious effects on ocular structures, potentially leading to the onset of light-induced retinal degeneration.

Research has shown that melatonin suppresses the phosphoinositide 3-kinase (PI3K)/ protein kinase B (Akt)/signal transducer and activator of transcription 3 (STAT3)/nuclear factor-kappaB (NF-κB) signaling pathway in experimental DR, thereby preserving the integrity of the blood-retinal barrier.[14] Genome-wide association studies have revealed that variations in genes encoding melatonin synthase and receptors are implicated in the pathogenesis of type 2 diabetes.[15,16] It has been hypothesized that melatonin may play a role in various forms of retinopathy; however, population-based studies have not investigated these potential associations. Melatonin exerts its effects through multiple mechanisms, such as antioxidant, anti-inflammatory, and neuroprotective actions. It scavenges free radicals, diminishes the release of inflammatory molecules, and shields ocular tissues from oxidative stress and inflammatory harm in AMD and DR.[17,18] Furthermore, melatonin inhibits neovascularization and vascular leakage, regulating the development of fundus degenerative lesions.[19]

Studies have found that exogenous melatonin is safe in the human body and has a high ability to cross the blood-retinal barrier.[20,21] Therefore, melatonin may become a potential novel therapy in degenerative eye diseases. Interestingly, research has found that the synthesis of melatonin in the retina decreases with age, further suggesting that melatonin may be involved in age-related pathologies.[22]

Melatonin Biosynthesis and Physiological Functions

Mechanisms of Melatonin Synthesis and Release

Melatonin, a neurohormone primarily synthesized by the pineal gland, undergoes complex regulatory mechanisms during its synthesis and release.[23] Various enzymes, hormones, and regulatory factors are involved in this process, and once produced, melatonin diffuses freely out of the cell.[24,25] Understanding the processes involved in the production and secretion of melatonin is crucial to uncovering its significance in fundus degeneration.

Melatonin is synthesized from tryptophan, an essential amino acid, through a series of enzymatic reactions, among which tryptophan hydroxylase is involved.[26] In the following step, 5-hydroxytryptophan is converted into 5-hydroxytryptophan via the hydroxytryptophan decarboxylase. The cytochrome P450 enzyme is also involved in the regulation of the conversion to 5-hydroxytryptamine.[27] Melatonin is eventually converted from 5-hydroxytryptophan inside the cell through a variety of enzyme-catalyzed modifications.[28] Key enzymes in this pathway include the melatonin N-acetyltransferase (AANAT) and the hydroxytryptamine-O-methyltransferase (HIOMT).[29] The enzyme AANAT catalyzes the transfer of an acetyl group to serotonin, forming N-acetylserotonin, which is then methylated by HIOMT to produce melatonin.[30]

The Regulation of Melatonin Synthesis and Release

Light primarily regulates melatonin synthesis and release through the retino-pineal pathway.[31] Light signals are transmitted from the retina, the light-sensitive tissue of the eye, to the pineal gland.[32] Retinoid molecules in photoreceptor cells trigger a series of biochemical reactions that ultimately lead to neural signals. As these signals travel

through the optic nerve to the pineal gland, the pineal gland modulates melatonin synthesis and release by releasing neurotransmitters and activating melatonin receptors. During daytime light exposure, neurotransmitters released from the retina inhibit the activity of melatonin synthase and AANAT in the pineal gland, decreasing melatonin production.[33] In contrast, in darkness or at night, the absence of light signaling reduces the release of retinal neurotransmitters, increasing the activity of melatonin synthase and AANAT, thus promoting melatonin synthesis and release.[34]

In addition to light, melatonin synthesis and release are influenced by endogenous factors, involving various systems such as the nervous, endocrine, and immune systems.[35] Neurotransmitters in the nervous system, including dopamine, norepinephrine, and epinephrine, can inhibit melatonin synthesis and release, whereas neuropeptides such as oxytocin can promote it.[36] Hormones within the endocrine system, such as cortisol, thyroid hormones, and sex hormones, also affect melatonin synthesis by binding to receptors in pineal cells and regulating intracellular signaling pathways.[37] Additionally, immune system cytokines and inflammatory responses can influence melatonin production and release. Cytokines involved in inflammatory processes, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), have been shown to inhibit melatonin synthesis and release.[38]

The pineal gland plays a crucial role as an endogenous regulator in the synthesis and release of melatonin. Pineals are small brain glands that are primarily responsible for melatonin synthesis and release.[39] Various hormones, such as β-adrenoceptors and cholinergic neurons, control pineal gland activity.[40] Adrenaline suppresses melatonin synthesis, while cholinergic neurons stimulate it.[41] The synthesis of melatonin in the pineal gland is regulated by the daily rhythm of β-adrenergic receptor stimulation, which initiates the transcription of AANAT genes and activates the corresponding enzymes.[42] Melatonin demonstrates a protective and enhancing influence on cholinergic neurons responsible for the regulation of circadian rhythm and sleep. However, a definitive correlation between these two systems has not been established.[43] These hormones and neuromodulators regulate intracellular signaling pathways by binding to receptors on the surface of pineal gland cells, thereby affecting melatonin synthesis and release.

Melatonin receptors have been identified in many retinal neurons, including intrinsic photosensitive retinal ganglion cells (ipRGCs) containing melanopsin, suggesting that melatonin modulates the physiological function of these photoreceptors in the inner layers of the retina.[44] ipRGCs are located in the inner layers of the retina are responsible for circadian regulation, and are directly stimulated by light through the activation of the photoreceptor pigment melanopsin, which projects to the supraoptic nucleus of the optic cross, and eventually projects to the pineal gland and controls the release of the sleep hormone melatonin.[45]

In summary, the production and secretion of melatonin is an intricate and carefully controlled process. It is regulated by several factors, including enzymes in the synthesis pathway, pineal hormone regulation, light exposure, and endogenous regulation of the nervous, endocrine, and immune systems. An in-depth understanding of the mechanisms of melatonin synthesis and release is important for revealing its role and therapeutic potential in fundus degenerative diseases.

The Presence and Role of Melatonin in the Structure of the Eye

Melatonin is prevalent in ocular structures and plays a critical role in several physiological processes. Below are the key aspects of melatonin's presence and function in ocular tissues.

Melatonin in the Retina

Melatonin is synthesized in retinal photoreceptors and acts as a local neuromodulator.[46] In addition to endogenous production, melatonin can be transported into ocular tissues via the bloodstream. Melatonin receptors have been identified in multiple retinal structures, including retinal pigment epithelium (RPE), photoreceptors, horizontal cells, bipolar cells, amacrine cells, ganglion cells, and the inner and outer plexiform layers.[47] The melatonin hormone has paracrine and autocrine impacts that are controlled by its G-protein-coupled receptors, melatonin receptor type 1 (MT1) and MT2, as well as potentially MT3, or can occur without receptor involvement.[48] It is currently believed that it is the MT1 and MT2 receptors that play a major role in the eye.[49] The retinal cells with receptors play several crucial roles, such as absorbing light that is scattered, preserving the well-being of photoreceptor cells in the retina, and offering nutritional assistance.[50] Melatonin is present in the eye's retina, with a high concentration in the RPE.[51] Melatonin is

released in the dark and dopamine in the light within the eye, with melatonin suppressing the release of dopamine from anaplastic cells.[52] MT1 receptors, present on dopaminergic and GABAergic amacrine cells in guinea pigs, humans, and rhesus monkeys, have the potential to induce this effect.[53] Furthermore, exposure to light stimulates the release of dopamine from anaphase cells, which bind to D2 and D4 receptors on photoreceptors, thereby inhibiting the activity of AANAT and modulating cAMP and calcium concentrations, ultimately leading to a reduction in melatonin production.[54] Therefore, the widespread distribution of melatonin receptors in the retina suggests an intricate interplay between neuronal processes involving melatonin, dopamine, and melanopsin.

Research indicates that melatonin supports retinal health by controlling RPE cell activity, reducing oxidative stress, and protecting against damage.[55] Knockout studies in mice have shown that defects in MT receptors lead to lipofuscin accumulation and decreased cell survival.[56] Melatonin also influences phototransduction and modulates photoreceptor and bipolar cell sensitivity.[57] Additionally, it mitigates cell death and inflammation in RPE cells, thereby maintaining retinal function.[58]

Melatonin in the Sclera and Uvea

Melatonin is present in the uvea, where it plays several physiological roles. It regulates ocular blood flow by modulating vasoconstriction and vasodilation and exhibits anti-neovascularization properties, inhibiting endothelial cell proliferation and migration.[59–61] Melatonin also reduces ocular inflammation by modulating immune responses and decreasing cytokine levels and inflammatory mediator production.[62] Melatonin receptors are expressed in the sclera, which may contribute to the maintenance of scleral elasticity.[63] Melatonin receptors in the sclera may be involved in the progression of ocular axial length due to myopia in adolescents. As a result of the blue light (480 nm) interacting with the retina and sclera, melanopsin synthesis is specifically stimulated and melatonin MT1 receptor expression and melatonin concentration were decreased.[64] The findings are consistent with those of a study in guinea pigs in which melatonin protease was inhibited by an antagonist administered intravitreally.[65] This melatonin protease inhibition leads to an abnormal increase in eye growth, which is directly related to increased melatonin levels in the retina.

Melatonin in the Lens and Vitreous

Melatonin is also found in the lens, where it contributes to lens transparency and health.[66] It was once thought that melatonin reached the lens via atrial fluid absorption, but recent studies suggest that it is also synthesized by human lens epithelial cells. Light activates melanopsin, reducing melatonin synthesis. Likewise, darkness increases AANAT expression and melatonin production in lens epithelial cells.[67] Lenses are transparent tissues inside the eyes used for focusing light.[68] Oxidative stress and inflammatory responses affect lens clarity and function. Melatonin, which has antioxidant and anti-inflammatory effects in the lens, can maintain lens health by inhibiting the production of free radicals and reducing oxidative stress, protecting lens cells from oxidative stress damage.[69] The lens is unable to avoid UV exposure, and after UV exposure, exogenously administered melatonin interventions result in decreased lipid peroxidation, increased antioxidant enzyme activity, and decreased CA^{2+}, thereby reducing cataract formation.[70] Furthermore, melatonin reduces inflammatory damage to lens cells by modulating the inflammation response and inhibiting the production of inflammatory mediators.[71] Located between the lens and retina, vitreous humor is a clear gel-like substance that maintains the shape of the eye and supports the retina. There is no melatonin production in the vitreous, it is generally secreted and delivered to the vitreous and has been shown to be effective in rescuing photoreceptor degeneration in experimental studies.[72]

Melatonin in the Ciliary Body

The unpigmented ciliary epithelium is also thought to provide melatonin, and the fact that AANAT and HIOMT are localized to the human ocular ciliary body supports a ciliary source for melatonin.[73] Researchers have identified melatonin receptors in rabbit iris and ciliary body, as well as melatonin metabolites in the ciliary bulge Melatonin receptors have been identified in the iris and ciliary body of rabbits, as well as localized to the ciliary epithelium.[74,75] The ciliary body secretes melatonin, which is responsible for aqueous humor production and maintaining intraocular pressure variations throughout the day.[76] Melatonin is highest at night, when intraocular pressure (IOP) is generally lowest;

therefore, melatonin may be negatively correlated with IOP. Moreover, topical administration of melatonin analogs has been shown to lower IOP, thereby altering the circadian pattern of IOP.[77] Currently, it is believed that the mechanism of action is to reduce chloride ion efflux, which in turn reduces the formation of aqueous humor caused by fluid movement in the unpigmented ciliary body.[78] It is possible that melatonin plays a role in the pathophysiology and treatment of glaucoma because of its association with an increase in aqueous humor production and intraocular pressure.[79] Glaucoma-induced damage to the inner retina layer can impact retinal ganglion cells, potentially causing disruptions in melatonin levels and contributing to the prevalence of sleep disorders among individuals with glaucoma.[80,81] Melatonin, on the other hand, has the potential to be a new treatment option for glaucoma if it has both IOP-lowering and neuroprotective effects.

Melatonin in the Cornea

The distribution of melatonin receptors is also detected in the cornea, which is mainly localized in the epithelium, stroma, and endothelium of the rabbit cornea.[82] Both rabbits and humans have melatonin in their tears. Various potential impacts of melatonin on the eye surface have been observed. Melatonin facilitates the shedding of epithelial cells by controlling the development of tight junctions and the detachment of surface cells.[83] Melatonin has been shown in in vitro study to affect corneal hydration and corneal wound healing.[84] Furthermore, melatonin may play a part in the growth of corneal epithelial cells.[85] Melatonin has also been shown to have antioxidant properties that protect corneal epithelial cells from ultraviolet (UV) irradiation damage, and melatonin-treated rabbit corneal epithelial cells showed a decrease in lipid peroxidation and an increase in mitochondrial viability after UV exposure compared to untreated control tissue.[86]

In Conclusion, melatonin plays a significant role in various physiological functions within the eye, including phototransduction and photoreceptor renewal, aqueous humor production regulation, intraocular pressure, wound healing, and providing antioxidant protection (Figure 1). Melatonin receptors are widely distributed across ocular tissues, enabling diverse responses to melatonin.[87] Understanding melatonin's synthesis and effects in ocular tissues highlights its importance in maintaining ocular health and its potential therapeutic applications in treating ocular diseases.

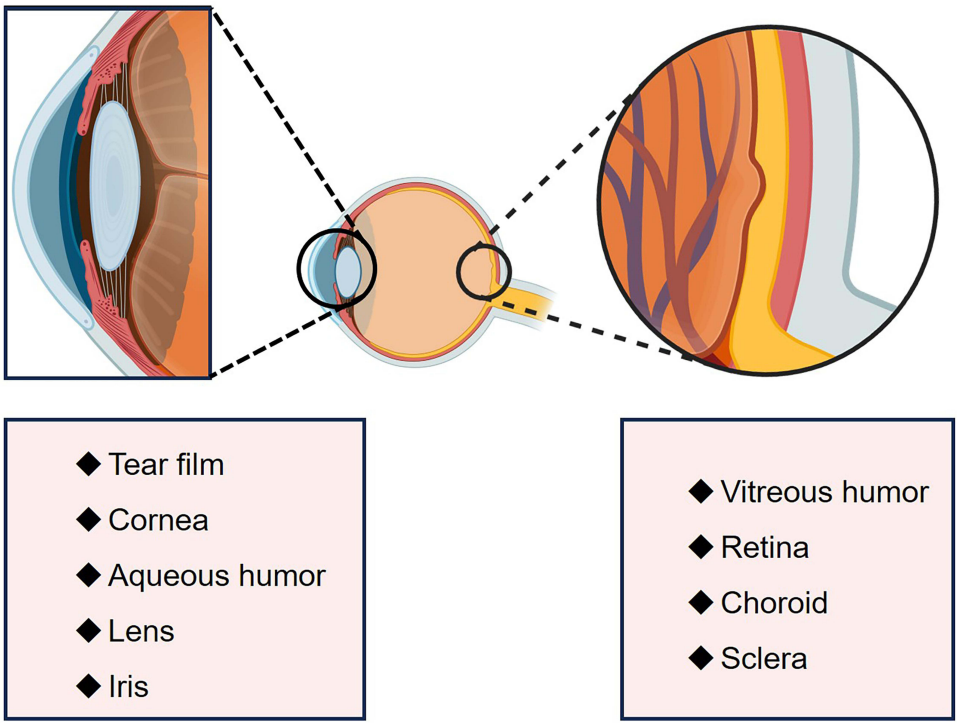

Figure 1 The distribution of melatonin in various tissues of the eye.

Melatonin Exerts Antioxidant, Anti-Inflammatory, Cytoprotective, Cell-Cycle-Regulating and Proliferative Effects in Degenerative Fundus Lesions

Antioxidant Effects

Melatonin exerts significant antioxidant and anti-inflammatory effects in degenerative diseases of the fundus, playing a crucial role in maintaining ocular tissue health and mitigating lesion progression Oxidative stress is a primary factor in the development of degenerative fundus lesions, causing irreversible damage to cellular and tissue structures. Melatonin plays a neuroprotective role by activating its receptor MT1 to inhibit the expression of amyloid precursor protein processing enzyme in the hyperglycemia induced diabetes cell model.[88] Additionally, melatonin inhibits mTOR and autophagy markers (LC3-II and Beclin-1) through its MT2 receptors, promoting autophagy to reduce retinal oxidative stress.[89] It also modulates the expression of antioxidant enzymes and neuronal-type nitric oxide synthase (nNOS), while triggering the activation of inducible nitric oxide synthase (inNOS).[90,91]

Melatonin serves as a mitochondria-targeted antioxidant, protecting retinal cells from oxidative stress.[92] It enhances the survival of retinal cells, including photoreceptors, retinal ganglion cells, and Müller cells, which are affected by DR.[93] In diabetic retinas, melatonin prevents nitro-oxidative stress and the inflammatory response induced by high glucose levels.[94] Studies have shown that melatonin synthesis is reduced in the retinas of diabetic rats, correlating with the progression of DR.[95–97]

In age-related macular degeneration (AMD), reduced nocturnal melatonin production contributes to oxidative damage, highlighting the importance of melatonin's antioxidant effects.[98,99] Melatonin regulates antioxidant gene transcription via nuclear factor erythroid 2–related factor 2 (Nrf2), which is compromised in aging RPE cells.[100,101] Exogenous melatonin may thus play a role in preventing and treating AMD by modulating oxidative stress and Nrf2-mediated defenses.[102] Additionally, in fundus oxidative stress injury, reactive oxygen species (ROS) can facilitate telomere erosion, thereby contributing to the senescence of RPE cells.[103] The retina contains active telomerase, and defects in telomerase activity in AMD can also lead to RPE cell damage; melatonin, which regulates telomerase activity, may play a role in slowing the damage.[104] Melatonin appears to modulate telomerase, suggesting it may be useful to prevent or treat AMD.[105] Since melatonin is an antioxidant, a mitochondrial protector, and an inflammatory modulator, its deficiency may promote the progression of DR and AMD lesions. Further clinical trials are necessary to evaluate its efficacy and safety.

Melatonin's direct antioxidant effects should not be overlooked.[106] It neutralizes free radicals, reducing oxidative stress and protecting eye tissues from damage.[107–109] It also enhances mitochondrial function and intracellular antioxidant capacity by boosting the activity of enzymes like superoxide dismutase and glutathione peroxidase.[110] Melatonin has demonstrated efficacy in protecting mitochondrial DNA from oxidative damage, although it did not confer protection against ischemia/reperfusion-induced retinal damage.

Melatonin demonstrated efficacy in safeguarding the mitochondrial DNA of ARPE-19 cells against damage induced by hydrogen peroxide.[111] Ischemia/reperfusion is an important source of free radical production, and subcutaneous injection of melatonin can provide protection against retinal damage caused by ischemia/reperfusion in many rats.[112] In autopsy studies of AMD-affected eyes, mitochondrial DNA was found to be excessively damaged by oxidative stress.[113] Furthermore, melatonin's antioxidant properties are expressed in its ability to reduce oxidative damage to DNA.[114] Inflammation can also be triggered by mitochondrial signaling pathways. Melatonin attenuates mitochondrial damage and oxidative stress generated during inflammation by modulating mitochondrial function and the activity of the mitochondrial respiratory chain. Regulation of the mitochondrial pathway reduces the production and release of inflammatory mediators, thereby attenuating the inflammatory response and cellular damage. Melatonin reduces ocular inflammatory responses and damage by regulating the production and release of cytokines and maintaining the balance of cytokines and inflammatory mediators.[115] Thus, the involvement of melatonin in mitochondrial regulation may be one of the ways to address AMD fundus lesions. It is predicted that mitochondria may play a significant role in melatonin synthesis, which supports the relationship between melatonin and mitochondria.[116]

Anti-Inflammatory Effects

Inflammatory responses play an important role in the development of degenerative fundus lesions, leading to tissue damage and apoptosis. Moreover, the inflammatory process plays a significant role in the pathogenesis of DR, rendering it a low-grade chronic inflammatory condition. Upregulation of inflammatory mediators including nNOS, Cyclooxygenase-2, vascular endothelial growth factor (VEGF), mitogen-activated protein kinases (MAPK) and NF-κB is observed in DR, with NF-κB activation leading to cytokine release and increased production of ROS.[117] A significant part of melatonin's anti-inflammatory effect is its ability to reduce the inflammatory response and inflammatory mediator production.[118] There are several mechanisms by which melatonin exerts its anti-inflammatory effects. First, it inhibits the production and release of inflammatory mediators, such as cytokines and inflammatory mediators. Specifically, melatonin suppresses the synthesis of inflammatory cytokines, including (TNF-α) and interleukin-6, leading to a decrease in inflammatory response.[119] Second, melatonin also regulates inflammatory signaling pathways such as NF-κB and mitochondrial pathways.[120] NF-κB is a key transcription factor involved in the regulation of inflammatory responses and apoptosis, among other processes. Melatonin inhibits NF-κB activation through multiple mechanisms. It inhibits the nuclear translocation and nuclear transcriptional activity of NF-κB, thereby suppressing the expression of inflammation-related genes.[121] As well as blocking NF-κB activation signaling, melatonin inhibits the activity of IKK receptors.[122] Furthermore, melatonin regulates cytokine signaling pathways, including the Janus kinase/signal transducer and activator of transcription (JAK/STAT) family pathway, impacting immune cell function and the development of inflammatory responses.[123]

These signaling pathways play an important role in the inflammatory response, and melatonin inhibits the onset and progression of the inflammatory response by regulating their activity.[124] In addition, melatonin reduces inflammation-induced apoptosis and cellular damage. It protects eye tissues from inflammation-induced damage by inhibiting oxidative stress and regulating the expression of proteins associated with cell survival and apoptosis.

Regulates Cell Activity and Exerts Cytoprotective and Anti-Apoptotic Effects

Melatonin also affects the activity of immune cells, regulates the immune response and inflammatory processes, and modulates immune cells such as macrophages and T-lymphocytes that play an important role in fundus degeneration.[125] In dendritic cells, melatonin influences immune function via the Nrf2/hemoglobin oxygenase-1 (HO-1) axis.[126] Melatonin regulates dendritic cells to modulate the body's immune system, but further basic and clinical studies are needed to confirm this in the field of ophthalmology.[127] Melatonin was effective in ameliorating retinal degeneration in a mouse model, and the 5'-nucleotidase ecto/Tet methylcytosine dioxygenase 2 (NT5E/TET2) pathway in Tregs may be the mechanism of the anti-retinal degeneration response to melatonin treatment, which was first demonstrated to regulate immune homeostasis through Tregs.[128] Melatonin also affects the proliferation and differentiation of immune cells and regulates their function. By affecting the function of immune cells, it reduces the aggregation and activation of inflammatory cells and decreases the secretion and release of inflammatory mediators. In addition, melatonin can inhibit the migration of immune cells and reduce the inflammatory response and damage to ocular tissues.[129] In addition, melatonin acts as a cytoprotectant, reducing apoptosis and damage to eye tissue.[130] The apoptotic pathway is inhibited by melatonin, thereby increasing cell survival and functional recovery. According to a study, melatonin inhibits the expression of apoptosis-related proteins, including members of the Bcl-2 family and cysteine protease family.[131] The expression and activity of these proteins play an important role in apoptosis, and melatonin inhibits it in ocular tissues. The action of melatonin interferes with cell survival signaling pathways, thereby regulating the balance between cell survival and apoptosis. A study showed that melatonin can promote cell survival and proliferation by activating the PI3K/Akt pathway.[132] Furthermore, in terms of neuroprotection, melatonin treatment increased levels of brain-derived neurotrophic factor (BNDF) and its downstream phosphorylated tropomyosin receptor kinase B (Trkb)/Akt/extracellular regulated protein kinase (ERK)/p-cAMP response element binding protein (CREB) levels, and hypoxia-ischemia-induced increases in cleaved caspase-3 and Bax protein levels, as well as reductions in Bcl-2 protein levels, were reduced.[133] Besides, activation of the NF-κB signaling pathway triggered apoptosis of retinal capillary cells in the DR, increasing the production of ROS and inflammatory factors.[134] Melatonin regulates dendritic cells to modulate the body's immune system, but further basic and clinical studies are needed to confirm this in the field of

ophthalmology.[135] Melatonin induces the expression of SIRT1 gene to reduce the expression of BAX and caspase 3, increase the expression of Bcl2, and play a role in reducing mitochondrial and nuclear DNA damage.[136] Melatonin exerts its cytoprotective effects against DR and AMD through these cytoprotective and anti-apoptotic mechanisms, attenuating cellular damage and inflammatory responses in ocular tissues.

In summary, melatonin's mechanism of action in degenerative fundus diseases involves its antioxidant, anti-inflammatory, cytoprotective, cell proliferation regulator and anti-apoptosis (Figure 2). A comprehensive understanding melatonin's role in fundus degenerative disease is crucial for revealing its therapeutic potential and developing appropriate therapeutic strategies.

Vasomodulation of Melatonin in Degenerative Fundus Lesions

Abnormal neovascularization is an important feature in fundus degenerative diseases such as AMD and DR. Melatonin exerts a role in reducing neoangiogenesis, decreasing vascular damage due to inflammatory responses in vascular tissue

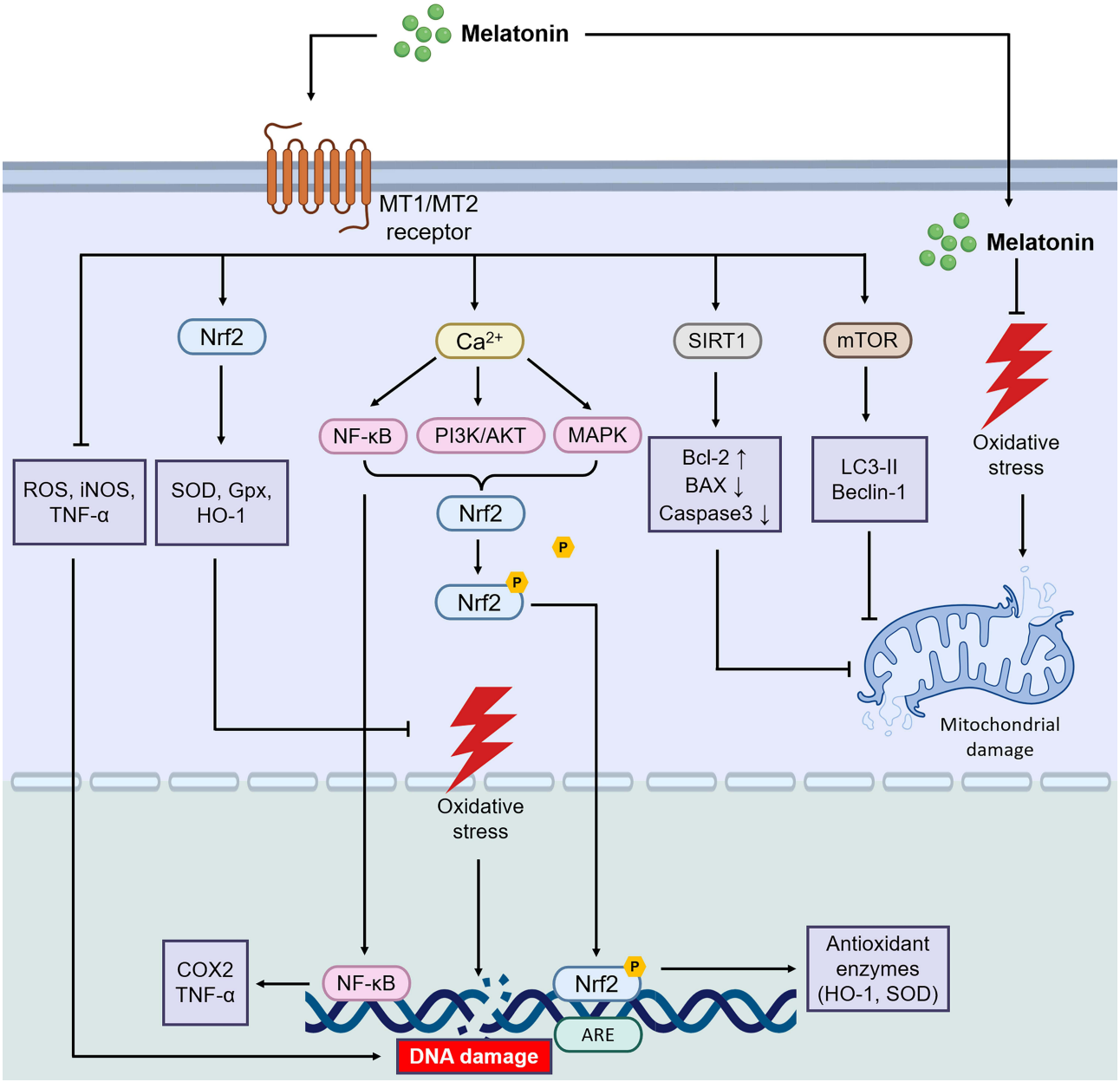

Figure 2 Melatonin plays a role in antioxidant, anti-inflammatory, and reducing cell apoptosis in degenerative fundus lesions.

and regulating vasoconstriction (Figure 3). Melatonin regulates retinal VEGF secretion, promoting physiologic secretion to protect the retina from oxidative stress and reducing pathologic secretion to inhibit neovascularization.[137] Inhibition of proliferation and migration of vascular endothelial cells is one way in which melatonin inhibits neovascularization.[138] In addition, melatonin inhibits the production and release of VEGF and matrix metalloproteinase (MMP) in vascular endothelial cells, which are involved in regulating the process of neovascularization.[139,140] VEGF is a major cause of neovascularization, and melatonin protects the retina from oxidative stress and hemorrhage by regulating VEGF secretion in the retina and reducing pathological secretion to inhibit neovascularization.[141] The antioxidant and antiangiogenic characteristics of melatonin position it as a promising therapeutic option for addressing AMD and DR. The diminished synthesis of melatonin in the retinas of DR rats, in comparison to control subjects, may be linked to the advancement of DR fundus lesions.[142] As well, serum melatonin concentrations are reduced at night in diabetics with PDR.[97] Furthermore, studies have shown that melatonin exhibits a protective effect against pathological retinal neovascularization, preservation of glial cells, and mitigation of inflammatory response through the inhibition of the HIF-1α/VEGF signaling pathway.[143] Additionally, melatonin has been found to suppress the activity of angiopoietin receptors, crucial

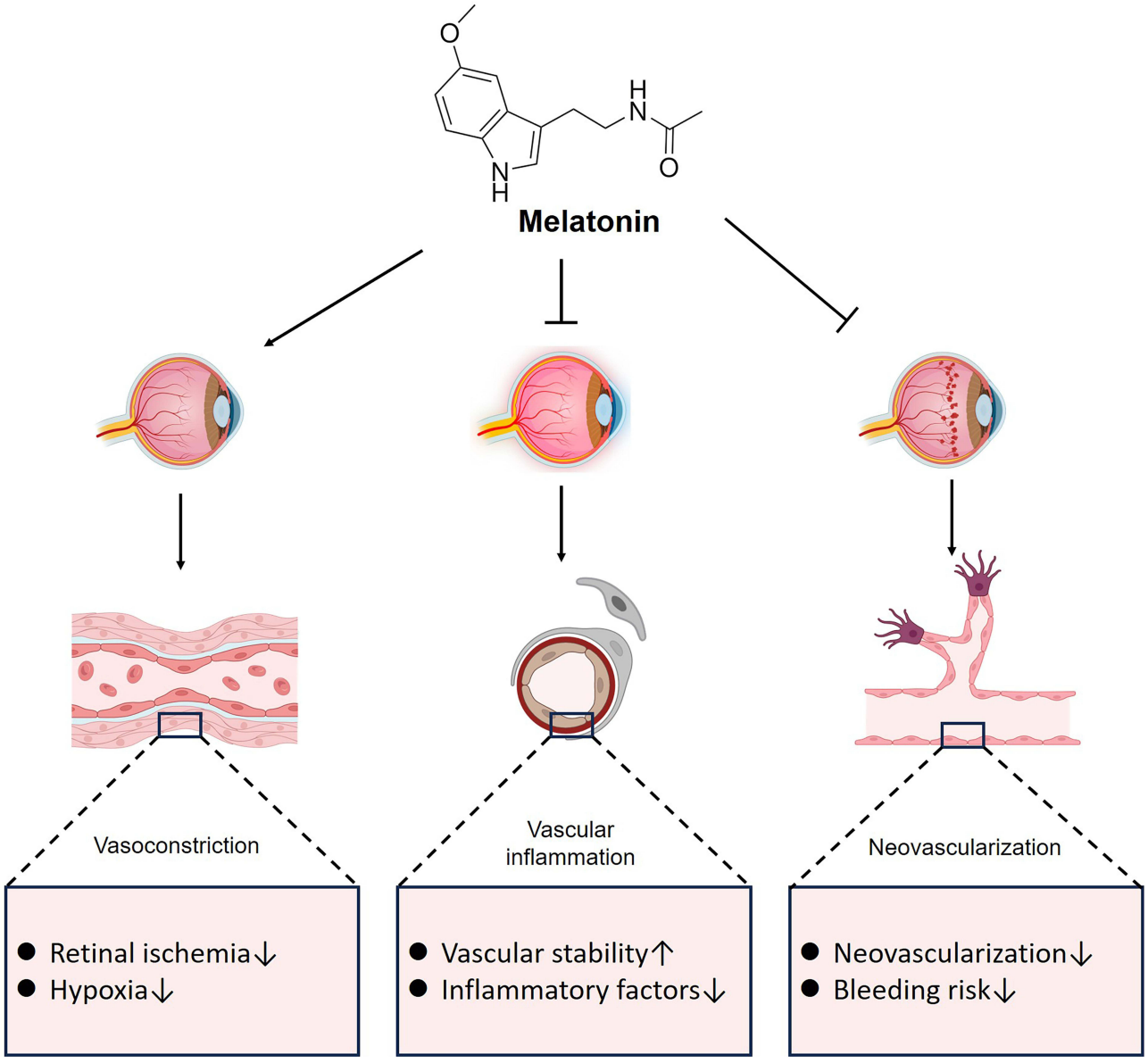

Figure 3 The vascular regulatory role of melatonin in retinal degenerative diseases.

components of angiogenesis-related signaling pathways that contribute significantly to angiogenesis and tissue remodeling.[137] Melatonin has been shown to suppress RhoA/ROCK signaling in mouse models of choroidal neovascularization, leading to a transition of macrophages and microglia from M2 to M1 phenotypes following prolonged laser exposure.[144] These findings indicate the potential for melatonin intervention as a novel therapeutic approach for AMD and DR. Through the regulation of key molecules, melatonin can impact the proliferation, migration, and lumen formation of vascular endothelial cells, ultimately influencing vascular structure and function.

In regulating vasoconstriction, melatonin has been shown to have different effects on blood vessels and blood flow in different organs and tissues of the body. Mechanisms of melatonin action on the vasculature have been shown to include direct activation of melatonin receptors and through intercellular pathways.[145,146] The prevalence of MT1 receptors in retinal vascular endothelial cells suggests that melatonin binding to these receptors on vascular smooth muscle cells can induce vasoconstriction through the enhancement of norepinephrine signaling.[147] The presence of MT1 has been identified in the outer membranes of retinal arteries and veins, particularly in the papillary region rather than in the ciliary and choroidal vessels.[148] The localization of MT1 in retinal vessels to the outer membrane of the vessel wall aligns with previous observations in human cerebral vessels.[149] The primary role of MT1 receptors is thought to be mediating vasoconstriction.[150] Therefore, we hypothesized that melatonin may act in an indirect manner on retinal vascular smooth muscle to regulate contraction. And there is also a study demonstrating that the onset of AMD may lead to smaller diameters of small blood vessels.[151] In addition, patients with DR also show narrowing changes in the diameter of the lumen of the retinal blood vessels in the fundus, resulting in decreased blood flow to the fundus.[152] Thus, the possible vasoconstrictive effect of melatonin on the fundus has the potential to exacerbate fundus changes in patients at an early stage. In spite of melatonin's ability to modulate vasoconstriction, its effect on blood pressure appears to be dose-dependent. A reduction in arterial blood pressure was observed in subject men and women with 1 mg of melatonin.[153] However, in another study it was found that ingesting 3mg of melatonin did not change the subjects' blood pressure.[154] In order to better understand the relationship between melatonin levels and vascular changes, adrenal nerve activity, and hormonal responses, additional studies are needed for various doses of the drug.[146,155] Melatonin's protective effects on retinal inflammation, oxidative stress, angiogenesis, and apoptosis have been demonstrated in animal models, suggesting that melatonin may help prevent diabetic-related retinal damage.[156] However, due to a lack of clinical studies, it is still unknown whether melatonin has clinical benefits, despite having been taken as a supplement by a relatively large number of people worldwide.

Melatonin for Stem Cell Therapy in Fundus Degenerative Disease

Melatonin has demonstrated effective application in various diseases when used in pretreatment or in combination with scaffolds including chronic kidney disease, neurodegenerative diseases, and orthopedic disorders, whereas its use in ocular diseases is rare.[157,158] It has been widely demonstrated that stem cells are effective in treating eye diseases.[159] Melatonin promotes the proliferation, differentiation and survival of stem cells and improves their effectiveness in therapy.[160] For treatment of retinal diseases and vision restoration, reprogramming endogenous neural stem cells is considered to be the most promising approach.[161] In vitro, melatonin inhibits cell apoptosis pathways and regulates DNA methylation to promote the survival of endogenous neural stem cells derived from bovine retina.[162] The proliferation of pluripotent stem cells induced by endogenous neural stem cells can be further enhanced through activation of the ERK1/2 signaling pathway downstream of melatonin. Additionally, melatonin has been shown to significantly increase retinal neural stem cell proliferation and expression of the marker nestin via the ERK and TGF-β/Smad pathway-mediated MT1.[163]

Moreover, melatonin has been shown to impact signaling pathways and gene expression in stem cells, modulate the equilibrium between cell proliferation and differentiation, and serve as an antioxidant to mitigate oxidative stress-induced apoptosis and augment stem cell functionality.[164,165] However, the specific role of melatonin in the regulation of corneal epithelial stem cells and its efficacy in the treatment of ocular diseases in animal models have yet to be elucidated. Given the demonstrated superiority and significant potential of melatonin in stem cell therapy, it is imperative to prioritize further investigation into its therapeutic modalities, effects, and mechanisms. Additionally, preliminary small-scale

clinical trials in patients may be warranted to assess the potential for melatonin's clinical application to enhance therapeutic outcomes, promote improvements in visual acuity, and facilitate the repair of fundus tissues.

Melatonin Dosing Patterns

Clinical trials have focused on oral melatonin administration, with early results showing protection of the retina and slow progression of AMD when administered daily (3 mg).[166] In recent studies, however, it has been demonstrated that due to the liver's first pass metabolism, its bioavailability is only about 15%.[167] Whereas the efficacy of melatonin varies by dosage form, with continuous-release and absorbed forms being more efficacious than immediate-release forms, the short half-life and ultra-high maximal plasma concentration may further contribute to the low bioavailability of melatonin due to under-absorption and tolerability issues.[168] Ocular surface drug delivery is convenient and safe, and is currently the most common route of administration in the treatment of ophthalmic diseases. The ophthalmic administration of melatonin has been widely used in animal experiments, and nano micelle formulation eye drops can penetrate into the eyes of rats.[169] However, if clinical application is required, further research is needed on the concentration, safety, and bioavailability of drugs entering the human eye. The use of vitreous cavity injections, which circumvent the ocular barrier and facilitate the delivery of drugs to the targeted treatment site, is currently under observational investigation for the treatment of retinal diseases. Nevertheless, a prior study documented the occurrence of adverse effects, specifically retinal cell degeneration, following high-dose melatonin injections.[170] Hence, it is imperative to conduct further research on the mechanism of action and potential toxicity of melatonin in the treatment of ocular diseases, as well as to establish the optimal therapeutic dosage for varying ocular conditions and individual patients. Additionally, the optimal timing of melatonin administration and the therapeutic efficacy of alternative routes of delivery, such as subconjunctival injection, warrant exploration through extensive clinical trials.

Efforts to enhance melatonin's efficacy in treating degenerative fundus lesions focus on developing drug delivery systems that sustain release, increase local tissue drug concentrations, improve therapeutic efficacy, and reduce side effects. The delivery of ocular drugs using nanotechnology can penetrate the surface of the eye and provide sustained release. Nanocarriers can be classified into four distinct categories according to their geometries: 0D-like nanoparticles, 1D-like nanofibers, 2D-like nanomembranes, and 3D-like nanogels.[171] Research has demonstrated that the encapsulation of melatonin within 0D and 1D nanocarriers enhances both bioavailability and therapeutic effectiveness.[172] Melatonin-loaded PLGA-PEG nanoparticles synthesized by solvent substitution method can also reduce IOP twice as long as melatonin aqueous solution, and the results show good tolerance.[173] Moreover, melatonin is delivered through cationic and mucus carriers, which enhance its ability to cross the ocular surface barrier and prolong its retention.[174] A recent study discovered that melatonin solution encapsulated within ethylcellulose nanoparticles exhibited enhanced corneal penetration attributed to its adhesion to mucin and slower release kinetics in comparison to free melatonin solution. This formulation significantly augmented retinal thickness and decreased apoptosis of retinal ganglion cells by approximately 16% in a retinal detachment model, indicating a superior retinoprotective effect.[175] Nevertheless, there remains a scarcity of advanced high-dimensional nanocarriers with high drug loading capacity and stimulus responsiveness for the loading of melatonin in ocular drug delivery, necessitating further development and exploration for potential clinical application. We learned that synergistic therapeutic effects based on melatonin, including co-administration strategies with glial cell-derived neurotrophic factors and neuroprotective drugs, have also been proposed, and the prognosis of co-administration may be better compared with single drugs. The incorporation of melatonin into multidrug systems results in improved sustained release of formulations, while advancements in drug delivery systems facilitate enhanced detection and monitoring. However, it is important to acknowledge potential challenges such as competition for drug delivery sites and the formation of drug co-crystals.[176] Therefore, despite the development of nano-loading technologies, mass production of melatonin nanomedicines for ophthalmic applications remains challenging and clinical trials are still lacking. In addition to short-term clinical studies, it is important to evaluate the long-term efficacy and safety of the application of various dosage forms of melatonin in the treatment of fundus degenerative diseases.

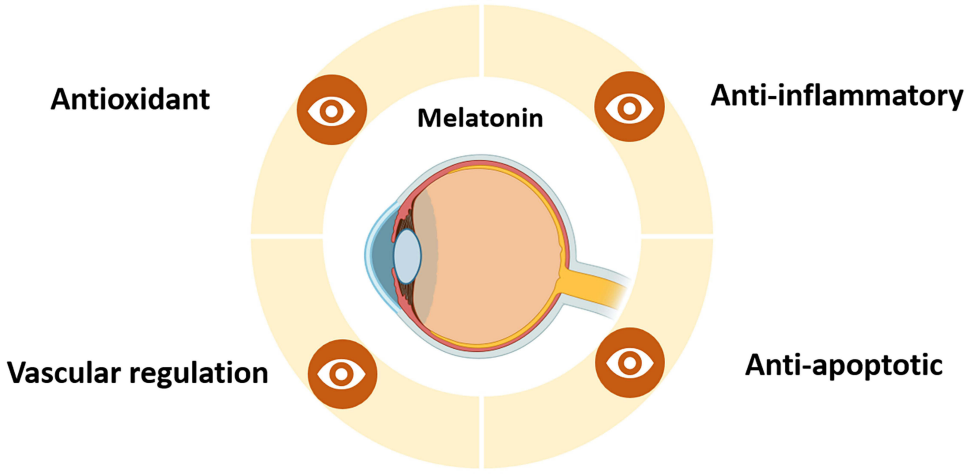

Figure 4 Melatonin is primarily responsible for fundus degeneration.

Conclusion

Melatonin exhibits diverse mechanisms of action and therapeutic potential in managing fundus degenerative diseases (Figure 4). Clinical and laboratory research underscores its role in modulating vasomotor function, maintaining fundus vasculature, and mitigating complications like fundus hemorrhage through anti-angiogenic and anti-inflammatory effects. Melatonin's antioxidant properties neutralize free radicals, reduce oxidative stress, and protect retinal cells from apoptosis, promoting cell survival, repair, and normal turnover in retinal tissue. Despite these promising findings, further research is essential to optimize melatonin's clinical application. Long-term studies are crucial for evaluating its efficacy, safety, and individualized treatment approaches tailored to genetic predispositions, age, and health status. Comprehensive understanding of melatonin's molecular mechanisms in fundus degenerative diseases will inform clinical practice and guide development of optimized drug delivery systems. Continued exploration of melatonin's therapeutic potential and refinement of delivery systems represent promising avenues for advancing treatment outcomes in ocular diseases.

Funding

This study is funded by the Joint construction project of Henan Medical Science and technology (LHGJ20220370) and Natural Science Foundation of Henan (232300420237).

Disclosure

The authors report no conflicts of interest in this work.

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