# Melatonin and melanopsin in the eye: friends or foes?

**Title in Spanish:** *Melatonina y melanopsina en el ojo: ¿amigos o enemigos?*

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**ABSTRACT:** Melatonin is a neurohormone synthesized in several ocular structures apart from its original source, the pineal gland. It is of great importance in several functions such as maintaining a healthy values of intraocular pressure. Moreover, it decreases intraocular pressure in the case of glaucoma. This nuerohormone is controlled by the activation of a photopigment responible for non-image forming tasks in the eye, this photopigment is Melanopsin, present in a subclass of retinal ganglion cells, and very recently, it was discovered in different ocular structures. When Melanopsin is activated by the short wavelength component of light, it supresses Melatonin synthesis. This action is controlled mainly by light could affect several functions including the regulation of intraocular pressure. In this sense, the present work highlights the history and importance of the relationship between both Melatonin and Melanopsin to maintain a healthy ocular homeostasis.

**RESUMEN:** La Melatonina es una neurohormona sintetizada en varias estructuras oculares, aparte de su fuente original, la glándula pineal. Es de gran importancia por varias funciones, como el mantenimiento de valores saludables de presión intraocular. Además, disminuye la presión intraocular en el caso de glaucoma. Esta nuerohormona se controla mediante la activación de un fotopigmento responsable de las tareas no relacionada con la formación de imágenes en el ojo, este fotopigmento es la Melanopsina, presente en una subclase de células ganglionares de la retina y, muy recientemente, se descubrió en diferentes estructuras oculares. Cuando la melanopsina se activa por el componente de longitud de onda corta de la luz, suprime la síntesis de melatonina. Esta acción está controlada principalmente por la luz que podría afectar varias funciones, incluida la regulación de la presión intraocular. En este sentido, el presente trabajo destaca la historia y la importancia de la relación entre la melatonina y la melanopsina para mantener una homeostasis ocular saludable.

## 1. INTRODUCTION

When someone mention the eye to a professional in this field, the first thing that comes to mind is vision, and ocular pathologies which can lead to blindness. All the possible ocular diseases starting from the tear-film until the retina, could result in either reversible or irreversible blindness. However, the ocular organ exceeds this very important function, and it is rather a window for both out- and inside of the body. It is the organ which permits us to capture the daylight and all the information about the time of the day, and it is the first vehicle for photo-entrainment.

In order to accomplish the function of photo-entrainment, the ocular organ contains a small number of cells laying in the inner retina, which comprise a photopigment named melanopsin (1). This photopigment is responsible of capturing light and passing its signals through a series of chemical reactions to several brain regions, until it reaches the pineal gland, where it suppresses melatonin synthesis (2).

With modern life, and the use of artificial light instead of depending on daylight, a serious debate was generated regarding the risk of light pollution. Melanopsin containing retinal ganglion cells receives confusing signals and it is activated when light is switched on at night; hence disrupting the circadian rhythm and leading to serious health issues as a consequence of suppressing melatonin synthesis (3).

Melatonin (N-acetyl-5-methoxytryptamine) is a neurohormone classically known to be produced by the pineal gland (4). This hormone is considered the chemical expression of darkness, because of its role in regulating the circadian rhythm. Melatonin levels raise during the night and its levels are lower at daytime, hence, it is the natural sleep aid our body has (5). However, from the moment this hormone was discovered and characterized, numerous researchers investigated it, and they detected its presence not only by the blood stream, but also because it is synthesized in several organs and cells (6).

Several studies indicated the pharmacological effect of melatonin in the eye, moreover, the eye is a very special organ since it synthesizes this hormone and comprises its local machinery giving that several ocular structures are able to produce it. For instance, melatonin synthesizing enzymes were found first in the retina (7), then it was shown to be present in the iris, ciliary body, crystalline lens, and the harderian gland (8-10). Furthermore, studies confirmed its multitasking characteristics, exceeding the classical and once thought to be the only function of regulating the circadian rhythm (11).

An interesting observation about melatonin and the physiology of the eye is the synchronization between melatonin levels and the intraocular pressure, where the later reaches its lowest levels at night while melatonin is at the highest (12, 13). Intraocular pressure is one of main factors in maintaining our ocular system healthy, since its elevation could lead to the second leading cause of blindness worldwide, glaucoma disease (14).

Glaucoma is defined as a heterogenous group of progressive disorders characterized by optic neuropathy and retinal ganglion cell death (15). Many risk factors are involved in the development of this disease, such as the age, gender, genetics, intraocular pressure (IOP), and ethnicity. For instance, glaucoma cases accounts 8% of all blindness worldwide, but this percentage raise to 15% in African population (16). Glaucoma lacks primary symptoms and it leads gradually to a loss of the peripheral vision, as it is an under-diagnosed disease (17). In all the cases, intraocular pressure is the only risk factor which can be controlled in order to slow the progression of glaucoma. A variety of glaucoma medication are currently in use, and all of them function in order to keep IOP within healthy and normal limits (18).

In the current review, light will be shed on melatonin in the eye with a special focus on glaucoma disease. Also, melanopsin role in regulating melatonin levels within the eye and its signalling pathways will be discussed.

## 2. MELATONIN HISTORY AND SYNTHESIS

The history of melatonin goes back to many cultures and ages, by the reason of the pineal gland´s shape and location, and before being conscious about the neurohormone itself. For instance, in the greek culture, the pineal gland was given this name because it is shaped similar to the pine nut (19), and in the pharaonic Egypt, the pineal was considered the eye of Horus. Another speculation by the Hindu, describing the pineal gland as the third eye for spiritual enlightenment (20). However, one of the most remarkable historical definition of this curious gland was by the philosopher Descartes (1594–1650), where he described the pineal gland as the seat of the soul and the region where our thoughts were formed (21).

The pineal gland gained its importance through history, until 1958, when the dermatologist Aaron Lerner was looking for a cure for vitiligo, and he discovered the hormone secreted by this gland, melatonin (4). Therefore, this hormone was given the name melatonin as "mela" from melanin and "toni" from serotonin (4).

Melatonin is first synthesized from tryptophan which is converted into serotonin (22). Certain amount of this hormone goes through acetylation by the first enzyme in melatonin synthesis, arylalkymine N-acetyltransferase (AANAT), to get N-acetylserotonin (NAS), which in turn is converted to melatonin with the help of the last enzyme involved in this process, hydroxyindole O-methyltransferase (HIOMT), which catalyses the O-methylation of NAS by S-adenosyl methionine to form melatonin (Fig.1) (23). Several studies haves indicated the importance of AANAT enzyme in the process of melatonin synthesis, and it is named the Timezyme, since its activity increases up to 100-fold at night, thus it is considered a key in regulating melatonin levels (24, 25).

As commented in the introduction, melatonin was found to be produced by several ocular structures. But more importantly, in 1984 the synthesis of melatonin in the eye has gained additional interest after some experiments done in white leghorn cockerels, when Rohde and collaborators performed a pinealectomy procedure and then measured melatonin in several structures in the eye. Two important discoveries were made from this work, first, melatonin was measured in the retina, iris, and ciliary body resulted similar to the control. And second, melatonin concentration in the studied structures followed the same pattern as the pineal gland, raising during the night and decreasing at daylight (26).
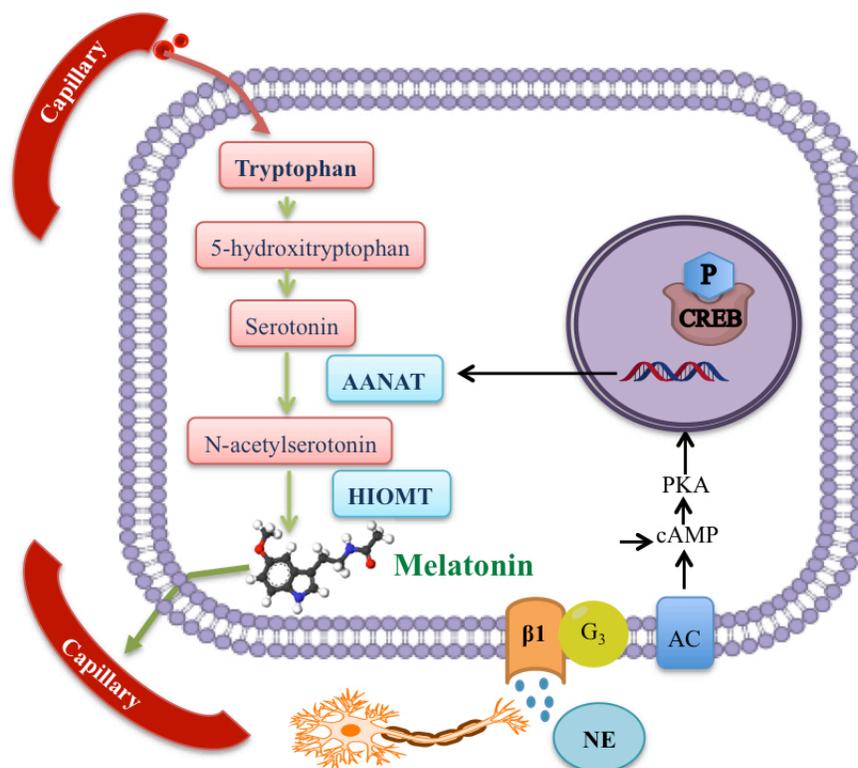
**Figure 1.** Diagramatic resprestentation of melatonin synthesis in the pineal gland. Starting from tryptophan in the blood stream, which is converted into serotonin. The rise in AANAT activity results in an increase in the intracellular concentration of N-acetylserotonin which is further converted to melatonin by hydroxyindole-O-methyltransferase (modified from Klein, 1974). AANAT, arylalkylamine *N*-acetyltransferase; AC, adenylate cyclase; HIOMT, hydroxyindole-*O*-methyltransferase; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element-binding protein;NAS, N-acetyl 5-methoxytryptamine; NE, norepinephrine; PKA, protein kinase A.

## 2.1. Melatonin receptors and functions

Melatonin has the ability to function through its receptors, but also it have direct actions as a free radical scavenger. Melatonin have two cloned and characterized membrane receptors in mammals, $MT_1$ and $MT_2$. A putative *MT₃* was suggested by several authors, and in some cases it was claimed to belong to the quinone reductase family, specifically, quinone reductase 2 (NQO2) (27, 28), although in other studies using different species through silencing this enzyme, melatonin still had functional properties (29).

Melatonin receptors signalling pathways were extensively studied. In a canonical way, $MT_1$ and $MT_2$ stimulation would lead to adenylate cyclase (AC) inactivation in a Gαi subunit process of the G protein coupled to the membrane receptor (30). When AC is inactivated, it would lead to a decrease in intracellular cAMP concentration, and finally a decrease in activated protein kinase A (PKA). The action of these receptors has been shown to inhibit forskolin-induced cAMP formation (31). However, melatonin receptors are also able to couple to different subtypes of G protein (32). Therefore the mentioned classical signal transduction is not the case in all cells and models, melatonin receptors activation also could lead to different intracellular signalling. For instance, some studies showed that $MT_1$ receptor activation would activate phospholipase C-α (PLC-α) pathway (33); While $MT_2$ receptor, in addition to classical inhibition of AC, has been described in inhibition processes of the enzyme guanylate cyclase (GC) (Fig. 2) (34).
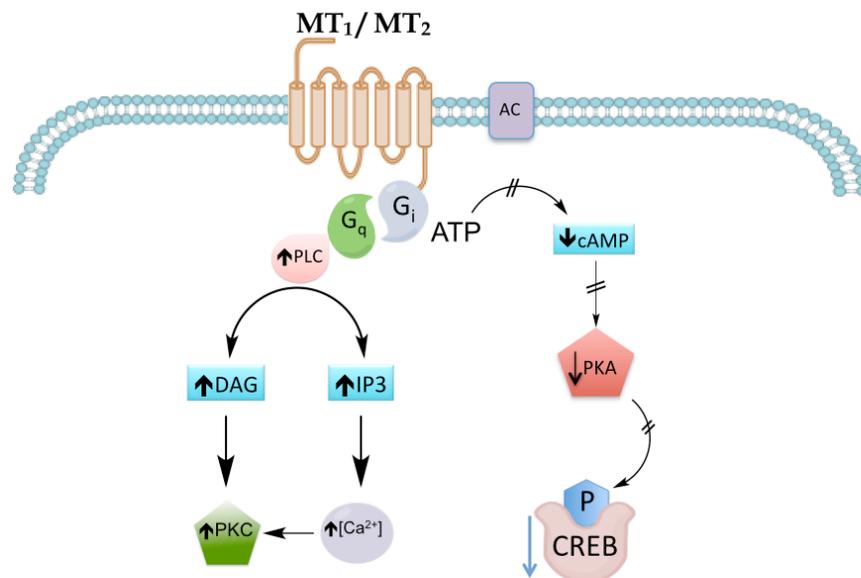
**Figure 2.** Scheme showing membrane signalling by melatonin receptors $MT_1$ and $MT_2$, both G-protein coupled receptors. On the right is shown the interaction of $G_i$ with adenyl cyclase (AC) to decrease cAMP levels and therefore cyclic AMP-dependent protein kinase activity (PKA). On the left is shown the interaction of $G_q$ with phospholipase C (PLC) leading to the cleavage of phosphatidyl inositol diphosphate (PIP2) into inositol triphosphate (IP3) and diacylglycerol (DAG). These second messengers stimulate increased intracellular Ca2+ and protein kinase C (PKC), respectively. The downstream effects of these events at the membrane vary with cell type.

## 2.2. Melatonin and glaucoma

One of the most important risk factors for developing glaucoma disease in elevated intraocular pressure. Intraocular pressure consists of an equilibrium between the formation of the aqueous humor in the ciliary process and its drainage by the trabecular meshwork and the to some extent, the uveoscleral pathway (35, 36).

The aqueous humor composed mainly of water and electrolytes to complete one of its functions apart from regulating IOP, to provide nutrients to the avascular structures bathe in it (37). Aqueous humor also contains melatonin, which also plays an important role in regulating IOP. Melatonin content in the aqueous humor originates from both the ciliary processes and the crystalline lens. In this sense, both exogenous and endogenous melatonin has been extensively investigated.

Before coming into the interesting relationship between melatonin and melanopsin, it is worthy to explain the role melatonin have over IOP when applied or consumed exogenously. Melatonin consumption prior to cataract surgery showed a positive effect on the post-operative outcome and it reduced IOP (38). Moreover, melatonin and its analogue agomelatine showed an ocular hypotensive effect when applied topically to a normotensive and hypertensive model of New Zealand white rabbits (39) as well as in a glaucomatous animal model (40), same effect observed after oral consumption of agomelatine in human glaucoma patients (41). This effect of reducing IOP is mediated by melatonin receptors, since it triggers cAMP production and consequently inhibits chloride efflux in the ciliary processes, hence reduces aqueous humor production (42). Different studies

used mice lacking melatonin receptor 1 showed that they suffered from elevated intraocular pressure and retinal ganglion cells death, both signs for developing glaucoma (43). Beside that effect, melatonin is known also as a free radical scavenger, it functions as an oxidative stress and it was shown to have a protective effect against retinal cells death by reducing the damage produced by oxidative stress (44, 45).

All of the mentioned studies used melatonin as an external pharmacological agent, however, melatonin content in the aqueous humor without any exogenous addition is not equal among all subjects. Analysis showed that certain conditions could lead to changes in melatonin levels in the aqueous humor. For instance, patients with elevated intraocular pressure have higher levels of melatonin in the aqueous humor. These results are in parallel to the analysis of melatonin levels in a mice model of glaucoma, both before and after developing the disease, and in comparison to the control healthy mice (46). These results were not only observed in the aqueous humor, but also seen in the serum melatonin level, were glaucoma patients had a significant increment of melatonin in blood compared to healthy patients (47). Human donor eyes were examined by immunohystochemistry assay against melatonin synthesizing enzyme AANAT, in both glaucomatous donors and healthy eyes, demonstrated an increased staining of AANAT in the ciliary body of glaucoma donors (48). In order to investigate these results, in vitro studies took place using immortalized human non-pigmented ciliary body epithelial cells. To mimic the elevation of intraocular pressure, a vanilloid channel belonging to to the superfamily of TRPs present in these

cells, the TRPV4 channel was stimulated since this protein is sensitive to mechanical pressure. The activation of this channel leaded to and increment of both melatonin levels extracellularly and an increase in the expression of the protein AANAT (48, 49). Other studies showed that the activation of this channel has a short term effect when activated, similar to a sudden increase of IOP, where it phosphorylate the enzyme AANAT, hence protecting it from degradation and leading to an increment of melatonin (50, 51). TRPV4 was silenced in the non-pigmented ciliary body epithelial cells to confirm the effect of melatonin increment, confirming the importance of this channel in regulating melatonin synthesis in the ciliary processes (52). This difference in melatonin levels in the aqueous humor was also reported for other diseases. A study analyzing melatonin levels in patients with proliferative diabetic retinopathy showed that those patients had a significant increase of melatonin in the aqueous humor compared to healthy subjects, and interestingly, this increment was not seen in serum samples taken from the same patients. This indicates that melatonin synthesis is increased in the eye only and its origin is not the circulating melatonin from the pineal gland (53). In fact, in a different study, melatonin decreased in blood serum of patients with type 2 diabetes with cardiac autonomic neuropathy (54), also urinary 6-sulfatoxymelatonin level in were found lower in patients with diabetic retinopathy with type 2 diabetes (55).

All the mentioned studies are evidence of a possible melatonin modification or changes in the eye due to ocular diseases. However, a different perspective of melatonin regulation has rose due to a public serious issue; light pollution. Light at night is currently associated to several pathologies, and it is considered as a possible risk factor to develop many diseases, starting from obesity to a more serious pathologies such as cancer (56, 57). Light can disrupt the circadian rhythm and when it activates the non-image forming photoreceptor situated in a small number of the retinal ganglion cells, melanopsin: It directly projects its signals to the pineal gland to shut-off melatonin synthesis, and it is associated directly or indirectly to a wide range of pathologies (58).

## 3. MELANOPSIN, THE HIDDEN RECEPTOR IN OUR EYES

In the 1920s, a Harvard university graduate student, Clyde Keeler, discovered that blind mice due to rod and cone dystrophy, can still respond to ambient light by pupil constriction, and moreover, they conserved their ability for photo-entrainment (59). This was the first evidence of the presence of a different photoreceptor in the eye, however, since the retina is an extensively studied tissue, with all its layers, rods and cones were the only photoreceptors recognized by scientists for decades after Keeler´s

observation. Nonetheless, all posterior studies confirmed that the eyes are essential as the primary source of light information for photo-entrainment, and eye loss in mammals abolishes this characteristic (60).

Decades after Keeler´s discovery, in 2000, the scientist Provencio identified a small subclass of retinal ganglion cells which are photosensitive. This is because they contain a photopigment, melanopsin, sensitive to short wave length content of light (corresponding to blue light) (1). In fact, this photoreceptor was identified earlier in dermal melanophores, eye, and the brain of *Xenopus laevis*, but it was not found in extra-ocular regions in mammals (61). This discovery explained the reason why rodless and coneless eyes can still react to light.

Interestingly, this photopigment have different characteristics than ones found in mammals. For instance, it presents greater homology to invertebrate opsin than those of vertebrate; melanopsin in mammals belongs to the rhabdomeric receptors unlike the ciliary receptors in rods and cones (62). Moreover, this photoreceptor depolarize in reaction to light, whereas rods and cone hyperpolarize. Moreover studies using pharmacological approaches suggested the biochemical phototransduction cascade to be similar to invertebrate rhabdomeric photoreceptors acting through $G_q$ protein coupled opsin (63). After light stimulation, the photopigment of the intrinsically photosensitive retinal ganglion cells (ipRGC) triggers signalling, presumably, through Gq/11-class G-superfamily, which in turn activates a phospholipase C (PLC) (Fig. 3), provoking the hydrolysis of phosphatidylinositol 4,5-bisphosphate (PI(4,5)P2) in the membrane generating inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG) and the later increase in cytoplasmic $Ca^{2+}$ and ultimately causing membrane depolarization. Furthermore, the participation of TRP and TRPL channels, the $Ca^{2+}$-permeable light-sensitive channels, made clear since treatments with a $Ca^{2+}$ chelator or a TRP channel blocker were able to reduce the light effect. Treating chicken primary retinal ganglion cells (RGCs) cultures with PLC inhibitors abolished the light-suppressive effect on ^{3}H-melatonin synthesis. These findings demonstrated the chemical components of the phototransduction cascade operating in vertebrate embryonic RGCs is involving a Gq-protein (64-66).

When light reaches the inner retina and activate melanopsin containing ganglion cells, signals passes to different regions than the image forming pathway. They travel from the retina through the retinohypothalamic tract to the suprachiasmatic nucleus (SCN) and to the cervical superior ganglion and the pineal gland where light signals suppresses melatonin synthesis (Fig. 3) (67).
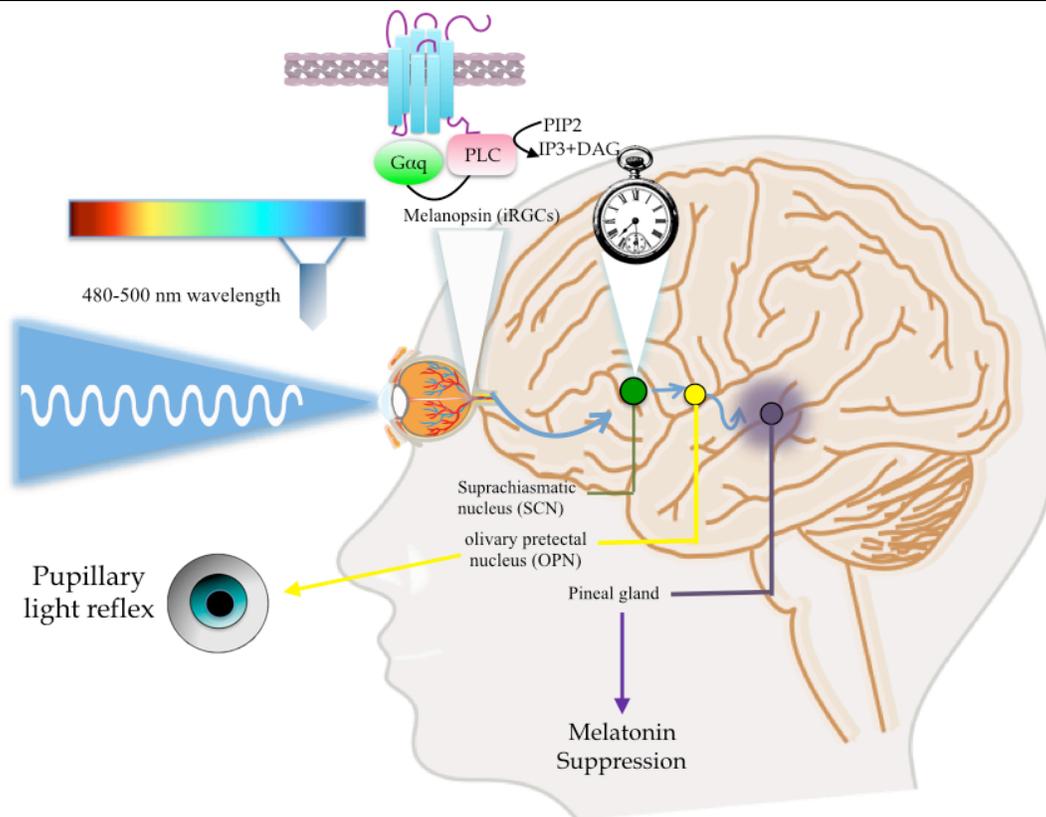
**Figure 3.** Scheme of melanopsin pathway through retinal iRGCs to the suprachiasmatic nucleus for photoentrainment, reaching the paraventricular nucleus where it participate in pupillary light reflex. Finally signals reachs the pineal gland where melatonin synthesis is inhibited/activated by the intracellular pathway shown at the bottom of the photo.

It is fascinating to think that the eye has much more functions other than image forming vision, and it participates in several physiological roles. In fact, being the first vehicle in regulating the circadian rhythm is of great importance since numerous biological activities follows a circadian manner (68). For instance, several evidence showed that fully blind humans with no light perception suffers from desynchronized circadian processes due to a lack of light input. This leaded to alteration of the pattern of alertness, mood, performance, alteration of core body temperature; which interferes with their social and professional lives even more seriously than the fact of being blind (67, 69).

Very recently, melanopsin was detected in other ocular structures than the retina, it was found to be present in the crystalline lens as well as in the cornea (70, 71). Experiments showed that human epithelial crystalline lens reacts differently under light and darkness conditions, melatonin synthesizing enzyme AANAT as well as melatonin levels significantly increased when cells were submitted to total darkness compared to white light. Moreover, experiments done under different wave lengths showed that melatonin was suppressed in response to blue light, corresponding to an action mediated by melanopsin. This action was through phospholipase C (PLC) pathway, similar to melanopsin containing retinal ganglion cells (70). In the cornea, melanopsin expression was detected in

the epithelium and near the endothelial surface. Surprisingly, experiments showed no light response in the mentioned study, suggesting a different sensory role for melanopsin in the cornea (71). Although the trigeminal ganglia in the source of most corneal nerve fibers, a different study showed that melanopsin is also expressed in the trigeminal ganglion neurons, and that it responded to light. This is specially interesting since these neurons are a classic pain sensory cells and the ability for light to cause pain is paradoxical, besides the fact that fiber endings in the cornea are specialized to respond to pressure, temperature, and caspaicin. All these findings together opens a new possible role for melanopsin in the cornea (72).

*3.1. The impact of melanopsin activation over melatonin synthesis: timing is everything*

One of the most fascinating facts about melanopsin is its unconscious response to light. Light is an ancient prehistorical phenomena which exists before any living being. Throughout the history, sun light have been a subject of amusement. In numerous cultures and societies sun light was considered as a source of life and nourishment, for example, ancient Egyptians were the first to report beneficial properties from sun exposure 6000 years ago was reported. The Chinese introduced the art of morning sun gaze, and exercises such as yoga or tai chi has strong ties to sunlight (73). These potential benefits of sun

exposure were translated to the western world during the 18th century, when light therapy was introduced for *lupus vulgaris* treatment; a discovery by Niels Finsen (1860-1904) who was awarded the Nobel Prize in Medicine and Physiology (74, 75).

Apart from sunlight, humans have come up with numerous ways to create artificial light along the history. From around 500,000 years ago, evidence showed that *Homo erectus* started to use fire light in caves. In Greece, bronze lamps were used around 700 B.C (76). Until the nineteenth century, the commonly used artificial light was the wax candle, which in comparison to the current lighting, wax candles had very low intensities and low color temperature; hence they produced a very little effect on the circadian system (77). In 1801, Humphrey Davey discovered the incandescence of an energized conductor, a process put in use by Joseph Swan and Thomas Alva Edison developed the incandescent light bulb (78). Nowadays, electricity has proliferated all around the world, because of its increased efficiency and reduced costs. As a result, in the current modern life, homes and work places lack the complete dark nights, indeed, 2/3 of the population in Europe usually experience nights brighter than under a full moon (79). In addition to all, sine the 1960s, artificial lighting has improved to higher intensities, and they mainly contain short wave length light, correspondent to blue light. The exact wave length which is able to activate melanopsin, and hence alter the natural circadian cycle, leading to some serious pathophysiological consequences (77).

Although light has proven benefits, and melanopsin activation by the blue component of either artificial or sunlight is crucial for the whole circadian system, however, studies has shown that timing is very important, and light at night, leading to melanopsin activation and, as a consequence, melatonin suppression, is harmful in many levels. The first evidence of the damaging effect the circadian disruption has, is demonstrated with jet lag; a condition resulted from rapid travel across multiple time zones, resulting in rhythm desynchronization, depressed mood, gastrointestinal complaints and cardiovascular problems (80). Another relevant condition is shift work, a condition affecting around 20% of workers in Europe and the US. Epidemiological studies linked shift-workers to increased risk of developing breast, prostate, colorectal, and endometrial cancers (81-83). All studies highlighting the problem of chronodisruption because of the exposure to artificial light at night resulting in melatonin suppression (77). From the other hand, Can some ocular diseases affect the expression of melanopsin? Hence, can it affect our ability to synchronize the circadian rhythm?

Interesting studies indicated that melanopsin is among the first developing photosensitive cells in the mammalian retina (84), moreover, experiments in mice has proven their ability to detect light during embryonic stages (85). However, although they develop first, they have a longer period of proliferation and may be some of the last retinal neurons to die in the course of an organism's lifetime.

They are considered atypical central nervous system neurons, acting both as photoreceptors responding directly to environmental stimuli, as well as standard neurons integrating synaptic input and generating action potentials (86-88). Many studies have raised awareness towards these cells being resistant or less vulnerable to damage and disease compared to conventional RGCs. For instance, studies in some rodent glaucoma model examined the sparing of ipRGCs, suggesting that IOP threshold to damage these cells is much higher than it is in conventional RGCs (86). Different studies indicate melanopsin resistance to damage in optic nerve damage in inherited optic neuropathy, as well as studies indicating that these cells may be resistant to glutamate-induced excitotoxicity (87-90). Little is known about the cellular and molecular mechanisms that provide neuroprotection to these RGCs, however, it appears that along the development of glaucoma, melanopsin cells come to their fate. Different studies showed that melanopsin expressing ganglion cells deteriorated with ocular diseases, resulting in unfavorable outcomes, for example, a study to evaluate melanopsin response in patients with retinitis pigmentosa showed that blue light had a better effect over pupillary response in comparison to red light, however, the effect of short wave length was proportional to the ERG abnormality; patients with non-recordable ERG had significantly reduced response to melanopsin mediated effect "blue light" (91). Another study of melanopsin function in patients with glaucoma demonstrated that melanopsin could be used as an indicator of the progression of this disease, based on clinical evidence that showed that subjects with moderate and severe glaucoma had dysfunctional melanopsin mediated pupillary response in comparison to patients with early stage glaucoma (92). This study supports the facts that melanopsin containing retinal ganglion cells are more resisting to stress during the development of ocular pathologies, moreover, suggesting it as a biomarker to follow up the progressive deterioration noted in glaucoma patients.

### 3.2. Light, melanopsin, and melatonin: possible therapeutical approach

Very recently, an article published by Jesús Pintor was introducing the concept of pharmacology without drugs (93). In this article, the scientist made the following statement: " *Receptor-drug interaction is necessary to obtain a given effect; nevertheless, in some cases, instead of using a chemical messenger or drug it is possible to play with something that surrounds us: light*". In fact, the blue component of light is the specific agonist for melanopsin receptor, hence, stimulating or inhibiting this receptor could be achieved by means of switching the lights off and/or. This suggestion is based on some published evidence, for instance, in vivo experiments on New Zealand white rabbits showed that light triggered ATP release in the aqueous humor (94). As the crystalline lens is the richest structure in ATP compared to the whole body, it have an important role in the lens by keeping all the active transporters working besides its protective effect

over the retina by absorbing the harmful UV light (95). Also, ATP release in the aqueous humor would activate P2X receptors in the ciliary body which leads to IOP decrease; in other words, this could be a method of controlling IOP (96). Another study supporting this suggestion was mentioned previously (for more details, see section 2.), where crystalline lens cells responded variably under different light conditions in terms of melatonin synthesis, another important natural component in regulating IOP (70).

Another striking fact about melanopsin in the retinal ganglion cells is that light conditions not only regulate its response, but also it regulates melanopsin expression itself. Experiments showed that melanopsin, in addition of being a key participant in photo-entrainment, its expression is also controlled by light conditions, and it increases significantly at night (97). The mechanism and functional implication of the changes of melanopsin expression are still unclear, however, this could explain the higher sensitivity children face when they suffer light at night, based on a study showed that melatonin suppression in children is more sensitive that adults due to light at night (98).

As new discoveries are emerging since the discovery of melanopsin, the mutual relationship between both melanopsin and melatonin in the control of ocular physiology is becoming obvious., though more studies are necessary. Indications propose that melatonin may directly modulate the activity of melanopsin containing retinal ganglion cells as these cells express melatonin receptors (99), however most studies are speculative and the actual answer is still unclear.

## 4. CONCLUSION

Melatonin and melanopsin tight bond is out of doubts, and light could become a new era of ocular pharmacology. In this sense, the current review highlighted the most recent discoveries in the eye and ocular pathologies with a special interest over glaucoma disease, being the second leading cause of blindness and giving its complexity in term of the effect of aqueous humor dynamics leading to retinal cells death and the positive effect of melatonin over regulating IOP. Melanopsin presence and activation is crucial during the day to favor melatonin production at night, however, modern life and artificial light are an important factor for harmony between both melatonin and melanopsin.

### Abreviations:

IOP: Intraocular Pressure.
AANAT: Aralalkymine N-acetyltransferase.
NAS: N-acetylserotonin.
HIOMT: Hydroxyindole O-methyltransferase.
$MT_{1-2}$: Melatonin receptor 1, 2
NQO2: Quinone reductase 2.
AC: Adenylate cyclase.
cAMP: Cyclic adenosine mono- phosphate
PKA: Protein kinase A.

PLC: Phospholipase C.
GC: guanylate cyclase.
TRP: Transient Receptor Potential Ion Channels.
TRPV4: Transient Receptor Potential vanilloid Channel 4.
ipRGC: Intrinsically photosensitive retinal ganglion cells.
PI(4,5)P2: Phosphatidylinositol 4,5-bisphosphate.
IP3: Inositol 1,4,5-triphosphate
DAG: Diacylglycerol.
SCN: Suprachiasmatic nucleus.
ERG: Electroretinogram.
ATP: Adenisine triphosphate
UV: Ultraviolet

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