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Melatonin: An Underappreciated Player in Retinal Physiology and Pathophysiology

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Abstract

In the vertebrate retina, melatonin is synthesized by the photoreceptors with high levels of melatonin at night and lower levels during the day. Melatonin exerts its influence by interacting with a family of G-protein-coupled receptors that are negatively coupled with adenylyl cyclase. Melatonin receptors belonging to the subtypes MT_1 and MT_2 have been identified in the mammalian retina. MT_1 and MT_2 receptors are found in all layers of the neural retina and in the retinal pigmented epithelium. Melatonin in the eye is believed to be involved in the modulation of many important retinal functions; it can modulate the electroretinogram (ERG), and administration of exogenous melatonin increases light-induced photoreceptor degeneration. Melatonin may also have protective effects on retinal pigment epithelial cells, photoreceptors and ganglion cells. A series of studies have implicated melatonin in the pathogenesis of age-related macular degeneration, and melatonin administration may represent a useful approach to prevent and treat glaucoma. Melatonin is used by millions of people around the world to retard aging, improve sleep performance, mitigate jet lag symptoms, and treat depression. Administration of exogenous melatonin at night may also be beneficial for ocular health, but additional investigation is needed to establish its potential.

Introduction

Melatonin is a neurohormone that plays important roles in the temporal regulation of many aspects of physiology (review in: Wiechmann and Summers, 2008). Accumulating evidence indicates that melatonin plays important roles in retinal physiology and pathophysiology. However, the mechanisms by which melatonin can affect the physiology and pathophysiology of the retina are not well defined. This lack of data is partially due to the fact that the vast majority of mouse strains are genetically incapable of synthesizing melatonin (see Goto et al., 1989, Tosini and Menaker, 1998) and therefore this important animal model has not been used to dissect the action and the mechanisms by which melatonin can influence retinal functions. Our laboratories have recently developed transgenic mice on a melatonin-proficient background (C3H-f+/+) in which melatonin receptors have been genetically removed. These new models are providing important clues on the mechanisms by which melatonin affects retinal function. The aim of this review is to

summarize the current literature on the role that melatonin plays in vertebrate retinal physiology.

Regulation of Melatonin Synthesis and Metabolism

Melatonin is synthesized in the retina of many vertebrate species (from lamprey to mammals) via a well-defined biosynthetic pathway (Tosini and Meanker, 1996; Menaker et al., 1997). Melatonin synthesis starts with the uptake of the amino acid tryptophan from the blood. Tryptophan is converted to melatonin by a series of enzymatic reactions producing serotonin and *N*-acetylserotonin as important intermediates (Figure 1). In the retina, melatonin is almost exclusively produced by the photoreceptors cells (Cahill and Besharse, 1993; Liu et al., 2004) and under some pathological conditions by other retinal cell types (Sakamoto et al., 2004). In addition, it has been reported that melatonin can also be produced – in smaller amounts - by ganglion cells in the chicken retina (Garbarino-Pico et al., 2004). Once produced, melatonin is not stored but freely diffuses out of the cells. The amount of melatonin produced by the retina is small compared to that in the pineal gland, the primary source of circulating melatonin, and retinal melatonin is thought to act as a local neuromodulator within the eye. However, in a few instances (e.g., quails) retinal melatonin may contribute to the levels of the hormone in the blood (Underwood et al., 1984). In most vertebrate species, retinal melatonin synthesis and levels are high during the night and low during the day (reviewed in: Tosini et al., 2008); however, in a few species (i.e., trout and European sea bass) retinal melatonin levels are high during the daytime (Iigo et al., 1997; Besseau et al., 2006). In the vast majority of the species investigated thus far melatonin synthesis in the retina is under control of retinal circadian clocks since the retinae of fish, amphibians, reptiles, birds and mammals synthesize melatonin in the rhythmic fashion when they are maintained in vitro under constant darkness (reviewed in: Iuvone et al., 2005). In many species, the retinal clock that controls melatonin synthesis appears to be in photoreceptor cells. In *Xenopus*, chicken and rat, rhythmic melatonin synthesis persists in retinae in which the inner retina has been destroyed (Cahill and Besharse, 1993; Zawilska and Iuvone, 1992; Thomas et al., 1993; Sakamoto et al., 2006; Tosini et al., 2007). In addition, melatonin synthesis and clock gene expression are rhythmic in monolayer cultures of embryonic chick photoreceptors (Chaurasia et al., 2006a).

The key regulatory step in melatonin synthesis is catalyzed by arylalkylamine *N*-acetyltransferase (AANAT), which converts serotonin to *N*-acetylserotonin. AANAT is subject to both transcriptional and posttranslational regulation (Iuvone et al., 2005, Figure 2). The control of the transcription of the *Aanat* gene in photoreceptors is under direct control of the circadian clock (Chen and Baler, 2000) and is independent from suprachiasmatic nuclei (SCN) of the hypothalamus, the master circadian clock. *Aanat* mRNA rhythmicity in retinal photoreceptors persists after the SCN has been lesioned (Sakamoto et al., 2000) and in cultured photoreceptor cells (Chaurasia et al., 2006a). The chicken and rat *Aanat* genes contain circadian E-box enhancer elements in their promoters that are directly activated by the Bmal1/Clock and Bmal1/NPAS2 heterodimers (Chen and Baler, 2000; Chong et al., 2000; Haque et al., 2010). Thus, *Aanat* is considered to be a clock-controlled gene. The *Aanat* promoter also contains cyclic AMP-response elements that contribute to the circadian expression of the gene (Baler et al., 1997; Baler et al., 1999; Haque et al., 2011)

AANAT is also subject to posttranslational regulation (Fig. 2). Retinal AANAT is phosphorylated at night (Pozdeyev et al., 2006). Phosphorylation of AANAT promotes its binding to 14:3:3 proteins, which stabilizes and activates the enzyme (Ganguly et al., 2001; Obsil et al., 2001; Pozdeyev et al., 2006). This process is regulated by the retinal circadian clock by controlling the circadian expression of *Adcy1*, which encodes the type 1 Ca^{2+}/

calmodulin-stimulated adenylyl cyclase (AC1) (Fukuhara et al., 2004; Chaurasia et al., 2006b). The rhythm in AC1 in turn generates circadian rhythms of cyclic AMP and PKA-dependent phosphorylation of AANAT (Ivanova and Iuvone, 2003; Fukuhara et al., 2004; Chaurasia et al., 2006b).

Post-translational mechanisms ensure that melatonin levels are maintained at extremely low levels in presence of light. For example, AANAT activity is abolished in animals maintained in constant light (Nowak et al., 1989) and light exposure in the middle of the night induces a very rapid decrease in AANAT activity in the pineal gland and retina (Klein et al., 1997; Hamm et al., 1983). Light exposure rapidly decreases cAMP levels in photoreceptor cells (Orr et al., 1976; DeVries et al., 1978; Nir et al., 2002; Ivanova and Iuvone, 2003) and promotes the dephosphorylation of AANAT, its dissociation from 14–3–3, and its degradation by proteasomal proteolysis (Fukuhara et al., 2001; Iuvone et al., 2002; Pozdeyev et al., 2006). This effect of light appears to be partially a direct effect on photoreceptor cells, combined with an effect of dopamine. Dopamine is released from amacrine and interplexi form cells in response to light and acts on dopamine D4 receptors on the photoreceptor cells to further suppress cyclic AMP synthesis and Ca^{2+} levels and to inhibit melatonin biosynthesis (Cohen et al., 1992; Zawilska et al., 1994; Tosini and Dirden, 2000; Nir et al., 2002; Ivanova et al., 2008). Such tight control of retinal melatonin levels suggests that high melatonin levels during the light-phase may be deleterious for the photoreceptor cells (Wiechmann and O'Steen, 1992; Sugarawa et al., 1998).

Melatonin biosynthesis is also regulated by circadian control of tryptophan hydroxylase, which converts tryptophan to 5-hydroxytrptophan (5HTP). *Tph* mRNA, the transcript that encodes tryptophan hydroxylase, is expressed in a circadian fashion in the retinas of many species, including *Xenopus laevis*, chicken, and rat (Green et al., 1994, 1995; Chong et al., 1998; Liang et al., 2004), and tryptphan hydroxylase activity and AANAT activity show similar daily rhythms (Thomas and Iuvone, 1991; Valenciano et al., 1999; Iuvone et al., 1999). Tryptophan hydroxylase activity may be rate limiting for melatonin biosynthesis at night in darkness, as exogenous 5HTP enhances melatonin synthesis in *Xenopus* and chicken retinas (Cahill and Besharse, 1990; Iuvone et al., 1999). In contrast to AAANAT, tryptophan hydroxylase is much less sensitive to acute light exposure and AANAT appears to be rate limiting under these conditions (Iuvone et al., 1999).

Another interesting aspect of retinal melatonin regulation is its metabolism. In non-mammalian vertebrates, retinal melatonin is metabolized within the eye (Grace et al., 1991; Cahill and Besharse, 1989; Li et al., 1997) via a well-defined pathway that involves melatonin deacetylation (see Figure 1). Several attempts to detect this pathway in the mammalian retina have failed (Rogawski et al., 1979; Hsu 1982; Grace et al., 1991) and therefore it is not clear whether melatonin is metabolized in the retina of mammals.

While melatonin synthesis in the retina is well established in many mammalian and non-mammalian species, its synthesis in the retina of primates, including humans, has been questioned. Melatonin has been detected in human retina using a specific gas chromatography mass spectrometric assay (Leino, 1984) and AANAT mRNA is expressed in human and macaque retinas (Coon et al., 1996; Coon et al., 2002). Melatonin receptors are present in human retina (Reppert et al., 1995; Scher et al., 2002; Savaskan et al., 2002; Savaskan et al., 2007). However, ASMT transcripts and activity are barely detectable in human and macaque retinas (Rodriguez et al., 1994; Coon et al., 2002). These observations suggest that primate retinas may not contain the complete melatonin biosynthetic pathway and that the source of melatonin in the retina is the circulating pool of pineal gland-derived hormone. Thus, retinal melatonin receptors may be occupied by pineal melatonin. Alternatively, retinal melatonin receptors might by occupied by *N*-acetylserotonin, the

AANAT product, but the affinity of human melatonin receptors for *N*-acetylserotonin is several orders of magnitude lower than for melatonin (Yuan et al., 1991). The role of AANAT in primate retina is uncertain. In addition to binding to melatonin receptors, *N*-acetylserotonin activates TrkB receptors in the retina (Jang et al., 2010) and may provide neuroprotection to photoreceptors and retinal neurons (review in: Tosini et al., 2012). It has also been proposed that AANAT may serve to detoxify reactive arylalkylamines in the retina to prevent them from reacting with retinaldehyde (Klein 2004).

Melatonin: Site of Action and Signaling

Melatonin exerts its influence by interacting with a family of G-protein-coupled receptors (GPCR) that are negatively coupled with adenylyl cyclase (Reppert, 1997, Jockers et al., 2008) although cAMP-independent transduction pathways are also involved (Dubocovich et al., 2010). Two subtypes of melatonin receptors have been identified in mammals, the MT_1 and MT_2 receptors, which are encoded by the *MTNR1A* and *MTNR1B* genes, respectively. Both subtypes are expressed in the retina (reviewed in: Wiechmann and Summers, 2008). In rats MT_1 receptors are found in the inner nuclear layer (horizontal and amacrine cells), the inner plexiform layer, retinal ganglion cells (RGCs), and the retinal pigmented epithelium (RPE) (Fujieda et al., 1999). Dopaminergic neurons in the guinea pig express MT_1 receptors (Fujieda et al., 2000), suggesting that melatonin can directly modulate the activity of these cells. In humans, melatonin receptors (MT_1 and MT_2) have been located on the rod photoreceptors and on GCs (Savaskan et al., 2002; Scher et al., 2002; Meyer et al., 2002; Savaskan et al., 2007). In the mouse, MT_1 receptors have been localized to photoreceptors, inner retinal neurons and RGCs (Baba et al., 2009; Sengupta et al., 2011). The fact that melatonin receptors are expressed on the same cells responsible for its synthesis raises the intriguing hypothesis that melatonin may feedback on the photoreceptors to regulate its own levels.

The signaling pathways activated by MT_1 and MT_2 receptors are very similar for the two subtypes when expressed heterologously (Jockers et al., 2008). The widely observed co-expression of MT_1 and MT_2 and their potential to form heteromeric complexes *in vitro* are of particular interest in this context. MT_1 and MT_2 were indeed among the first GPCRs that have been shown to homo- and heteromerize in a constitutive manner when transfected in HEK 293 cell at physiological levels (Ayoub et al., 2002). Interestingly, the propensity of melatonin receptors to form homo- and heteromers is not identical. Whereas the propensity of MT_1/MT_2 heteromer and MT_1 homomer formation is similar, that of MT_2 homomer formation is 3 to 4-fold lower, suggesting that the MT_2 receptor preferentially exists as heteromeric complexes with MT_1 or as monomers (Ayoub et al., 2004). Hence, it is possible that in the retina - and more specifically in the photoreceptors - MT_1 and MT_2 form functional melatonin receptor heteromeric units that may activate different pathways from those activated by MT_1 and MT_2 monomers.

Finally it is worth noting that there is a very large body of evidence documenting melatonin as an antioxidant (Reiter et al., 2009). In the retina melatonin acts as antioxidant in retinal photoreceptors (Marchiafava and Longoni, 1999). It decreases lipid peroxidation of polyunsaturated fatty (Guajardo et al., 2003), reduces NO-induced lipid peroxidation in rat retinal homogenates (Siu et al., 1999) and may also reduce retinal oxidative damage from ischemia-reperfusion injury (Celebi et al., 2002).

Role of Melatonin in the Modulation of Retinal Functions

Melatonin may alter the sensitivity of photoreceptors and second-order neurons at night when photopic input is at its lowest level (Wiechmann et al., 1988). In the carp retina melatonin can modulate glutamatergic transmission from cones to cone-driven bipolar cells

(Huang et al., 2005) and may potentiate responses of ON bipolar cells to rod signals (Ping et al., 2008). In *Xenopus laevis,* melatonin, acting through melatonin receptors on rod photoreceptor membranes, directly stimulates the responsiveness of rod photoreceptors to light (Wiechmann et al., 2003). This supports the hypothesis that melatonin acts both as an autocrine and a paracrine signal and binds to specific receptors in photoreceptors and other retinal cells to increase visual sensitivity. Administration of exogenous melatonin in *X. laevis* and in the carp increases the amplitude of the scotopic ERG (Wiechmann et al., 2003; Ping et al., 2008). In chickens and pigeons, administration of exogenous melatonin during the day reduces the amplitude of the b-wave (Lu et al., 1995), and constant administration of melatonin abolishes rhythmicity of a-wave and b-wave implicit times and b-wave amplitude (McGoogan and Cassone, 1999). In humans, oral administration of melatonin decreases the amplitude of the cone ERG (Gagne et al., 2009) and the amplitude of the cone and mixed rod-cone response was negatively correlated with the concentration of endogenous salivary melatonin (Rufiange et al., 2002). In mice, administration of exogenous melatonin (1 mg/kg) during the day increases the amplitudes of a- and b- waves and lowers the scotopic threshold response to levels observed at night under control conditions (Baba et al., 2009); removal of MT_1 receptors abolishes these effects (Baba et al., 2009). In melatonin proficient mice (C3H-f+/+) there are daily rhythms in both the scotopic and photopic ERG responses; these are absent in MT_1 knock-out ($MT_1^{-/-}$) mice (Baba et al., 2009; Sengupta et al., 2011). Therefore, it is clear that melatonin has influence over many different visual functions, although the precise mechanisms by which this hormone mediates these functions are likely to vary in a species-dependent manner.

Photoreceptor rod outer segments (ROS) are continuously renewed by the assembly of new membrane disks at the base of the ROS and by displacement of older disks at the top of the outer segment. These old disks are shed from the apical part of the ROS and phagocytized by the RPE. These two phenomena occur every day in a synchronized fashion shortly after the onset of light in the rod photoreceptors, and at the onset of night in the cones. Moreover, the daily rhythms of disk shedding and phagocytosis persist in constant darkness, indicating that they are under the control of circadian clocks located in the retina (LaVail, 1976; Teirstein et al., 1980; Terman et al., 1993; Grace et al., 1996).

Earlier studies suggested a role for melatonin in the regulation of disk shedding. Exogenous melatonin led to activation of disk shedding in *Xenopus* retina (Besharse and Dunis, 1983) and an increase in the frequency of large phagosomes in rat RPE cells (White and Fisher, 1989). However, a study in which the circadian regulation of disk shedding was compared between in melatonin proficient mice ($C3H/f^{+/+}$) and melatonin-deficient mice (C57/BL6) questioned the contribution of melatonin in the regulation of disk shedding in mice (Grace et al., 1999). This study reported that disk shedding was rhythmic in both strains and was not affected by administration of exogenous melatonin, thus suggesting that circadian factors other than melatonin are important for the regulation of the circadian rhythm in disk shedding. Additional studies are needed to determine the mechanisms regulating circadian disk shedding in mammals.

Melatonin as a Key Regulator of Retinal Circadian Rhythms

Several studies have shown that melatonin and dopamine play opposing roles in the regulation of retinal adaptive physiology (reviewed in: Green and Besharse, 2004; Tosini et al., 2008). Dopamine functions as a humoral signal for light, producing light adaptive physiology. Melatonin, on the other hand, produces dark-adaptive effects. In many species, the synthesis and release of both melatonin and dopamine are under circadian control, with melatonin released at night and dopamine during the daytime. Melatonin inhibits the release of dopamine through an action on melatonin receptors (Dubocovich, 1983; Boatright et al.,

1994; Ribelayga et al., 2004a), and dopamine inhibits the synthesis and release of melatonin from photoreceptor cells by acting on D2-like dopamine receptors (Zawilska and luvone, 1992; Nguyen-Legros et al., 1996; Tosini and Dirden, 2000). Thus, the melatonin secreting photoreceptors and dopamine secreting amacrine/interplexiform cells form a cellular feedback loop functioning to regulate circadian retinal physiology. The circadian rhythm of dopamine release and metabolism appears to be dependent on melatonin. Retinal dopamine content and metabolism are circadian in mice that synthesize melatonin, but not in mice that are genetically incapable of synthesizing melatonin (Nir et al., 2000; Doyle et al., 2002, Pozdeyev et al., 2008); and daily injections of melatonin induce circadian rhythms of dopamine in retinas of mice that are unable to synthesize the neurohormone (Doyle et al., 2002). The role of melatonin in controlling DA rhythmicity is not unique to mice. Previous work in *Xenopus laevis* has also indicated that DA and D_2-like receptors are involved in the entrainment of circadian rhythm of retinal melatonin synthesis (Cahill and Besharse, 1991; Hasegawa and Cahill, 1999). DA and quinpirole, a D_2R-like agonist, induce *Per2* mRNA levels in *Xenopus* photoreceptors (Steenhard and Besharse, 2000; Besharse et al., 2004) suggesting that DA -- via D_2R-like receptors -- and *Per2* are involved in the entrainment of the circadian clock located in the photoreceptors of *X. laevis* and thus in the regulation of retinal melatonin synthesis. In fish, regulation of rhythmic dopamine release also depends on activation of melatonin receptors (Ribelayga et al., 2004b).

Melatonin may have a profound impact of the function of the molecular clockwork. For example, disruption of MT_1 melatonin signaling has a profound impact on the regulation of clock genes and clock-controlled genes in many tissues. Von Gall et al. (2002) reported that rhythmic expression of *Period 1* (gene and protein) in the pituitary gland depends on melatonin via MT_1 signaling and that melatonin affects the amplitude and phase of the transcripts of others clock genes (e.g., *Per1, and Cry1*) in the mouse retina (Dinet and Korf, 2007; Dinet et al., 2007). Such results indicated that melatonin, at least in some tissues, is not only a clock output, but can also regulates the expression of canonical clock genes. In this context, is important to mention that circadian clocks are directly involved in the regulation of cellular metabolism (Bass and Takahashi, 2010) and, consequently, alteration of the clock in cells like the photoreceptors with a high metabolic rate may result in adverse outcomes.

Melatonin and Retinal Pathophysiology

Melatonin has been implicated in the modulation of intraocular pressure (IOP) (Samples et al., 1988; Osborne and Chidlow 1994; Pintor et al., 2001; Wiechmann and Wirsig-Wiechmann, 2001; Alarma-Estrany et al., 2008) and it has been suggested that melatonin or melatonin analogs may be useful in the treatment of glaucoma (Lundmark et al., 2007; Belforte et al., 2010). In rabbits, topical application of melatonin or 5-methoxycarbonylamino-N-acetyltryptamine (5-MCA-NAT, a melatonin analogue) leads to a reduction in IOP, whereas luzindole (a MT_1 and MT_2 receptor antagonist) abolishes the effect of both compounds, supporting a role for MT_1 or MT_2 in the regulation of IOP (Pintor et al., 2001). 5-MCA-NAT application also reduces IOP in glaucomatous monkey eyes (Serle et al., 2004). Additional studies have reported that many melatonin antagonists, such as prazozin, DH-97 and 4-P-PDOT, reverse the effect of 5-MCA-NAT in a dose-dependent manner (Pintor et al., 2003). A recent study demonstrated that 5-MCA-NAT acts via MT_1 or MT_2 to reduce IOP (Alarma-Estrany et al., 2009). In humans, administration of oral melatonin causes a small but significant decrease in the IOP of individuals kept in bright light to suppress endogenous melatonin (Samples et al., 1988) and in patients undergoing cataract surgery (Ismail and Mowafi, 2009).

A recent study further supports a role for melatonin in the modulation of IOP levels and the development of glaucoma that is consistent with the pattern of melatonin synthesis. IOP in $MT_1^{-/-}$ mice was higher (about 2 mmHg) than in the wild type mice during the night, but not during the day (Alcantara-Contreras et al., 2011). $MT_1^{-/-}$ mice also showed a significant decrease in the number of cells in the ganglion cell layer during aging compared to wild type mice (Baba et al., 2009; Alcantara-Contreras et al., 2011), suggesting that even a small increase in nocturnal IOP may have a significant effect of RGCs survival. The observation that administration of exogenous melatonin in WT mice reduced IOP at night but not during the day further suggests a role for melatonin in the modulation of nocturnal IOP. Interestingly, removal of MT_2 receptors did not affect the daily rhythm in IOP. However, exogenous melatonin was ineffective at lowering IOP in MT_2 knock-out mice, suggesting that MT_2 receptors, as well as MT_1 receptors, may be involved in the regulation of the IOP. The observation that melatonin receptors (MT_1 and MT_2) are present in the ciliary body (Osborne and Chidlow 1994; Wiechmann and Wirsig-Wiechmann, 2001; Alarma-Estrany et al., 2008) further suggests a role for melatonin receptors in the regulation of IOP.

Altogether these results indicate that melatonin and its analogues could be a promising resource in the management and treatment of glaucoma, but further studies are required to understand the mechanism(s) by which melatonin and its receptors regulate IOP and possibly protect ganglion cells.

Melatonin may also have protective effects on other retinal cell types, including retinal pigment epithelial cells and photoreceptors. Melatonin protects cultured RPE cells from oxidative stress and ischemia-induced cell death (Osborne et al., 1998; Liang et al., 2004; Fu et al., 2012) and delays photoreceptor degeneration in *rds* mutant mice (Liang et al., 2001). In addition, the age-related loss of photoreceptors cells is accelerated in $MT_1^{-/-}$ mice compared to wild type controls (Baba et al., 2009; Alcantara-Contreras et al., 2011). A series of studies have implicated melatonin in the pathogenesis of age-related macular degeneration (AMD). Yi et al. (2005) reported that daily administration of melatonin (3mg) may protect the retina and delay the progression of AMD. Rosen et al. (2009) reported that production of melatonin is decreased in AMD patients with respect to age-matched controls, suggesting that a deficiency in melatonin may play a role in the occurrence of AMD. In pseudophakic patients with AMD, daytime levels of melatonin were significantly higher than in pseudophakic patients without ocular pathology (Schmid-Kubista et al., 2009), suggesting that the daily rhythm of melatonin may be disrupted in AMD patients. Elevated daytime levels of melatonin may have a detrimental effect since melatonin enhances light-induced retinal degeneration (see below). Expression of melatonin receptors is altered in retinas of Alzheimer's disease patients with degenerating photoreceptor cells, with increased expression of MT_1 receptors and decreased expression of MT_2 receptors (Savaskan et al., 2002, 2007). A further indication of the possible role of melatonin in age-related pathologies can be found in the observation that retinal melatonin synthesis decreases during aging (Pulido and Clifford, 1986; Tosini et al., 2006) and that the responsiveness to the administration of exogenous melatonin steadily decreases during aging (Baba et al. 2012). The mechanisms by which melatonin influences photoreceptor viability during aging are unknown, but it is reasonable to speculate that melatonin can affect the circadian clocks in photoreceptors and RPE cells and, thereby, metabolism in these cells.

Circadian clocks prevent the occurrence of high melatonin levels in the presence of light. It may be critical that melatonin levels are low during the daytime, as melatonin potentiates light-induced oxidative damage in the retina. Albino rats injected with melatonin and exposed to bright light showed significantly greater photoreceptor cell death than vehicle-treated controls (Wiechmann and O'Steen, 1992). Administration of luzindole (a melatonin receptor antagonist) at night significantly reduced light-induced photoreceptor degeneration

of rats exposed to bright light on the following day (Sugawara et al., 1998). In addition, there is a circadian rhythm of sensitivity to light-induced retinal degeneration (Organisciak et al., 2000; Vaughn et al., 2002), which peaks at night when melatonin levels are high. The mechanisms by which melatonin increases the susceptibility of the retina to light damage are still unknown.

Conclusions and Future Research Directions

Recent genome wide association studies (GWAS) have indicated that polymorphisms in genes encoding melatonin receptors or melatonin synthesizing enzymes are associated with the pathogenesis of type 2 diabetes, polycystic ovary syndrome, and autism spectrum disorders (Bonnefond et al., 2012; Li et al., 2011; Chaste et al., 2010). Melatonin may be involved in several retinal pathologies but, unfortunately, no population studies using GWAS have examined the association of polymorphisms in melatonin-related genes with ocular diseases. Little is known about the mechanisms whereby melatonin regulates retinal physiology or affects retinal cellular viability. We believe that the transgenic mice generated by our laboratories may provide useful tools to probe the mechanisms by which melatonin affects retinal physiology and pathology. Finally, it is important to note that melatonin and its analogues are currently used by millions of people around the world to retard aging, improve sleep performance, ameliorate jet-lag symptoms and treat depression. Administration of exogenous melatonin at night may also benefit ocular health, but further translational and clinical investigations are needed to establish its potential.

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Highlights

- Regulation of melatonin synthesis and metabolism.
- Distribution of melatonin receptors in the vertebrate eye
- Role of melatonin receptors in the regulation of retinal physiology
- Role of melatonin in the development of retinal pathology
- Use of melatonin to treat ocular diseases

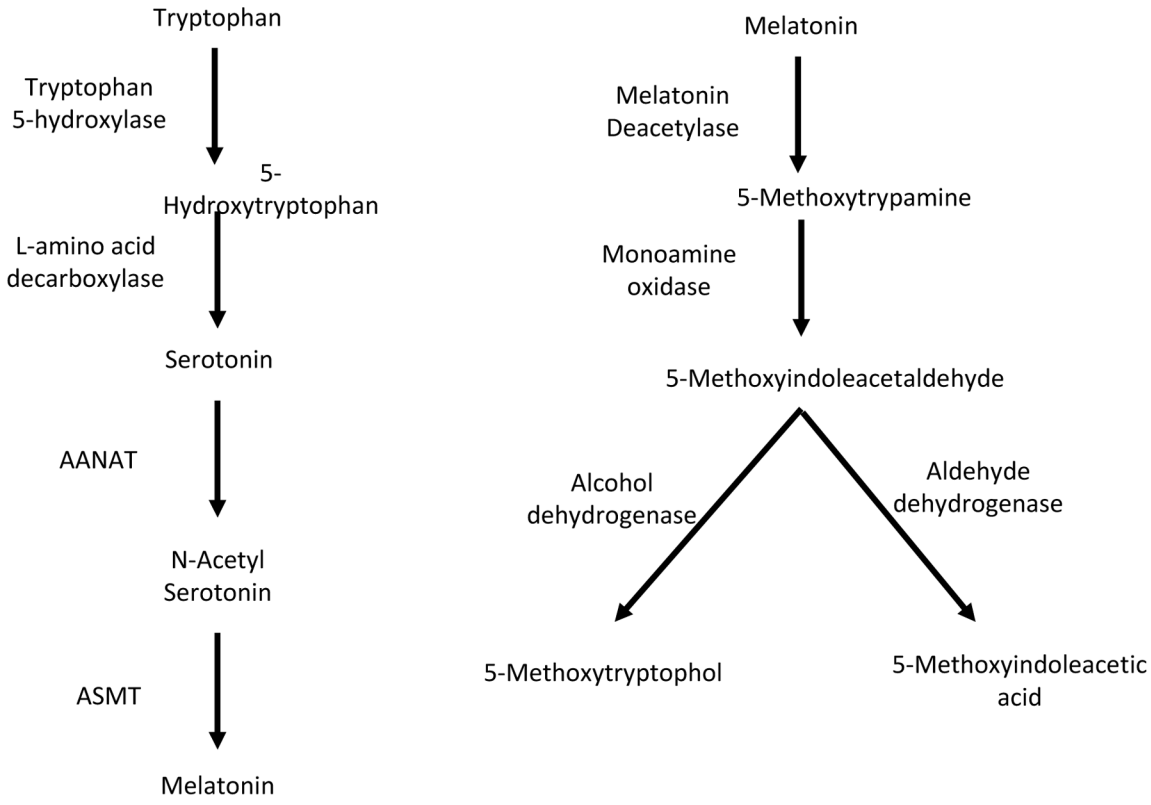

Figure 1.

Melatonin synthesis starts with up-take of the circulating amino acid tryptophan and the subsequent 5-hydroxylation by tryptophan hydroxylase. 5-Hydroxytryptophan is then converted to serotonin by the action of aromatic L-amino acid decarboxylase. Serotonin is acetylated by arylalkylamine *N*-acetyltransferase (AANAT) to N-acetylserotonin, which is subsequently *O*-methylated and converted to melatonin by acetylserotonin methyltransferase (ASMT), which is also known as hydroxyindole-*O*-methyltransferase. The metabolism of retinal melatonin illustrated on the right has been demonstrated for *Xenopus,* reptiles, teleost fish, and chicken but not in mammals (see text).

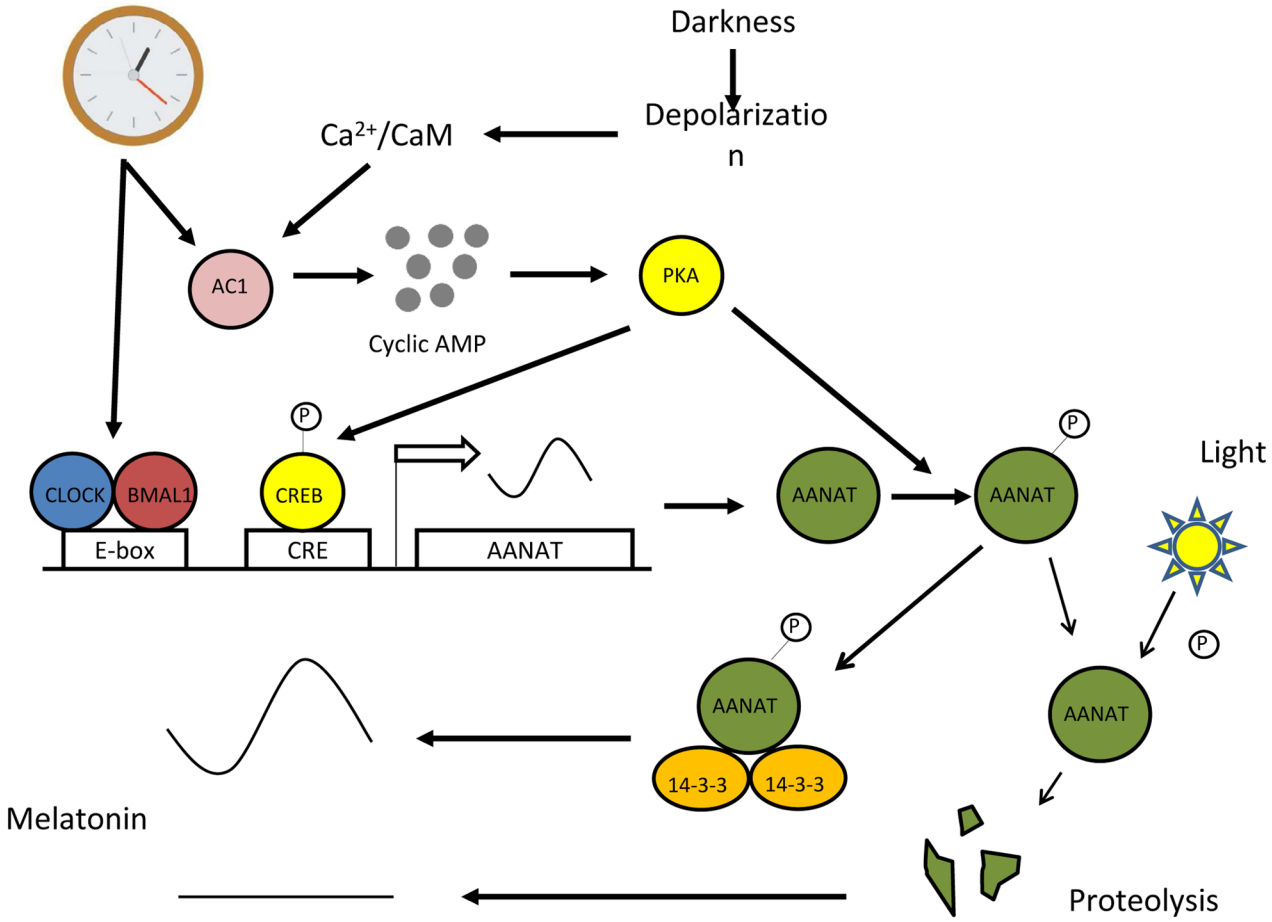

Figure 2.

Regulation of retinal melatonin levels by light and the circadian clock. At night in darkness cAMP levels are elevated, activating PKA, which induces *Aanat* gene transcription and phosphorylates AANAT protein. Phosphorylated AANAT (pAANAT) associates with 14-3-3 proteins, which activate and stabilize the enzyme resulting in increased conversion of serotonin to *N*-acetylserotonin, and ultimately to melatonin. Light exposure decreases cAMP levels resulting in dephosphorylation of AANAT and its subsequent degradation by proteasomal degradation. The circadian clock controls melatonin levels by directly regulating *Aanat* transcription and by gating the cAMP signaling cascade.

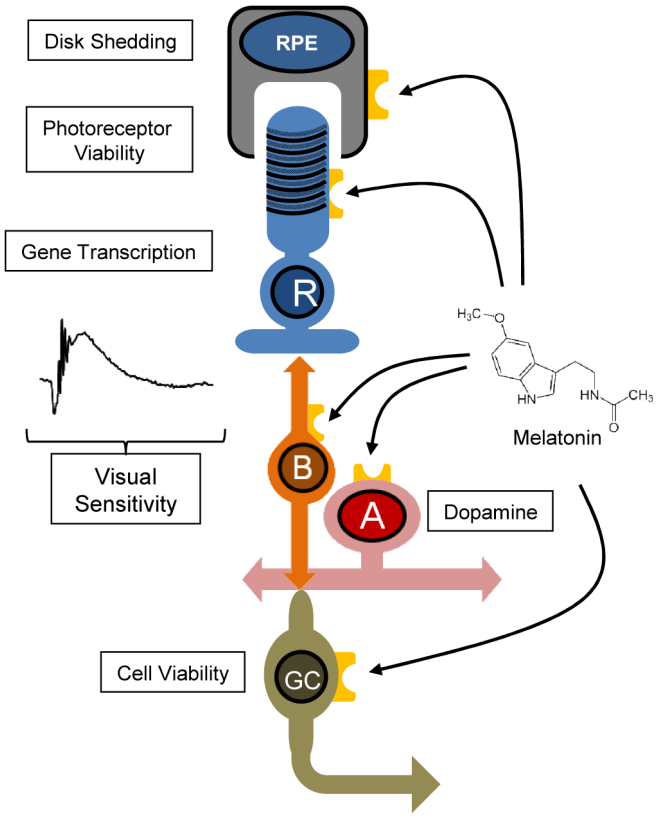

Figure 3.
Melatonin receptors are expressed in many retinal cell types. Activation of these receptors may modulate several retinal functions such as: disk shedding, retinal cell viability; visual sensitivity; and dopamine levels and metabolism. RPE=retinal pigmented epithelium; R= rod photoreceptors; B= bipolar cells; A= amacrine cells; GC= retinal ganglion cells.