CHAPTER SIX

Role of Melatonin and Its Receptors in the Vertebrate Retina

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Abstract

Melatonin is a chemical signal of darkness that is produced by retinal photoreceptors and pinealocytes. In the retina, melatonin diffuses from the photoreceptors to bind to specific receptors on a variety of inner retinal neurons to modify their activity. Potential target cells for melatonin in the inner retina are amacrine cells, bipolar cells, horizontal cells, and ganglion cells. Melatonin inhibits the release of dopamine from amacrine cells and increases the light sensitivity of horizontal cells. Melatonin receptor subtypes show differential, cell-specific patterns of expression that are likely to underlie differential functional modulation of specific retinal pathways. Melatonin potentiates rod signals to ON-type bipolar cells, via activation of the melatonin MT2 (Mel1b) receptor, suggesting that melatonin modulates the function of specific retinal circuits based on the differential distribution of its receptors. The selective and differential expression of melatonin receptor subtypes in cone circuits suggest a conserved function for melatonin in enhancing transmission from rods to second-order neurons and thus promote dark adaptation.

1. INTRODUCTION

Melatonin is an indolamine hormone produced at nighttime by the pineal gland and retinal photoreceptors. Melatonin produced by the pinealocytes enters the circulation as an endocrine hormone, and binds to receptors on a variety of target tissues to exert their physiological responses. In contrast, melatonin produced by retinal photoreceptors appears to have a local action within the retina, and thus acts as a paracrine neuromodulator of retinal function. A wide range of functions have been attributed to circulating melatonin, including regulation of seasonal reproduction, entrainment of sleep rhythms, rhythms of locomotor activity, and modulation of immune responsiveness. In the retina, melatonin appears to influence retinomotor movements, modulation of neurotransmitter release, and sensitivity to light. It is currently thought that melatonin is produced and released from photoreceptors at night, and diffuses throughout the neural retina to bind to specific melatonin receptor subtypes to modulate the activity of second-order retinal neurons. We will review the source and regulation of melatonin synthesis in the retina, its subsequent effects on the activity of retinal neurons and potential to increase retinal sensitivity at night as part of a dark-adaptation response.

2. PHYLOGENIC RELATIONSHIP BETWEEN RETINA AND PINEAL GLAND

The ability of photoreceptors and pinealocytes to synthesize melatonin may be the result of an ancestral relationship between the retina and the pineal
gland. The pineal glands of many nonmammalian vertebrates display photoreceptive structures and functions similar to the retinal photoreceptors of the lateral eyes. The mammalian pineal gland is thought to have evolved from a primitive third photosensory organ into a secretory endocrine gland receiving photic information indirectly from the retinas (Eakin, 1973; Flight, 1979). Mammalian pinealocytes express some proteins that are generally unique to retinal photoreceptors (Vigh and Vigh-Teichmann, 1981; Somers and Klein, 1984).

The pineal photoreceptors of many nonmammalian vertebrates (e.g. amphibians and birds) are directly photosensitive (Hamasaki, 1968; Solessio and Engbretson, 1999), synthesize melatonin, and are morphologically similar to retinal photoreceptors, including the presence of opsin-containing outer segments (Vigh and Vigh-Teichmann, 1981). Moreover, during embryological development of the mammalian pineal gland, there is a transient photoreceptor-like differentiation of the pinealocytes (Clabough, 1973; Zimmerman and Tso, 1975) although mature mammalian pinealocytes do not resemble photoreceptors. It has been suggested that the melatonin-producing cells of the lateral eyes evolved into photoreceptors specialized for phototransduction, but maintained their ability to synthesize melatonin. The synthesis of melatonin by mammalian retinal photoreceptors may be the consequence of an ancestral relationship between the pineal gland (“third eye”) and the lateral eyes. Some prehistoric animals possessed three eyes, perhaps all of which may have both produced melatonin and were directly photosensitive. It is hypothesized that the two lateral eyes became more specialized for phototransduction, whereas the third eye became specialized for secretion of melatonin into the circulation. Furthermore, genes encoding melatonin receptors in the peripheral organs may have come to be expressed in inner retinal neurons for local paracrine signaling of melatonin in the eye.

3. MELATONIN BIOSYNTHESIS IN RETINA

3.1. Circadian Regulation of Melatonin Synthesis

Studies on the pineal gland have revealed the biosynthetic pathway of melatonin, which is synthesized from tryptophan in four enzymatic steps: (1) tryptophan hydroxylase (TPH) converts tryptophan to 5-hydroxytryptophan; (2) 5-hydroxytryptophan is converted to 5-hydroxytryptamine (serotonin) by aromatic amino acid decarboxylase (AADC; Lovenberg et al., 1967;
Snyder and Axelrod, 1964); (3) serotonin is converted to N-acetylserotonin by arylalkylamine N-acetyltransferase (AANAT; Weissbach et al., 1975); (4) N-acetylserotonin is converted to melatonin (N-acetyl-5-methoxytryptamine) by hydroxyindole-O-methyltransferase (HIOMT; Axelrod and Weissbach, 1960). The enzyme activities and mRNA encoding both TPH and AANAT exhibit circadian rhythms of expression, with peak levels during the dark period (Thomas and Iuvone, 1991; Green and Besharse, 1994; Hamm and Menaker, 1980; Besharse and Iuvone, 1983; Iuvone and Besharse, 1986). A daily cyclic rhythm of melatonin occurs in the retina of several vertebrates, with highest levels at nighttime (Pang et al., 1980; Wiechmann, 1986; Cahill and Besharse, 1992). Since melatonin is a highly lipophilic molecule, it diffuses out of the photoreceptors at the time it is synthesized and diffuses freely into neighboring cells.

### 3.2. Distribution of Melatonin-Synthesizing Enzymes in Retina

The photoreceptor cells have been identified as the melatonin-producing cells in the retina. Melatonin immunoreactivity is present in the outer nuclear layer (Bubenik et al., 1978; Vivien-Roels et al., 1981), which is the location of the photoreceptor cell soma and nuclei. mRNA encoding the final enzyme in the melatonin-synthesizing pathway, HIOMT, is localized to photoreceptors in the chick retina (Wiechmann and Craft, 1993; Wiechmann, 1996; Guerlotte et al., 1996). mRNA encoding AANAT is localized to photoreceptors in the mammalian retina (Bernard et al., 1997; Niki et al., 1998; Liu et al., 2004). In addition, TPH mRNA is expressed in retinal photoreceptors in chicken (Chong et al., 1998) and *Xenopus* (Green et al., 1995).

### 4. MELATONIN RECEPTOR STRUCTURE AND FUNCTION

#### 4.1. Melatonin Receptor Nomenclature

Melatonin receptors are members of the superfamily of seven–pass transmembrane G-protein coupled receptors (GPRCs) and are expressed in the retina of many species. Melatonin receptors were initially classified as Mel1a, Mel1b, and Mel1c subtypes (Reppert et al., 1995a, 1995b). The Mel1a, Mel1b, and Mel1c nomenclature applies only to the three subtypes of lower vertebrates such as amphibians, fish, and birds. Mammalian melatonin receptors are classified not only according to their sequence homology to the nonmammalian receptors but also according to their pharmacological
properties (Dubocovich et al., 1998). In mammals, the MT1 receptor subtype is the ortholog of the Mel1a receptor, and the MT2 receptor subtype is the ortholog of the Mel1b receptor. The mammalian ortholog of the Mel1c subtype is GPR50, which does not bind melatonin (Dufourmy et al., 2008). Nuclear melatonin receptors are members of the RZR/ROR receptor superfamily (Mor et al., 1999), and a melatonin–binding site on the enzyme quinine reductase 2 has been identified and has been designated as the MT3 melatonin receptor (Nosjean et al., 2000).

### 4.2. Melatonin Receptor Signaling

In most tissues studied, the G-proteins coupled to melatonin receptors are inhibitory (G_i) to the activation of adenylate cyclase and the subsequent cyclic AMP (cAMP) production (Iuvone and Gan, 1994; Nash and Osborne, 1995; Weaver et al., 1990). However, receptor coupling to other signaling pathways and G-proteins (G_iα2, G_iα2, G_iαq, G_iα5, G_iαz, G_iα16) have also been reported. The Mel1a receptor may be coupled to several different G-proteins (Brydon et al., 1999). Mel1a receptor stimulation appears to potentiate phospholipase activation (Godson and Reppert, 1997) in addition to the inhibition of adenylate cyclase activity. In some tissues, Mel1a receptor stimulation does not result in inhibition of cAMP synthesis (Conway et al., 1997). Mel1b or Mel1c receptor expression has been reported to inhibit cyclic GMP (cGMP) synthesis (Jockers et al., 1997; Petit et al., 1999). Cells that express only Mel1a receptors may inhibit cAMP synthesis only, whereas cells that also express Mel1b or Mel1c receptors may inhibit both cAMP and cGMP synthesis (Jockers et al., 1997; Petit et al., 1999). Inhibition of cAMP accumulation may therefore be a general feature of melatonin receptor signaling, and be complemented by modulation of cGMP synthesis, depending on the combination of receptor subtypes expressed in a cell (Petit et al., 1999).

Activation of different melatonin receptor subtypes exerts opposite effects on GABA_A receptor-mediated currents in different brain regions (Wan et al., 1999). Melatonin potentiates GABA_A receptor-mediated current via the MT1 receptor in the rat suprachiasmatic nucleus, but inhibits the GABA_A current in the hippocampus via the MT2 receptor. Differences in GABA_A receptor responses within the same transfected cells, via two different melatonin receptor subtypes, indicate that different second-messenger systems must be involved in the signaling mediated by MT1 and MT2 activation (Wan et al., 1999). Together, these studies suggest that
multiple signaling pathways may be stimulated by the binding of melatonin to various combinations of melatonin receptor subtypes.

4.3. Melatonin Receptor Dimerization

Many GPCRs interact with each other to form dimers (Gomes et al., 2001). GPCRs can form dimers either with an identical receptor (homo-dimerize) or with a different form of the receptor (heterodimerize). These

Figure 1  Mel1b receptors are expressed by OFF bipolar cells. Double labeling for Mel1b receptors (A) and the ON bipolar cell marker G_{o}\alpha (B) shows that Mel1b receptor immunoreactivity is absent from the cell bodies of ON bipolar cells (ON), identifying the Mel1b receptor immunoreactive bipolar cells as OFF bipolar cells (OFF). Confocal image stack comprised of seven optical slices of 400 nm each. Apparent colocalization of Mel1b and G_{o}\alpha immunoreactivity in processes in the outer plexiform layer (OPL) is due to their close proximity and the relative thickness of the image stack, and does not represent genuine colocalization. Immunolabeling for both Mel1b and G_{o}\alpha is present in the inner plexiform layer (IPL), with strongly Mel1b-positive processes (small arrows) present along the inner margin of the layer. Mel1b immunoreactive puncta (small arrowheads) are also present at the level of the outer limiting membrane, which is located between the photoreceptor inner segments (IS) and the outer nuclear layer (ONL). Nuclei are counterstained with DAPI (blue). INL, inner nuclear layer; OS, photoreceptor outer segments. See Wiechmann and Sherry, 2012 for similar images in color.
homodimers and heterodimers can exhibit distinct functional properties, and may provide a mechanism by which receptor function can be modulated.

MT1 and MT2 melatonin receptors can exist as either homodimers or heterodimers when studied in a cell culture model (Ayoub et al., 2004). Heterodimerization of GPCRs appears to play a role in receptor affinity, trafficking and signaling (Gazi et al., 2002). The expression of different combinations of melatonin receptor subtypes in retinal cells may have an impact on the function of melatonin in the target cells (See Figs. 1 and 2).

![Figure 2](image-url)

**Figure 2** Melatonin increases rod input and decreases cone input to goldfish retinal L-type cone horizontal (H1) cells. A, superfusion of melatonin (1 μm) during the late subjective day (ZT 09) introduced rod input and decreased cone input to H1 cells, so that light responses resembled those typically obtained during the subjective night. B, superfusion of luzindole (10 μm) during the subjective night (ZT 15, 21) decreased rod input and increased cone input to the cells. The recordings shown are representative of results obtained from 14 (A) and 8 (B) cells. (Modified from Ribelayga et al. (2003), with permission).
5. CELL TYPES AND ORGANIZATION OF VISUAL CIRCUITS IN RETINA

The neural retina of vertebrates contains six basic classes of neuron (photoreceptor, horizontal, bipolar, amacrine, interplexiform, and ganglion cells) that perform the initial processing of visual information (Masland, 2011). There is a single major type of specialized retinal glial cell, which is the Müller cell that regulates the ionic environment and provides metabolic support for the neurons. Neuronal connectivity patterns in the retina are well studied and the basic functional organization of retinal circuits has been established although there are important differences in cell populations and circuits between nonmammalian and mammalian species, and at the species-specific level (Fig. 3).

Visual signals originate in the rod and cone photoreceptors, which transduce the energy from photons striking the retina into neural signals. Rods are exquisitely sensitive and mediate dim-light (scotopic) vision. Mammals possess a single type of rod, but some nonmammalian species contain more than one rod type and potentially could possess scotopic color vision. Cones are less sensitive, usually comprise multiple types, and mediate high acuity and color vision under relatively bright-light (photopic) conditions. Rods and cones encode light information and transmit it synaptically to second-order horizontal and bipolar cells in the outer plexiform layer (OPL). Horizontal cells mediate lateral processing within the OPL, and comprise one to four types depending on species. Bipolar cells comprise several morphologically and functionally distinct types and transmit signals from the OPL to third-order neurons, amacrine, ganglion, and interplexiform cells via their synaptic terminals in the inner plexiform layer (IPL). Amacrine cells typically make inhibitory synapses with bipolar, amacrine, and ganglion cells in the IPL. Ganglion cells are the only output neurons in the retina, projecting via the optic nerve to higher visual centers in the brain. Amacrine and ganglion cells are highly diverse, and each comprises 20 or more anatomically and functionally distinct types. Interplexiform cells receive their input in the IPL, then project back to the OPL to form a feedback loop; however, little is known about the function and diversity of these cells. Thus, retinal neurons are connected in sequences of photoreceptors, bipolar cells, and ganglion cells that carry information vertically through the retina and then to the brain, and there are local circuits within the OPL and the IPL that process information laterally within a synaptic layer.
One theme in the functional organization of the retina is the processing of visual information in several parallel pathways dedicated to extracting information about different visual attributes (Field and Chichilnisky, 2007; Wässle, 2004; Wu, 2010). These parallel pathways initially arise at the level of the OPL, based on precise patterns of connectivity between specific classes of photoreceptors and bipolar cells (Famiglietti and Kolb, 1976; Famiglietti et al., 1977; Hare et al., 1986; Lasansky, 1973, 1978; Ishida et al., 1980; Li and DeVries, 2006; Smith et al., 1986; Stell et al., 1977; Wässle et al., 2009; Witkovsky and Stone, 1983). These pathways are maintained in the inner retina by the stratified organization of bipolar cell terminals at specific depths within the IPL, which organizes precise connections between specific classes of bipolar cells and specific classes of amacrine and ganglion cells (Famiglietti and Kolb, 1976; Famiglietti et al., 1977; Maple et al., 1999; Stell et al., 1977; Wu et al., 2000). Particularly important pathways include those dedicated to processing of inputs from rods and cones and for processing information related to increases and decreases in light intensity (known as “ON” and “OFF” pathways, respectively; Fig. 3). Parallel processing streams are preserved in the projections of ganglion cells to higher visual centers in the brain, where further visual processing occurs (Nassi and Callaway, 2009). Because melatonin is a key signal modulating rod- and cone-driven signaling in the retina, differences in the organization of connectivity patterns in the OPL of mammalian and nonmammalian retinas are likely to affect the functional and anatomical organization of melatonin receptors in rod–cone pathways and ON–OFF pathways.

One key difference between mammalian and nonmammalian species in the organization of rod and cone pathways in the OPL is the specificity of connections between photoreceptors and bipolar cells (Fig. 3). In mammals, bipolar cells typically receive input exclusively from either cones or rods, and are called “cone” or “rod” bipolar cells, and mediate photopic and scotopic vision, respectively (Dowling, 1968; Famiglietti and Kolb, 1976; Li and DeVries, 2006; Smith et al., 1986; Wässle et al., 2009). In contrast, many nonmammalian bipolar cells receive mixed inputs from rods and cones (Dowling, 1968; Famiglietti et al., 1977; Hare et al., 1986; Lasansky, 1973, 1978; Ishida et al., 1980; Stell et al., 1977; Witkovsky and Stone, 1983). Some specific subtypes of mammalian cone bipolar cells can receive some direct input from rods (Hack et al., 1999; Li et al., 2004; Protti et al., 2005; Tsukamoto et al., 2001), and photoreceptor terminals can be electrically coupled via gap junctions, permitting rod signals to enter
Figure 3  Organization of retinal cell types in the rod and cone circuits of mammalian and nonmammalian retina. See text for details. (A) Nonmammalian retina. Abbreviations: C, cone; R, rod; ON B, ON bipolar cell receiving mixed rod and cone input; OFF B,
cone circuits and contribute to transmission of rod signals at mesopic light levels (DeVries and Baylor, 1995; Hornstein et al., 2005; O’Brien et al., 2012; Smith et al., 1986). Horizontal cell connectivity also can differ between mammalian and nonmammalian retinas (Lasansky, 1978; Leeper, 1978; Peichl and Gonzalez-Soriano, 1994; Stell and Lightfoot, 1975; Witkovsky et al., 1988). In mammalian species, horizontal cell dendrites specifically contact cones, whereas the axons contact rods exclusively. In contrast, the dendrites and axons of horizontal cells contact both rods and cones in some nonmammalian species, including *Xenopus laevis* (Witkovsky et al., 1988b), which is a major model system for investigating retinal melatonin.

Another important difference between mammalian and nonmammalian species is the organization of ON and OFF circuits for processing rod-driven signals (Fig. 3). Bipolar cells are classified as either ON or OFF cells according to their light-driven response, which is determined by their response to the light-induced decrease in glutamate released from presynaptic photoreceptor terminals according to the type of glutamate receptor expressed on their dendrites (Wässle, 2004; Wu, 2010). ON bipolar cells express the metabotropic mGluR6 glutamate receptor, and depolarize in response to light, terminate in the inner portion of the IPL, and serve to detect increases in light. OFF bipolar cells express AMPA or kainite-type ionotropic glutamate receptors, hyperpolarize in response to light, terminate in the outer portion of the IPL, and serve to detect decreases in light. In both mammals and nonmammals, cones provide roughly symmetrical input to separate populations of ON and OFF cone bipolar cells that then transmit cone-driven signals to the ON and OFF amacrine and ganglion cells that stratify in the inner and outer portions of the IPL, respectively.
In contrast, the organization of rod-driven inputs to ON and OFF circuits differs substantially between mammals and nonmammals (Fig. 3). In nonmammals, rods also provide roughly symmetrical input to separate populations of ON and OFF bipolar cells, which, in turn, provide direct input to the processes of ON and OFF amacrine and ganglion cells in the IPL, respectively (Hare et al., 1986; Ishida et al., 1980; Sherry and Yazulla, 1993; Wu et al., 2000). The primary rod circuit of the mammalian retina, which mediates rod-driven vision near visual threshold, lacks the anatomically symmetrical bipolar cell populations that mediate transmission of rod signals to the ON and OFF sublayers of the nonmammalian IPL (Bloomfield and Dacheux, 2001). In mammals, rod-driven signals in the primary rod circuit are mediated exclusively by the rod bipolar cell, which comprises a single ON bipolar cell type that terminates in the innermost portion of the IPL, where it makes output synapses onto two types of amacrine cells, the AII and A17 amacrine cells. Importantly, the mammalian rod bipolar cell does not transmit directly to ganglion cells, the output neurons of the retina. This requires that rod signals in the mammalian IPL be processed by circuits that differ substantially from those of nonmammals in order to produce rod-driven ON and OFF responses and retinal output. This is accomplished via the AII amacrine cell, which has a bistratified dendritic architecture characterized by large lobular processes in the OFF portion of the IPL that make inhibitory glycinergic chemical synapses onto the terminals of OFF-cone bipolar cells, and thin arboreal processes in the ON portion of the IPL that make electrical synapses onto the terminals of ON cone bipolar cells and other AII cells (Strettoi et al., 1992, 1994). Rod-driven signals are transmitted from the rod bipolar cell to the AII amacrine cell via an excitatory glutamatergic synapse that depolarizes the AII cell. This depolarization then spreads through the arboreal processes of the AII cell in the ON portion of the IPL to the electrically coupled terminals of ON cone bipolar cells, causing glutamate release from those terminals onto the dendrites of ON ganglion cells, generating rod-driven ON output from the retina. Simultaneously, the depolarizing signal from the rod bipolar cell spreads to the lobular processes of the AII cell in the OFF portion of the IPL, inducing synaptic release of glycine onto the terminals of the OFF-cone bipolar cells, in turn causing those terminals to hyperpolarize and cease releasing glutamate onto the dendrites of OFF ganglion cells, thus generating rod-driven OFF output from the retina. The electrical coupling of AII cells to other AII cells permits pooling of rod signals, and increases the sensitivity of the system.
The A17 amacrine cells are an ON amacrine cell type that provides local inhibitory feedback to the rod bipolar cell terminals to truncate rod signals.

Because melatonin is an important signal in the circadian switching of the retina from cone-driven to rod-driven function in both mammals and nonmammals, it is expected that the organization of melatonin receptors would ultimately result in a conserved end-point of reducing cone signaling and enhancing rod signaling. However, the differences in the anatomical organization of rod and cone circuits between mammalian and non-mammalian retinas may result in distinctly different anatomical organization of melatonin receptors in mammalian and nonmammalian retinas. Although some data regarding the distribution of melatonin receptors in the retinas of mammals and nonmammals are available, our current understanding of melatonin receptor distribution and function in specific cell types and circuits remains limited.

6. EXPRESSION OF MELATONIN RECEPTORS IN RETINA

6.1. Localization of Melatonin-Binding Sites in Retina

$I^\text{25}$-melatonin binding has been demonstrated to occur in the IPL of many species (Blazynski and Dubocovich, 1991; Laitinen and Saavedra, 1990; Wiechmann and Wirsig-Wiechmann, 1991, 1994). The IPL is the location of the synaptic connections between bipolar cells, amacrine cells, horizontal cells, and ganglion cells. On the basis of a variety of physiological studies (Section 6), the dopaminergic and GABA-ergic amacrine cells, both of which form synaptic contacts in the IPL, have long been considered to be candidates for the sites of action of melatonin in the inner retina (Dubocovich, 1983; Boatright et al., 1994). Melatonin inhibits dopamine release from the retina (Dubocovich, 1983) and GABA\textsubscript{A} receptor antagonists block melatonin-induced suppression of dopamine release (Boatright et al., 1994). These observations suggest that the inhibition of dopamine release by melatonin may be mediated by both direct action on dopaminergic cells and indirect action on GABA-ergic amacrine cells.

6.2. Localization of Melatonin Receptor RNA Expression in Retina

Mel1b and Mel1c RNA expression is localized to the inner nuclear layer (INL), ganglion cell layer, and photoreceptor inner segments in *Xenopus* retina (Wiechmann and Smith, 2001). The INL contains the cell soma of
bipolar, amacrine, horizontal, and Müller cells. In the chicken retina, mRNA encoding the Mel1a, Mel1b and Mel1c receptor subtypes is present in the INL, ganglion cell layer, and photoreceptor inner segments (Natesan and Casonne, 2002). In the human retina, MT2 (Mel1b) receptor mRNA is expressed at higher level than the mRNA encoding the MT1 (Mel1a) receptor (Reppert et al., 1995a).

6.3. MT1 and MT2 Receptors Distribution in Retina

The MT1 (Mel1a) receptor is localized to photoreceptors of the human and chicken retina (Savaskan et al., 2002; Natesan and Casonne, 2002). In the *Xenopus* retina, Mel1b receptor immunoreactivity appears as a punctate pattern in the proximal portion of photoreceptor inner segments, whereas Mel1c immunoreactivity is observed in the plasma membrane of photoreceptor inner segments (Wiechmann, 2003; Wiechmann et al., 2004; Wiechmann and Sherry, 2012).

Melatonin receptor immunoreactivity is present in the outer and inner retina of several species (Fujieda et al., 2000; Huang et al., 2005; Meyer et al., 2002; Scher et al., 2002; Wiechmann and Wirsig-Wiechmann, 2001; Wiechmann, 2003; Wiechmann et al., 2004; Wiechmann and Sherry, 2012). In human, monkey, rat, and carp, the MT1 receptor is present in horizontal cells in the IPL (Fujieda et al., 2000; Meyer et al., 2002; Scher et al., 2002; Huang et al., 2005). In *X. laevis* retina, all three melatonin receptor subtypes (Mel1a, Mel1b, and Mel1c) are localized to horizontal cells (Wiechmann, 2003; Wiechmann et al., 2004; Wiechmann and Sherry, 2012). In the human and monkey retina, the MT1 (Mel1a) receptor is also present in AII amacrine cells (Fujieda et al., 2000; Scher et al., 2002), and in the guinea pig retina, MT1 is localized to dopaminergic and GABA-ergic amacrine cells (Fujieda et al., 2000).

The presence of MT1 receptors on dopaminergic and GABA-ergic neurons is consistent with the reports that melatonin modulates the cyclic release of GABA and dopamine from amacrine cells (Dubocovich, 1983; Boatright et al., 1994). In the *X. laevis* retina, Mel1b (MT2) receptor immunoreactivity does not colocalize to dopaminergic and GABA-ergic neurons. This suggests that melatonin may not act directly on GABA-ergic and dopaminergic amacrine cells via the Mel1b receptor in *Xenopus* (Wiechmann et al., 2004).

In *X. laevis*, the Mel1a and Mel1b receptors are differentially distributed throughout the retina (Wiechmann, 2003; Wiechmann et al., 2004;
Horizontal cell processes are immunoreactive for Mel1a receptors in the OPL (Wiechmann and Sherry, 2012). Mel1a and Mel1b immunoreactivities are present in cell somas of the INL, but are not colocalized to the same population of cells. This suggests that there are two separate populations of neurons in the INL that express either the Mel1a receptor or the Mel1b receptor, but not both.

The OPL is the site of synaptic connections between photoreceptors, bipolar cells and horizontal cells. The Mel1a and Mel1b receptor immunoreactivities are located in distinctively different cell processes that are in very close proximity to each other, and often appear to contact the same population of cone photoreceptors (Wiechmann and Sherry, 2012). Although all three melatonin receptor subtypes are expressed in ganglion cells in the *Xenopus* retina, they appear to be distributed in different ganglion cell populations (Wiechmann et al., 2003).

Melatonin receptor mRNA and protein is rhythmically expressed in *Xenopus* and chicks, with peak levels of Mel1a and Mel1b expression occurring at night (Wiechmann and Smith, 2001; Summers Rada and Wiechmann, 2006). The rhythm of Mel1c receptor protein in chicks appears to be opposite that of Mel1a and Mel1b, with higher levels occurring during the day (Natesan and Casonne, 2002; Summers Rada and Wiechmann, 2006). The daily rhythms of melatonin receptor expression may be superimposed on the rhythm of retinal melatonin levels to provide an additional level of regulation of melatonin responsiveness of inner retinal neurons.

### 6.4. Circadian Rhythms in Melatonin Receptor Expression in Retina

Melatonin receptor mRNA is expressed rhythmically in chickens and *X. laevis*, (Wiechmann and Smith, 2001; Natesan and Casonne, 2002; Summers Rada and Wiechmann, 2006). Peak levels of Mel1c RNA occur during the day. In the chick retina, Mel1c receptor protein exhibits higher levels during the early morning than during the night (Summers Rada and Wiechmann, 2006). The rhythms of Mel1a and Mel1b receptor proteins generally appear to be opposite that of Mel1c, with lower levels occurring in the early morning and higher levels in the evening (Summers Rada and Wiechmann, 2006). Therefore, distinct diurnal rhythms for each melatonin receptor subtype appear to be present in the retina.

There are several specialized processes that occur in the retina that are thought to be regulated in a circadian manner, potentially through
activation of melatonin receptors. Melatonin may be involved in circadian events such as photoreceptor outer segment disc shedding and phagocytosis (Besharse and Dunis, 1983; Ogino et al., 1983; White and Fisher, 1989), photomechanical movements (Chéze and Ali, 1976; Krause-Ruppert and Lembeck, 1965; Pierce and Besharse, 1985), visual sensitivity (Wiechmann et al., 1988, 2003; Cosci et al., 1997; Ping et al., 2008; Baba et al., 2009; Yang et al., 2011), and neurotransmitter release (Dubocovich et al., 1983; Boatright et al., 1994).

7. PHYSIOLOGICAL ACTIONS OF MELATONIN IN RETINA

7.1. Influences of Melatonin on Circadian Functions of Retina

The cell-specific expression of the melatonin receptor types and the physiological responses to melatonin receptor binding are essential factors that determine the influence of melatonin on retinal function. One potentially important role of melatonin in the normal retina is in the modulation of daily renewal of photoreceptor outer segment membrane. The distal tips of photoreceptor outer segments are shed on a daily rhythm as part of a renewal process, and are subsequently phagocytized by the adjacent retinal pigment epithelial (RPE) cells. Melatonin is thought to be involved in this process (Besharse and Dunis, 1983) but the molecular mechanism is not well understood, and the specific melatonin receptor types mediating this effect and their cellular localization have not been determined definitively.

Some functions of melatonin in the retina appear to be mediated indirectly through antagonism of dopamine signaling (Dubocovich, 1983; Iuvone and Besharse, 1986; Tosini and Dirden, 2000). Dopamine and melatonin serve as chemical messengers of day and night, respectively, and exert some of their influences by a mutual antagonism. For example, melatonin, synthesized at night, may bind to receptors to increase visual sensitivity and facilitate dark adaptation by increasing horizontal cell coupling through inhibition of dopamine release (Harsanyi and Mangel, 1992; Iuvone and Gan, 1995; Witkovsky et al., 1988a).

As one function of melatonin may be to increase the sensitivity of the retina to light as part of a dark-adaptation mechanism, an undesirable consequence of this may be an increased sensitivity to the damaging effects of light. Inappropriate exposure of retinal cells to melatonin may be detrimental to photoreceptor survival (Cahill and Besharse, 1992; Sugawara
et al., 1998; Wiechmann and O’Steen, 1992) as melatonin increases the degree of light–induced photoreceptor cell death in albino rats (Wiechmann and O’Steen, 1992; Bubenik and Purtill, 1980). Furthermore, the melatonin receptor antagonist luzindole protects photoreceptors from light–induced damage, thus demonstrating that the deleterious effect of melatonin is mediated through a retinal melatonin receptor (Sugawara et al., 1998). However, the precise melatonin receptor type responsible and whether it is expressed directly on photoreceptors or is mediated by activation of melatonin receptors located on cells in the inner retina has not been definitively determined to date.

7.2. Modulation of Neurotransmitter Release

Melatonin likely has a paracrine signaling influence on neurons of the inner retina. Paracrine signaling may exchange information between the melatonin-synthesizing photoreceptors and the dopaminergic amacrine cells (Dearry et al., 1991; Museran et al., 1993) of the INL and IPL. It is thought that melatonin diffuses throughout the retina to bind to melatonin receptors on target cells of the inner retina. Stimulation of melatonin receptors on specific amacrine cells modulates the release of dopamine and GABA (Boatright et al., 1994; Iuvone and Gan, 1995). Melatonin may inhibit the release of dopamine from amacrine cells by binding directly to receptors on dopaminergic amacrine cells. In addition, melatonin may act indirectly on dopaminergic amacrine cells by binding to melatonin receptors located on GABA-ergic amacrine cells to stimulate the release of GABA, which may then affect dopamine release. Since dopamine suppresses the synthesis of melatonin in the photoreceptor cells by binding to D2 dopamine receptors, which results in the suppression of AANAT activity (Iuvone and Besharse, 1986), melatonin and dopamine act as chemical signals of darkness and light, respectively, and have mutually antagonistic influences on retinal activities.

D₁ receptors are present on horizontal cells (Krizaj and Witkovsky, 1993; Zarbin et al., 1986) and are positively coupled to cyclic AMP synthesis. The dopamine–induced uncoupling of horizontal cell gap junctions (Lasater et al., 1984) suggests a potential scenario by which melatonin can influence the cyclic rhythm of light sensitivity. Melatonin released by photoreceptors at night may bind to melatonin receptors on dopaminergic amacrine cells to suppress dopamine release. Additionally, melatonin may bind to receptors on GABA-ergic amacrine cells, further inhibiting release from dopaminergic
amacrine cells (Boatright et al., 1994). The lower dopamine levels could then increase horizontal cell coupling and receptive field size. This would result in lower visual acuity, but would increase the sensitivity of the retina to light during the dark period since light-driven responses from photoreceptors would be pooled by more second-order neurons. Horizontal cells are hyperpolarized in response to reduction in dopamine levels (Dowling, 1991; Witkovsky and Shütte, 1991; Witkovsky et al., 1988b).

Additionally, melatonin may bind directly to receptors located on horizontal cells to increase horizontal cell coupling. Melatonin receptor RNA and protein are expressed in horizontal cells (Fujieda et al., 1999; Huang et al., 2005; Wiechmann and Sherry, 2012). Melatonin may also regulate horizontal cell activity postsynaptically by inhibiting the cAMP response to D1 receptor activation (Iuvone and Gan, 1995). Melatonin may therefore modulate dopaminergic transmission in the inner retina by a combination of reduced dopamine release from dopaminergic amacrine cells in the inner retina and inhibition of postsynaptic D1 receptors on horizontal cells. Melatonin potentiates glutamate-induced currents from isolated cone-driven horizontal cells in the carp retina by increasing the binding activity of the glutamate receptor (Huang et al., 2005), causing a depolarization of the H1 horizontal cell membrane potential, and a reduction in their light responses. The melatonin receptor antagonist luzindole blocks the effects of melatonin on H1 cell depolarization, but the melatonin effect persists in the presence of dopamine, GABA, and glycine receptor antagonists, suggesting that melatonin can also act directly on H1 cells (Huang et al., 2005). Therefore, melatonin potentially could provide circadian modulation of retinal sensitivity and transmission of photoreceptor signals at multiple levels of the retina by several different mechanisms: inhibition of dopamine release from amacrine cells, inhibition of D1 receptor-mediated uncoupling of horizontal cells, modulation of GABA-ergic amacrine cell signaling, and modulation of glutamatergic signaling from photoreceptors to second-order neurons.

7.3. Role of Melatonin in Visual Sensitivity

Melatonin may also act directly on retinal photoreceptors by binding to melatonin receptors located on the photoreceptors. Melatonin induces membrane conductance changes in isolated frog rod photoreceptors (Cosci et al., 1997) and binds with low affinity to structures in the OPL in frog retina (Wiechmann, 1986).
In a transgenic *Xenopus* model that overexpresses functional Mel1c receptors in rod photoreceptors, treatment with melatonin increases the electroretinogram (ERG) response to light (Wiechmann et al., 2003). Melatonin stimulates an increase in the amplitude of the $a$-wave of rod photoreceptors as well as the $b$-wave, which reflects an increased response from the cells of the inner retina, in transgenic animals. This lends further support to the general hypothesis that melatonin increases retinal sensitivity to light as part of a dark-adaptation mechanism. Although melatonin may enhance dark adaptation by affecting inner retinal cells as discussed above, melatonin may also act directly on rod photoreceptors to facilitate dark adaptation.

Melatonin reduces the circadian rhythm of the ERG $b$-wave amplitude and the $b$-wave, but not the $a$-wave peaks in the daytime (Miranda-Anaya et al., 2002), and both the $a$-wave and $b$-wave show a circadian rhythm in implicit time (Shaw et al., 1993). When circulating levels of melatonin are reduced, the ERG circadian rhythm is abolished. ERG $b$-wave amplitudes, but not the $a$-wave amplitudes have a circadian rhythm with peak amplitude in the daytime in chickens (Lu et al., 1995). In addition, the $a$-wave and $b$-wave implicit times are higher during the day than during the night (McGoogan and Cassone, 1995). In continuous darkness, melatonin treatment abolishes the rhythm of $a$-wave and $b$-wave implicit times and $b$-wave amplitude (McGoogan and Cassone, 1995). Therefore, the circadian system appears to regulate retinal sensitivity at least partially through melatonin.

### 7.4. Potential Role of Melatonin in Specific Retinal Circuits

Although it is well known that both MT1 and MT2 receptors are present in the retina, much less is known about the specific cell types that express each receptor and the specific circuits in which the various receptor subtypes are localized. However, studies in several species do provide some insight into the organization of MT1 and MT2 receptors in retinal circuits.

#### 7.4.1. Outer Plexiform Layer (OPL)

Both MT1 and MT2 receptors are present in the OPL across vertebrate species (Fujieda et al., 1999, 2000; Meyer et al., 2002; 2002, 2003; Wiechmann, 2003; Wiechmann and Summers, 2008; Wiechmann and Sherry, 2012; Wiechmann and Wirsig-Wiechmann, 2001; Wiechmann et al., 2003, 2004) although details of their precise functions and localization are scarce.
A common feature of melatonin receptor organization in the OPL is expressed by horizontal cells although the receptor subtype is expressed and their precise localization is species-dependent (Fujieda et al., 1999; Huang et al., 2005; Meyer et al., 2002; Ping et al., 2008; Scher et al., 2002, 2003; Wiechmann and Sherry, 2012). Physiological studies support a functional role for melatonin receptors in horizontal cells as melatonin reduces signaling to cone-driven horizontal cells in carp retina, probably via an MT1 receptor-mediated mechanism (Huang et al., 2005). Melatonin signaling may also modulate transmission to bipolar cells at the level of the OPL. Melatonin enhances transmission of rod-driven signals to bipolar cells via an MT2 receptor-mediated mechanism in the carp retina (Ping et al., 2008). MT2 receptors have also been localized to rod bipolar cells in the rat retina where they suppress K⁺ currents and depolarize the rod bipolar cells, potentially enhancing visual sensitivity (Yang et al., 2011). Melatonin also increases the amplitude of the rod-driven b-wave of the ERG in the mouse retina; however, this effect is mediated by MT1 receptors (Baba et al., 2009).

A recent study directly examining the relative distributions of MT1 and MT2 receptors in the OPL show that they are differentially localized on horizontal and bipolar cell processes in the X. laevis retina (Wiechmann and Sherry, 2012; Fig. 4), suggesting that MT1 and MT2 receptor-mediated signaling has discrete functions in the OPL. MT1 and MT2 receptors are differentially expressed, but localize specifically to the processes of second-order neurons with hyperpolarizing (OFF) light responses at contacts with cones. MT1 receptors are expressed selectively by axon-bearing horizontal cells and localize to the axon. MT2 receptors are expressed selectively on the dendrites of OFF bipolar cells at contacts with cone terminals. This arrangement implies that melatonin, which is at its highest levels in darkness when vision is dominated by rod-driven function, likely functions to suppress cone-driven noise to horizontal and OFF bipolar cells in order to enhance rod signaling although this has not been tested directly. It also remains uncertain whether all types of OFF bipolar cell in the Xenopus retina express MT2 receptors or whether MT2 expression is restricted to specific OFF bipolar cell subpopulations. It is also unclear presently whether MT1 and/or MT2 receptors localize selectively to contacts with specific classes of cone cells.

Melatonin acts to enhance rod-driven signaling during the dark portion of the light cycle. Differences in the distributions of melatonin receptors in the OPL of different species suggest that multiple mechanisms must exist to generate this enhancement. The available evidence suggests that at least two
different types of melatonin-driven mechanisms exist: decreasing cone-driven noise, as is likely to be present in the *Xenopus* retina, and/or direct enhancement of rod signaling to rod-driven bipolar cells, as is likely to be present in mammals.

### 7.4.2. Inner Plexiform Layer (IPL)

Melatonin receptors are broadly expressed by neurons projecting to the IPL including bipolar, amacrine and ganglion cells in mammals and nonmammals (Baba et al., 2009; Fujieda et al., 1999, 2000; Scher et al., 2002, 2003; Meyer et al., 2002; Sengupta et al., 2011; Wiechmann, 2003; Wiechmann and Summers, 2008; Wiechmann and Sherry, 2012; Wiechmann and Wirsig-Wiechmann, 2001; Wiechmann et al., 2003, 2004; Zhao et al., 2010).

Studies to determine the distribution of melatonin receptors in the inner retina have focused mainly on MT1 receptors. In situ hybridization studies...
show that the MT1 message is expressed by neurons at all levels of the INL and in the GCL, suggesting that the MT1 receptor is expressed by bipolar, amacrine and ganglion cells (Baba et al., 2009; Fujieda et al., 1999; Natesan and Casonne, 2002; Wiechmann, 2003; Wiechmann et al., 2004; Wiechmann and Sherry, 2012). Immunolabeling studies have demonstrated that the MT1 receptor is expressed by multiple types of amacrine cells across species (Baba et al., 2009; Fujieda et al., 1999, 2000; Scher et al., 2002, 2003; Sengupta et al., 2011; Wiechmann, 2003; Wiechmann et al., 2004; Wiechmann and Sherry, 2012). In the mammalian retina, amacrine cells shown to express the MT1 receptor include GABA-ergic amacrine cells, dopaminergic amacrine cells, and AII amacrine cells (Fujieda et al., 1999, 2000; Scher et al., 2002, 2003). The MT1 receptor is also expressed widely in retinal ganglion cells across species (Baba et al., 2009; Fujieda et al., 1999, 2000; Scher et al., 2002, 2003; Wiechmann, 2003; Wiechmann et al., 2004; Wiechmann and Sherry, 2012). A recent study performed in the mouse retina specifically identified MT1 expression by intrinsically photosensitive retinal ganglion cells (ipRGCs; Sengupta et al., 2010).

Although it is clear that the MT2 receptor is expressed in the retina (Natesan and Casonne, 2002; Reppert et al., 1995a; Scher et al., 2002; Wiechmann et al., 2004; Wiechmann and Sherry, 2012; Yang et al., 2011; Zhao et al., 2010), less is known about the cell-specific distribution of the MT2 receptor in the inner retina and IPL. Recent studies suggest that the MT2 receptor may be present on rod-driven bipolar cells in the carp and rat retinas (Ping et al., 2008; Yang et al., 2011), and on OFF bipolar cells in the Xenopus retina (Wiechmann and Sherry, 2012). Immunolabeling studies have confirmed MT2 expression in amacrine cells and ganglion cells as well (Wiechmann et al., 2004; Wiechmann and Sherry, 2012), however, the identities of the specific amacrine and ganglion cell types expressing MT2 receptors are poorly characterized. We should not discount the possibility of distinct species-specific differences in the expression of MT2 receptors. For example, in situ hybridization and immunolabeling studies suggest that MT1 and MT2 receptors are expressed in the retinal ganglion cells in Xenopus and mouse retina, however, it has been reported that rat retinal ganglion cells express only MT2 receptors (Zhao et al., 2010). More detailed studies of the specific cell types expressing MT1 and MT2 receptors and their synaptic localization will be needed to resolve these questions.

Less is known about the distribution and function of the Mel1c receptor in the retina. However, in the inner retina of X. laevis, Mel1c shows a distribution similar in some respects to the MT1 receptor and has been localized to
GABA-ergic and dopaminergic amacrine cells as well as ganglion cells (Wiechmann, 2003; Wiechmann and Wirsig-Wiechmann, 2001). Specific functions in the retina have not yet been assigned to the Mel1c receptor. As discussed above, GPR50, the mammalian homolog of the nonmammalian Mel1c receptor, does not bind melatonin (Dufourny et al., 2008).

Melatonin is likely to perform multiple functions in the IPL that lead to increased retinal sensitivity and enhanced transmission of rod-mediated signals. A key function of retinal melatonin is to suppress the release of dopamine (Dubocovich, 1983), a key signal in light adaptive changes in the retina (Witkovsky, 2004). The expression of MT1 receptors by dopaminergic amacrine cells suggests direct modulation of dopamine amacrine cell function (Fujieda et al., 2000; Scher et al., 2002), and is consistent with the ability of melatonin to inhibit dopamine release (Dubocovich, 1983). However, a recent study in the retina of mice lacking MT1 receptors showed that melatonin did not regulate dopamine levels or the numbers of dopaminergic amacrine cells (Sengupta et al., 2011). Melatonin is also positioned to modulate the function of the AII amacrine cell, which expresses the MT1 receptor (Scher et al., 2003) and is essential for transmission of rod-driven signals through the primary rod pathway of the mammalian retina (Bloomfield and Dacheux, 2001). The effects of melatonin on AII cell physiology, however, have not been reported. The recent finding of MT1 receptor expression specifically by ipRGCs, which have important functions related to circadian activity and light–dark adaptation in the retina (Pickard and Sollars, 2012), suggests that melatonin may be an important modulator of ipRGC function (Sengupta et al., 2011). However, the precise role of melatonin in modulating ipRGC function is currently unknown. Finally, melatonin signaling also appears to have long-term roles in maintaining the health of retinal neurons, as MT1 receptor deficiency leads to enhanced photoreceptor and ganglion cell loss with aging (Baba et al., 2009).

7.5. Potential Role of Melatonin in Adaptive Changes in Synaptic Structure

The structure of photoreceptor synaptic complexes undergo adaptive remodeling in a light-dependent and circadian manner. The length of the synaptic ribbons in photoreceptor terminals is altered in a circadian manner (Adly et al., 1999; Vollrath and Spiwoks-Becker, 1996; Spiwoks-Becker et al., 2004). Autocrine signaling via the melatonin receptors expressed by
photoreceptors potentially may contribute to these remodeling events (Baba et al., 2009; Sengupta et al., 2011; Wiechmann, 2003; Wiechmann et al., 2003, 2004) although that has not been directly established. In the retinas of fish, horizontal cells show reversible light-dependent extension of small protrusions known as “spinules” (Behrens et al., 2000; Raynauld et al., 1979; Wagner and Douglas, 1983). The light/dark adaptive extension and retraction of these spinules is sensitive to melatonin agonists and antagonists, which have been proposed to modulate spine formation and retraction indirectly by modulating dopamine release (Behrens et al., 2000; Wagner et al., 1992; Yazulla et al., 1996; Yazulla and Studholme, 1995; Wagner, 1980). MT1 receptor expression by photoreceptors and horizontal cells suggests that melatonin also could contribute directly to these adaptive processes although this has not been tested directly.

Similar light- and dark-adaptive changes in synaptic ribbons and the extension and retraction of spinules also occur in the synaptic terminals of Mb bipolar cells in the goldfish retina (Hull et al., 2006; Yazulla and Studholme, 1992). Rat rod bipolar cells also show light–dark remodeling of their terminals (Behrens et al., 1998). It is not known currently if melatonin signaling is involved in the adaptive remodeling of bipolar cell terminals.

8. CONCLUDING REMARKS

Horizontal cell axons that express Mel1a (MT1) receptors form synaptic contacts with cone terminals that synapse with Mel1b (MT2) receptor-positive OFF-cone bipolar cell dendrites. Physiological studies indicate that melatonin potentiates rod signals to ON type bipolar cells, via activation of the melatonin MT2 (Mel1b) receptor. Together, these studies suggest that melatonin signaling in the outer retina is positioned specifically to play a role in modulating cone-driven signals in OFF circuits in the OPL.

Given that retinal melatonin levels are highest in darkness, when visual function is dominated by rods, Mel1a and Mel1b receptors activation would be expected to lead to enhanced signaling in rod pathways in some manner. On the basis of the selective localization of Mel1a and Mel1b receptors to OFF bipolar and horizontal cell processes contacting cone terminals, these receptors may serve to reduce noise from signaling by cone terminals in darkness. This would presumably result in increased sensitivity of the retina to light at nighttime, and may represent a component of dark adaptation.
Melatonin may be an important signal in the daily switching of the retina from cone-driven to rod-driven function in both mammals and non-mammals. It is therefore not surprising that the organization of melatonin receptors would ultimately result in a conserved end-point of reducing cone signaling and enhancing rod signaling. However, the differences in the anatomical organization of rod and cone circuits between mammalian and nonmammalian retinas may result in distinctly different anatomical organization of melatonin receptors across species.

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