Circadian regulation in the retina: from molecules to network

Y.-P. Ko Gladys

Department of Veterinary Integrative Biosciences, Texas A&M University, College Station, Texas, USA; Texas A&M Institute of Neuroscience, Texas A&M University, College Station, Texas, USA.

Abstract

The mammalian retina is the most unique tissue among those that display robust circadian/diurnal oscillations. The retina is not only a light sensing tissue that relays light information to the brain, it has its own circadian "system" independent from any influence from other circadian oscillators. While all retinal cells and retinal pigment epithelium (RPE) possess circadian oscillators, these oscillators integrate by means of neural synapses, electrical coupling (gap junctions), and released neurochemicals (such as dopamine, melatonin, adenosine, and ATP), so the whole retina functions as an integrated circadian system. Dysregulation of retinal clocks not only causes retinal or ocular diseases, it also impacts the circadian rhythm of the whole body, since the light information transmitted from the retina entrains the brain clock that governs the body circadian rhythms. In this review, how circadian oscillations in various retinal cells are integrated, how retinal diseases affect daily rhythms, and how modern electronic displays might affect human health are discussed.

Keywords

retina; photoreceptor; circadian rhythm

Introduction

The vertebrate retina is the most unique tissue among those that display robust circadian/diurnal oscillations. The retina is not only a light sensing tissue that relays light information to the brain, it has its own circadian "system" that prepares the retina to anticipate the upcoming dawn or dusk. In lower vertebrates and invertebrates, there are multiple light sensing tissues or organs in addition to the retina, such as the pineal gland, regions in the deep brain, skin, and even the entire body. In higher mammalian species, these tissues or organs lose the ability to detect light except the retina, even though they still have their circadian oscillator machinery intact.

The neural retina is not a homogenous tissue. It is packed with different types of neurons and glia cells and is highly organized in stratified layers (Dowling, 1970). All of the retinal cells are known to have circadian oscillators, so the circadian signals from retinal cells have

§Correspondence addressed to: Gladys Y.-P. Ko, Ph. D., Department of Veterinary Integrative Biosciences, College of Veterinary Medicine and Biomedical Sciences, Texas A&M University, 4458 TAMU, College Station, TX 77843-4458, USA., Tel: 979-845-1797, gko@cvm.tamu.edu.

to integrate to allow the retina to function as an independent circadian system. The major retinal neurons and glial cells are the photoreceptors, bipolar cells, ganglion cells, horizontal cells, amacrine cells, and the Müller glia (Dowling, 1970; Dowling & Werblin, 1971). The electroretinogram (ERG) is often used to record retinal light responses under various illuminating conditions with the a-wave reflecting the photoreceptor responses of the outer retina while the b-wave reflects the inner retinal responses. The ERG a-wave, b-wave, or both display circadian rhythms in a species-dependent manner (Dearry & Barlow, 1987; Fowlkes *et al.*, 1987; Hawlina *et al.*, 1992; Hankins *et al.*, 1998; Manglapus *et al.*, 1998; Manglapus *et al.*, 1999; McGoogan & Cassone, 1999; Hankins *et al.*, 2001; Miranda-Anaya *et al.*, 2002; Ren & Li, 2004; Cameron *et al.*, 2008; Cameron & Lucas, 2009; Danilenko *et al.*, 2009; Danilenko *et al.*, 2011; Sengupta *et al.*, 2011; Jackson *et al.*, 2012), indicating that the retinal light sensitivities and responses are governed by the internal circadian system (Barlow, 2001). Thus, retinas do not merely respond to ambient light passively, the circadian system in the retina actively regulates the overall light responses and prepares the retina to adapt to the upcoming dawn or dust (Green & Besharse, 2004). The canonical circadian core genes (such as *Per 1–3*, *Bmal1*, *Clock*, *Cry 1–2*, *RevErb*, and *Ror*) and their molecular mechanisms are detected in the retina [for a review of the molecular mechanism of circadian oscillation, please see Bell-Pedersen *et al.*, 2005; Storch *et al.*, 2007; Tosini *et al.*, 2008; McMahon *et al.*, 2014; Besharse & McMahon, 2016]. While we will not address the specific molecular mechanism of circadian oscillation in this review, we will address the circadian oscillations in various retinal neurons and how they integrate.

I. Circadian oscillation in the photoreceptors

Among retinal cells, the circadian oscillation in photoreceptors is studied the most (Young, 1978; LaVail, 1980; Burnside *et al.*, 1982; Fisher *et al.*, 1983; Cahill & Besharse, 1993; Pierce *et al.*, 1993; Stenkamp *et al.*, 1994; Cahill & Besharse, 1995; Green & Besharse, 2004; Menger *et al.*, 2005; Hasegawa & Cahill, 1998; 1999b; a; Manglapus *et al.*, 1999; Valenciano *et al.*, 1999; Ko *et al.*, 2001; 2003; Hasegawa & Cahill, 2004; Ko *et al.*, 2004a; Menger *et al.*, 2005; Chaurasia *et al.*, 2006; Ko *et al.*, 2006; Sakamoto *et al.*, 2006; Ko *et al.*, 2007; Ivanova *et al.*, 2008; Ribelayga *et al.*, 2008; Jackson *et al.*, 2009; Ko *et al.*, 2009b; Haque *et al.*, 2010; Ko *et al.*, 2013; Li *et al.*, 2013; Jin *et al.*, 2015; Zhang *et al.*, 2015; Baba *et al.*, 2018; Pierce & Besharse, 1985; 1988; Pierce *et al.*, 1993; Manglapus *et al.*, 1999; Tosini *et al.*, 2007). Rod and cone photoreceptors are the first neurons to detect light and relay this information to the bipolar cells and then to ganglion cells for vision. Photoreceptors in lower vertebrates have autonomous circadian oscillators, and they function independently in the absence of other retinal inputs (Hasegawa & Cahill, 1998; Ko *et al.*, 2001; Hasegawa & Cahill, 2004). While the core circadian clock genes and proteins are all detected in mammalian photoreceptors (Tosini *et al.*, 2007; Schneider *et al.*, 2010; Sandu *et al.*, 2011; Liu *et al.*, 2012; Dkhissi-Benyahya *et al.*, 2013), whether the mammalian photoreceptors are as autonomous as the ones in lower vertebrates remains controversial. As the photoreceptors strongly rely on lighting conditions to drive their circadian oscillation shown in rodents (Sandu *et al.*, 2011; Besharse & McMahon, 2016), the isolated rat photoreceptors display circadian oscillations of clock genes in cultures, which demonstrates that photoreceptor clocks can function independently without inputs from other retinal cells (Tosini *et al.*, 2007). The photoreceptor oscillators lead to morphological, physiological,

biochemical, and molecular changes that ultimately regulate photoreceptor function and physiology in a circadian fashion (Figure 1; Green & Besharse, 2004; Tosini *et al.*, 2008; Ko *et al.*, 2009a; Ko *et al.*, 2010; Besharse & McMahon, 2016). In vertebrate rod photoreceptors, outer segment shedding and renewal is a continuous process, but the rate of which is under circadian control (Young, 1978; LaVail, 1980; Reme *et al.*, 1986; Dearry & Barlow, 1987; Grace *et al.*, 1999). In some lower vertebrates such as teleosts, amphibian, and fish, the inner segments of rod and cone photoreceptors undergo sustained contraction and elongation, known as retinomotor movement, in response to changes in ambient illumination as well as the circadian cycles (Burnside & Ackland, 1984; Pierce & Besharse, 1985; 1988; Stenkamp *et al.*, 1994; Burnside, 2001; Menger *et al.*, 2005). While cones remain in a contracted state during the day and elongated at night or after dark adaptation, rods contract at night (Menger *et al.*, 2005). The molecular machinery regulating photoreceptor elongation requires microtubule shuttling and assembly by dynein-1 (Lewis *et al.*, 2018). It is reasonable to postulate that the rate of dynein-1 movement might be governed by the photoreceptor oscillators, with rods and cones anti-phase to each other.

Photoreceptors form specialized ribbon synapses with bipolar cells and horizontal cells. The numbers and ultrastructure of synaptic ribbons in both photoreceptors and bipolar cells undergo changes depending on the time of day and light intensities (Vollrath *et al.*, 1989; Vollrath & Spiwoks-Becker, 1996; Adly *et al.*, 1999; Balkema *et al.*, 2001; Spiwoks-Becker *et al.*, 2004; Hull *et al.*, 2006). In addition to the circadian oscillator genes, several photoreceptor-specific genes such as opsin and rhodopsin (Korenbrot & Fernald, 1989; Pierce *et al.*, 1993; Green & Besharse, 1996; Bernard *et al.*, 1997; von Schantz *et al.*, 1999; Yu *et al.*, 2007), ion channels (Ko *et al.*, 2001; Ko *et al.*, 2004a; Ko *et al.*, 2007; Ko *et al.*, 2010), and enzyme activities (Besharse & Iuvone, 1983; Ko *et al.*, 2001; 2004b; Ko *et al.*, 2009b; Ko *et al.*, 2009c; Huang *et al.*, 2012; Huang *et al.*, 2013; Ko *et al.*, 2013; Huang *et al.*, 2015) are also under circadian control that ultimately contribute to the circadian regulation of photoreceptor physiology and function. Photoreceptors are more susceptible to light damage during the subjective night (Organisciak *et al.*, 2000; Vaughan *et al.*, 2002), which likely reflects circadian regulation of the expression and distribution of retinal crystallins, the chaperone proteins trafficking in and out of the photoreceptor outer segments that is protective to photoreceptors (Organisciak *et al.*, 2011).

The cGMP-gated cation channel (CNGC) is the last step of the phototransduction process that takes place in the outer segments in response to light-induced hyperpolarization of photoreceptors. Light induces a G-protein mediated phototransduction cascade that results in a fall in local intracellular cGMP and leads to the closure of CNGCs, reduced cation influx, and membrane hyperpolarization. In the absence of photon stimulation, the intracellular cGMP concentration is relatively high, which causes the opening of CNGCs and influx of cations (Na^+ and Ca^{2+}) to depolarize photoreceptors in the dark. Thus, CNGCs carry the photoreceptor "dark current" and serve essential roles in the light-dependent changes in photoreceptor membrane potential and subsequent neural processing (Cobbs *et al.*, 1985; Pugh Jr. & Lamb, 2000; Kramer & Molokanova, 2001; Lamb & Pugh, 2004). Even though the opening or closure of CNGCs is dependent on light stimulation, the affinity of CNGCs to cGMP is under circadian regulation in avian cone photoreceptors (Ko *et al.*, 2001; Chae *et al.*, 2007). The apparent affinity of CNGCs to cGMP is higher at the subjective night than

during the subjective day suggesting a substantially larger dark current during the subjective night than subjective day. The complex cell-signaling involving adenylyl cyclase, cAMP, Ras-MAP kinase (MAPK), calcium/calmodulin-dependent kinase II (CaMKII), and tyrosine kinase leads to the circadian rhythmicity of tyrosine phosphorylation on the 85-kDa auxiliary subunit of cone CNGCs and provides one of the final steps in the circadian regulation of CNGCs (Ko *et al.*, 2001; 2003; 2004b; Chae *et al.*, 2007). Because the CNGCs in photoreceptors are essential components of the visual phototransduction cascade, they may also play a role in the light entrainment of photoreceptor circadian oscillators. Since the gating of CNGCs is under circadian control in cone photoreceptors, these channels represent an example of an entity that is both an input to and an output from the circadian oscillator (Ko *et al.*, 2001). Roenneberg and Merrow (Roenneberg & Merrow, 1999) have presented models of circadian oscillator systems in which pathways that lead to entrainment of the core oscillators (i.e. the circadian inputs) can themselves be regulated by the oscillators (i.e. they are also components of circadian outputs). One feature of these models is that they contain additional feedback loops that can markedly enhance the stability of the overall oscillator system. Therefore, the circadian regulation of CNGCs in retinal photoreceptors represents an adaptation to enhance the stability of retinal circadian oscillators.

L-type calcium channels (LTCCs) mediate a voltage-dependent and depolarization-induced calcium influx and regulate diverse biological processes such as contraction, secretion, neurotransmission, differentiation, and gene expression in many different cell types (Barnes & Kelly, 2002; Benitah *et al.*, 2002; Catterall *et al.*, 2005; Thorneloe & Nelson, 2005; Dolphin, 2006; Catterall & Few, 2008; Dolphin, 2009; Joiner & Lee, 2015). There are three major LTCCs expressed in the vertebrate retina: Cav1.2, Cav1.3, and Cav1.4 (Ahlijanian *et al.*, 1990; Strom *et al.*, 1998; Firth *et al.*, 2001; Morgans, 2001; Barnes & Kelly, 2002; Xu *et al.*, 2002; Haeseleer *et al.*, 2004; Morgans *et al.*, 2005; Cristofanilli *et al.*, 2007; Ko *et al.*, 2007; Wu *et al.*, 2007; Kersten *et al.*, 2010; Mizuno *et al.*, 2010; Xing *et al.*, 2012; Zou *et al.*, 2012; Knoflach *et al.*, 2013; Liu *et al.*, 2013; Lee *et al.*, 2015; Haeseleer *et al.*, 2016; Shi *et al.*, 2017a). In photoreceptors, Cav1.4 is exclusively expressed at the synaptic terminals and responsible for the tonic release of glutamate in the dark as a result of depolarization-evoked activation of LTCCs (Morgans, 2001; Haeseleer *et al.*, 2004; Knoflach *et al.*, 2013; Haeseleer *et al.*, 2016). Cav1.3 is also detected at the synaptic terminal (Firth *et al.*, 2001; Shi *et al.*, 2017a), but it might not be as essential for mediating neurotransmitter release as Cav1.4 (Shi *et al.*, 2017a; Shi *et al.*, 2017b). Both Cav1.2 and Cav1.3 are largely expressed in the inner segments and cell bodies, in which calcium influx into this part of the photoreceptors is involved in calcium-dependent gene expression, metabolism, and homeostasis (Miller *et al.*, 1994; Korenbrot, 1995; Wilkinson & Barnes, 1996; Firth *et al.*, 2001; Barnes & Kelly, 2002; Krizaj & Copenhagen, 2002; Xu *et al.*, 2002; Ko *et al.*, 2007; Ko *et al.*, 2009a; Krizaj, 2012; Joiner & Lee, 2015).

Circadian regulation of LTCCs has been observed in gold fish retinal bipolar cells (Hull *et al.*, 2006), chick cone photoreceptors (Ko *et al.*, 2007; Ko *et al.*, 2009b; Shi *et al.*, 2009; Huang *et al.*, 2012; Huang *et al.*, 2013; Ko *et al.*, 2013; Huang *et al.*, 2015), and other non-retinal neurons (Kim *et al.*, 2005; Nahm *et al.*, 2005). In both retinal cases, the average maximal current amplitudes of LTCCs are significantly larger at midnight than at midday, while the activation and channel gating kinetics do not change throughout the course of a

day. In chick retinas, the main factor contributing to the circadian regulation of LTCC current amplitudes is the expression of functional L-VGCCα1 subunits, with mRNA levels and protein expression of Cav1.3 being rhythmic (Ko *et al.*, 2007). The Ras-MAPK-CaMKII signaling pathway that regulates the circadian rhythms of CNGCs also serves as part of the circadian output to regulate LTCCs. However, the circadian regulation of LTCCs and CNGCs are different. While the expression of Cav1.3 varies throughout the day with varying maximal amplitudes, the CNGC currents remain constant, but its gating properties exhibit changes throughout the day (Ko *et al.*, 2001; Ko *et al.*, 2007). In addition to Ras-MAPK-CaMKII signaling, phosphatidylinositol 3 kinase (PI3K)-protein kinase B (AKT) signaling (Ko *et al.*, 2009b), calcineurin (Huang *et al.*, 2012), mechanistic/mammalian target of rapamycin complex 1 (mTORC1, (Huang *et al.*, 2013), and AMP-activated protein kinase (AMPK, (Huang *et al.*, 2015) are all involved in the circadian regulation of LTCCs. Furthermore, microRNA-26a regulates LTCCs at the post-transcriptional level (Shi *et al.*, 2009). In photoreceptors, not only is the activation (phosphorylation) of the complex signaling network rhythmic, these networks further regulate the circadian rhythms of LTCCs and CNGCs and thus the physiology of photoreceptors. Several molecules in the signaling network including AKT, mTORC1, and AMPK that regulate LTCCs are also involved in cellular metabolism. The overall production of ATP displays a diurnal rhythm in avian retinas (Huang *et al.*, 2015). Thus, it is reasonable to assume that at the cellular level, metabolism and energy production in photoreceptors is under circadian regulation.

While cone photoreceptors are responsible for daytime and color vision and rod photoreceptors are for nighttime and dim-light vision (Dowling, 1987), there is a circadian regulation in the interaction between rods and cones (Wang & Mangel, 1996; Manglapus *et al.*, 1998; Manglapus *et al.*, 1999; Ribelayga *et al.*, 2002; Ribelayga *et al.*, 2008; Ribelayga & Mangel, 2010). The ERG recordings using monochromatic light sources indicate a day and night difference in the dynamics of rod- or cone-dominance (Manglapus *et al.*, 1998; Manglapus *et al.*, 1999). There is a day-night change in spectral sensitivity as the cones dominate during the day while the rods dominate during the night, even when animals are kept in constant darkness for several days. The process is mostly governed by the photoreceptor circadian clocks. As cone photoreceptors specifically form synapses with cone bipolar cells and rod photoreceptors synapse onto rod bipolar cells, this rod-cone shift takes place at the photoreceptor-to-bipolar cell synapses (Manglapus *et al.*, 1998). Furthermore, the rod-cone shifts are modulated by dopamine, a neurotransmitter released from the amacrine cells in the inner retina (Manglapus *et al.*, 1999). The modulatory action of dopamine in the retinal circadian system will be discussed in the following section.

Even though the synapse between a photoreceptor and a bipolar cell is rod/cone specific, rod and cone photoreceptors in the vertebrate retina are anatomically connected or coupled by gap junctions (Raviola & Gilula, 1973; Yang & Wu, 1989; Krizaj *et al.*, 1998; Bloomfield & Dacheux, 2001; Hornstein *et al.*, 2005) meaning rod inputs can enter the cone circuitry (Ribelayga *et al.*, 2008). The rod-cone coupling is remarkably strong at night but weak during the day in goldfish, rabbit, and mice (Ribelayga *et al.*, 2008; Ribelayga & Mangel, 2010). This rhythmic rod-cone coupling is mediated by the circadian regulation of the phosphorylation of connexin 36 (Cx36), the gap junction protein between rods and cones, in which Cx36 phosphorylation is higher at night than during the day (Zhang *et al.*, 2015). The

rod-cone coupling is also subjected to modulation by dopamine (Witkovsky *et al.*, 1988; Wang & Mangel, 1996; Krizaj *et al.*, 1998; Ribelayga *et al.*, 2002; 2004; Jin *et al.*, 2015), since both rods and cones express dopaminergic receptors, while horizontal cells do not (Witkovsky *et al.*, 1988; Cohen *et al.*, 1992; Yazulla & Lin, 1995; Krizaj *et al.*, 1998; Ko *et al.*, 2003).

II. Circadian oscillators in the inner retinal cells

The core clock genes are all detected in the inner retinal neurons (bipolar, horizontal, amacrine, and ganglion cells) especially in the dopaminergic (DA) amacrine cells (Witkovsky *et al.*, 2003; Gabriel *et al.*, 2004; Ruan *et al.*, 2006; Liu *et al.*, 2012). Based on morphological characteristics and neurotransmitters released, there are 30–40 types of amacrine cells in the inner retina (Remington, 2012). While the core clock genes oscillate in amacrine cells, whether these gene transcripts cycle rhythmically in other inner cells (bipolar neurons, horizontal neurons, and ganglion neurons) are not clear. Imaging of a bioluminescent reporter of *Per2Luc* shows the circadian cycling of the core circadian gene *Per2* across the whole retina (Ruan *et al.*, 2008), as well as in isolated retinal layers, including the photoreceptor layer, inner retinal layer, and the ganglion cell layer (Jaeger *et al.*, 2015). Interestingly, in mixed dissociated retinal cell cultures excised from the PERIOD2 (PER2)::LUC (*Per2Luc*) knock-in mice, the *Per2Luc* bioluminescent oscillation maintains similar amplitudes without dampening, while the *Per2Luc* oscillations show dampening after a few cycles in the individual retinal layers (Jaeger *et al.*, 2015), which might imply that the overall circadian rhythm in the retina requires the integration from all cellular oscillators. Müller glial cells are proposed to play a role in integrating the whole retinal circadian system, since all the core clock genes oscillate in these glial cells, and the circadian rhythmicity of these glial cells is able to sustain in isolation from other cell types (Ruan *et al.*, 2006; Xu *et al.*, 2016). A single Müller cell extends the entire thickness of the retina and makes contacts with multiple retinal neurons. Furthermore, there are gap junctions (or tight junctions) between Müller cells, as well as between Müller cells and photoreceptors (Dowling, 1987; Rich *et al.*, 1995). Light or dark information coming from the photoreceptors could have been relayed to these glial cells through the junctions. As Müller cells are critical in regulation of ion buffering and neurotransmitter recycling (Dowling, 1987), it is reasonable to postulate that Müller glial cells are able to synchronize the circadian rhythm of the whole retina. However, within the retina, not all signals are synchronized in the same circadian phase. For example, the dopamine released from the DA amacrine cells peaks during the day time, while melatonin diffused from the photoreceptors and the pineal cells peaks at night (Besharse & Iuvone, 1983; Robertson & Takahashi, 1988; Zatz, 1989; Iuvone, 1990; Benloucif & Dubocovich, 1996; Nikaido & Takahashi, 1996; Adachi *et al.*, 1998; Tosini, 2000; Tosini & Dirden, 2000; Iuvone *et al.*, 2002; Miranda-Anaya *et al.*, 2002; Besharse *et al.*, 2004; Fukuhara *et al.*, 2004; Iuvone *et al.*, 2005; Peters & Cassone, 2005; Baba *et al.*, 2009; Tosini *et al.*, 2012; Bernard *et al.*, 1997; Ebihara *et al.*, 1997). These neurochemical signals serve as synchronizing signals to integrate various circadian oscillators in the retina.

III. Circadian integration in the retina

a. The retinal dopamine-melatonin anti-phase relationship.—The two major neurotransmitters that serve as "day" and "night" signals in the retina are dopamine and melatonin, respectively (Figure 2; Dubocovich, 1983; Adachi *et al.*, 1998), and the retinal dopamine is always in an opposite circadian/diurnal phase to retinal melatonin (Besharse & Iuvone, 1983; Dubocovich, 1983; Adachi *et al.*, 1998). Dopamine has long been known to regulate retinal physiology (Dowling, 1990; 1991). While dopamine is synthesized and release from the DA amacrine cells (Iuvone *et al.*, 1978; Dubocovich *et al.*, 1985; Dowling, 1990), dopamine receptors are distributed throughout the whole retina (Krizaj *et al.*, 1998; Witkovsky, 2004; Jackson *et al.*, 2009; Keeley & Reese, 2010; Jackson *et al.*, 2012). The synthesis and release of dopamine is light-driven as well as circadian regulated in birds and amphibians, but in mammalian retinas that are melatonin-deficient, their retinal dopamine content only displays a diurnal rhythm (Iuvone *et al.*, 1978; Nir *et al.*, 2000a; b; Valenciano *et al.*, 2000; Zhang *et al.*, 2018). While previous studies showed that light stimulated DA amacrine cells by activating rods, cones, and the melanopsin-expressing intrinsically photosensitive retina ganglion cells (ipRGCs; please see a later section for details on ipRGCs; Zhang *et al.*, 2007; Zhang *et al.*, 2008; Newkirk *et al.*, 2013; Vuong *et al.*, 2015), a more comprehensive examination shows that it is the cone photoreceptors that drive the light signals through multiple neural circuits, including both ON and OFF bipolar cells, as well as a cone-driven retrograde signaling pathway from ipRGCs, to modulate the dopamine release from DA amacrine cells (Qiao *et al.*, 2016).

As the light stimulates dopamine synthesis (Iuvone *et al.*, 1978), dopamine is able to modulate retina daytime vision by enhancing the contrast sensitivity and spatial resolution of light-adapted retinas (Jackson *et al.*, 2012). In retina-specific dopamine deficient mice, their light-adapted ERG responses, contrast sensitivity, acuity, and the retinal circadian rhythms are dampened, but their dark-adapted ERG responses appear normal (Jackson *et al.*, 2012). Thus, dopamine is critical for regulating retinal light adaption and daytime vision. In addition, dopamine is able to act like the light/daytime signal (Manglapus *et al.*, 1999) to entrain (Hasegawa & Cahill, 1999b) and phase-shift the retinal clocks in amphibians (Green *et al.*, 1995; Steenhard & Besharse, 2000), and exogenous dopamine inhibits melatonin production from the photoreceptors at night (Hasegawa & Cahill, 1999b; a; Zawilska & Iuvone, 1992; Nguyen-Legros *et al.*, 1996; Tosini & Dirden, 2000). Dopamine shifts the rod-cone dominance (Manglapus *et al.*, 1999) as well as the rod-cone coupling toward the "daytime" phase in birds, fish, and mammals (Witkovsky *et al.*, 1988; Wang & Mangel, 1996; Krizaj *et al.*, 1998; Ribelayga *et al.*, 2002; 2004; Jin *et al.*, 2015). Interestingly, while dopamine is able to phase-shift and modulate photoreceptor properties as mentioned above, cone photoreceptors are involved in the photic regulation of retinal DA amacrine cells (Qiao *et al.*, 2016).

The expression of dopamine receptors in the retina is also under circadian control (Nir *et al.*, 2002). In the mouse retina, the D1, D2, D4, and D5 dopamine receptors mediate dopamine's bioactivities (Jackson *et al.*, 2009). However, not all dopamine receptors contribute to the circadian regulation of the retina. Through binding to the D2/D4 receptors, administering dopamine during the subjective night shifts CNGCs from its high affinity to cGMP to a

lower daytime-like affinity in avian cone photoreceptors, while inhibition of D1 receptors does not have any effects on cone photoreceptors (Ko *et al.*, 2003). In mice, deletion of D5 receptors have no impact on retinal function, but knock out of D4 or D1 receptors have distinct visual deficits (Jackson *et al.*, 2012). Even though dopamine acting through D1 receptors is necessary to maintain retinal spatial resolution in mice, it is the D4 receptors that mediate the circadian regulation of light-adapted ERG (Jackson *et al.*, 2012). Dopamine shifts the rod-cone coupling toward the "daytime" phase through D2-like receptors in fish and mice (Ribelayga & Mangel, 2003; 2007; Ribelayga *et al.*, 2008). Furthermore, it is through D2-like receptors that dopamine inhibits melatonin synthesis in the photoreceptors (Nguyen-Legros *et al.*, 1996). Hence, it is reasonable to conclude that through D2/D4 receptors, dopamine serves as a daytime signal to modulate the retinal circadian rhythm.

As mentioned earlier, both dopamine and melatonin are important circadian signals in the retina that have reciprocal and antagonistic relationships with each other (Iuvone, 1986; Nguyen-Legros *et al.*, 1996; Ebihara *et al.*, 1997; Adachi *et al.*, 1998; Tosini & Dirden, 2000). Melatonin is synthesized and secreted from the retina photoreceptors in lower vertebrates (such as avian, amphibian, reptile, fish) and most mammalian species, and all retinal cells express melatonin receptors (Dubocovich, 1985; 1991; Tosini *et al.*, 2008; Tosini *et al.*, 2012; Acuna-Castroviejo *et al.*, 2014). While it is still debatable whether the retina is able to synthesize and secrete melatonin in humans and higher primates (Reiter *et al.*, 2010; Hardeland *et al.*, 2012; Acuna-Castroviejo *et al.*, 2014; Bonmati-Carrion *et al.*, 2014), it is clear that the retinal melatonin level is higher at night than during the day, in part through the melatonin released from the pineal gland at night reaching the retina through blood circulation (Acuna-Castroviejo *et al.*, 2014; Bonmati-Carrion *et al.*, 2014; Blasiak *et al.*, 2016). The transcription of arylalkylamine N-acetyltransferase (AANAT), the key melatonin synthesis enzyme, is under circadian control, so at night, the content of retinal melatonin is higher than the day time (Besharse & Iuvone, 1983; Iuvone & Besharse, 1983; Dubocovich, 1988; 1991; Bernard *et al.*, 1999; Iuvone *et al.*, 2005; Tosini *et al.*, 2008; Haque *et al.*, 2010; Tosini *et al.*, 2012). In the carp retina, melatonin serves as an autocrine or paracrine signal and modulates neurotransmission from cones and cone-driven bipolar cells (Huang *et al.*, 2005). Administration of exogenous melatonin in *Xenopus* and carps increases the amplitude of dark-adapted scotopic ERG (Wiechmann *et al.*, 2003; Ping *et al.*, 2008). Administration of exogenous melatonin during the daytime reduces the ERG b-wave amplitude in diurnal birds (Lu *et al.*, 1995) but increases the ERG a- and b-wave amplitudes in nocturnal mice (Baba *et al.*, 2009). In humans, oral intake of melatonin during the day decreases the amplitude of the cone ERG (Gagne *et al.*, 2009), and the amplitude of the cone and mixed rod-cone responses are negatively correlated with the endogenous melatonin concentration in the saliva (Rufiange *et al.*, 2002). Constant administration of melatonin abolishes the ERG circadian rhythms in chickens (McGoogan & Cassone, 1999). Interestingly, although melatonin is known to regulate the disk shedding of photoreceptor outer segments in *Xenopus* and rats (Besharse & Dunis, 1983; White & Fisher, 1989), when comparing the circadian rhythm of disk shedding between melatonin-proficient (C3H+/+) and melatonin-deficient (C57/BL6) mice, the disk shedding is rhythmic in both mouse strains, and exogenous melatonin does not affect the circadian rhythmicities, which questions the contribution of melatonin in regulating the rhythmic disk shedding in mice

(Grace *et al.*, 1999). Thus, how disk shedding in mammalian species is regulated requires further investigation (Tosini *et al.*, 2012).

The synthesis of melatonin is not only governed by the photoreceptor circadian clock, light and dopamine are also able to inhibit the production and secretion of melatonin from photoreceptors as mentioned previously. As dopamine through D2/D4 receptors inhibits the synthesis and release of melatonin, melatonin appears to regulate the circadian rhythm of dopamine in the retina. At night, melatonin inhibits the dopamine production from amacrine cells (Dubocovich, 1983; Adachi *et al.*, 1998). In fish, the rhythmic dopamine release in the retina depends on the activation of melatonin receptors (Ribelayga *et al.*, 2002). In mice, melatonin also regulates the circadian rhythm of retinal dopamine. In a comparison between melatonin-proficient (C3H+/+) and melatonin-deficient (C57BL6) mice, C3H+/+ mice display strong circadian oscillations of retinal dopamine content and metabolism, while C57BL6 mice do not (Doyle *et al.*, 2002). However, if the melatonin-deficient (C57BL6) mice are given daily injections of melatonin, these mice exhibit a robust circadian rhythm of retinal dopamine content even if the mice are kept in constant darkness (Doyle *et al.*, 2002). Therefore, in the retina, not only do dopamine and melatonin reciprocally regulate each other, dopamine serves as a "day signal" while melatonin serves as a "night signal" to orchestrate the circadian oscillators existing in various retinal cell types enabling the whole retina to function and adjust across 12 magnitudes of ambient light changes harmoniously throughout the course of a day (Green & Besharse, 2004; Besharse & McMahon, 2016).

b.   Adenosine triphosphate (ATP): the circadian regulation of retinal metabolism and the role of ATP in inter-retinal communication.—In addition to melatonin and dopamine that serve as neural signals in the retina to regulate the overall retinal circadian rhythm, ATP has been proposed as an inter-retinal signal to synchronize the retinal clocks, and the metabolic state in the retina is under circadian regulation (Dmitriev & Mangel, 2000; 2001; 2004; Huang *et al.*, 2015). As shown in the fish and rabbit retina, the retinal pH values oscillate in a circadian fashion (Dmitriev & Mangel, 2000; 2001), and overall pH changes in the retina reflects changes in its metabolic state (Dmitriev & Mangel, 2004). In the avian retina, the overall ATP level displays a diurnal rhythm that is nearly antiphase to the circadian oscillation of AMP-activated protein kinase (AMPK) activation (Huang *et al.*, 2015). AMP-activated protein kinase (AMPK) is a cellular energy sensor (Hardie, 2007a). When the intracellular AMP to ATP ratio rises, AMPK is activated (phosphorylated) and promotes catabolic pathways while inhibiting anabolic ones so that more ATP is generated (Hardie, 2007a; b; Towler & Hardie, 2007). Among all retinal neurons, the photoreceptors consume the most energy (Wong-Riley, 2010), and their energy consumption is highly compartmentalized (Linton *et al.*, 2010; Wei *et al.*, 2012). There is heavy energy expenditure in the outer segments of photoreceptors where phototransduction and protein transport for outer segment renewal are taking place in response to various light intensities (Korenbrot, 1995; Koutalos & Yau, 1996). In the dark, most of the energy consumption is in the inner segments and synaptic terminals to maintain the dark currents and neurotransmitter release (Wong-Riley, 2010). The retinal photoreceptors have a higher metabolic activity in the dark, which means that on one hand, ATP is hydrolyzed in an accelerated rate to support tonic neurotransmitter release. On the other hand, mitochondria

will have to produce more ATP to sustain photoreceptor activities. As a result, the mitochondrial enzymes that are responsible for ATP production should be more active in darkness, which is supported by Huang *et al.* (2004) where the mitochondrial enzymes cytochrome C oxidase III and adenosine triphosphatase-6 are down-regulated by higher light intensity (Huang *et al.*, 2004). The overall ATP production might be lower in the presence of bright light. Therefore, the retinal energy expenditure and production can be light intensity-dependent as a reflection of acute light/dark adaptation, as well as circadian clock-regulated.

In addition to serving as a cellular energy source, ATP is also a neurotransmitter in the retina, and ATP receptors are present in all retinal neurons (Ho *et al.*, 2014). ATP and other purines (ADP, AMP, adenosine, adenine, and hypoxanthine) are tonically released in the retina particularly in the dark (Perez *et al.*, 1986), and such release is increased by neuronal activity (Neal & Cunningham, 1994). However, Müller glia cells are also able to generate, release, and accumulate extracellular ATP (Loiola & Ventura, 2011). Interestingly, in cultured cortical glia cells, extracellular ATP accumulation displays circadian rhythms (Womac *et al.*, 2009; Burkeen *et al.*, 2011). Hence, extracellular ATP could serve as a neurotransmitter to communicate among multiple circadian oscillators that exist in different retinal cell types (Ruan *et al.*, 2006; Liu *et al.*, 2012). In addition, the extracellular ATP can further be converted into adenosine, which could contribute to the circadian rhythm of retinal adenosine with a higher concentration at night than during the day (Ribelayga & Mangel, 2005). Retinal adenosine is known to regulate circadian rhythms of photoreceptor coupling, as well as retinal light/dark adaptation (Ribelayga & Mangel, 2005; 2007; Ribelayga *et al.*, 2008; Li *et al.*, 2013). Therefore, the circadian rhythm of retinal ATP might not only reflect the circadian control of energy status, but it might implicate that ATP and its metabolite adenosine could serve as neuromodulators to coordinate the various circadian oscillators in the retina to integrate the overall retinal circadian rhythm in the whole retina. As evidence, there is a circadian regulation of retinal light responses as measured by electroretinogram (ERG) in humans and animals (Dearry & Barlow, 1987; Fowlkes *et al.*, 1987; Hawlina *et al.*, 1992; Hankins *et al.*, 1998; Manglapus *et al.*, 1998; Manglapus *et al.*, 1999; McGoogan & Cassone, 1999; Hankins *et al.*, 2001; Miranda-Anaya *et al.*, 2002; Ren & Li, 2004; Cameron *et al.*, 2008; Cameron & Lucas, 2009). As heterogeneous as the retina is, through multiple mechanisms, including the rod-cone coupling, Muller glial cells, inter-retinal synaptic network, dopamine / melatonin inverse regulation, and ATP / adenosine, the retina as a whole has its own circadian system that allows it to anticipate the upcoming light changes at dawn and dusk and adapt to daily ambient illumination.

IV. The relationship between retinal photoreceptors and the retinal pigment epithelium (RPE)

As stated above, the outer segments (OS) of photoreceptors are constantly shedding and renewing, the rate of which is under circadian control. The outermost tips of photoreceptor OS are surrounded by RPE cells. RPE cells phagocytose the shed tips of the OS, degrade the shed disk membrane, and further recycle molecules involved in phototransduction back to the photoreceptors (Mazzoni *et al.*, 2014). If phagocytosis is defective and the OS debris accumulates in the interphotoreceptor space, it causes photoreceptor degeneration (Dowling & Sidman, 1962; Bok & Hall, 1971; Mullen & LaVail, 1976; Anderson *et al.*, 1983; Sheedlo

et al., 1989) as seen in inherited retinal degeneration diseases such as retinitis pigmentosa and inherited maculopathies (LaVail & Mullen, 1976; Mullen & LaVail, 1976; Bertolotti *et al.*, 2014), and in Royal College of Surgeons Rats (Caldwell & McLaughlin, 1985). While the rod OS tip clearance occurs at dawn or with light stimulation (LaVail, 1976b; a; Besharse *et al.*, 1977; Fisher *et al.*, 1983; LaVail, 1980; Reme *et al.*, 1986; Ruggiero *et al.*, 2012; Laurent *et al.*, 2017), the timing of cone OS clearance varies by species, depending on whether the animal's retina is rod-dominant (Young, 1977; O'Day & Young, 1978; Fisher *et al.*, 1983) or cone-dominant (Anderson *et al.*, 1978; Young, 1978; Immel & Fisher, 1985; Bobu *et al.*, 2006; Bobu & Hicks, 2009). Even though photoreceptor oscillators appear to control the OS shedding and renewal, the rate of phagocytosis of shed OS requires circadian control from the RPE, as RPE cells also have intact circadian oscillators (Baba *et al.*, 2010; Ruggiero *et al.*, 2012; Baba *et al.*, 2017; Laurent *et al.*, 2017), and cultured RPE isolated from the *Per2Luc* mouse displays circadian oscillations in luciferase activities (Baba *et al.*, 2017). Thus, the rhythmic oscillations of the autophagy process in RPE cells are controlled by RPE cells themselves. In this regard, while photoreceptors and RPE cells have independent circadian oscillators, the shed disks from photoreceptor OS that are to be engulfed and degraded in RPE cells require synchronization from both. Even though administration of melatonin induces disk shedding in *Xenopus* retinas (Besharse & Dunis, 1983) and increases phagocytosis in rat RPE cells (White & Fisher, 1989), the rhythmic disk shedding is still present in melatonin-deficient mice (Grace *et al.*, 1999). Since dopamine is able to phase-shift the circadian rhythm of RPE via the D2 receptors expressed in the RPE (Baba *et al.*, 2017), dopamine is likely to be the neurochemical signal that synchronizes photoreceptors and the RPE.

Like photoreceptors, the protein expression of Cav1.3 is under circadian control in the RPE (Muller *et al.*, 2014; Reichhart & Strauss, 2014; Genewsky *et al.*, 2015). Interestingly, in Cav1.3 knockout mice, the RPE lacks peak phagocytic activity following morning photoreceptor shedding and retained a higher number of phagosomes at a later time of the day. The big potassium (BK) channel is a voltage-dependent and calcium-modulated large conductance potassium channel and is also expressed abundantly in the RPE, but its mRNA expression is not under circadian control (Muller *et al.*, 2014). In BK knockout mice, the RPE retains normal phagocytic capability, but its rhythmic phagocytosis is phase-shifted out of synchronization from the photoreceptor disk shedding. Thus, both Cav1.3 and BK channels might be important to regulate the circadian timing in RPE phagocytosis in synchronization with photoreceptors for the disk shedding.

V.   Melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs): their role in photoentrainment

The primary visual pathway starts with the rods and cones transmitting light information to bipolar cells, ganglion cells, and onto the lateral geniculate nucleus in the thalamus for image processing (Dowling, 1987). About 2–5% of retinal ganglion cells are able to detect light directly, the intrinsically photosensitive retinal ganglion cells (ipRGCs; Provencio *et al.*, 1998; Berson *et al.*, 2002; Hattar *et al.*, 2002; Hattar *et al.*, 2003; Lucas *et al.*, 2003; Chaurasia *et al.*, 2005; Hannibal *et al.*, 2014). After leaving the eye, the axons of ipRGCs directly project to the suprachiasmatic nucleus (SCN), the central clock, through the

retinohypothalamic tract (Hendrickson *et al.*, 1972; Moore & Lenn, 1972; Hattar *et al.*, 2002; Hattar *et al.*, 2003; Lucas *et al.*, 2003). This is the non-visual pathway mediating circadian inputs of light information into the SCN for photoentrainment. There are major electrical properties of ipRGCs that are different from the traditional photoreceptors (rods and cones). When light reaches the photoreceptor OS, through a G protein-coupled phosphodiesterase-mediated phototransduction process, it causes a decrease of intracellular cGMP, closure of CNGCs, and hyperpolarization of photoreceptors, which further decreases the release of glutamate from photoreceptors to other inner neurons (Edwards, 1995; Zagotta & Siegelbaum, 1996; Kaupp & Seifert, 2002). When light reaches the ipRGCs, it initiates an intracellular phosphoinositide signaling cascade leading to transient receptor potential (TRP) channels opening and cell depolarization, as such, ipRGCs fire action potentials and release glutamate onto SCN neurons (Berson *et al.*, 2002; Panda *et al.*, 2005; Warren *et al.*, 2006; Hartwick *et al.*, 2007; Sekaran *et al.*, 2007). The traditional photoreceptors use rhodopsin and opsins as their chromophores (Yau & Baylor, 1989; Edwards, 1995), but the ipRGCs use melanopsin, a chromophore first identified from the skin of amphibians (Provencio *et al.*, 1998; Hattar *et al.*, 2002; Hattar *et al.*, 2003; Lucas *et al.*, 2003).

There are at least 5 subtypes of ipRGCs (M1-M5), and they have different morphological characteristics, retinal distribution, and possibly different functions (Schmidt *et al.*, 2011b). Even though these ipRGCs directly send light information to the SCN, they still receive inputs from rods and cones, and their light responses and mRNA levels are modulated by these inputs (Berson *et al.*, 2002; Sakamoto *et al.*, 2004; Lucas *et al.*, 2012). In addition, these ipRGCs have complex relationships with other retinal neurons. Dopamine receptors are expressed in retinal ganglion cells (McMahon *et al.*, 2014), and dopaminergic amacrine neurons directly interact with ipRGC dendrites (Vugler *et al.*, 2007). As such, not only does dopamine regulate melanopsin expression in ipRGCs (Sakamoto *et al.*, 2005), it directly modulates the light responses of ipRGCs through D1 receptors (Van Hook *et al.*, 2012). Furthermore, ipRGCs might send retrograde signals that modulate the retinal light responses. The intraretinal axon collaterals of ipRGCs project to dopaminergic amacrine cells and influence retinal light adaptation, since the deletion of M1 ipRGCs attenuates retinal light adaptation (Prigge *et al.*, 2016). During development, ablation of ipRGCs causes mislocalization of a subset of cone photoreceptors in dark-reared animals (Tufford *et al.*, 2018).

Even though rods, cones, and ipRGCs all provide light information for circadian entrainment, ipRGCs play a more significant role in overall photoentrainment and circadian regulation of the whole body. Patients with glaucoma, in which their RGCs (including ipRGCs) are degenerated, often suffer from circadian dysregulation related syndromes, such as sleep disorders (Gracitelli *et al.*, 2015; Guo *et al.*, 2017) and autonomic nervous system dysfunction (Kashiwagi *et al.*, 2000) that are caused in part by a deficiency of circadian entrainment (Guido *et al.*, 2010). Other ocular diseases related to retinal degeneration (such as macular degeneration, diabetic retinopathy, or inherited blindness) that dampens or prevents light inputs to the SCN may also impact the overall circadian rhythm of patients. Patients with Smith-Magenis Syndrome, a genetic disorder, have abnormal daily rhythms with sleep disturbances (daytime sleepiness, nocturnal awakenings, difficulty falling asleep at night), and they have high melatonin levels during the day but low levels at night. These

patients apparently have a deficit in melanopsin positive ipRGC photoreception (Barboni *et al.*, 2018), which reinforces the importance of ipRGCs in photoentrainment.

As mentioned earlier, light suppresses melatonin release from the pineal gland and the retina. This is because the pineal gland is under the control of the SCN through the autonomic system, and the SCN directly receives light inputs from ipRGCs (for reviews see (Macchi & Bruce, 2004; Guido *et al.*, 2010; Hardeland, 2012). Among the wavelengths of visible light, the 460 nm blue light suppresses melatonin twice as much as the 555 nm green light and shifts the circadian rhythms by twice the duration (3.5 hr versus 1.5 hr; Gooley *et al.*, 2010). Evidently, some blind people are not able to see images due to degenerated photoreceptors, but they still have conscious light perception with intense light stimulus at 481 nm, which is the peak spectral sensitivity of melanopsin (Zaidi *et al.*, 2007). This discovery led to intensive research on the influence of blue lights and health (Tosini *et al.*, 2016). Most modern electronic displays (including cell phones, computers, tablets, and televisions) emit blue lights through their screens, and energy efficient lighting such as the light-emitting diode (LED) and curlicue compact fluorescent lightbulbs emit more blue lights than the traditional incandescent lightbulbs, which has raised concerns on possible adverse effects of human health (Tosini *et al.*, 2016). People who wear "blue-light goggles" that allow more blue light into the eyes while concurrently looking at computer monitors have significantly decreased nighttime melatonin levels compared to subjects only exposed to monitor light at night (Figueiro *et al.*, 2011). Attenuation of blue light by wearing short wavelength-blocking glasses prior to bedtime significantly increases the night time melatonin level and improves the sleep quality and duration (Ostrin *et al.*, 2017).

While ipRGCs project to the SCN, they also project to other brain areas (Schmidt *et al.*, 2011a; Schmidt *et al.*, 2011b), including the limbic system (amygdala, habenula, and dorsal thalamus), which is important in mood regulation and cognitive function (Lazzerini Ospri *et al.*, 2017). The amygdala plays an important role in learned fear (fear-conditioning), but light enhances mice fear-conditioning responses, in which rods, cones, and ipRGCs are required (Warthen *et al.*, 2011). Keeping adult diurnal rodents in a short photoperiod (such as light:darkness at 5:19 hr) for a period of time causes depression-like behavior (Ashkenazy-Frolinger *et al.*, 2010; Leach *et al.*, 2013). When animals are entrained to 12:12 light-dark cycles with dim light during the light-phase, they also display depressive behavior similar to animals in a short photoperiod (Deats *et al.*, 2015; Ikeno *et al.*, 2016). If diurnal rodents are entrained to light-dark cycles but with dim light at night, they have impaired cognition and depression without circadian alterations (Fonken *et al.*, 2012). Thus, because ipRGCs receive light information from rods and cones and project to the limbic system, different light settings (such as dim lights or short photoperiods) might affect mood and cognitive function (Lazzerini Ospri *et al.*, 2017).

VI. The circadian clocks and ocular diseases

As the circadian clocks in the retina regulate retinal metabolism, signaling, gene expression, and light sensitivity, altered clock function is likely to affect retinal health. Dysregulation of the core clock genes has been regarded as a key factor in the pathogenesis of several ocular diseases. The *Bmal1* knockout mice display premature aging symptoms, and their ocular

abnormalities include corneal neovascularization, keratinization, and progressive inflammation (Yang *et al.*, 2016), while *Clock*-deficient mice have cataracts (Kondratov *et al.*, 2006). In addition, photoreceptor viability during aging is significantly reduced in *Bmal1* knockouts, as they lose 20–30% of their photoreceptors at 8–9 months old compared to the wild type mice of the same age (Baba *et al.*, 2018). *Per1/Per2* knockout mice have scattered retinal deformations as well as reduced cone opsin expression (Ait-Hmyed *et al.*, 2013). These data suggest that either disruption of circadian rhythms in the eye or the retina would cause these ocular diseases, or the core circadian genes (*Bmal1*, *Clock*, *Per1*, *Per2*) might have other functions such as supporting the proper development and health of the retina. Disruption of retinal dopamine rhythms causes myopia in chickens (Stone *et al.*, 1989; Stone *et al.*, 1990; McMahon *et al.*, 2014), while lens-induced myopia changes the expression of circadian clock genes and melatonin receptors in the retina (Stone *et al.*, 2011). Thus, the circadian rhythm in the retina is important for refractive error development (Stone *et al.*, 2013; Chakraborty *et al.*, 2018). As mentioned previously, photoreceptors are more sensitive to light damage during the subjective night (Organisciak *et al.*, 2000; Vaughan *et al.*, 2002). In rodent models of type 1 or type 2 diabetes, the expression of several circadian genes is down regulated in the retina (Kuriyama *et al.*, 2004; Busik *et al.*, 2009; Wang *et al.*, 2014; Lahouaoui *et al.*, 2016), but there is no such change in the SCN. It is possible that changes in retinal circadian genes correlate to the diabetic disease progression. However, it also implies that dysregulation of the retinal circadian clocks in diabetes might exacerbate or even contribute to diabetic retinopathy.

While the dysregulation of the retinal clock genes might lead to various ocular diseases mentioned above, certain ocular diseases that manifest death of RGCs (such as glaucoma) or decreased light input to the retina (such as in aging eyes or eyes with cataracts) affect the whole body circadian timing. Glaucoma is a widespread ocular disease and a major cause of blindness (Quigley & Broman, 2006). Dysregulation of intraocular pressure (IOP) due to aging, hypertension, or the inability of diurnal oscillations of IOP contributes to the pathogenesis of glaucoma (Quigley, 1993; Friedman *et al.*, 2004; Boland & Quigley, 2007; Choi & Kook, 2015). Patients with glaucoma often have disturbed sleep problems and dampened diurnal rhythms (Zizi *et al.*, 2002; Jean-Louis *et al.*, 2008; Lanzani *et al.*, 2012). In a rat model of glaucoma with ~50–70% of RGCs degenerated, these glaucomatous rats require higher light intensities for entrainment, take more days to re-adjust to a shifted light-dark cycle, and show significantly higher variability in locomotor activity onsets compared to normal rats (Drouyer *et al.*, 2008). Age-related eye changes such as crystalline lens yellowing, cataract development, or miosis progression (decreased pupillary area) cause a progressive loss of light transmission into the retina, which leads to a decrease of light inputs to the SCN for circadian photoreception (Turner *et al.*, 2010). Deficiency in light reception eventually causes a significant decrease in systemic melatonin even to undetectable levels, along with decreased amplitudes in daily oscillations of several hormones (Monk *et al.*, 1997; Oren *et al.*, 1997; Van Someren *et al.*, 2002; Danilenko *et al.*, 2009). Thus, weakened SCN control of the body circadian rhythms due to decreased light inputs from the retina, aging, or both may increase the risk of all-cause morbidity (Hastings *et al.*, 2003; Turner *et al.*, 2010). Cataract surgery not only recovers vision, it further improves circadian photoreception and reduces the adverse effect of chronodisruption in these patients (Turner

& Mainster, 2008; Turner *et al.*, 2010). Therefore, the deficiency in light reception into the retina due to ocular diseases or aging contributes to dysregulation of the whole body circadian rhythm that has a profound adverse impact on health.

VII. Summary

The retina has a fascinating circadian system in that all retinal cells have their own oscillators, and yet all of these circadian oscillators are integrated for the rhythmic regulation of retinal physiology and function. Thus, the retina does not just passively respond to ambient light, its circadian system actively prepares the retina to anticipate the changes in light intensity that come with dawn and dust. Dysregulation of the retinal circadian system has adverse impacts on photoreceptors, RPE, RGCs, and possibly the lens and the cornea (McMahon *et al.*, 2014), which implies that the retinal circadian system further affects other ocular tissues beyond the neural retina. In disease states such as diabetes, downregulation of the clock genes in the retina might further exacerbate the development of diabetic retinopathy. Since the retina transmits light information to the SCN that further controls the circadian rhythm of the entire body, degenerated retinas dampen the light input to the SCN which further affects the body's daily rhythms. As we live in a modern society with advanced lighting for both day and night, excessive illumination not only has adverse impacts on the retina, light pollution may have a strong impact on human health that has been underestimated (Contin *et al.*, 2016). While advancements in technology shifts usage from the old incandescent lightbulbs to more energy efficient LED lighting and with many electronics emitting blue lights, the adverse effects of blue lights on human daily rhythms and health have been a research focus in recent years. As more research on the use of LEDs on health will be needed, maybe with the continued evolution of scientific technology, future illumination devices will be more environment and human health friendly.

Acknowledgements

Abbreviations list:

AANAT	arylalkylamine N-acetyltransferase
AKT	protein kinase B
AMPK	AMP-activated protein kinase
BK	big conductance potassium channel
Bmal1	Brain and muscle Arnt-like protein-1
Ca^{2+}	calcium
CaMKII	Calcium/calmodulin-dependent kinase II
CNGC	cGMP-gated cation channel

Na⁺	sodium
Cry	Cryptochrome
Cx36	connexin 36
DA	dopaminergic
ERG	electroretinogram
ipRGC	intrinsically photosensitive retinal ganglion cell
K⁺	potassium
LED	light-emitting diode
LTCC	L-type calcium channel
Luc	lucerferase
MAPK	mitogen-activated protein kinase
mTORC1	mechanistic/mammalian target of rapamycin complex 1
OS	outer segment of the photoreceptor
Per	Period
PI3K	phosphatidylinositol 3 kinase
Ror	retinoic acid receptor-related orphan receptors
RPE	retinal pigment epithelium
SCN	suprachiasmatic nucleus
TRP	transient receptor potential

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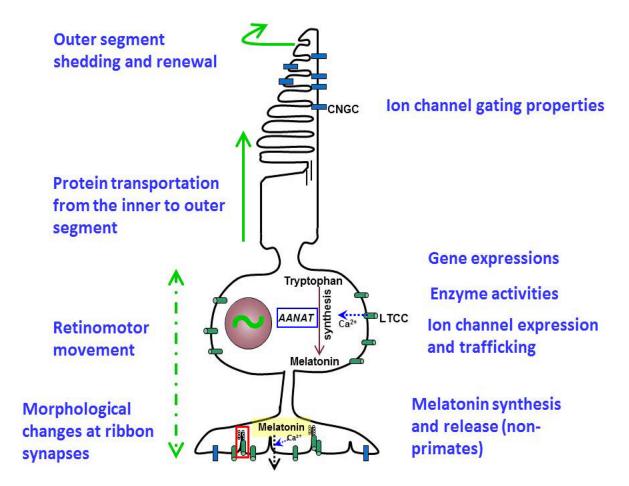
Figure 1. There is circadian regulation in the vertebrate photoreceptor.
CNGC: cGMP-gated cation channel; LTCC: L-type voltage-gated calcium channel;
AANAT: Aralkylamine N-acetyltransferase, also known as arylalkylamine N-
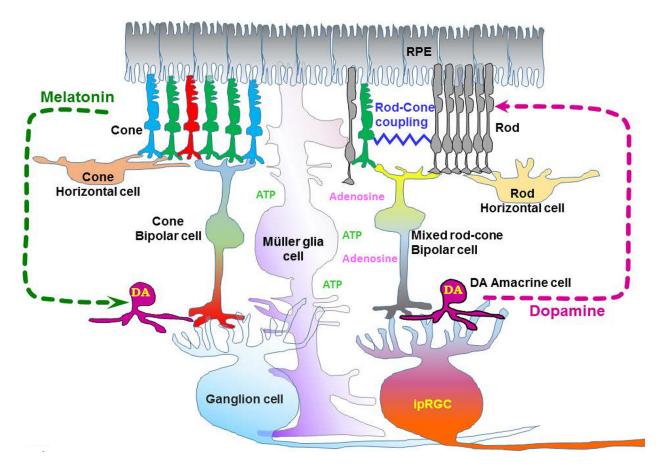acetyltransferase or serotonin N-acetyltransferase, the key enzyme of melatonin synthesis.

Figure 2. A schematic diagram of the circadian system in the retina.
All retinal cells and retinal pigment epithelium (RPE) have circadian oscillators.
Photoreceptors release melatonin at night that inhibits dopaminergic amacrine cells (DA)
from releasing dopamine. During the day, dopamine released from the amacrine cells
inhibits the melatonin synthesis and release from the photoreceptors. As the gap junction
couplings between rods and cones are stronger at night, the intrinsic clock-driven signals, as
well as dopamine, uncouple these electric synapses between rods and cones. The intrinsic
photosensitive retinal ganglion cell (ipRGC) receives inputs from photoreceptors through
bipolar cells, as well as receiving dopamine from AII amacrine cells. The ipRGCs directly
relay the light signal to the SCN for photoentrainment.