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Circadian organization of the mammalian retina: From gene regulation to physiology and diseases

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ABSTRACT

The retinal circadian system represents a unique structure. It contains a complete circadian system and thus the retina represents an ideal model to study fundamental questions of how neural circadian systems are organized and what signaling pathways are used to maintain synchrony of the different structures in the system. In addition, several studies have shown that multiple sites within the retina are capable of generating circadian oscillations. The strength of circadian clock gene expression and the emphasis of rhythmic expression are divergent across vertebrate retinas, with photoreceptors as the primary locus of rhythm generation in amphibians, while in mammals clock activity is most robust in the inner nuclear layer. Melatonin and dopamine serve as signaling molecules to entrain circadian rhythms in the retina and also in other ocular structures. Recent studies have also suggested GABA as an important component of the system that regulates retinal circadian rhythms. These transmitter-driven influences on clock molecules apparently reinforce the autonomous transcription–translation cycling of clock genes. The molecular organization of the retinal clock is similar to what has been reported for the SCN although inter-neural communication among retinal neurons that form the circadian network is apparently weaker than those present in the SCN, and it is more sensitive to genetic disruption than the central brain clock. The melatonin–dopamine system is the signaling pathway that allows the retinal circadian clock to reconfigure retinal circuits to enhance light-adapted cone-mediated visual function during the day and dark-adapted rod-mediated visual signaling at night. Additionally, the retinal circadian clock also controls circadian rhythms in disk shedding and phagocytosis, and possibly intra-ocular pressure. Emerging experimental data also indicate that circadian clock is also implicated in the pathogenesis of eye disease and compelling experimental data indicate that dysfunction of the retinal circadian system negatively impacts the retina and possibly the cornea and the lens.

Contents

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1. Introduction

Daily rhythms are a common feature of living systems. Generally, these rhythms are not just passive consequences of cyclic fluctuations in the environment, but instead originate within the organism. In mammals, including humans, the master pacemaker controlling 24-h rhythms is localized in the suprachiasmatic nuclei of the hypothalamus (SCN). This circadian clock is responsible for the temporal organization of a wide variety of functions, ranging from sleep and food intake, to physiological measures such as body temperature, heart rate and hormone release.

Experimental evidence has shown that the mammalian retina contains a complete circadian clock system – biochemical machinery that generates temperature-compensated 24 h oscillations, an input pathway by which light synchronizes the cycling of the retinal clock to the environmental light/dark cycle, and neurochemical output pathways that transmit the clock's influence throughout the retina and into the rest of the brain. The retinal circadian clock drives many processes within the retina including gene expression, synaptic communication and metabolism, which reconfigure retinal circuits and shape the functioning of the retina according to time of day. The circadian clock system in the retina allows the anticipation of the normal cycle of photopic and scotopic visual conditions that alternate with the cycling of solar day and night. Another important function of the circadian clock resides in the capability to act as the gate for sensory information, and this function is a fundamental property of sensory organs and systems in a wide variety of species. Here, we focus on the mammalian retinal circadian clock and recent advances in its understanding, while previous reviews have covered studies of circadian rhythms in non-mammalian retinas, where this line of research began (Besharse, 1982; Besharse et al., 1988; Cahill and Besharse, 1995).

Several studies have clearly established that many aspects of mammalian retinal physiology and function are under the control of a retinal circadian clock (Fig. 1). Melatonin release (Besharse and Iuvone, 1983; Tosini and Menaker, 1996, 1998), dopamine synthesis (Nir et al., 2000; Doyle et al., 2002a, 2002b), gamma-aminobutyric acid (GABA) turnover rate and release (Jaliffa et al., 2001), extracellular pH (Dmitriev and Mangel, 2001), electroretinogram (ERG) b-wave amplitude (Barnard et al., 2006; Storch et al., 2007), rod disk shedding (Teirstein et al., 1980), and UV opsin and rhodopsin gene expression (von Schantz et al., 1999), are all regulated in a

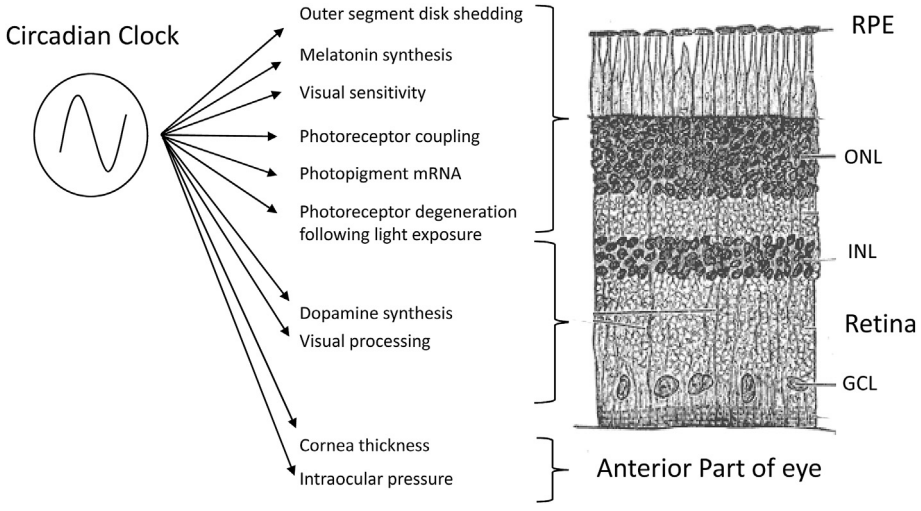

Fig. 1. The circadian clock system in the mammalian retina controls several functions. Many studies have shown that rhythms in the eye are under direct control of the retinal circadian clock system. Recent studies have also indicated that the many different cell types within the eye contain circadian clocks that interact to modulate many ocular functions. Shown here are several known circadian processes in the retina and the eye, with their approximate location identified by retinal layer. RPE = retinal pigment epithelium, ONL = outer nuclear layer, INL = inner nuclear layer, GCL = ganglion cell layer.