Progress in Neurobiology 92 (2010) 484–504

Contents lists available at ScienceDirect

Progress in Neurobiology

journal homepage: www.elsevier.com/locate/pneurobio

Inner retinal circadian clocks and non-visual photoreceptors: Novel players in the circadian system

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ARTICLE INFO

Article history:
Received 4 December 2009
Received in revised form 8 August 2010
Accepted 11 August 2010

Keywords:
Phototransduction
Retina
Circadian rhythms
Non-visual functions
Clock genes
Photoreceptors
Ganglion Cells
Retinal diseases
Melatonin
Lipids
Dopamine
Metabolic oscillators

ABSTRACT

Daily and annual changes in ambient illumination serve as specific stimuli that associate light with time and regulate the physiology of the organism through the eye. The eye acts as a dual sense organ linking light and vision, and detecting light that provides specific stimuli for non-classical photoreceptors located in the inner retina. These photoreceptors convey information to the master circadian pacemaker, the hypothalamic suprachiasmatic nuclei (SCN). Responsible for sensing the light that regulates several non-visual functions (i.e. behavior, pupil reflex, sleep, and pineal melatonin production), the retina plays a key role in the temporal symphony orchestra playing the musical score of life: it is intrinsically rhythmic in its physiological and metabolic activities. We discuss here recent evidence in support of the hypothesis that retinal oscillators distributed over different cell populations may act as clocks, inducing changes in the visual and circadian system according to the time of the day. Significant progress has recently been made in identifying photoreceptors/photopigments localized in retinal ganglion cells (RGCs) that set circadian rhythms and modulate non-visual functions. Autonomous retinal and brain oscillators could have a more complex organization than previously recognized, involving a network of "RGC clock/SCN clock cross-talk". The convergence of oscillatory and photoreceptive capacities of retinal cells could deeply impact on the circadian system, which in turn may be severely impaired in different retinal pathologies. The aim of this review is to discuss the state of the art on inner retinal cell involvement in the light and temporal regulation of health and disease.

Contents

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doi:10.1016/j.pneurobio.2010.08.005

1. The circadian timing system and the suprachiasmatic nuclei (SCN) as the Orchestra Director of the circadian system

Most living organisms, from cyanobacterias to plants, insects, and mammals, display spontaneously sustained oscillations in approximately 24 h-cycles known as circadian rhythms (from the Latin *circa dies*). These rhythms evolved as an adaptation to environmental changes – day/night cycles – deriving from the Earth's rotation, they can occur in constant conditions, and are therefore endogenous (Dunlap et al., 2004). Body temperature, hormonal levels, sleep and countless other physiological variables exhibit daily oscillations, attesting to the importance of biological clocks in regulating these daily rhythmic activities. Such clocks form the circadian system that enables organisms to anticipate daily and seasonal changes in environmental conditions, and adjust their rhythms accordingly.

The circadian timing system in vertebrates is composed of central pacemakers located in the brain and of several peripheral oscillators distributed throughout the body (Dibner et al., 2010; Dunlap et al., 2004). The circadian system is essential for temporally regulating physiology and behavior and has to be adjusted daily by environmental signals such as light, food availability, temperature, social interactions and others.

In mammals, the master biological clock that commands the temporal organization of physiology and behavior lies in the suprachiasmatic nuclei (SCN) of the hypothalamus, a pair of small nuclei located above the optic chiasm and laterally to the third ventricle. There is strong evidence supporting the functional role of the SCN as the master circadian clock (for review see (Hastings, 1991; Meijer and Schwartz, 2003; Morin, 2007; Rusak and Boulos, 1981; Rusak and Zucker, 1979; Vidal and Morin, 2007)). In addition, the SCN is a major site of retinal projections coming through the retinohypothalamic tract (RHT) (Hendrickson et al., 1972; Moore and Lenn, 1972; Morin, 2007).

Nearly all circadian clocks have free-running periods that do not conform to a 24 h-cycle. To maintain synchronism with the 24 h-day, the circadian clock is mainly reset by light. Photic cues from the daily light–dark cycle reach the SCN directly from the retina *via* the RHT, or indirectly from the intergeniculate leaflet (IGL) of the lateral geniculate complex, serving to maintain the organism in phase with the outside world. In this way, the SCN generates output signals that reach the rest of the organism to ensure the synchronization of the temporal organization of the entire body (reviewed in (Dibner et al., 2010; Dunlap et al., 2004; Morin and Allen, 2006; Welsh et al., 2010)).

Mammalian circadian entrainment occurs exclusively *via* the eyes and optic nerves. The RHT connects a small subset of retinal ganglion cells (RGCs) with the SCN, and plays an essential role in photic entrainment (Meijer and Schwartz, 2003; Morin, 2007; Morin and Allen, 2006; Rusak and Boulos, 1981; Rusak and Zucker, 1979). Besides the master circadian pacemaker located in the SCN, many peripheral tissues also contain independent or quasi-independent circadian oscillators (Dibner et al., 2010; Dunlap et al., 2004). Since the retina plays a key role in SCN synchronization and therefore in circadian physiology, the existence of an autonomous retinal circadian clock was investigated. Indeed, several lines of evidence strongly support the existence of a clock in the retina (Doyle et al., 2002a; Grace et al., 1996; Iuvone et al., 2005; Niki et al., 1998; Tosini and Menaker, 1996, 1998), serving to regulate a variety of cellular, biochemical, and physiological processes.

2. The retina: a leading player in the rhythmic symphony orchestra

2.1. General features of the retina

The retina is made up of five major classes of neurons (photoreceptors, horizontal cells, bipolar cells, amacrine cells, and ganglion cells) and glia (Tessier-Lavigne, 1991) (see Scheme 1). Retinal neurons are linked in a complex pattern of connections, but with an orderly, layered anatomical arrangement. The structural organization of the retina comprises three nuclear layers: outer nuclear layer (ONL), inner nuclear layer (INL), and ganglion cell layer (GCL). The retina is apposed to the retinal pigment epithelium (RPE) at the back of the eye. Photoreceptors (PRC), bipolar, and horizontal cells form synaptic connections with each other in the outer plexiform layer (OPL), whereas bipolar, amacrine and retinal ganglion cells (RGCs) make contact in the inner plexiform layer (IPL) (see Scheme 1). In most parts of the retina, light passes through layers of nerve cells (GCL and INL) and their processes (IPL and OPL) before reaching the PRCs. After photoreception, information flows vertically from PRCs to bipolar cells and to RGCs. Information also flows laterally, mediated by horizontal cells in OPL and amacrine cells in the IPL.

2.2. Visual photoreceptors

Rods and cones are the visual PRCs for all vertebrate species, and are made up of similar functional regions: the outer segment (OS), a specialized region for phototransduction located at the distal surface of the retina, the inner segment (IS), the cell's nucleus containing most of the biosynthetic machinery which is located more proximally within the retina, and a synaptic terminal that makes contact with the target cells (see Scheme 1). The OS of rods and cones are very specialized light captors, packed with different opsin photopigments contained in stacked membranous discs, which are constantly renewed. OS membranes have a high turnover involving an elaborate mechanism of new disc assembly at the base of the OS, and disc shedding at the tip of the segment leading to phagocytosis and digestion by the RPE (Bobu and Hicks, 2009; Strauss, 2005). RPE cells are also involved in the regulation of nutrients and ion movements toward the PRCs and in visual processes including vitamin A storage, isomerization and recycling, as well as absorbing excess light that impacts the eye (Bok, 1985).

One of the most striking features of the vertebrate retina is the presence of a variety of photopigments distributed in different cell layers, presumably displaying defined and diverse functions associated with image-forming and non-image-forming tasks (see Table 1 and Peirson et al., 2009 for further details). Indeed, the pathways for vision encode complex information such as color, motion, spatial relations and feature detection among others, whereas the pathway relevant to photic entrainment relies mainly on information related to the irradiance and duration of photic stimuli (Devlin and Kay, 2001; Nelson and Takahashi, 1991; Roenneberg and Foster, 1997). However, in physiological conditions a variety of photoreceptors (visual and non-visual) coexists in