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Neuromodulatory role of melatonin in retinal information processing

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ABSTRACT

The neurohormone melatonin is implicated in a variety of physiological processes. In the retina, a major source for melatonin production, melatonin is involved in modulation of neuronal activities. In this article we review recent advances in this research field, which is preceded by a concise account of general information about melatonin, melatonin receptors and intracellular signaling pathways for melatonin actions.

Melatonin is mainly synthesized in and released from photoreceptors in the retina. Different subtypes of melatonin receptors are present on major types of retinal neurons, and the expression of these receptors is highly species- and neuron subtype-dependent. By activating different melatonin receptor subtypes, melatonin modulates activities of retinal neurons. In the outer retina, melatonin regulates the activity of photoreceptors. In addition, melatonin reduces the light responsiveness of cone-driven horizontal cells, but potentiates rod signal to rod-dominant ON type bipolar cells in teleost fish or inhibits the TEA-sensitive potassium channel of rod-driven ON type bipolar cells in rats. In the inner retina, melatonin potentiates inputs from glycinergic amacrine cells to ganglion cells in rats. These actions of melatonin on retinal neurons are mediated by distinct intracellular signaling pathways via different subtypes of melatonin receptors and all serve to improve visual performance in a world of changing ambient illumination. The topics, concerning allosteric action of melatonin, interplay between melatonin and dopamine systems, and potential interaction between melatonin and melanopsin systems, are also discussed. An in-depth discussion of future directions in this research field is presented.

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1. Introduction

Melatonin (5-methoxy-N-acetyltryptamine) was first isolated and discovered by Lerner and co-workers in the late 1950s (Lerner et al., 1958, 1959, 1960). In vertebrates the synthesis of melatonin takes place primarily in the pineal gland and the retina, and the synthesis and release of melatonin show a marked circadian variation, being at higher levels during the night and at lower levels during the daytime (Cahill, 1996; Cahill and Besharse, 1992; Tosini and Menaker, 1996, 1998). Whilst it is well-established that melatonin is a major regulator of circadian rhythm, abundant evidence suggests that this hormone may be involved in the regulation of a variety of physiological processes, such as sleep, reproduction, immune and vascular response, etc. (see Dubocovich et al., 2010; Hardeland et al., 2011; Pandi-Perumal et al., 2008 for reviews). In recent years it has been demonstrated that melatonin may modulate the function of various types of neurons in the central nervous system (CNS) by modifying the activity of ligand- and voltage-gated ion channels (Dijk et al., 1995; Gillette and McArthur, 1996; Hou et al., 2004; Huang et al., 2005; Jiang et al., 1995; Larson et al., 2006; Liu et al., 1997, 2007; Mason and Brooks, 1988; Musshoff et al., 2002; Nelson et al., 2001, 1996; Ping et al., 2008; Shibata et al., 1989; Starkey et al., 1995; Wang et al., 2005; Wu et al., 1999; Yang et al., 2011; Zhang et al., 2007; Zhao et al., 2010). These actions of melatonin on central neurons are mediated by distinct intracellular pathways via activation of different subtypes of melatonin receptors.

The vertebrate retina, as a full-fledged part of the CNS, is generally thought to be an excellent model for exploring the neuronal mechanisms underlying elementary information processing in the brain. Melatonin is synthesized in and released from photoreceptors (Bernard et al., 1997; Cahill and Besharse, 1992; Chong et al., 1998, 2000; Wiechmann and Craft, 1993). Moreover, the presence of melatonin receptors has been demonstrated in the retinas of various species by *in situ* hybridization and immunohistochemistry (Fujieda et al., 1999; Huang et al., 2005; Natesan and Cassone, 2002; Reppert et al., 1995; Sallinen et al., 2005; Savaskan et al., 2002, 2007; Scher et al., 2002; Sengupta et al., 2011; Wiechmann, 2003; Wiechmann et al., 2004; Yang et al., 2011; Zhao et al., 2010). Numerous evidence suggests that melatonin is implicated in many retinal functions, such as retinomotor responses (photomechanical movements) (Kemali et al., 1986; Pang and Yew, 1979; Pierce and Besharse, 1985; Stenkamp et al., 1994), rod disc shedding (Besharse and Dunis, 1983; White and Fisher, 1989), dopamine release (Behrens et al., 2000; Boatright et al., 1994; Dubocovich, 1983; Nowak et al., 1989) and activities of retinal neurons (Behrens et al., 2000; Cosci et al., 1997; Huang et al., 2005; Li et al., 2001; Ping et al., 2008; Spiwoks-Becker et al., 2004; Wiechmann et al., 1988; Yang et al., 2011; Zhang et al., 2007; Zhao et al., 2010).

In this article, we first provide some basic information concerning melatonin and its receptors, which is followed by a brief account of general signal transduction mechanisms of melatonin receptors. Against a background regarding the synthesis and release of melatonin in/from photoreceptors and the expression profiles of melatonin receptors in the retina, we then concentrate on reviewing how melatonin modulates the functions of major retinal neurons and discussing the possible underlying mechanisms. We do not attempt to make a comprehensive treatment of the topic, complete with references. Rather, we tend to illustrate the main points by presenting examples, including ones from the work of the authors' laboratory. Readers interested in biology of melatonin and its receptors and more general physiological actions of melatonin are suggested to refer to excellent prior reviews (Dubocovich et al., 2010; Ekmekcioglu, 2006; Hardeland et al., 2011; Iuvone et al., 2005; Jockers et al., 2008; Lundmark et al., 2006; New et al., 2003; Pandi-Perumal et al., 2008; Reiter et al., 2010; Sugden et al., 2004; Tosini et al., 2008; von Gall et al., 2002; Wiechmann and Summers, 2008; Witt-Enderby et al., 2003).

2. Synthesis and degradation of melatonin

2.1. Two melatonin synthesis systems: pineal gland and retina

The pineal gland that is located in the center of the vertebrate brain is the major organ for melatonin synthesis. Historically, as early as in 1893, Robert Wiedersheim considered the pineal gland, along with other 85 organs, as a "vestigial remnant" of evolution or development (Wiedersheim, 1893). While extracts of cow pineal gland were found to lighten the frog skin in 1917 (McCord and Allen,