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Review

Melatonin in the eye: Implications for glaucoma

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Abstract

Melatonin synthesis occurs in the retina of most animals as well as in humans. Circadian oscillators that control retinal melatonin synthesis have been identified in the eyes of different animal species. The presence of melatonin receptors is demonstrable by immunocytochemical studies of ocular tissues. These receptors may have different functional roles in different parts of the eye. In view that melatonin is a potent antioxidant molecule, it can be effective in scavenging free radicals that are generated in ocular tissues. By this mechanism melatonin could protect the ocular tissues against disorders like glaucoma, age-related macular degeneration, retinopathy of prematurity, photo-keratitis and cataracts. Although an increased intraocular pressure is an important risk factor in glaucoma, other concomitant phenomena like increased glutamate levels, altered nitric oxide metabolism and increased free radical generation seem to play a significant role in its pathogenesis. Data are discussed indicating that melatonin, being an efficient antioxidant with antinitridergic properties, has a promising role in the treatment and management of glaucoma.

Keywords: melatonin; glaucoma; intraocular pressure; antioxidant properties; glutamate excitotoxicity; free radicals

1. Introduction

Melatonin is a ubiquitous natural substance widely distributed in nature, both in plants and animals. It is probably one of the first regulatory compounds that appeared in living organisms (Claustrat et al., 2005; Pandi-Perumal et al., 2006). In all mammals including humans, circulating melatonin derives primarily from the pineal gland. Local synthesis of melatonin also occurs in several peripheral organs (Kvetnoy, 2002) such as bone marrow, gut, gastrointestinal tract, lymphocytes and various parts of the eye including the retina (Cardinali and Rosner, 1971a,b; Tosini and Menaker, 1998), ciliary body (Martin et al., 1992) and lacrimal gland (Mhatre et al., 1988).

In the eye, locally synthesized melatonin may regulate retinomotor movements (Pierce and Besharse, 1985), rod outer segment disc shedding (Wiechmann and Rada, 2003), dopamine synthesis and release (Doyle et al., 2002) and intraocular pressure (IOP) (Wiechmann and Wirsig-Wiechmann, 2001). Moreover, melatonin can be an effective antioxidant in the retina, acting as a direct and indirect free radical scavenger. In this sense, melatonin was shown to protect photoreceptor outer segment membranes from free radical attack induced by light (Marchiafava and Longoni, 1999; Siu et al., 1999, 2006). The reduction in antioxidant defenses has been suggested as one of the causes for early stage glaucoma (Bunin et al., 1992; Moreno et al., 2004). Selective death of retinal ganglion cells (RGCs) that occurs in glaucoma leads to optic neuropathy (Osborne et al., 1999).

Intraocular hypertension and vascular insufficiency in the optic nerve are suggested as main risk factors for glaucoma

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(Ritch, 2000). Although the current management of glaucoma is mainly directed at the IOP control, the use of neuroprotective agents represents a new avenue for effective therapy in glaucoma (Chew and Ritch, 1997; Osborne et al., 1999; Weinreb and Levin, 1999).

In the last decade melatonin has emerged as a promising neuroprotective agent in experimental animal models of various neurological and neurodegenerative disorders (Reiter, 1998; Srinivasan et al., 2005, 2006). In the present review, we will discuss the evidence supporting the use of melatonin as a useful therapeutic strategy in the management of glaucoma.

2. Melatonin biosynthesis in the eye

In the eye, melatonin is synthesized through the same pathway as that described in the pineal gland. Tryptophan is taken up from the blood and is converted to serotonin. Serotonin is then converted into *N*-acetyl serotonin by the enzyme arylamine *N*-acetyl transferase (AA-NAT). *N*-acetyl serotonin is converted to melatonin by the enzyme hydroxyindole-*O*-methyl transferase (HIOMT). The existence of melatonin biosynthetic pathway in the mammalian retina was initially supported by the discovery of retinal HIOMT activity (Cardinali and Rosner, 1971b) and by the finding that labeled serotonin is converted into melatonin in the rat retina (Cardinali and Rosner, 1971a). The presence of HIOMT in the retina (both protein and mRNA) has been confirmed in other animals (Bernard et al., 1999; Liu et al., 2004). The gene encoding HIOMT is selectively expressed in retinal photoreceptors. In a recent study, the promoter of HIOMT gene *Otx*2 was localized in the retina and the pineal gland (Dinet et al., 2006). The findings are significant in view of the fact that the Otx2 protein is present at ''the right place and at right time'' to play a role in the onset of HIOMT gene expression in retinal photoreceptors and pineal gland of chickens (Dinet et al., 2006). Although available data strongly support that photoreceptors synthesize melatonin independently from the rest of the retina, recent evidence indicates that melatonin could also be synthesized by chick RGCs (Garbarino-Pico et al., 2004).

As in the pineal gland, retinal melatonin content significantly changes during the 24-h cycle (Hamm and Menaker, 1980; Zawilska and Nowak, 1989). The enzyme AA-NAT exhibits a circadian rhythm with peak concentration occurring at night (Niki et al., 1998; Iuvone et al., 2002). It has been suggested that retinal melatonin synthesis is related to cyclic events that normally occur in the retina (Wiechmann, 1986). The existence of a diurnal rhythm of melatonin in the retina of rats suggests its involvement in the regulation of the diurnal rhythm of eye pigmentation in vertebrates (Pang et al., 1980).

3. Regulation of melatonin biosynthesis in the eye

Melatonin biosynthesis by the pineal gland is regulated by the light/dark cycle (Moore, 1997). Specialized melanopsin-containing neurons that respond to light has been detected in the eye (Brainard et al., 2001a,b; Foster and Hankins, 2002) and this is the neural source of light input to the suprachiasmatic nuclei (SCN). This unique subset of intrinsically photosensitive retinal ganglion cells express melanopsin, the primary circadian photopigment in rodents and primates. Action spectra of melatonin suppression by light have shown that light in the 446–477 nm range, distinct from the visual system's peak sensitivity, is optimal for stimulating the human circadian system (Brainard et al., 2001a,b; Foster and Hankins, 2002).

The finding that isolated photoreceptor cells rhythmically secrete melatonin suggests that photoreceptors contain an endogenous ''clock'' that regulates melatonin biosynthesis (Cahill and Besharse, 1993). This has been confirmed in the mammalian retina; photoreceptors, either rods or cones, contain circadian oscillators (Tosini and Menaker, 1996, 1998). The genes that have been recognized as components of the core oscillator in the SCN are also present in the retina. The clock genes *Cry* 1 and *Cry* 2 are expressed in inner retinal neurons and ganglion cell layer (Bailey et al., 2002; Haque et al., 2002). Other genes, like *Per* 1 and *Per* 2 were identified in the inner retina (Namihira et al., 2001), in the inner nuclear layer, and in few ganglion cells of mouse and human retina (Witkovsky et al., 2003; Thompson et al., 2004). Experiments with the rd (rodless) mouse have shown that melatonin synthesis is not abolished by the complete loss of photoreceptors but its circadian expression disappears (Tosini and Menaker, 1998; Tosini, 2000). This finding suggests that rods are necessary for the rhythmic synthesis of melatonin.

Retinal melatonin levels are regulated by the interaction between the circadian clock and the photic environment. Retinal melatonin levels rise rapidly during darkness and decrease after exposure to light (Fukuhara et al., 2001). The depolarization of photoreceptors that takes place during darkness induces AA-NAT activity by a Ca^{2+}- and cAMP-dependent mechanism (Ivanova and Michael, 2003). Depolarization of the photoreceptor membrane opens dihydropyridine sensitive voltage gated Ca^{2+} channels resulting in a sustained increase of intracellular Ca^{2+} concentration in the inner segments of photoreceptors which in turn stimulates cAMP formation through activation of a calmodulin-dependent adenyl cyclase (Gan et al., 1995; Uchida and Iuvone, 1999). This increased formation of cAMP induces AA-NAT gene transcription and increases AA-NAT activity, thus causing the increased production of melatonin (Alonso-Gomez and Iuvone, 1995; Greve et al., 1999).

A circadian clock that gates melatonin synthesis and that involves transcription factors has recently been proposed (Fukuhara et al., 2004). The gating is effected through E box-mediated transcriptional activation of the *AC1* gene. This regulates melatonin synthesis through the expression of type 1 adenyl cyclase and the synthesis of cAMP in photoreceptors (Fukuhara et al., 2004). The gating of cAMP signaling presumably plays a key role as input and output components of the central circadian axis, i.e., the retina, the SCN and the pineal gland.