

Improving Melatonin Delivery Within the Eye

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Abstract

Melatonin is a neurohormone synthesized in the pineal gland as well as in other organs and it plays an important role in many ocular functions, as it is synthesized in numerous eye structures. Melatonin can reduce the intraocular pressure and to serves as an antioxidant preventing against free radicals, hence cataract formation as well as retinal damage due to glaucoma, among other functions. Ocular pharmacology is a challenging field giving the difficulties of drug delivery inside the eye due to its low bioavailability. In this sense, the present brief commentary is summarizing the latest advances in non-invasive ocular drug delivery focused on the effect of melatonin in different ocular diseases.

Short Commentary

Melatonin is an ancient molecule which was first identified in the late 1950s [1]. It exists in almost every organism starting from the primitive ones as prokaryotes to the very complex organisms as the humans. Melatonin is known as a circadian rhythm regulator [2]. This indoleamide is a neurohormone considered classically to be secreted by the pineal gland, nonetheless, it is currently known to be synthesized in other organs and tissues such as the retina and cerebellum [3,4], iris, ciliary body [5], crystalline lens [6,7], Harderian gland [8] and the lacrimal gland [9], spleen, heart, skeletal muscle, liver, stomach, gut, placenta, testes, ovaries, cerebral cortex and striatum [10].

Melatonin levels in the body are variable giving the time of the day, it increases at night and when light enters the eye and reach the retina, melatonin is suppressed [11], such photoreception being due to specific ganglion cells in the retina containing the pigment melanopsin [12]. This neurohormone is of great importance in the eye, apart from the retina it has numerous functions, such as working as an antioxidant protecting ocular structures against free radicals. For instance, melatonin intraperitoneal injection on rats instantly following an oxidative stress has shown to protect the lens against cataract [13]. Melatonin is inversely related to intraocular pressure since IOP decreases at night while melatonin increases [14]. It also has been proved to reduce intraocular pressure (IOP) by decreasing the rate of aqueous humour secretion by the non-pigmented ciliary epithelium, resulting in a modulation of IOP [15]. More importantly, melatonin is important for the cornea. Studies showed that melatonin accelerate corneal wound healing, and it has been possible to demonstrate that the effect of melatonin is to increase the rate of cell migration rather than mitosis [16]. Besides, melatonin has the ability to potentiate the effect of diadenosine tetraphosphate, a tear secretion inducer, being suitable to treat one of the most prevalent ocular conditions: Dry eye [17].

Treating ocular conditions have many challenges due to poor drug delivery because of effective multiple barriers to drug entry, comprising nasolacrimal drainage, epithelial drug transport barriers and clearance from the vasculature in the conjunctiva [18]. While topical ocular bioavailability is extraordinary poor, in the order of 5% or less, sustained delivery systems for diseases of the posterior segment such as various vitreoretinal disorders through intraocular delivery systems are used *via* implantable devices or injections [19]. However, independently of the fact that intraocular drug delivery systems are invasive, up to date, long-term drug delivery for diseases of the anterior segment of the eye does not exist.

There are several ways for drugs to reach the ocular system, for

instance, melatonin orally administered at a concentration of 10 mg to patients before performing cataract surgery have shown to lower intraocular pressure, consequently, they had better operating condition [20]. Melatonin was also investigated for the treatment of uveitis in hamsters, experiments were done by injecting 5 mg of melatonin before the induction of uveitis, and results suggested that melatonin prevents the clinical and biochemical consequences of this disorder [21].

Among several factors leading to poor bioavailability of drug administered topically, the cornea is the primary barrier of the anterior segment due to lipophilicity and tight junctions which restrain the entrance of pharmacological substances [22]. In this sense, experiments have demonstrated that when melatonin or any of its analogues is topically applied, the amount that appears within the eye was between 3 and 4 orders of magnitude lower than the instilled amount [23]. This relevant fact is suggesting that it is necessary to improve the delivery ways to permit better results with less amount of melatonin.

There are three main ideas that can be highlighted: One can be to facilitate the entrance through the cornea by modifying the barrier effect. Second, to permit melatonin to remain longer on the ocular surface to allow a slow but a sustained entrance of this substance. Third to induce the intraocular synthesis of melatonin by modulating light wavelength.

Concerning the first idea, an interesting study showed that the molecule diadenosine tetraphosphate (Ap4A), has the ability to make transiently disappear the corneal tight junctions permitting efficient drug delivery to the eye. A study showed that 5-MCA-NAT, a melatonin analog, had more hypotensive effect when instilled topically on New Zealand white rabbits when diadenosine tetraphosphate was applied two hours before the melatonin analogue. Indeed, when 5-MCA-NAT was topically applied after using diadenosine tetraphosphate, the amount of this melatonin analogue found within the eye was 3-fold the one measured when it was instilled alone [24]. This is indicating that

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the transient elimination of the corneal tight junctions is an effective mechanism to permit the entrance of molecules into the eye [25].

The second idea consists of permitting melatonin to remain longer on the ocular surface. A possible alternative for a long-term drug delivery is the use of contact lenses, in such a way, ocular bioavailability will be improved considering reduced tear mixing between the lens and the cornea besides the extended drug release [26]. The traditional method is to soak the lens in drug solution in order for the drug to be absorbed into the polymeric lenses, this way permits limited and slow release of the drugs into the post-lens lacrimal fluid [18,27]. Melatonin and analogues can be soaked in contact lenses overnight and the lenses can be fitted to obtain a sustained release of these substances. In this way, when melatonin is topically instilled it lasted no more than 2 min on the ocular surface as happens with all compounds applied in this way [18]. When melatonin and analogues are released from contact lenses the maximal release occurs 2 hours after the lens fitting, their presence being measurable for more than 300 min, as it happens with other naturally occurring substances [27]. This slow but sustained release of melatonin will permit the entry of this substance and therefore a more robust intraocular effect.

The third idea is based on modifying the light that enters the eye in order to induce the natural production of melatonin in the lens, instead of applying it exogenously. Recently, it has been possible to describe the presence of melanopsin in the lens epithelium [28]. This pigment abolishes the synthesis of melatonin when the lens is illuminated with blue light (including the blue component of white light). Therefore, it is possible to induce the synthesis of melatonin by reducing the blue component of white light (460-490 nm wavelength) by means of filters. Interestingly, white light permits a discrete synthesis of melatonin in lens epithelial cells (about 20 pmol/10⁶ cells), but the blockade of blue light permits levels which are 3-fold higher (60 pmol/10⁶ cells) [28]. This regulation of the local synthesis of melatonin by filtering light, could be an interesting approach to induce melatonin synthesis intraocularly and to help in processes such as the reduction of IOP and cataract prevention.

In summary, melatonin has proven effective for several ocular disorders and it could be interesting to investigate the best possible way for its delivery giving the challenges ophthalmologists are facing due to limited non-invasive drug delivery systems to the eye.

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