

Melatonin and derivatives as promising tools for glaucoma treatment

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Core tip: This mini review depicts the main features of melatonin and derivatives as interesting agents for the treatment of the ocular hypertension associated with glaucoma.

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Abstract

Neurohormones melatonin and its analogues are present with an important physiological and pharmacological ability to reduce intraocular pressure (IOP); thus, they are suitable for the treatment of ocular hypertension often associated with glaucoma. It is demonstrated that two of its analogues, 5-MCA-NAT and IIK7, are more effective than melatonin to reduce IOP for a longer period of time. The research for the discovery of better compounds resulted in the development of newer and improved analogues compared to 5-MCA-NAT and IIK7. Furthermore, already commercially available drugs currently used as treatment for other pathologies, presenting a resemblance to the melatonin structure, are being tested as potential glaucoma drugs. In this sense, agomelatine, which is already used as an anti-depressant medicine, is recognized as a worthy candidate since it reduces IOP, even under hypertensive conditions. To sum up, the use of melatonin and its analogues as promising anti-glaucomatous substances is of great importance and should be given serious consideration.

INTRODUCTION

There is a general interest in searching for novel compounds capable of reducing intraocular pressure (IOP) as an improved alternative to the existing drugs. IOP can be lowered through the reduction of aqueous humor production or by increasing its outflow through the trabecular meshwork or uveoscleral pathways. The interest for searching for new compounds relies on the fact that most of the existing drugs produce important side effects, hampering the treatment of certain patients. Side effects are a common issue in glaucoma medications. β -blockers such as timolol can cause bradycardia and hypotension and they are unsuitable for patients suffering from cardiovascular problems^[1], asthma, obstructive pulmonary disease or corneal dystrophy^[2]. Cholinergic agonists such as pilocarpine produce fixed pupils and induce myopia and cataracts^[1], whereas prostaglandins (*e.g.*, latanoprost) cause eyelash growth, iris pigmentation^[3], muscle and joint pain^[2]. Frequently, ocular redness and ocular surface discomfort obligates patients to abandon the treatment.

Several new compounds and approaches are under development in companies' pipelines or in academic institutions. Among the plethora of substances, the naturally occurring are more attractive as its administration is expected to result in fewer side effects^[4]. Among these, the neurohormone melatonin emerges as a promising substance with interesting hypotensive properties^[5]. The use of 5-MCA-NAT (a melatonin analogue, see below) when applied to the eye does not produce severe side effects. It does not affect corneal and lens transparency nor cause redness or corneal edema. No negative effects were noticed in general ocular examinations^[5]. It is important to bear in mind that most of melatonin intake is not by prescription as it is considered a dietetic supplement. In this case, high dosages and an elevated number of intakes could produce some minor side effects. The Mayo Clinic indicates that the most common side effects are drowsiness, headache and dizziness. Moreover, large doses of melatonin can interfere with some medications, such as anticoagulants, immunosuppressants, diabetes medications and birth control pills.

There are two interesting works describing the melatonin effect and its analogues on reducing IOP. Serle *et al.*^[6] demonstrated that a melatonin analogue was able to reduce IOP in glaucomatous monkeys, suggesting these molecules as a possible treatment of ocular hypertension related to glaucoma. Additionally, a group of ophthalmologists started to use melatonin during cataract surgery because it reduces IOP substantially, which is recommendable during phacoemulsification^[7].

From these two relevant works, the question arises as why these groups decided to use melatonin and its analogues for clinical purposes and mainly for reducing IOP. The present mini review introduces the reader to the basis of why melatonin is an attractive molecule to reduce IOP and why it should be considered in the future as a respectable alternative to the current ocular hypertension and glaucoma therapies.

MELATONIN, MORE THAN A PINEAL GLAND HORMONE

Melatonin is a molecule known by its chemical name N-acetyl-5-methoxytryptamine (Figure 1). It has been traditionally related to a particular area of brain, termed the pineal gland, where it is synthesized in low illumination conditions like during the night^[8] and it regulates many day-night processes, called circadian rhythms^[9]. It is necessary to emphasize that this substance is also synthesized in other tissues and ocular structures such as the retina, the ciliary body or the lens. This clearly suggests that melatonin can exert some local actions on the tissues where it is synthesized or in surrounding areas. Keeping in mind that melatonin is released by the lens or the ciliary body, its presence in the aqueous humor, modifying the physiology of these structures being bathed in the fluid, can be speculated about. Interestingly, one of the possible physiological processes to be modified is IOP.

It is documented that in many animal models there are changes in IOP during the day (high IOP) and night (low IOP). It is possible that both processes are associated considering the circadian pattern of melatonin production. Consequently, we should study what happens if we topically apply melatonin during the day when IOP is high.

MELATONIN REGULATES INTRAOCULAR PRESSURE

When melatonin is topically applied at a single dose of 100 µmol/L in a volume of 10 µL, there is a transient reduction in IOP and values return quickly to initial figures in about 2 h^[10]. This effect is similar to that of endogenous melatonin at night which reduces IOP. Despite the acquired hypotensive effect, the rapid return to normal pressure values suggests that either it is necessary to regulate the doses or to look for an alternative compound to produce a more sustained effect^[11].

There are several commercially available melatonin analogues depicting similar behavior to melatonin. Two compounds present sharper and long lasting effects on reducing the IOP compared to melatonin. In particular, the compound N-butanoyl-2-2-methoxy-6H-isindolo ([2,1-a]indol-11-yl) ethanamine (abbreviated as IIK7) has a hypotensive effect that lasts up to 7 hours and the compound 5-methylcarboxyamino-N-acetyltryptamine (also known as 5-MCA-NAT), which can reduce IOP for up to 9 h (Figure 1)^[12]. Consequently, 5-MCA-NAT is more interesting since it presents a longer term effect with a significant reduction of IOP for up to 96 h. This remarkable effect has been taken into consideration as we indicate below^[11] (Table 1).

5-MCA-NAT was tested in normotensive models as well as under hypertensive conditions, including glaucomatous monkeys (Table 1). Interestingly, the effects on the monkeys, a model closer to the human glaucomatous pathology, were extremely interesting. Compared to vehicle treatment, twice daily administration of 5-MCA-NAT for 5 d reduced IOP from 1 to 5 h after the first dose and the IOP-lowering effects were shown to last at least 18 h following administration, based on IOP measurements made after the fourth and eighth doses^[6].

One interesting characteristic to take into account was that the ocular hypotensive effect of 5-MCA-NAT was enhanced by repeated dosing. The maximum reduction of IOP was acquired 3 h after each morning dose and was 10% on day 1, 15% on day 3, and 19% on day 5 (control = 100%). No adverse ocular or systemic side effects were observed during the 5 treatment days, suggesting that this compound could be used perfectly as ocular hypertension treatment^[6] (Table 1).

IIK7 reduced intraocular pressure by acting through MT₂ melatonin receptors, presumably decreasing aqueous humor formation. Its effect is concentration dependent and it can reduce IOP 38.5% ± 3.2% when compared to controls (Table 1). It is important to notice that these

Table 1 Hypotensive effects of melatonin analogues: animal models, conditions and receptors involved

| Compound species | IOP reduction | Receptor involved | Ref. |
|-----------------------|----------------|-----------------------------------|---------|
| Melatonin | | | |
| Human | 32.0% ± 3.2% | Unknown | [7] |
| Rabbit | 22.0% ± 1.6% | MT ₂ , MT ₃ | [10,11] |
| Mouse (glaucomatous) | 33.4% ± 2.5% | MT ₂ | UD |
| 5-MCA-NAT | | | |
| Monkey (hypertensive) | 19.2% ± 2.1% | MT ₃ | [6] |
| Rabbit | 42.5% ± 1.6% | MT ₃ | [10,11] |
| IIK7 | | | |
| Rabbit | 38.5% ± 3.2% | MT ₂ | [12] |
| INS48848 | | | |
| Rabbit | 36.0% ± 2.0% | MT ₃ | [22] |
| INS48852 | | | |
| Rabbit | 33.1% ± 1.4% | MT ₂ | [22] |
| INS48862 | | | |
| Rabbit | 26.0 V ± 1.3 V | MT ₂ | [22] |
| Agomelatine | | | |
| Rabbit | | | |
| Normotensive | 20.8% ± 1.4% | MT ₂ | [25] |
| Hypertensive | 68.8% ± 5.7% | MT ₂ | [25] |

The values represent the mean ± SEM for the indicated compounds in the respective animal model. IOP: Intraocular pressure; UD: Unpublished data.

experiments have not been performed in glaucomatous monkeys yet but only in rabbits^[12].

In summary, it seems that some compounds, such as melatonin, 5-MCA-NAT and IIK7, clearly reduce IOP. But what is the mechanism for this IOP reduction? What receptors activate these substances in order to produce the observed effects?

MELATONIN AND ITS ANALOGUES ACTIVATE MELATONIN RECEPTORS

Melatonin exerts its effect *via* membrane and nuclear receptors. The protein membrane receptors are better understood and until recently three proteins have been cloned. Two of these membrane receptors, termed MT₁ and MT₂, are melatonin receptors belonging to the 7-transmembrane G protein-coupled receptor family (GPCR). There have been claims that a third receptor exists, the MT₃ melatonin receptor, although it has not been cloned yet. Some authors have identified it as quinone reductase 2 (QR2), demonstrating features of a melatonin receptor in some animal models (for a review see^[9]).

MT₁, MT₂ and the probable MT₃ melatonin receptors are present in several ocular structures, according to pharmacological, biochemical and immunological studies^[13,14]. This evidence suggests that melatonin plays a role in physiological processes in ocular tissues, such as the modulation of IOP, and it has been documented that MT₂ and MT₃ are responsible for IOP reduction.

When melatonin, 5-MCA-NAT and IIK7 are applied to normotensive or hypertensive eyes, they produce a dissimilar IOP reduction, depending on the compound

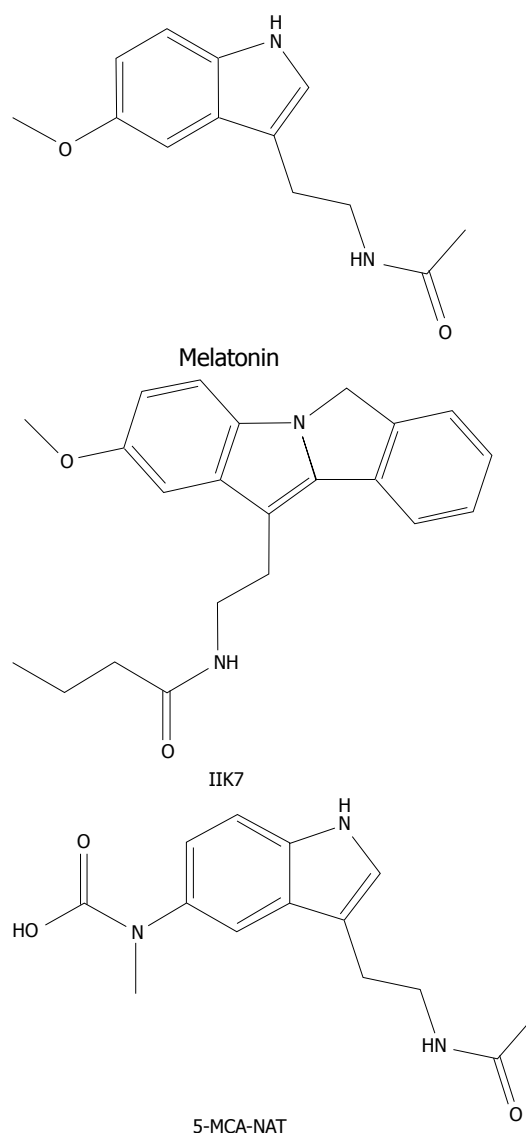


Figure 1 Chemical structure of melatonin and analogues. Melatonin (N-acetyl-5-methoxytryptamine), IIK7 (N-butanoyl-2-(2-methoxy-6H-isoindolo[2,1-a]indol-11-yl)ethanamine) and 5-MCA-NAT (5-methylcarboxyamino-N-acetyltryptamine).

under study. The use of selective antagonists for melatonin receptors has allowed identification of the presence of MT₂ melatonin receptors in the ciliary body of experimental animals, such as New Zealand white rabbits. This has been confirmed through immunohistochemical studies. In these studies it has been possible to verify the presence of MT₂ melatonin receptors on pigmented and non-pigmented ciliary epithelia. Accordingly, the application of melatonin or IIK7, which is a selective MT₂ agonist, results in a reduction in the production of the aqueous humor^[12] (Figure 2).

5-MCA-NAT has been suggested as an MT₃ melatonin receptor agonist that reduces IOP. To date, the location of the receptor is unknown. As there is a controversy with the possible identification of the MT₃ receptor which is tentatively identified in some animal models as QR2, some sophisticated experiments were performed to

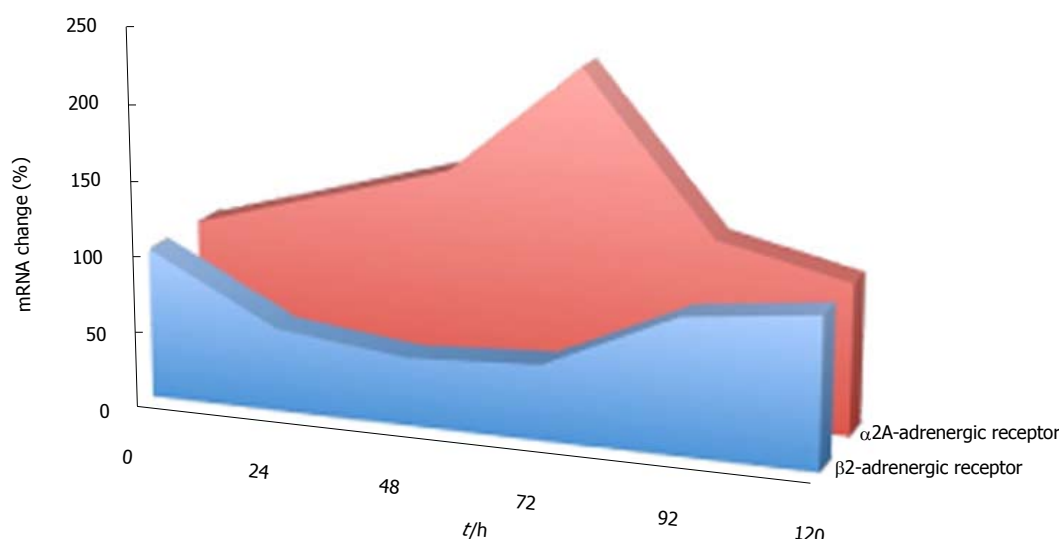


Figure 2 Expression of mRNA levels in ciliary body cells. The amounts of mRNA and concomitant adrenoceptors were changed after the application of 5-MCA-NAT. While there was an increase of α 2A-adrenoreceptors (in red), there was a decrease in the levels of β 2-adrenoreceptors (in blue).

clarify the issue^[15-17]. In New Zealand rabbits, the use of a siRNA silencing QR₂ (therefore avoiding the expression of this enzyme) did not abolish the hypotensive effect of 5-MCA-NAT, clearly indicating that, in this animal model, MT₃ \neq QR₂, opening the possibility of speculating about the existence of a receptor that needs to be cloned to fully understand its functioning and location^[18].

Apart from melatonin and its derivatives, some other compounds, like 5-MCA-NAT, can keep IOP below normal values for up to 5 d. This long-term effect is mediated by the action of melatonin receptors on the expression of genes expressing proteins important for the homeostasis of the aqueous humor.

To date, it has been possible to demonstrate that the 5-MCA-NAT long-term effect is in part the result of the expression inhibition of carbonic anhydrases. This down-regulation means that 24 h after 5-MCA-NAT application there is a reduction in IOP because the amounts of carbonic anhydrases are severely reduced. In particular, when 5-MCA-NAT is applied, carbonic anhydrase 2 is reduced 32% (protein levels), while carbonic anhydrase 12 is reduced 39% (protein levels). This reduction in protein expression mimics the carbonic anhydrase inhibitor action, such as dorzolamide or acetazolamide^[19].

Likewise, the expression of adrenergic receptors is modified by the application of 5-MCA-NAT. Interestingly, this melatonin analogue is able to produce a sequential process consisting of an initial reduction in the β 2-adrenoreceptors expression, followed by an increase in α 2A-adrenoreceptors^[20]. Altogether, these consecutive effects produce a sustained reduction in IOP lasting for at least 96 h^[21].

In summary, 5-MCA-NAT, apart from a sharp hypotensive effect, exerts a long term effect, maintaining low IOP for 4 d.

SO, WHAT IS NEXT NOW?

Several aspects need to be studied, taking into account that melatonin and analogues can significantly reduce IOP.

It is clear that it is necessary to research and design new melatonin analogues with more profound and long lasting effects^[5]. Inspire Pharmaceuticals Inc. (now absorbed by Merck) has designed several melatonin analogues with interesting hypotensive properties to reduce IOP. In recent studies, melatonin analogues, termed INS48848, INS48852 and INS48862, demonstrated similar behavior to melatonin, 5-MCA-NAT and IIK7^[22]. Indeed, these three compounds decreased IOP in a dose-dependent manner similar to melatonin, 5-MCA-NAT and IIK7, confirming their efficiency in decreasing IOP (Table 1). Concerning their selectivity on melatonin receptors, the effects of INS48848 were completely blocked by prazosin, an antagonist of MT₃ melatonin receptors, and were potently inhibited by luzindole, a non-selective antagonist of melatonin receptors. However, DH97, a selective MT₂ receptor antagonist, had a limited effect against INS48848 and the results obtained from INS48862 and INS48852 were contradictory. Luzindole and prazosin had no significant effects against those two compounds, whereas DH97 blocked them completely. These results strongly suggest that INS48848 could be acting through the MT₃ melatonin receptors and that INS48862 and INS48852 could be acting preferentially through MT₂ melatonin receptors. In any case, all these compounds are worthy candidates to reduce IOP, especially when it is abnormally elevated^[22].

Another alternative to the development of newly synthesized compounds is to search for melatonergic compounds already used for other medical purposes. Compounds such as ramelteon ((S)-N-[2-(1,6,7,8-tetrahyd-

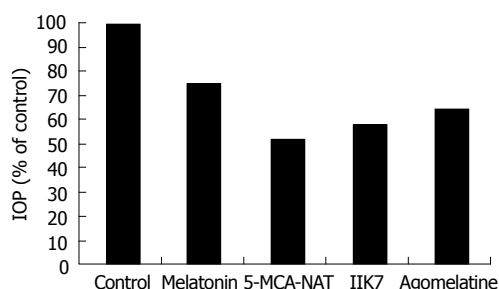


Figure 3 Comparative effects of melatonin and analogues in an animal model. Equal doses of melatonin or the corresponding analogues (100 $\mu\text{mol/L}$, 10 μL), reduced intraocular pressure in New Zealand white rabbits. Differences among the compounds rely on the activation of different receptors in each case (see text).

ro-2H-indeno-[5,4-b]furan-8-yl)ethyl]propionamide), also known as *Rozzerem*, used for sleep disorders^[23] or agomelatine (N-[2-(7-methoxynaphthalen-1-yl)ethyl]acetamide), known also by the names *Valdoxan*, *Melitor*, *Thymanax*^[24], used for the treatment of depression, could be candidates to reduce IOP since their structure is similar to melatonin.

There is a lack of information regarding the use of ramelteon in IOP studies. Agomelatine significantly reduces IOP when topically applied on rabbit eyes. Agomelatine (10 μL , 100 $\mu\text{mol/L}$) reduced IOP by $20.8\% \pm 1.4\%$ and its maximal IOP reduction was 180 minutes after the compound application. Interestingly, this compound exhibited an ability to reduce IOP in hypertensive conditions. It is noteworthy to stress that under high IOP the ability of this melatonin analogue to reduce IOP was $68.8\% \pm 5.7\%$ (Figure 3, Table 1)^[25].

There is a clear advantage in using compounds already commercialised for other conditions as the timeline for testing and clinical trials is significantly reduced.

CONCLUSION

It is necessary to perform an exhaustive study on the role of melatonin and its analogues in the different ocular structures since it is very probable that this knowledge will contribute to the discovery of more effective treatments for pathologies like glaucoma, corneal wound healing, cataracts or retinal pathology^[26].

Taking into account the importance of the role of melatonin and its analogues in hypertension, often associated with glaucoma, it is quite evident that these compounds should be used as treatment to reduce IOP. Melatonin or agomelatine can simply and rapidly reduce IOP, although further research is required to prove that they can be safely used as treatment for ocular hypertension.

Most of the presented data resulted from experiments assaying melatonin or its analogues on animal models. We still have a long way to go to test these compounds on human beings. Nevertheless, there are a lot of positive points regarding the efficacy of certain melatonin-ergic compounds. For instance, melatonin itself is able to reduce IOP in normotensive humans, as previously described^[7]. These authors reported an approximate

30% reduction in IOP during cataract surgery compared to the initial patient's pressures. This is quite interesting because the IOP reduction has been obtained in normotensive patients and it could be even more substantial in hypertensive (glaucomatous) patients. Several experiments in animal models demonstrated that melatonin and analogues are able to reduce IOP equally in normotensive and hypertensive animals, being more effective in hypertensive than in normotensive animals (Table 1). Also, experiments performed with 5-MCA-NAT on hypertensive monkeys, a step before human clinical trials, have proved that this melatonin analogue reduced IOP.

In conclusion, agomelatine is the compound that we strongly believe should be tested in glaucomatous patients for its ability to reduce IOP. Agomelatine is already used as a depression treatment drug under the commercial name Valdoxan^[24]. Since many of the pre-clinical tests have already been completed, we should not be surprised if agomelatine clinical trials start and it becomes the first melatoninergic compound to join the group of glaucoma treatment substances.

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